Medicinrådet

Bilag til Medicinrådets vurdering af neoadjuverende durvalumab i kombination med kemoterapi efterfulgt af adjuverende durvalumab til behandling af ikke-småcellet lungekræft

Voksne patienter med resektabel stadie II-IIIB-sygdom (AJCC TNM vers. 8)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab til NSCLC
2. Forhandlingsnotat fra Amgros vedr. durvalumab til NSCLC
3. Ansøgers endelige ansøgning vedr. durvalumab til NSCLC

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København

24.10.2025

Draft assessment report regarding durvalumab in combination with PDC for perioperative treatment of resectable non-small cell lung cancer

AstraZeneca would like to thank DMC for the assessment of durvalumab in the above-mentioned setting and appreciates the opportunity to comment on the draft assessment report.

Initially AstraZeneca would like to emphasize that as there are no other products available for perioperative treatment of resectable NSCLC that has been approved by DMC and as the relevance of the clinical studies on the approved products in the neoadjuvant and adjuvant respectively only to a certain extend are relevant as basis for an indirect treatment comparison, in general it is a challenge to perform an optimal analysis. Based on this, the application included 3 different comparators (neoadjuvant PDC, neoadjuvant nivolumab plus PDC and adjuvant PDC) in order to try and provide as detailed a picture of the relative benefit of durvalumab in this perioperative indication as possible.

In the assessment report, DMC mention that durvalumab is most likely to have more serious AEs compared to nivolumab in the AEGEAN and CheckMate-816 study regime respectively and mention that longer treatment duration may associate with more toxicity. However, AEGEAN and CheckMate-816 differ materially, e.g. stage distribution, TNM version, number of neoadjuvant cycles, platinum agent, and regional composition. As acknowledged in the assessment report, unadjusted direct comparisons between the two studies are not justified. Similarly, without appropriate statistical methods, any conclusions should not be drawn for safety comparisons. Notably, in AEGEAN, the control arm - which received no active treatment other than placebo after surgery - showed similar rates of serious adverse events as the intervention arm. This indicates that adjuvant durvalumab monotherapy after surgery did not contribute additional serious toxicity.

DMC notes that the AEGEAN study population may not be fully generalizable to Danish clinical practice for resectable NSCLC (e.g., higher proportions of stage III/N2, multiregional enrolment, and differences in neoadjuvant chemotherapy composition). These factors may attribute to uncertainty about real world effectiveness. However, no additional evidence is provided by the DMC in the evaluations report that would suggest the benefits of Durvalumab as a perioperative treatment would be overestimated, compared to standard of care in the Danish clinical setting.

In general, AstraZeneca considers that the patient population in scope has a potential severe prognosis, with a five-year survival between 46% and 57%, despite patients being treated with IO in the neoadjuvant phase. As this is a developing area, AstraZeneca has proposed to collect further evidence via an innovative agreement (conditional recommendation) to support the decision to use perioperative treatment of NSCLC in Danish clinical practice.

We look forward to receiving the DMC decision with the hope that durvalumab will be made available for patients with resectable NSCLC, and that DMC sees the relevance of providing more evidence on possible selection criteria for eligible patients for perioperative treatment.

Kind regards,

Mette Lange, Market Access Manager

Kun Kim, HTA Manager

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27.10.2025

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	19.11.2025
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Indikation	Durvalumab i kombination med platinbaseret kemoterapi som neoadjuverende behandling, efterfulgt af durvalumab som monoterapi som adjuverende behandling, er indiceret til behandling af voksne med operabel ikke-småcellet lungekræft (NSCLC) med høj risiko for recidiv og ingen EGFR-mutationer eller ALK-omlejringer.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende priser på Imfinzi (durvalumab).
[redacted]:

Tabel 1: Aftalepris [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	SAIP, pr. 01.11.2025 (DKK)	Forhandlet rabat ift. AIP
Imfinzi	50 mg/ml (10 ml)	16.943,88	[redacted]	[redacted]
Imfinzi	50 mg/ml (2,4 ml)	4.091,83	[redacted]	[redacted]

Aftaleforhold

Imfinzi indgår i udbuddet på immunterapier.

[redacted] Der er mulighed for at aktivere en prisregulering i aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ikke andre lægemidler anbefalet som peri-operativ behandling af NSCLC. Keytruda (pembrolizumab) er tidligere blevet vurderet til samme indikation af Medicinrådet, men blev ikke anbefalet.

Opdivo i kombination med kemoterapi er anbefalet af Medicinrådet til neoadjuverende behandling af patienter med PD-L1 ≥ 1 %, men patienter som får neoadjuverende behandling, skal ikke tilbydes adjuverende behandling efter operation jf. Medicinrådets anbefaling. Tecentriq (atezolizumab) er anbefalet som adjuverende behandling til patienter med PD-L1 ≥ 50 %.

Tabel 2 viser lægemiddeludgifter for hhv. neoadjuverende og adjuverende behandling. For neoadjuverende behandling gives behandling med Imfinzi i 4 serier (svarende til 12 uger), mens behandling med Opdivo gives i 3 serier (svarende til 9 uger). For adjuverende behandling gives behandling med Imfinzi i højst 12 serier (svarende til 48 uger), mens behandling med Tecentriq gives i højst et år (svarende til 52 uger). Tabel 2 nedenfor viser den samlede lægemiddeludgift for de enkelte behandlingsregimer beregnet på den maksimale behandlingslængde, behandlingsvarigheden er derfor ikke ens. Lægemiddeludgifter til kombinationsbehandling med kemoterapi er ikke medtaget i beregningen.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for hhv. neoadjuverende og adjuverende behandling af NSCLC.

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsregime (SAIP, DKK)
Neoadjuverende behandling				
Imfinzi	50 mg/ml (2,4 ml)	1.500 mg (i.v.) hver 3. uge i 4 serier *12 ugers behandling*	[redacted]	[redacted]
Opdivo	100 mg/10 ml (1 stk.)	4,5 mg/kg* (i.v.) hver 3. uge i 3 serier *9 ugers behandling*	[redacted]	[redacted]
Adjuverende behandling				
Imfinzi	50 mg/ml (2,4 ml)	1.500 mg (i.v.) hver 4. uge i 12 serier *48 ugers behandling*	[redacted]	[redacted]
Tecentriq	1.200 mg, 1 stk.	1.200 mg (i.v.) hver 4. uge i 52 uger *52 ugers behandling*	[redacted]	[redacted]

*Gennemsnitsvægt på 72 kg., jf. Medicinrådets evidensgennemgang vedr. uhelbredelig ikke-småceller lungekræft

Tabel 3 nedenfor viser den samlede lægemiddeludgift for peri-operativ behandling (neoadjuverende + adjuverende behandling) med Imfinzi.

Tabel 3: Samlede lægemiddeludgifter pr. patient for peri-operativ behandling med Imfinzi

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Peri-operativ behandling med Imfinzi				
Imfinzi	50 mg/ml (2,4 ml)	1.500 mg (i.v.) hver 3. uge i 4 serier	[redacted]	[redacted]
Imfinzi	50 mg/ml (2,4 ml)	1.500 mg (i.v.) hver 4. uge i højst 12 serier	[redacted]	[redacted]
Total lægemiddeludgift for peri-operativ behandling med Imfinzi				[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
England	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering

Opsummering

[redacted]

Imfinzi® (durvalumab) in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable non-small cell lung cancer (rNSCLC) at high risk of recurrence and no epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Description
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
BICR	Blinded Independent Central Review
BSC	Best Supportive Care
CI	Confidence interval
CrI	Credible interval
COPD	Chronic Obstructive Pulmonary Disease
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DCO	Data cut off
DFS	Disease-Free Survival
DIC	Deviance Information Criteria
DLCG	Danish Lung Cancer Group
DMC	Danish Medicines Council
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency

EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ESS	Effective sample size
GHS/QoL	Global Health Score/Quality of life
HCC	Hepatocellular Carcinoma
IASLC	International Association for the Study of Lung Cancer
IPD	Individual Patient Data
ITC	Indirect Treatment Comparison
ITT	Intent-To-Treat
MAIC	Matching-Adjusted Indirect Comparison
MID	Minimally Important Difference
mITT	Modified Intent-To-Treat
MMRM	Mixed Model Repeated Measures
mPR	Major Pathological Response
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
pCR	Pathological Complete Response
PDC	Platinum-based doublet chemotherapy
PD-L1	Programmed Death-ligand 1
PFS	Progression-Free Survival
PGIS	Patient Global Impression of Severity
PRO	Patient-Reported Outcome

QLQ-C30	Quality of life Questionnaire Core 30 questions
QLQ-LC13	Quality of life Questionnaire Lung Cancer module 13 items
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SCLC	Small Cell Lung Cancer
SLR	Systematic Literature Review
TLR	Targeted Literature review
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor, Node, Metastasis (Cancer Staging)
TPS	Tumor Proportion Score
TSD	Technical Support Document
TTD	Time to Treatment Discontinuation
TTDM	Time to Distant Metastasis
VAS	Visual Analogue Scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi®
Generic name	Durvalumab
Therapeutic indication as defined by EMA	Imfinzi® (durvalumab) in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable non-small cell lung cancer (rNSCLC) at high risk of recurrence and no epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements [1].
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01FF03
Combination therapy and/or co-medication	Neoadjuvant platinum-based doublet chemotherapy (PDC) [1].
(Expected) Date of EC approval	31/03/2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	NSCLC: • Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. • Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic

Overview of the medicine	
	NSCLC with no sensitising EGFR mutations or ALK positive mutations. Small Cell Lung Cancer (SCLC): • Durvalumab as monotherapy is indicated for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy. • Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). Biliary Tract Cancer (BTC): • Durvalumab in combination with gemcitabine and cisplatin is indicated for the first line treatment of adults with unresectable or metastatic BTC. Hepatocellular Carcinoma (HCC): • Durvalumab as monotherapy is indicated for the first line treatment of adults with advanced or unresectable HCC. • Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC. Endometrial Cancer (EC): Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: • Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) • Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).
Other indications that have been evaluated by the DMC (yes/no)	Yes, in the following indications: NSCLC: On May 30, 2025 DMC recommended durvalumab for stage III NSCLC in adults with

Overview of the medicine	
	PD-L1 ≥ 1% and whose disease has not progressed following platinum based chemoradiation therapy SCLC: On September 25, 2024, the DMC recommended durvalumab in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with ES-SCLC. BTC: On 04 March 2025, the DMC recommended durvalumab in combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic BTC in performance status 0 or 1. HCC: On 05 December 2024, the DMC recommended durvalumab in combination with tremelimumab for the first-line treatment of adults with advanced or unresectable HCC. EC: On May 2, 2025, the DMC recommended Durvalumab in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent endometrial cancer. Ongoing assessments by DMC: SCLC: Durvalumab as monotherapy for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes Is the product suitable for a joint Nordic assessment? No, as this assessment includes an indication extension for Imfinzi® and follows the DMC 14-week assessment process without a health economic assessment.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	N/A

2. Summary table

Summary	
Indication relevant for the assessment	Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, for the treatment of adults with rNSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements [1].
Dosage regiment and administration	Durvalumab should be administered intravenously in combination with platinum-based chemotherapy at a dose of 1,500 mg every three weeks for up to four cycles prior to surgery, followed by 1,500 mg monotherapy every four weeks for up to 12 cycles after surgery [1]. Treatment should be given in the neoadjuvant phase until disease progression that precludes definitive surgery, unacceptable toxicity, or maximum of four cycles and in the adjuvant phase until recurrence, unacceptable toxicity or a maximum of 12 cycles after surgery [1].
Choice of comparator	1. Neoadjuvant platinum-based doublet chemotherapy (PDC) 2. Neoadjuvant nivolumab plus PDC (PD-L1 ≥ 1%) 3. Adjuvant PDC.
Prognosis with current treatment (comparator)	Surgical resection with curative intent is recommended for patients with Stage I-III NSCLC [2, 3]. Despite the curative intent of surgery and the addition of neoadjuvant or adjuvant systemic therapy, recurrence rates remain high, and PDC offers only modest benefit in reducing recurrence or death [4-7]. Immuno-oncology (IO) therapies have shown improved outcomes in both neoadjuvant and adjuvant settings [8-12], but neoadjuvant IO is reserved for a subgroup of patients with PD-L1 ≥ 1% in Denmark. In Denmark, about 35% experience recurrence after surgery. Overall, ~40% of NSCLC patients treated with curative intent relapse within five years and only ~20% are eligible for curative retreatment, and the five-year survival for stage IIA–IIIA rNSCLC is 46%-57% [13, 14].
Type of evidence for the clinical evaluation	Head-to-head study AEGEAN (NCT03800134) for perioperative durvalumab versus neoadjuvant PDC. An indirect treatment comparison (ITC) versus neoadjuvant nivolumab + PDC (CheckMate 816 NCT02998528) and versus adjuvant PDC (NATCH NCT00913705).

Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	Perioperative durvalumab versus neoadjuvant PDC HR in EFS, 0.69 (95% CI: 0.55, 0.88) [15, 16]. [redacted]
Most important serious adverse events for the intervention and comparator	The most common serious adverse events (SAEs) in AEGEAN were infections and infestations, pneumonias, blood and lymphatic system disorders and respiratory disorders. In the CheckMate 816 trial, the overall incidence of SAEs was 17% for nivolumab + chemotherapy and 14% for chemotherapy alone. No serious adverse events were reported in NATCH for adjuvant chemotherapy.
Impact on health-related quality of life	Patient reported outcomes (PRO) were included as secondary endpoints in the AEGEAN study measured in the neoadjuvant period, with European Organisation for Research and Treatment of Cancer (EORTC): 1) Quality of Life Questionnaire Core 30 (QLQ-C30) and 2) Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) module [17]. In CheckMate 816, health related quality of life (HRQoL) was an exploratory endpoint with the EuroQoL 5 dimension 3 levels and Visual Analogue Scale (EQ-5D-3L VAS) questionnaire [18]. In both AEGEAN and CheckMate 816 studies, HRQoL scores were generally similar between treatment arms throughout the neoadjuvant and adjuvant periods, with no clinically meaningful or consistent differences observed. The NATCH trial did not collect QoL data.
Type of economic analysis that is submitted	N/A
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A

Summary	
QALYs gained	N/A
Incremental costs	N/A
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: 10 annually Prevalence: N/A
Budget impact (in year 5)	N/A

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for between 80% to 90% of cases [19-23]. Lung cancer is categorised according to the American Joint Committee on Cancer (AJCC) staging criteria, which utilise the tumour, (lymph) node, metastasis (TNM) system [24, 25]. Patients with Stage I–III NSCLC, representing ~30% of patients at diagnosis [26-29], are considered resectable and amenable to surgery with curative intent, referred to as rNSCLC. The goal is to completely remove the primary tumour and any involved regional lymph nodes [2, 30, 31]. This strategy is recommended by the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN) and the Danish Lung Cancer Groups (DLCG) treatment guidelines for patients with Stage I-IIIA, and in selected cases, for stage IIIB (AJCC TNM 8th edition) [2, 30, 31]. In Denmark, approximately 30% of patients are diagnosed with local disease (Stage IIA-IIIA), and 25% present with locally advanced disease (IIIA-IIIC) [13, 14].

Systemic therapy can be administered before (neoadjuvant) or after (adjuvant) surgery to reduce the risk of recurrence and improve the chances of cure. It is typically offered to patients at higher risk of recurrence. The definition of high risk of recurrence is based on lymph node involvement, tumour size, and other tumour characteristics [2, 31, 32], as per the AJCC TNM 8th edition [1]: Tumour size ≥ 4 cm and N1 or N2 disease (regardless of

primary tumour size), including multi-station N2; patients with multiple tumour nodules in the same lobe or tumours that involve the main bronchus or tumours that invade visceral pleura, chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve or parietal pericardium; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves part or all of the lung [1].

Despite the curative intent of surgery and the addition of systemic therapy, recurrence rates remain high, and the addition of PDC in the neoadjuvant or adjuvant setting has resulted in only modest reductions in the risk of recurrence or death [4-7]. In Denmark, approximately 35% have recurrence after surgery, and ~ 40 % of those who are treated for NSCLC with curative intent in Denmark will experience a recurrence within 5 years after surgery. Of these, only about 20% will be candidates for renewed potential curative treatment [33]. Once recurrence occurs, curative-intent therapy is generally no longer feasible, particularly in patients with metastatic disease [2, 31]. Consequently, the prognosis after recurrence is very poor [34-36]. The risk of recurrence is highest in the initial years following surgery and is further elevated in more advanced stages of NSCLC. By five years post-surgery, the risk of recurrence decreases substantially [37-40].

In Denmark, the overall five-year survival rate for lung cancer is 26% [49, 50], and the five-year survival following surgery is 64% [47]. For patients with recurrent Stage IIA-IIIA rNSCLC, five-year survival is estimated between 46% and 57% [34, 35].

IO regimens in the neoadjuvant setting or in the adjuvant setting have been shown to reduce recurrence rates after surgery [8, 9, 11, 12, 41]. Notably, neoadjuvant IO may offer an advantage over adjuvant IO by priming anti-tumour immunity while the primary tumour and regional lymph nodes are still present [42]. Despite these improvements, outcomes remain suboptimal, and there is room for further advancement. The perioperative approach, which integrates neoadjuvant IO (in combination with chemotherapy), surgery, and subsequent adjuvant IO, may provide additional clinical benefit compared to neoadjuvant IO alone or adjuvant chemotherapy. This strategy aims to consolidate the immune response and maintain suppression/eradication of residual cancer cells after surgery [43, 44]. As such, the perioperative approach offers a more comprehensive treatment strategy to maximise the chances of successful long-term outcomes for patients treated with curative intent.

3.2 Patient population

The relevant patient population for this application is adults with rNSCLC at a high risk of recurrence and no EGFR mutations or ALK rearrangements, which aligns with the population in the pivotal clinical trial AEGEAN [16].

Of all patients diagnosed with lung cancer in Denmark (approximately 4,900), 85% are diagnosed with NSCLC [3, 13, 14]. In the latest report from the Danish Lung Cancer Register, the incidence (patients diagnosed) of NSCLC was 4,161 in 2023. Table 1 gives an overview of the incidence in Denmark over the last five years. As no incidence have been presented from the register for 2024, the 2023 estimate was used. The proportion of

NSCLC patients who underwent curative intent treatment, defined as either resection or curatively intended oncological treatment (e.g., radiotherapy), was relatively stable, around 28% [45-47]. Of all patients with NSCLC, it has been estimated that 30% have local disease (stage II-IIIA) and 25% have locally advanced disease (stage IIIA-IIIC) [13, 14].

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	4,876	4,075	4,103	4,161	4,161*
Prevalence in Denmark	N/A	N/A	N/A	N/A	N/A
Global prevalence	N/A	N/A	N/A	N/A	N/A

Note: The estimate for the incidence in 2020-2023 are based on the number of patients diagnosed with NSCLC presented in the Danish Cancer Register yearly reports. *The incidence estimated for 2024, is based on 2023.

Source : Danish Lung Cancer Register, DLCG yearly reports 2019-2020 [45], 2021 [46], and 2023 [47].

When calculating the expected number of eligible patients for durvalumab + platinum-based doublet chemotherapy (PDC) as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, in adults with rNSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements, it was assumed that only stage III (stage IIIA–IIIB) patients would be treated during the first five-year period. This assumption is based on the current use of neoadjuvant nivolumab + PDC in Denmark, which is primarily administered to stage III patients. The following steps were used to estimate the number of eligible patients for rNSCLC SCLC who are eligible for treatment with durvalumab in Denmark:

- Lung cancer incidence (total): 5,125 patients
- NSCLC cases (80%): ≈ 4,100 patients
- Stage IIIA–IIIB (<N3) subset (12%): ≈ 492 patients
- Resectable patients (32%): ≈ 154 patients
- EGFR-wildtype (92%): ≈ 142 patients
- Receiving systemic drug therapy (85%): ≈ 121 patients
- Perioperative treatment share (40%): ≈ 48 patients
- Expected to receive IO (90%): ≈ 44 patients
- Estimated treated in Year 1 (based on rollout phase-in): ≈ 10 patients (Table 2):

Over time as perioperative treatment with IO is expected to increase, stage II patients will be treated in accordance with the durvalumab indication. When including the stage II patients, an additional 43 patients with perioperative IO is estimated of which 22% (9 patients) are assumed to be treated with durvalumab.

In previous assessments by the DMC, larger patient numbers have been estimated for perioperative and neoadjuvant IO in resectable NSCLC [48, 49]. In the assessment of

perioperative pembrolizumab + PDC, for stage II–IIIB NSCLC regardless of PD-L1 expression, the eligible patient population was estimated to 242–300 patients per year [49]. These estimates, however, do not account for patients who may not receive systemic therapy or who are ineligible for IO. In the assessment of neoadjuvant nivolumab in combination with PDC (hereafter referred to neoadjuvant nivolumab + PDC), which is recommended only for resectable NSCLC with PD-L1 ≥ 1%, the DMC estimated around 120 patients per year to be eligible [48].

The DMC, however highlight that in practice, only 40 to 50 patients annually are treated with neoadjuvant IO [48]. While previous estimates for neoadjuvant IO suggest a higher number of eligible patients, the perioperative estimates presented here are more conservative, including only stage III, EGFR-wildtype and systemic therapy use, leading to lower numbers that might increase as the use of perioperative IO broadens. We assumed 20% of the patients who received neoadjuvant therapy might be eligible for peri-operative therapy. Neoadjuvant IO has been used only for a short period of time in Denmark, so it is challenging to estimate the proportion at this point of time.

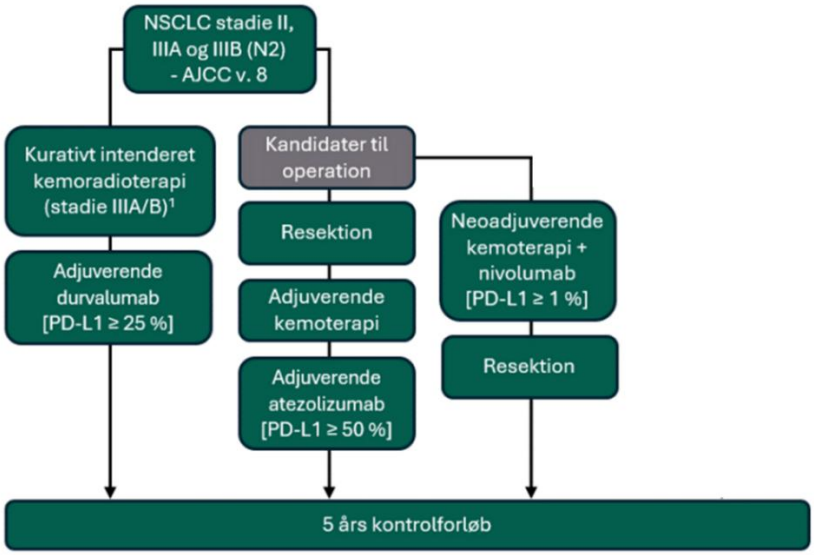
Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	10	10	10	10	10

3.3 Current treatment options

According to Danish treatment guidelines, patients with local or locally advanced NSCLC typically receive curative-intent treatment, which may involve surgery or chemoradiotherapy (CRT) [3, 13, 14]. An overview of the current treatment options is provided in Figure 1.

Figure 1 Current treatment algorithm and treatment options in Danish clinical practice



Source: Adapted from DMC assessment of perioperative pembrolizumab in adults with rNSCLC [49]

Abbreviation: PD-L1: Programmed Death-ligand 1;NSCLC: Non-small Cell Lung cancer

In Denmark, neoadjuvant treatment with nivolumab + PDC is recommended for operable patients with Stage II-IIIA (AJCC TNM 8th edition), PD-L1 expression ≥1%, and harbouring no targetable mutations [13]. Surgery should be performed within six weeks after completion of neoadjuvant therapy. This approach aims to improve outcomes by administering oncological therapy prior to surgery. The decision to initiate neoadjuvant therapy should always be made within a multidisciplinary medical team [13]. In general, patients who have received neoadjuvant treatment are not offered adjuvant therapy, though close follow-up is advised [13]. For patients who undergo surgery without prior neoadjuvant therapy, the adjuvant treatment strategy depends on stage and individual risk factors [14].

Adjuvant chemotherapy should be offered to NSCLC with stage IB, IIA (tumour >4cm), IIB and stage III disease (TNM 8th edition). PDC should be initiated 4-8 weeks post-surgery. The preferred regimen is cisplatin in combination with vinorelbine. If cisplatin is not suitable due to patient comorbidities or tolerability, carboplatin may be used as an alternative. Stage I patients may also be considered for adjuvant chemotherapy depending on recurrence risk. Stage II patients may receive adjuvant chemoradiotherapy in certain cases. Additionally, patients across stages I-III who are disease-free following curative treatment may be offered postoperative radiotherapy as part of adjuvant management.

In patients who have undergone curative-intent surgery, adjuvant immunotherapy may be offered to those at high risk of recurrence, provided they have [14]:

- Received platinum-based chemotherapy
- Tumours express PD-L1 ≥50%
- No EGFR mutations or ALK translocations.

In these cases, treatment with atezolizumab, an immune-check inhibitor, should begin within 8 weeks after completing adjuvant chemotherapy and continue for up to one year [14]. Close follow-up is recommended for all patients following curative treatment, particularly during the first two years, due to the elevated risk of local recurrence during this period [14].

Patients with stage III NSCLC who have undergone curative CRT and have PD-L1 Tumor Proportion Score (TPS) ≥25%, and no evidence of disease progression, may be eligible for adjuvant treatment with durvalumab for up to 12 months [14].

3.4 The intervention

Durvalumab is a high-affinity, human, recombinant IgG1κ monoclonal antibody that selectively blocks the interaction between PD-L1 and its receptors, PD-1 and CD80 (B7.1) [50]. PD-L1 is often overexpressed on tumour cells and antigen-presenting cells in the tumour microenvironment, where it downregulates immune responses by inhibiting T-cell activation. By preventing this interaction, durvalumab enhances T-cell-mediated immune responses against tumour cells, restoring cytotoxic activity, proliferation, and cytokine production [1, 50, 51].

The combination of PDC and durvalumab is believed to enhance anti-tumour responses through immunogenic effects and upregulation of PD-L1 expression, which may increase tumour sensitivity to immune checkpoint blockade. Chemotherapy-induced tumour cell death can promote antigen presentation, while increased PD-L1 expression may improve the efficacy of anti-PD-(L)1 therapies in poorly immunogenic tumours [52, 53]. Combining immunotherapy with chemotherapy has shown superior anti-tumour activity and response rates and may also help reduce the risk of treatment resistance [54, 55]. Clinical trial data in metastatic Stage IV NSCLC supports the effectiveness of this combination, suggesting potential utility in earlier treatment settings as well [56-59].

An overview of the intervention is provided in Table 3 below.

Table 3 Overview of the intervention, durvalumab (Imfinzi®)

Overview of intervention	
Indication relevant for the assessment	Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab monotherapy as adjuvant treatment, indicated for the treatment of adults with rNSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements [60]
ATMP	N/A
Method of administration	IV

Overview of intervention	
Dosing	Maximum of four cycles of PDC with durvalumab (1,500 mg) IV every three weeks, followed by surgery. Following surgery, durvalumab (1,500 mg) IV every four weeks for up to 12 cycles.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	Durvalumab is used in combination with platinum-based chemotherapy as neoadjuvant treatment.
Treatment duration / criteria for end of treatment	Prior to surgery patients receive up to four cycles of treatment every 3 weeks (12 weeks in total). Post-surgery patients can receive up to 12 cycles of treatment, with treatment every 4 weeks (total of 48 weeks).
Necessary monitoring, both during administration and during the treatment period	Patients are monitored during the administration of the drugs and during the course of the treatment period.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	The relevant biomarkers for ALK, EGFR mutations and PD-L1 expression are standard tests for these patients. Thus, no new tests are needed. N/A, as no CE-model is included in this application.
Package size(s)	50 mg/ml, 10 ml vial and 50 mg/ml, 2.4 ml vial.

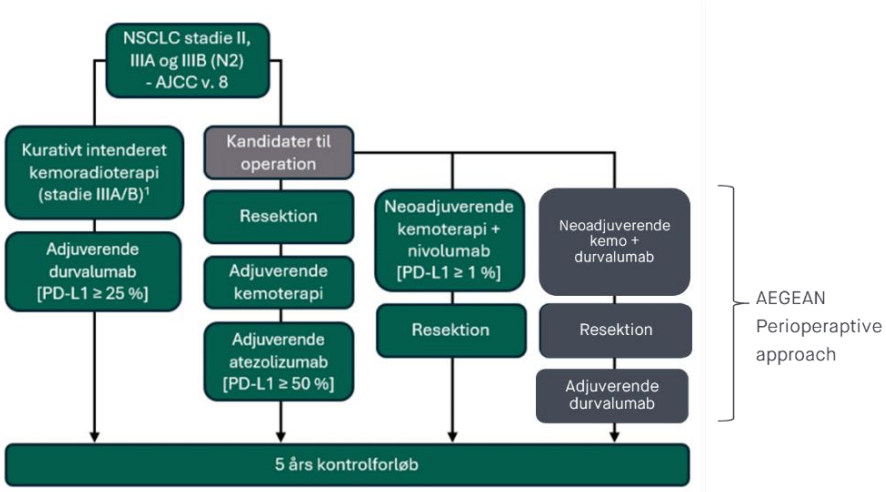
3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

When considering a perioperative setting (neoadjuvant therapy, surgery and adjuvant therapy), current clinical practice in Denmark includes the use of either neoadjuvant or adjuvant treatment (as presented previously in section 3.3 and Figure 1). The current standard of care (SoC) in the adjuvant setting consists of PDC. In Denmark the preferred PDC consist of cisplatin or carboplatin in combination with vinorelbine. In the neoadjuvant setting, PDC without nivolumab may still be considered in selected cases, for instance in patients with large tumours and N0 disease, where the intent is to reduce surgical morbidity (e.g., tumours adjacent to the chest wall). However, following the approval of neoadjuvant nivolumab + PDC by DMC, this has become the predominant SoC for patients with PD-L1 ≥1% [13]. The expected place in therapy for durvalumab + PDC as neoadjuvant treatment, followed by durvalumab monotherapy as adjuvant treatment after surgery, for adults with rNSCLC at high risk of recurrence and no known EGFR mutations or ALK gene rearrangements is presented in Figure 2.

Figure 2 Place in current treatment algorithm



3.5 Choice of comparator(s)

Durvalumab is indicated in combination with PDC (hereafter referred to as durvalumab + PDC or perioperative durvalumab) as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, for the treatment of adults with rNSCLC with no known EGFR mutations or ALK gene rearrangements and at high risk of recurrence.

As there are currently no nationally recommended treatments in the perioperative setting, the three comparators selected in this assessment are in line with DLCG treatment guidelines: neoadjuvant PDC (Comparator 1, see Table 4), neoadjuvant nivolumab + PDC in PD-L1 ≥1% (Comparator 2, see Table 5), and adjuvant PDC (Comparator 3, see Table 6).

Comparator 1, neoadjuvant PDC, follows the Danish clinical recommendations [3, 13] with cisplatin combined with vinorelbine as the first-choice regimen, since cisplatin causes less bone marrow toxicity than carboplatin. However, if cisplatin is not tolerated, carboplatin may be used in combination with vinorelbine. **Comparator 2**, neoadjuvant nivolumab + PDC, is recommended as SoC by the Danish guidelines in PD-L1 ≥1% [3, 13], with nivolumab administered at a dose of 360 mg alongside the same PDC regimen as, described for Comparator 1. **Comparator 3**, adjuvant PDC, is recommended as SoC by the Danish guidelines [14], the choice of PDC regimen can vary, but the preferred PDC is a as previously described for Comparator 1.

Other comparators were considered but excluded from the assessment. These included adjuvant atezolizumab following adjuvant chemotherapy, and CRT. Adjuvant atezolizumab treatment was not considered relevant, as results from the IMpower010 trial were not viewed as clinically convincing by clinical experts in Denmark [Section 14]. For example, at a median follow-up of 45.3 months, 25% of patients treated with atezolizumab had died, compared to a similar proportion of 24.9% in the best supportive care (BSC) treatment arm [61]. The 3-year disease-free survival (DFS) was 56% for the atezolizumab arm and 49% BSC, with a more pronounced effect observed in the PD-L1 ≥

50% subgroup, which showed a 3-year DFS of 75.1% compared to 50.4% [14, 61]. However, this subgroup does not align with the target population in this assessment.

Lastly, according to Danish guidelines, chemoradiotherapy is generally recommended only for patients who are not eligible for surgery or who decline surgical treatment, and is therefore not relevant as a comparator [3].

The other comparators considered were also discussed prior to the submission with DMC, who stated that although several comparators could be considered, it was acknowledged that not all could be expected to be included in this application.

Table 4 Overview of Comparator 1 - Neoadjuvant platinum-based chemotherapy

Overview of comparator	Cisplatin	Carboplatin	Vinorelbine
Generic name	Cisplatin "Accord"	Carboplatin "Accord"	Vinorelbine "Accord"
ATC code	L01XA01	L01XA02	L01CA04
Mechanism of action	Cisplatin binds directly to DNA, creating cross-links that block replication and transcription, leading to the death of cancer cells.	Carboplatin alters the supercoiled structure of DNA, disrupting replication and inhibiting the growth of cancer cells.	Vinorelbine blocks cancer cell division by disrupting microtubels, which are needed to separate chromosomes. This leads to cell death and slows tumour growth.
Method of administration	Intravenous infusion	Intravenous infusion	Orally
Dosing	80 mg/m², is given day 1 followed by every 22 days for 4 treatment cycles [62].	5* (GFR+25 mg), given day 1 and then at day 22 when a new cycle begins, 4 cycles in total [63].	60 mg/m², given on day 1 and 8 every cycle. Cycle is repeated 4 times [62].
Dosing in the health economic model (including relative dose intensity)	N/A	N/A	N/A
Should the medicine be administered with other medicines?	Can be administered together with vinorelbine.	Administered with vinorelbine.	Administered together with cisplatin or carboplatin.

Overview of comparator	Cisplatin	Carboplatin	Vinorelbine
Treatment duration/ criteria for end of treatment	4 cycles of treatment	4 cycles of treatment	4 cycles of treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No	No
Package size(s)	1mg/ml in a vial of 50 ml	10 mg/ml in a vial of 45 ml	20 mg, 1 capsule

Table 5 Overview of Comparator 2- Neoadjuvant nivolumab combined with platinum-based chemotherapy

Overview of comparator	Nivolumab	Cisplatin	Carboplatin	Vinorelbine
Generic name	Nivolumab "Opdivo"	Cisplatin "Accord"	Carboplatin "Accord"	Vinorelbine "Accord"
ATC code	L01FF01	L01XA01	L01XA02	L01CA04
Mechanism of action	Nivolumab is a human monoclonal antibody that blocks the PD-1 receptor on T-cells. By inhibiting PD-1 interaction with its ligands (PD-L1 and PD-L2), nivolumab restores T-cell activity and enhances the immune system's ability to recognise and destroy tumour cells.	Cisplatin binds directly to DNA, creating cross-links that block replication and transcription, leading to the death of cancer cells.	Carboplatin alters the supercoiled structure of DNA, disrupting replication and inhibiting the growth of cancer cells.	Vinorelbine blocks cancer cell division by disrupting microtubels, which are needed to separate chromosomes. This leads to cell death and slows tumour growth.
Method of administration	Intravenous infusion	Intravenous infusion	Intravenous infusion	orally

Overview of comparator	Nivolumab	Cisplatin	Carboplatin	Vinorelbine
Dosing	360 mg is given on day 1 and repeated every 3 weeks for 3 treatment cycles.	75 mg/m², is given day 1 followed by every 22 days for up to 4 treatment cycles.	900 mg, given day 1 and then at day 22 when a new cycle begins, up to 4 cycles in total.	60 mg/m², given on day 1 and 8 every cycle. Cycle is repeated up to 4 times.
Dosing in the health economic model (including relative dose intensity)	N/A	N/A	N/A	N/A
Should the medicine be administered with other medicines?	Administered together with either cisplatin+ vinorelbine or carboplatin+ vinorelbine.	Administered together with vinorelbine.	Administered with vinorelbine.	Administered together with cisplatin or carboplatin.
Treatment duration/ criteria for end of treatment	Up to 4 cycles of treatment	Up to 4 cycles of treatment	Up to 4 cycles of treatment	Up to 4 cycles of treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No	No	No
Package size(s)	40mg/4ml in a vial	1mg/ml in a vial of 50 ml	10 mg/ml in a vial of 45 ml	20 mg, 1 capsule

Table 6 Overview of Comparator 3 - Adjuvant platinum-based chemotherapy

Overview of comparator	Cisplatin	Carboplatin	Vinorelbine
Generic name	Cisplatin "Accord"	Carboplatin "Accord"	Vinorelbine "Accord"
ATC code	L01XA01	L01XA02	L01CA04

Overview of comparator	Cisplatin	Carboplatin	Vinorelbine
Mechanism of action	Cisplatin binds directly to DNA, creating cross-links that block replication and transcription, leading to the death of cancer cells.	Carboplatin alters the supercoiled structure of DNA, disrupting replication and inhibiting the growth of cancer cells.	Vinorelbine blocks cancer cell division by disrupting microtubules, which are needed to separate chromosomes. This leads to cell death and slows tumour growth.
Method of administration	Intravenous infusion	Intravenous infusion	Orally
Dosing	80 mg/m², is given day 1 followed by every 22 days for 4 treatment cycles [62].	5* (GFR+25 mg), given day 1 and then at day 22 when a new cycle begins, 4 cycles in total [63].	60 mg/m², given on day 1 and 8 every cycle. Cycle is repeated 4 times [62].
Dosing in the health economic model (including relative dose intensity)	N/A	N/A	N/A
Should the medicine be administered with other medicines?	Can be administered together with vinorelbine.	Administered with vinorelbine.	Administered together with cisplatin or carboplatin.
Treatment duration/ criteria for end of treatment	4 cycles of treatment	4 cycles of treatment	4 cycles of treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No	No
Package size(s)	1mg/ml in a vial of 50 ml	10 mg/ml in a vial of 45 ml	20 mg, 1 capsule

3.6 Cost-effectiveness of the comparator(s)

In this assessment, three comparators are included: neoadjuvant PDC, neoadjuvant nivolumab + PDC, and adjuvant PDC, in accordance with Danish clinical practice. Nivolumab combined with PDC has previously been assessed by DMC for the neoadjuvant treatment of NSCLC. PDC is well established in Danish clinical practice for the adjuvant treatment of NSCLC (see section 3.3) and is relatively low in cost compared to durvalumab due to generic competition. Therefore, no additional analysis of these comparators is presented in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The primary clinical efficacy outcome of the AEGEAN trial was event-free survival (EFS), which is the most relevant outcome for this application in comparing the perioperative approach to adjuvant and neoadjuvant treatment. Data for the EFS interim analysis 2 (IA2) with 25.9 months follow-up (Data cut off [DCO], 10 May 2024) are presented [15]. For neoadjuvant nivolumab + PDC, the CheckMate 816 study, one of the primary outcomes was EFS [9], with data from the 4-year update for EFS presented. For the NATCH study, which compared neoadjuvant PDC with adjuvant PDC, the primary outcomes were disease-free survival (DFS) and OS. The median follow-up was 51 months. The data presented in this application are from the randomised ITT population (N= 624). DFS is considered similar to EFS, and in the indirect comparison, they are treated as equivalent.

For this application, EFS is the most important clinical outcome, used both in the direct comparison and the indirect treatment comparisons (ITCs). Subgroup analysis of EFS in patients with a tumour PD-L1 expression level of in PD-L1 ≥1% is presented from AEGEAN and CheckMate 816, respectively.

An overview of the efficacy outcomes is given in Table 7.

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
EFS AEGEAN trial [15]	Median follow-up was 25.9 months	Defined as the time from randomisation to the first of the following: a) documented local or distant recurrence	Measured in the mITT population using BICR assessment, according to the RECIST v1.1 guidelines. Interim analysis 2, DCO May 10 2024

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		(RECIST v1.1); b) death due to any cause or c) disease progression that precludes surgery, or for patients who do not have surgery for a reason other than progression, disease progression (RECIST v1.1) after the surgery eligibility date, or d) disease progression discovered and reported by the investigator upon attempting surgery that prevents completion of surgery, or for patients who do not complete surgery for a reason other than progression, disease progression (RECIST v1.1) after the surgery date	
EFS CheckMate 816 [64]	Median follow-up of 57.6 months	Defined as the length of time from randomisation to any of the following events: any progression of disease precluding surgery, progression or recurrence of disease after surgery.	Based on BICR assessment per RECIST 1.1.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
DFS NATCH [65]	51 months	Defined as time from random assignment to recurrence for patients who underwent resection, to date of surgery for those with unresectable disease at thoracotomy, to first progression for patients not undergoing surgery, or to death for those who died without relapse – WHO tumour criteria.	According to the intention-to-treat principle, and included all randomized patients, eligible or not

Note: * Time point for data collection used in analysis (follow-up time for time-to-event measures)

Abbreviations: BICR: Blinded Independent Central Review; DCO: Data cut off, DFS: Disease-Free Survival; EFS: Event-Free Survival; EMA: European Medicines Agency; IASLC: International Association for the Study of Lung Cancer; mITT: Modified Intent-To-Treat; mPR: major Pathological Response; pCR: pathological Complete Response; RECIST: Response Evaluation Criteria in Solid Tumors

Source: [9, 16] [65]

Validity of outcomes

According to European Medicines Agency (EMA) guidelines on the evaluation of anticancer medicinal products [66], EFS as a primary or co-primary endpoint is especially accepted in neoadjuvant and adjuvant settings or treatments with potentially curative intent, and when there is a high likelihood of early events. EFS can provide earlier indications of treatment efficacy, especially in settings where long-term survival data may take extended periods to mature [66]. Therefore, when appropriately defined and justified, EFS serves as a meaningful endpoint in the assessment of anticancer therapies.

4. Health economic analysis

Not applicable.

4.1 Model structure

Not applicable.

4.2 Model features

Table 8 Features of the economic model N/A

Model features	Description	Justification
Patient population	N/A	N/A
Perspective	N/A	N/A

Model features	Description	Justification
Time horizon	N/A	N/A
Cycle length	N/A	N/A
Half-cycle correction	N/A	N/A
Discount rate	N/A	N/A
Intervention	N/A	N/A
Comparator(s)	N/A	N/A
Outcomes	N/A	N/A

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was originally conducted in July 2022 to identify clinical evidence (efficacy and safety) from randomised controlled trials (RCT) that enrolled adults with stage I to III NSCLC who were candidates for surgical resection and had received any or no treatment prior to surgery. Updates to the SLR were conducted in October 2023 and in April 2025 (the SLR is presented in Appendix H).

The SLR identified three trials relevant for the comparators of interest in Denmark:

1. AEGEAN (NCT03800134) for the comparison versus neoadjuvant platinum-based chemotherapy (PDC) (Comparator 1), at IA2 (DCO: May 10, 2024)
2. CheckMate 816 (NCT02998528), at 4-year update, (DBL: February 23, 2024) for the comparison versus neoadjuvant nivolumab+ PDC (Comparator 2).
3. NATCH (NCT00913705) for the comparison versus adjuvant PDC (DBL: March 1, 2009) (Comparator 3)

The literature used for the clinical assessment is presented in Table 9 below.

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Heymach JV et al. (2023). Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Nov 2;389(18):1672-1684 [16]	AEGEAN	NCT03800134	Start: 02/01/2019 Completion: ongoing Data-cut: 10/11/2022 and 10/05/2024	Perioperative durvalumab + neoadjuvant PDC versus PDC
Forde PM et al. (2022), Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung. Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985 [9]	CheckMate 816	NCT02998528	Start: 04/03/2017 Completion: 06/12/2024 Data cut-off: 20/10/2021	ITC, comparing EFS for perioperative durvalumab + PDC versus neoadjuvant nivolumab + PDC For other outcomes neoadjuvant nivolumab + PDC versus PDC
Jonathan Spicer, et al., Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. Journal of Clinical Oncology, meeting abstract: 2024 ASCO Annual meeting ll, (42):17 [64]	CheckMate 816	NCT02998528	Start: 04/03/2017 Completion: 06/12/2024 Data cut-off: 23/02/2024	ITC, comparing EFS for perioperative durvalumab + PDC versus neoadjuvant nivolumab + PDC For other outcomes neoadjuvant nivolumab + PDC versus PDC

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Felip E, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol. 2010 Jul 1;28(19):3138-45. doi: 10.1200/JCO.2009.27.6204. Epub 2010 Jun 1. PMID: 20516435. [65]	Neoadjuvant or Adjuvant Chemotherapy in Patients With Operable Non-small-cell Lung Cancer (NATCH)	NCT00913705	Start: 09/1999 Completion: 06/2009 Data cut-off: March 1, 2009	EFS network meta-analysis (NMA) comparing against adjuvant chemotherapy

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Refer to section 5.1, similar to the efficacy outcomes, health-related quality of life (HRQoL) outcomes were based on AEGEAN and CheckMate 816. No additional search was done.

Table 10 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Authors. Article title. Journal. Year; volume(issue): pp [reference number]	E.g. First line metastatic recurrence	

5.3 Literature used for inputs for the health economic model

As no health economic analysis was performed, no literature search was conducted

Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of durvalumab + PDC as neoadjuvant treatment, followed by durvalumab monotherapy as adjuvant treatment compared to neoadjuvant PDC (comparison 1) or neoadjuvant nivolumab + PDC (comparison 2) or adjuvant PDC (comparison 3) for patients with rNSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangement

6.1.1 Relevant studies

As previously described, there are three relevant studies to compare the efficacy of durvalumab + PDC as neoadjuvant treatment followed by durvalumab as adjuvant treatment for adults with rNSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements. In the absence of head-to-head comparisons, ITCs were required to assess the comparative effectiveness and safety of the perioperative durvalumab regimen in AEGEAN versus key comparators.

1) AEGEAN (versus neoadjuvant PDC)
2) CheckMate 816 (versus neoadjuvant nivolumab + PDC)
3) NATCH (versus adjuvant PDC)

AEGEAN is a pivotal Phase 3, randomised, multi-centre, double-blind, placebo-controlled global trial examining the efficacy and safety of perioperative durvalumab (neoadjuvant durvalumab + PDC followed by adjuvant durvalumab) for the treatment of patients with Stage IIA–IIIB (N2) rNSCLC [16]. The modified ITT (mITT) included 740 participants with documented EGFR mutations or ALK gene rearrangements. Patients received durvalumab + PDC (n=366) or placebo + PDC (n=374), followed by adjuvant durvalumab or placebo. The efficacy outcomes from AEGEAN are based on the most recent DCO, May 10, 2024. The safety analysis set (SAS) included all randomised patients in the global cohort who received at least one dose of study treatment, regardless of EGFR or ALK status.

CheckMate 816 is an open-label, phase 3 trial in patients with stage IB to IIIA rNSCLC examining the efficacy of nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection [9, 64]. The 4-year follow-up from DBL February 23, 2024, was used in this application for EFS, with a patient cohort of 358 participants (nivolumab + PDC: n=179, PDC: n=179) [10, 64]. Outcomes in PD-L1 ≥ 1% subgroup are presented with the DBL October 14, 2022.

NATCH was an open-label multicentre randomized phase 3 trial of preoperative (hereafter referred to as neoadjuvant) PDC or adjuvant PDC in patients with early-stage NSCLC [65, 68]. The primary endpoint was DFS. Between April 2000 and March 2007, a total of 624 patients from 42 centres in Spain, Germany, Portugal, Sweden, and

Switzerland were randomly assigned to one of three arms: neoadjuvant PDC, adjuvant PDC or surgery without PDC. The PDC regimen consisted of paclitaxel (Taxol) in combination with carboplatin. The median follow-up was 51 months. Analysis reflects the DBL March 1, 2009 [65].

An overview of the studies relevant for this application is presented in Table 12.

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
AEGEAN, NCT03800134) [16]	A Phase III, Double-blind, Placebo-controlled, Multi-centre [69]	From date of randomization to 5.5 years after randomization. [69]	Patients with resectable NSCLC (stage II to IIIB [N2 node stage] according to the eighth edition of the AJCC Cancer Staging Manual)	Neoadjuvant: Durvalumab in combination with platinum-based chemotherapy at a dose of 1,500 mg Q3W for up to 4 cycles Adjuvant: Durvalumab 1,500 mg Q4W as a single agent for up to 12 cycles	Neoadjuvant: Placebo in combination with platinum-based chemotherapy Q3W for up to 4 cycles Adjuvant: Placebo Q4W	Primary: EFS [Time Frame: Up to 5.5 years after first patient randomized.] pCR [Time Frame: Up to approximately 15 weeks after randomization] Secondary: OS [Time Frame: From date of randomization to 5.5 years after randomization] DFS Time Frame: From date of randomization to approximately 5.5 years after date of resection] mPR [Time Frame: Up to approximately 15 weeks after randomization] Subgroup analysis of all above outcomes in PD-L1-TC ≥1% patients in mITT population Disease-related symptoms and HRQoL (EORTC QLQ-C30) [Time Frame: From

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						date of screening to 6 months after last dose of IP] Disease-related symptoms and HRQoL (EORTC QLQ-LC13) in patients treated with durvalumab + chemotherapy prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy prior to surgery followed by placebo post-surgery [Time Frame: From date of screening to 6 months after last dose of IP]
CheckMate 816, NCT02998528 [9]	Randomized, Open Label, Phase III Trial [70]	From randomization up to a median of 30 months after randomization. [70]	patients with stage IB to IIIA resectable NSCLC [9]	Neoadjuvant treatment with 360 mg nivolumab iv in combination with platinum-based chemotherapy Q3W for 3 courses [70]	Neoadjuvant treatment with platinum-based chemotherapy Q3W for 3 courses [70]	Primary: EFS [Time Frame: From randomization to disease progression, reoccurrence, or death due to any cause. (Up to a median of 30 months)] pCR Rate [Time Frame: From randomization up to a median of 30 months after randomization.] Secondary: OS [Time Frame: From randomization to the date of death]

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						mPR Rate [Time Frame: From randomization up to a median of 30 months after randomization.] Time to Death or Distant Metastases (TTDM) [Time Frame: From randomization to the first date of distant metastasis or the date of death in the absence of distant metastasis (Up to a median of 30 months)] [70]
NATCH (NCT00913705) [65, 68]	Open-label multicenter randomized Phase III trial	Chemotherapy every 3 weeks for three cycles, starting as soon as possible after randomisation in patients allocated to the preoperative arm, and within 3 to 5 weeks after surgery in patients allocated to the adjuvant arm. Surgery had to take place ASAP after randomization in patients allocated	Patients with early stage NSCLC, clinical stage IA with tumour size more than 2 cm, IB, II, or T3N1 NSCLC considered resectable by the local multidisciplinary team	Treatment arm 1: Neoadjuvant chemotherapy (taxol and carboplatin) prior to surgery Taxol: 200 mg/m^2 IV infusion over 3 hours; followed by carboplatin: a at an area under the curve dose of 6.0 mg/mL/min, IV infusion over 30 to 60 minutes.	Treatment arm 2: Adjuvant chemotherapy post surgery Same as on arm 1. Treatment arm 3: Surgery without chemotherapy	Primary: Evaluate disease-free survival (DFS) and overall survival (OS) [Time Frame: 5 years] Secondary: Evaluate levels of response and the adverse effects of the chemotherapy [Time Frame: 5 years]: Occurrence and severity of adverse events

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
		to both the adjuvant and the surgery alone arms and within 3 to 4 weeks after the third chemotherapy cycle for those allocated to the preoperative arm. Follow-up continued beyond 5 years (median 51 months).		Administration of 3 cycles at 21-day intervals.		

6.1.2 Comparability of studies

A comparison of AEGEAN, CheckMate 816, and NATCH was done, as these trials were the basis for the ITCs. In general, the trial designs of AEGEAN, CheckMate 816 and NATCH were similar – all were phase 3, global, multicentre RCTs in rNSCLC.

Differences across the three trials were observed for how these were blinded, type of chemotherapy regimens used, number of chemotherapy cycles in the neoadjuvant phase, the trial setting (neoadjuvant versus perioperative) and the version of TNM classification used in the study. AEGEAN [16] included patients with stage II, IIA, or IIIB (N2 only) as defined by the AJCC 8th edition. CheckMate 816 [9, 71-75] included patients with stage IB (≥4 cm), II, IIIA according to the 7th edition. Patients with T2aN0 (4 cm) (IB in 7th edition) would be included in CheckMate 816 but not AEGEAN, and patients with T4N2 (IIIB in both 7th and 8th edition) would be included in AEGEAN but not CheckMate 816. In NATCH patients with IA stage with tumour size more than 2 cm, IB, II, or T2N1 NSCLC patients were included, which means patients with overall earlier disease-stage than in the other two trials [65].

For a comparison of baseline characteristics, see Table 13.

6.1.2.1 Comparability of patients across studies

The baseline characteristics of patients in the studies included in the comparative analysis of efficacy are presented in Table 13. For AEGEAN the mITT population is presented.

The imbalances in baseline characteristics between AEGEAN [16] and CheckMate 816 [9], as well as potential EMs, included a higher proportion of patients who received cisplatin at baseline (CheckMate 816), a higher proportion of patients with stage IIIA disease (CheckMate 816), a lower proportion of patients with stage IIIB disease (CheckMate 816), a higher proportion of patients enrolled in Asia (CheckMate 816), and a higher proportion of patients with PD-L1 <1% (CheckMate 816).

For NATCH, the ITT population is presented. Only the preoperative and adjuvant chemotherapy (PDC) arms are included in Table 13 as the surgery arm's outcomes were not relevant to AEGEAN in the ITC. The population in NATCH was different compared to AEGEAN, including resectable Stage IB, II, T3N1 NSCLC, as well as Stage IA with a tumour size larger than 2cm. There were no details on PD-L1 inclusion/exclusion. EGFR mutation and ALK translocation status were not part of the inclusion/exclusion criteria.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy

	AEGEAN, mITT [16]		CheckMate 816, ITT [9]		NATCH ITT [65]	
	Durva + PDC N=366	Placebo + PDC N=374	Nivo + PDC N=179	PDC N=179	Neoadjuvant PDC N=199	Adjuvant PDC N=210
Age						
Median (range) — yr	65 (30–88)	65 (39–85)	64 (41–82)	65 (34–84)	65 (35-80)	64 (33-81)
Distribution — no. (%)						
≥75 yr — no. (%)	44 (12.0)	36 (9.6)			NA	NA
<65 yr	NA	NA	93 (52.0)	83 (46.4)	55	64
≥65 yr	NA	NA	86 (48.0)	96 (53.6)	62	60
Sex — no. (%)						
Male	252 (68.9)	278 (74.3)	128 (71.5)	127 (70.9)	175 (87.9)	181 (86.2)
Female	114 (31.1)	96 (25.7)	51 (28.5)	52 (29.1)	24 (12.1)	29 (13.8)
ECOG performance-status score — no. (%)[1]						
0	251 (68.6)	255 (68.2)	124 (69.3)	117 (65.4)	88 (44.2)	95 (45.2)
1	115 (31.4)	119 (31.8)	55 (30.7)	62 (34.6)	108 (54.3)	111 (52.9)
2	NA	NA	NA	NA	1 (0.5)	3 (1.4)
Missing data	NA	NA	NA	NA	2 (1.0)	1 (0.5)
Race — no. (%)[2]						

	AEGEAN, mITT [16]		CheckMate 816, ITT [9]		NATCH ITT [65]	
	Durva + PDC N=366	Placebo + PDC N=374	Nivo + PDC N=179	PDC N=179	Neoadjuvant PDC N=199	Adjuvant PDC N=210
Asian	143 (39.1)	164 (43.9)	NA	NA	NA	NA
White	206 (56.3)	191 (51.1)	NA	NA	NA	NA
Other	17 (4.6)	19 (5.1)	NA	NA	NA	NA
Ethnic group — no.(%)						
Hispanic or Latino	63 (17.2)	56 (15.0)	NA	NA	NA	NA
Not Hispanic or Latino	303 (82.8)	318 (85.0)	NA	NA	NA	NA
Geographic region — no. (%)					European sites only	
Asia	142 (38.8)	163 (43.6)	85 (47.5)	92 (51.4)	NA	NA
Europe	141 (38.5)	140 (37.4)	41 (22.9)	25 (14.0)	NA	NA
North America	43 (11.7)	43 (11.5)	41 (22.9)	50 (27.9)	NA	NA
South America	40 (10.9)	28 (7.5)	NA	NA	NA	NA
Rest of the world[3]			12 (6.7)	12 (6.7)	NA	NA
Smoking status — no. (%)						
Current smoker	95 (26.0)	95 (25.4)	NA	NA	NA	NA
Former smoker	220 (60.1)	223 (59.6)	NA	NA	NA	NA

	AEGEAN, mITT [16]		CheckMate 816, ITT [9]		NATCH ITT [65]	
	Durva + PDC N=366	Placebo + PDC N=374	Nivo + PDC N=179	PDC N=179	Neoadjuvant PDC N=199	Adjuvant PDC N=210
Current or former smoker	315 (86.1)	318 (85.0)	160 (89.4)	158 (88.3)	NA	NA
Never smoked	51 (13.9)	56 (15.0)	19 (10.6)	20 (11.2)	NA	NA
Disease stage — no. (%)[4]						
I	NA	NA	NA	NA	Stage I: 74.4	
IB or II	104 (28.4)	110 (29.4)	65 (36.3)	62 (34.6)		
II	104 (28.4)	110 (29.4)	NA	NA	Stage II-T3N1: 25.6	
IIIA	173 (47.3)	165 (44.1)	113 (63.1)	115 (64.2)		
IIIB	88 (24.0)	98 (26.2)	0	0		
TNM classification, primary tumour — no. (%)[5]						
T1	44 (12.0)	43 (11.5)	NA	NA	10.1 (calculated)	
T2	97 (26.5)	108 (28.9)	NA	NA	78.4 (calculated)	
T3	128 (35.0)	129 (34.5)	NA	NA	11.1 (calculated)	
T4	97 (26.5)	94 (25.1)	NA	NA	0.5 (calculated)	
TNM stage, regional lymph nodes — no. (%)						
N0	110 (30.1)	102 (27.3)	NA	NA	NA	NA

	AEGEAN, mITT [16]		CheckMate 816, ITT [9]		NATCH ITT [65]	
	Durva + PDC N=366	Placebo + PDC N=374	Nivo + PDC N=179	PDC N=179	Neoadjuvant PDC N=199	Adjuvant PDC N=210
N1	75 (20.5)	87 (23.3)	NA	NA	NA	NA
N2	181 (49.5)	185 (49.5)	NA	NA	NA	NA
Single-station	141 (38.5)	132 (35.3)	NA	NA	NA	NA
Multistation	34 (9.3)	40 (10.7)	NA	NA	NA	NA
TNM classification overall clinical stage — no. (%)						
T1N0	NA	NA	NA	NA	16 (8.0)	30 (14.3)
T2N0	NA	NA	NA	NA	132 (66.3)	133 (63.3)
T1N1	NA	NA	NA	NA	4 (2.0)	3 (1.4)
T2N1	NA	NA	NA	NA	24 (12.1)	25 (11.9)
T3N0	NA	NA	NA	NA	18 (9.1)	18 (8.6)
T3N1	NA	NA	NA	NA	4 (2.0)	1 (0.5)
T4N0*	NA	NA	NA	NA	1 (0.5)*Patient not eligible	—
Histologic classification — no. (%)						
Squamous	169 (46.2)	191 (51.1)	87 (48.6)	95 (53.1)	107 (53.8)	103 (49.0)
Non squamous	196 (53.6)	179 (47.9)	92 (51.4)	84 (46.9)	92 (46.2)	107 (51.0)
PD-L1 expression — no. (%)[6]						
<1%	122 (33.3)	125 (33.4)	78 (43.6)	77 (43.0)	NA	NA

	AEGEAN, mITT [16]		CheckMate 816, ITT [9]		NATCH ITT [65]	
	Durva + PDC N=366	Placebo + PDC N=374	Nivo + PDC N=179	PDC N=179	Neoadjuvant PDC N=199	Adjuvant PDC N=210
≥1%	244 (66.7)	249 (66.6)	89 (49.7)	89 (49.7)	NA	NA
1-49%	135 (36.9)	142 (38.0)	51 (28.5)	47 (26.3)	NA	NA
≥50%	109 (29.8)	107 (28.6)	38 (21.2)	42 (23.5)	NA	NA
Tumour mutational burden — no. (%)[7]						
Could not be evaluated or was not reported	NA	NA	91 (50.8)	89 (49.7)	NA	NA
<12.3 mutations per megabase	NA	NA	49 (27.4)	53 (29.6)	NA	NA
≥12.3 mutations per megabase	NA	NA	39 (21.8)	37 (20.7)	NA	NA
Planned neoadjuvant platinum agent — no. (%)						
Cisplatin	100 (27.3)	96 (25.7)	124 (69.3)	134 (74.9)	NA	NA
Carboplatin	266 (72.7)	278 (74.3)	39 (21.8)	33 (18.4)	All patients, combined with paclitaxel	NA
Surgery procedure performed, n (%)						
Lobectomy	238 (65.0)	221 (59.1)	115 (77.2)	82 (60.7)	NR	NR
Lobectomy/ bilobectomy	NA	NA	NA	NA	131 (72.3)	139 (69)
Sleeve resection	7 (1.9)	14 (3.7)	NA	NA	NR	NR
Sleeve lobectomy	NA	NA	2 (1.3)	10 (7.4)	NR	NR

	AEGEAN, mITT [16]		CheckMate 816, ITT [9]		NATCH ITT [65]	
	Durva + PDC N=366	Placebo + PDC N=374	Nivo + PDC N=179	PDC N=179	Neoadjuvant PDC N=199	Adjuvant PDC N=210
Bilobectomy	13 (3.6)	20 (5.3)	3 (2.0)	4 (3.0)	NR	NR
Pneumonectomy	27 (7.4)	29 (7.8)	25 (16.8)	34 (25.2)	42 (23.2)	49 (24.4)
Sleeve resection (bronchial)	2 (0.5)	2 (0.5)	NA	NA	NR	NR
Sleeve resection (arterial)	0	1 (0.3)	NA	NA	NR	NR
Wedge resection	1 (0.3)	2 (0.5)	NA	NA	NR	NR
Other	7 (1.9)	13 (3.5)	24 (16.1)	21 (15.6)	NR	NR

Note: Characteristics for which there were missing or other responses were histologic classification (0.3% of the patients in the durvalumab group and 1.1% of those in the placebo group had other histologic classification), disease stage (0.3% in the durvalumab group had stage IV disease and 0.3% in the placebo group had stage III [not otherwise specified] disease, as reported on the electronic case-report form), and N2 lymph node station stage (1.6% in the durvalumab group and 3.5% in the placebo group had N2 disease with missing data on single-station vs. multistation classifi cation). [1]Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.[2] In the AEGEAN trial, race was reported by the patients.[3]This category includes Argentina and Turkey only. [4]in AEGEAN, patients with stage IIA disease to stage IIIB (N2 node stage) disease according to the eighth edition of the AJCC Cancer Staging Manual were enrolled [5] in AEGEAN, all patients had disease that was classified as M0 except for one patient in the durvalumab group who had disease that was classified as M1 (not otherwise specified).[6] in CheckMate 816, the percentages are based on the primary analysis population. The status of programmed death ligand 1 (PD-L1) expres sion was determined with the use of the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay (Dako); patients with tumor tissue that could not be assessed for PD-L1 expression (≤10% of all the patients who underwent randomisation) were stratified to the subgroup with a PD-L1 expression level of less than 1% at randomisation. [7] In CheckMate 816, tumour mutational burden was not analysed for patients in China, and these patients were included in the "not reported" category. Source: [9, 16] [65]

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The population in the AEGEAN study aligns with the expected patient population in Denmark. The Danish patient population expected to be treated with durvalumab is, according to the approved indication, adults with rNSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements. This aligns with the inclusion criteria in the AEGEAN trial.

When comparing the characteristics between AEGEAN and Danish patients, no specific published evidence for the Danish population was identified for this exact setting. Hence, data from the DLCG's yearly report (latest from 2023) was used, which includes an overall description of Danish lung cancer patients[45].

Based on this register data, a comparison was done with AEGEAN and CheckMate 816 (Table 14). Overall, patients diagnosed with lung cancer in Denmark were reported to be older than in AEGEAN [16], CheckMate 816 [9], and NATCH [65], around 72 years [45], whereas AEGEAN, CheckMate 816, and NATCH included patients with a median age of 64-65 years. The gender distribution in Denmark is equal, with 48% men [45], whereas in AEGEAN and CheckMate around 70% were men [9, 16] and in NATCH 86-88% were men [65]. Further squamous histology was seen less prevalent in Danish lung cancer patients, around 19% [45] whereas in the respective study arms from AEGEAN, CheckMate 816, and NATCH an equal distribution (around 50%) for non-squamous and squamous histology was seen at baseline [9, 16]. Lobectomies were the most common surgery performed in AEGEAN [16], CheckMate 816 [9], NATCH [65], and in Danish practice [45]. Besides, in a real-world practice some of rNSCLC may not be operable, while the trials included mostly operable patients.

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (Lung cancer overall) [45]	Value used in health economic model (reference if relevant)
Age	72 years (median)	N/A
Gender (men)	47,9%	N/A
Histology, squamous NSCLC	19%	N/A
PD-L1 expression <1%	31.8%	N/A
Surgery type, lobectomy	83%	N/A

Source: Danske Lunge Cancer Gruppe 2023 [45]

6.1.4 Efficacy – results per AEGEAN

6.1.4.1 Event-free survival

At the time of the second interim analysis (EFS IA2; DCO 10 May 2022) of AEGEAN, 289 EFS events (using BICR per RECIST v1.1) had occurred in the mITT population (Table 15) [15, 16]. Median follow-up for EFS in censored patients was 25.9 months (range, 0.0 to 58.6). [redacted] HR was 0.69 (95% CI: 0.55, 0.88), representing a 31% overall reduction in the risk of an EFS event [15, 16]. The median EFS was not reached (NR) for the durvalumab arm (95% CI: 42.3 months, NR) and 30.0 months (95% CI: 20.6 months, NR) for the placebo arm [15, 16].

[redacted]

After three months post-randomisation, there was clear and sustained separation of the curves that favoured the durvalumab arm, also reflected in the estimated EFS rates (Table 15) [15].

Table 15 Event-free survival mITT population (EFS IA2 10 May 2024) AEGEAN

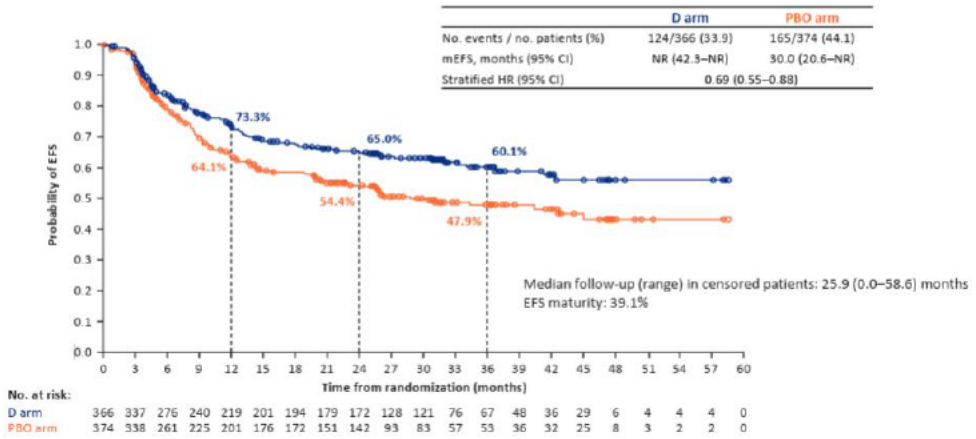
	Durvalumab arm (N = 366)	Placebo arm, PDC neoadjuvant (N = 374)
Events, n (%)[a]	124 (33.9%)	164 (44.1%)
Median EFS, months (95% CI)[e]	NR (42.3, NR)	30.0 (20.6, NR)
HR (95% CI)[c] p-value	0.69 (0.55, 0.88) NR	
Landmark EFS, % (95% CI)[e]		
12 months	73.3 (68.1, 77.7)	64.1 (58.7, 69.0)
24 months	65.0 (59.4, 70.0)	54.4 (48.7, 59.6)
36 months	60.1 (53.9, 65.8)	47.9 (41.8, 53.8)

Notes: DCO: 10th November 2022 (IA1), DCO: 10th May 2024 (IA2). [a]Two missed visit rule applied. [b]New malignancy that is not NSCLC as confirmed by pathology is not considered an EFS event. [c]Calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. An HR <1 favours the durvalumab arm. nr: Not reported. [e]Calculated using the KM technique.

Abbreviations: CI: confidence interval; DCO: data cut-off; EFS: event-free survival; HR: hazard ratio; IA: interim analysis; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: [15-17]

Figure 3 KM curves for event free survival, mITT population (EFS IA2 10 May 2024) AEGEAN



Note: DCO: 10th May 2024. Patients who have not experienced an EFS event at the time of analysis are censored at the time of the last disease assessment. If the event occurs after two or more consecutive missed visits, the patient is censored at the last disease assessment prior to the two missed visits. A new malignancy that is not NSCLC, as confirmed by pathology, is not considered an EFS event.

Source: [15]

6.1.4.2 Overall survival

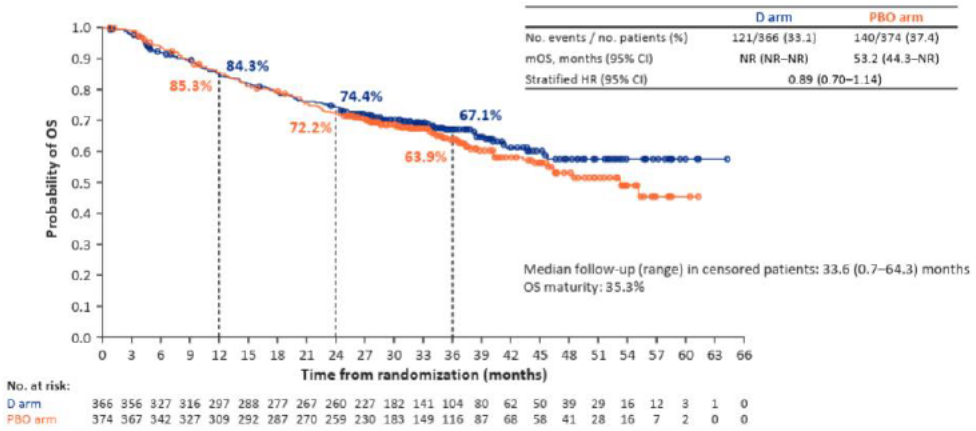
At the time of EFS IA2 (DCO: 10th May 2024), the median duration of OS follow-up in censored patients was 33.6 months (range: 0.7–64.3 months), and OS data had an overall maturity of 35.3% [15]. The median OS was not reached in in the durvalumab arm and was 53.2 months (95% CI: 44.3, NR) in the placebo arm, HR of 0.89 (95% CI: 0.70, 1.14), representing an 11% overall reduction in the risk of death and a trend toward improvement in favour of the durvalumab arm [15]. At EFS IA2, the OS KM curves were similar until approximately 20 months (Figure 4), after which there was a sustained separation that favoured the durvalumab arm [15]. The delayed curve separation arises from the treatment sequence in the placebo arm, where patients first had surgery before starting chemotherapy.

Table 16 Overall survival mITT population (EFS IA2 10 May 2024) AEGEAN

	Durvalumab arm (N = 366)	Placebo arm (N = 374)
Deaths, n (%)	121 (33.1)	140 (37.4)
Median OS, months (95% CI)[a]	NR	53.2 (95% CI: 44.3, NR)
HR (95% CI)[b] p-value	0.89 (0.70, 1.14)	

Note: [a] Calculated using the Kaplan-Meier technique [b]Calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A HR < 1 favors the durvalumab arm, to be associated with longer OS than placebo arm.

Figure 4 KM curves for overall survival, mITT (EFS IA2 10 May 2024) AEGEAN



Note: DCO: 10th May 2024. OS was defined as the time from the date of randomisation until death due to any cause. Patients who had not experienced an OS event at the time of analysis were censored at the date last known alive.

Source: [15]

6.1.4.3 Lung cancer specific deaths

Death related to lung cancer were reported in [redacted] and [redacted] in the durvalumab and placebo arm, respectively (Table 17). Considering the mean age at inclusion, the death not-related to the disease were most likely resulting from age-related causes.

Table 17 Deaths related to disease, mITT population (EFS IA2 10 May 2024) AEGEAN

Category	Durvalumab arm (N = 366)	Placebo arm (N = 374)
Total number of deaths	121 (33.1)	140 (37.4)
Death related to disease under investigation only[a]	[redacted]	[redacted]

[redacted]

6.1.4.4 Event free survival and overall survival in PD-L1 ≥1% subgroup

At EFS IA2 (DCO: 10th May 2024), 186 EFS events (using BICR per RECIST v1.1) had occurred in the PD-L1 expression ≥1% subgroup population [redacted]). Durvalumab demonstrated a clinically meaningful benefit in EFS, with an HR of 0.71 (95% CI: 0.53, 0.94). After three months post-randomisation, there was a clear and sustained separation in the EFS KM curves that favoured the durvalumab arm, similar to the mITT

population [redacted] This benefit is reflected in the estimated EFS rates at 12 months [redacted] for the durvalumab and placebo arms, respectively), 24 months [redacted] and 36 months ([redacted]) [17].

[redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

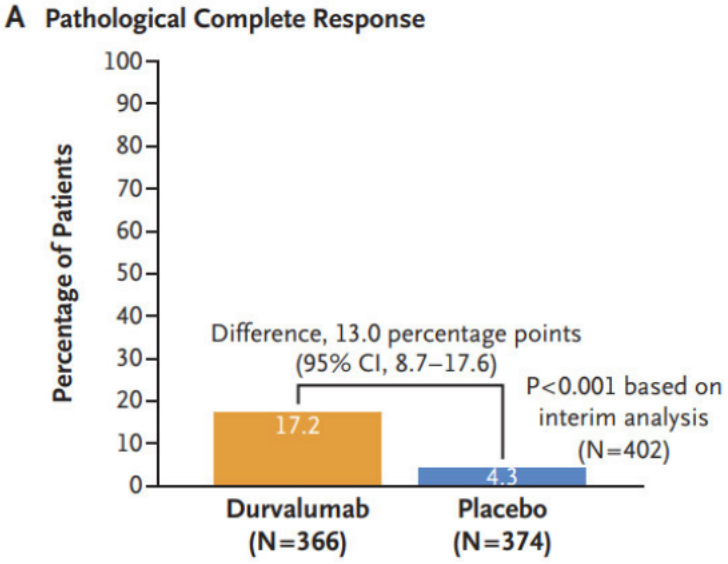
	Durvalumab arm (N = 244)	Placebo arm (N = 249)
Deaths, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)[a]	[redacted]	[redacted]
HR (95% CI)[b] p-value	[redacted]	

[redacted]

6.1.4.5 Pathological complete response

In the AEGEAN study (EFS IA2 10 May 2024), treatment with durvalumab resulted in a pathological complete response (pCR) rate of 17.2%, compared to 4.3% in the placebo arm, with a difference of 13.0 percentage points (95% CI: 8.7, 17.6). This difference was statistically significant, demonstrating a clinically meaningful improvement in pCR rates in favour of the durvalumab arm [16].

Figure 6 Pathological Complete Response in mITT (DCO, 10 November 2022)



Notes: Pathological complete response was defined as a lack of viable tumor cells after complete evaluation of the resected lung-cancer specimen and all sampled regional lymph nodes.

Abbreviation: CI: Confidence interval; DCO: data cut-off.

Source: **[16]**

6.1.5 Efficacy – results per CheckMate 816

6.1.5.1 Event-free survival

With the latest available update from CheckMate 816 (DBL 23 February 2024), with median follow-up of 57.6 months for ITT population, the median EFS (using BICR per RECIST v1.1) for nivolumab + PDC was 43.8 months versus 18.4 months for PDC alone, HR 0.66, (95% CI 0.49, 0.90) [64] (Table 20).

Table 20 Event-free survival ITT population (DBL 23 February 2024) CheckMate 816

	Nivolumab+PDC (N = 179)	PDC (N = 179)
Events, n (%)	75 (41.9%)	101 (56.4%)
Median (months) (95% CI)	43.8 (30.6–NR)	18.4 (14.0–26.7)
HR (95% CI)	0.66 (0.49–0.90)	

Note: DBL 23 February 2024

Abbreviation: PDC: Platinum-based chemotherapy

Source: [64]

6.1.5.2 Event free survival in PD-L1 ≥1% subgroup

With a minimum follow-up of 32.9 months (DBL 14 October 2022), EFS results for the subgroup of patients with tumour PD-L1 expression ≥ 1% are presented in Table 21, and the KM curve in Table 21 [78]. The median EFS was not reached with nivolumab+PDC and 26.71 months (95% CI, 13.4, NR) with PDC alone, HR 0.49 (95% CI 0.29,0.83) [78].

Table 21 Event free surival in patients with tumour PD-L1 ≥ 1% (DBL 14 October 2022) CheckMate 816

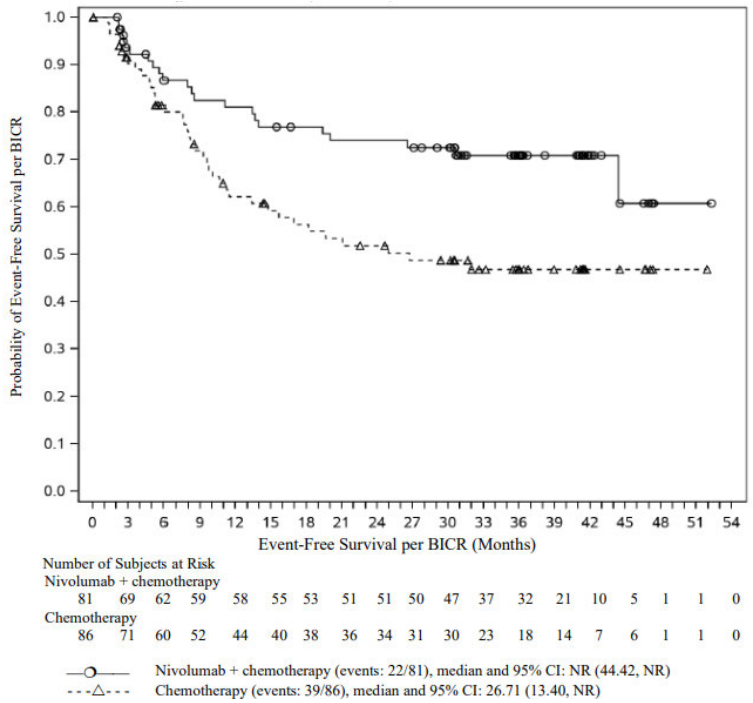
	Nivolumab + PDC (N= 81)	PDC (N=86)
Events, n (%)	22 (27.2%)	39 (45.3%)
Median (months)[b] (95% CI)	NR (44.42, NR)	26.71 (13.40, NR)
HR (95% CI)	0.49 (0.29, 0.83)	

Note: DBL 14 October 2022. [a]Based on an unstratified Cox proportional hazards model. [b]Kaplan-Meier estimate

Abbreviations: NR: not reached; DBL: data base lock; PD-L1: programmed death-ligand

Source: [78]

Figure 7 KM curve for EFS PD-L1 ≥1% subpopulation (DBL 14 October 2022) CheckMate 816

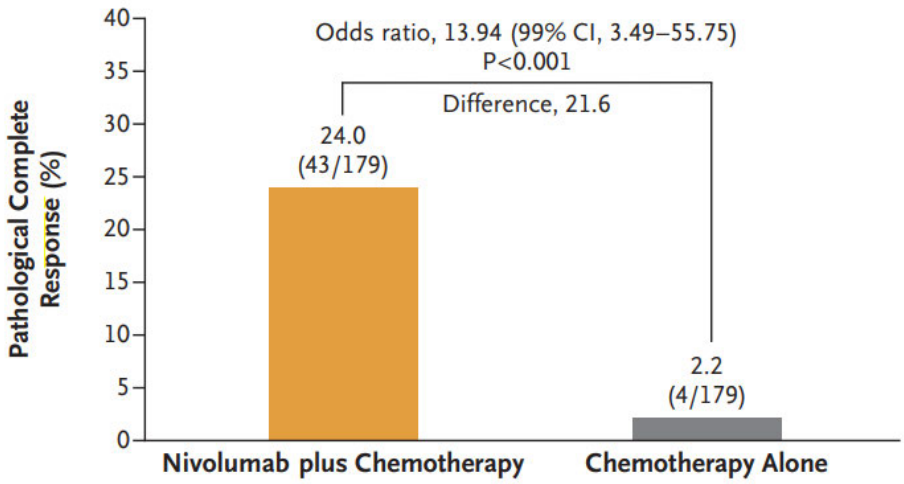


Source: [78]

6.1.5.3 Pathological complete response

In the CM816 study, the pCR rate observed in patients receiving nivolumab plus chemotherapy was 24.0%, compared with 2.2% for chemotherapy alone, corresponding to a difference of 21.6 percentage points. The odds ratio was 13.94 (99% CI: 3.49, 55.75), indicating a substantial benefit in pCR for the nivolumab combination over chemotherapy alone [9].

Figure 8 Pathological Complete Response in ITT (DBL, 16 September 2020)



Notes: Pathological complete response was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes. According to the intention-to-treat principle, patients who did not undergo surgery were counted as not having had a response for the primary analysis. The between-group difference was calculated by means of a stratified Cochran–Mantel–Haenszel method.

Abbreviation: CI: Confidence interval; DBL: Database lock.

Source: [9]

6.1.6 Efficacy – results per NATCH

6.1.6.1 Disease-free survival

In the NATCH study, with a median follow up of 51 months, 619 patients were included in the ITT analyses, surgery arm (N=210) preopreative/neoadjuvant PDC + surgery arm (N=199) and the surgery + adjuvant PDC arm (N=210). Summary results for DFS for adjuvant PDC and surgery are presented in Table 22. The adjuvant PDC group had 125 (59.5%) events and surgery group had 132 (62.9%) events (disease progression or death), with no statistically significant differences in DFS with the addition adjuvant PDC to surgery, HR = 0.96 (95% CI, 0.75 to 1.22) p=0.74 [65].

Table 22 Disease-free survival in NATCH

Outcome	Surgery (N=210)	Adjuvant PDC (N=210)
Events	132 (62.9%)	125 (59.5%)
Hazard ratio (95% CI) p-value	0.96 (0.75, 1.22) 0.74	
Median (months)[b] (95% CI)	N/A	

Source: [65]

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

For the comparison to neoadjuvant PDC, the head-to-head results from AEGEAN were used (see section 6.1.4). In the absence of head-to-head comparisons for neoadjuvant nivolumab + PDC and adjuvant PDC, two ITCs were performed.

Definitions of the time-to-event outcome, which included progression, recurrence, and death (EFS and DFS), in the studies used in the ITC were similar but not identical. All trials reported EFS or DFS as time until progression, recurrence, or death. For the ITCs the endpoints (EFS and DFS) were considered interchangeable, based on the similarity of

their outcome definitions (see Table 7). Also, specific PDC regimes are considered interchangeable.

The ITC did not include pCR between AEGEAN and CheckMate 816. Direct pairwise comparisons of pCR between AEGEAN (durvalumab) and CM816 (nivolumab) are not appropriate without proper statistical adjustment, as differences in study populations, trial designs, and other confounding clinical factors may impact efficacy estimates.

7.1.2 Method of synthesis

Two different methods were used for the indirect comparisons, network meta-analysis (NMA) and a matching-adjusted indirect comparison (MAIC). The ITC methods that were considered were primarily based on those recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) in Technical Support Documents (TSD) [79]. Given the differences in the patient populations across the trials, a MAIC was considered suitable for the ITCs, matching the AEGEAN mITT population to the populations in CheckMate 816 and NATCH, respectively. A feasibility assessment found that an MAIC was suitable for the ITC between AEGEAN and CheckMate 816, given that they are contemporary clinical studies with similar inclusion and exclusion criteria. However, it was found difficult to match the population of AEGEAN to better fit the population in NATCH, and the need to incorporate comparators for other settings led to the decision to perform the ITC against NATCH using an NMA approach. NMA is a generalisation of standard pairwise meta-analysis that permits the synthesis of relative effect estimates on three or more treatments in a connected network [80, 81].

In conclusion, to compare perioperative durvalumab with adjuvant PDC, an NMA was used, and for the ITC versus neoadjuvant IO + PDC (CheckMate 816), a population-adjusted ITC (pairwise) was chosen to account for differences in stage, PD-L1 expression, region and platinum-chemotherapy at baseline.

[redacted]

7.1.2.1 MAIC versus CheckMate 816

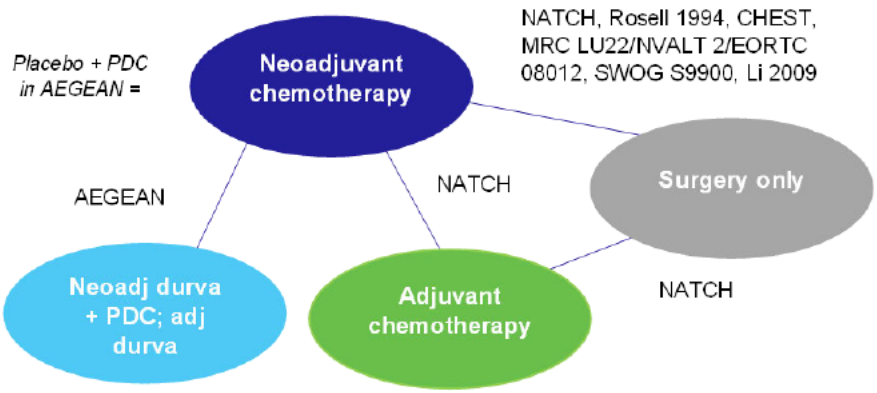
Anchored MAIC analyses were performed to compare the EFS of perioperative durvalumab + neoadjuvant platinum-based chemotherapy from the AEGEAN trial [16] vs neoadjuvant nivolumab + PDC from CheckMate 816 [9, 71-75] (in the AEGEAN mITT population).

The first step was to match the AEGEAN population to the population in CheckMate 816. The following characteristics were considered to be possible effect modifiers: disease stage, PD-L1 expression, region (Asia vs non-Asia), sex, histology, smoking status, and planned platinum chemotherapy. Details on the methodology are provided in C.2.

7.1.2.2 NMA versus adjuvant PDC

The EFS NMA (base case) in the mITT population is shown as a network diagram in Figure 9.

Figure 9 Network diagram of AEGEAN vs adjuvant PDC and surgery for EFS



The data inputs used in the NMA are shown in Table 23. For details on the NMA, please see section C.3.1.

Table 23 Overview of the mITT population NMA: sample size and number of events (overall period and piecewise)

Study	Treatment	Total subjects	Subjects with events	Subjects with event within 3 months	Subjects with event after 3 months
AEGEAN	Durvalumab	366	124 (33.9%)	18 (4.9%)	106 (29.0%)
	Neoadjuvant chemotherapy	374	165 (44.1%)	20 (5.3%)	145 (38.8%)
NATCH	Adjuvant chemotherapy	210	124 (59.0%)	37 (17.6%)	87 (41.4%)
	Neoadjuvant chemotherapy	199	120 (60.3%)	15 (7.5%)	105 (52.8%)
	Surgery	210	133 (63.3%)	30 (14.3%)	103 (49.0%)

Note: The number at risk and number of events in comparator trials were based on pseudo patient-level data generated from digitisation of the EFS KM curves.

7.1.3 Results from the comparative analysis

Tables below report the results of the comparative analysis of EFS for the three relevant comparators to perioperative durvalumab:

1) Direct evidence versus neoadjuvant PDC (AEGEAN) - Table 24
2) Indirect evidence versus neoadjuvant nivolumab + PDC (CheckMate 816) - [redacted] (piecewise MAIC), [redacted] (PD-L1 ≥ 1%)

3) Indirect evidence versus adjuvant PDC (NATCH) - [redacted]

Table 24 Results from the comparative analysis of perioperative durvalumab versus neoadjuvant PDC for patients with rNSCLC at high risk of recurrence

Outcome measure	Perioperative Durvalumab (N = 366)	Neoadjuvant+PDC (N = 374)	Result
EFS	N/A	N/A	HR = 0.69 (95% CI: 0.55–0.88)

Abbreviations: CI, confidence internval; EFS, event-free survival; HR, hazard ratio; NA, Not applicable; PDC, platinum-doublet chemotherapy; rNSCLC, resectable non-small cell lung cancer

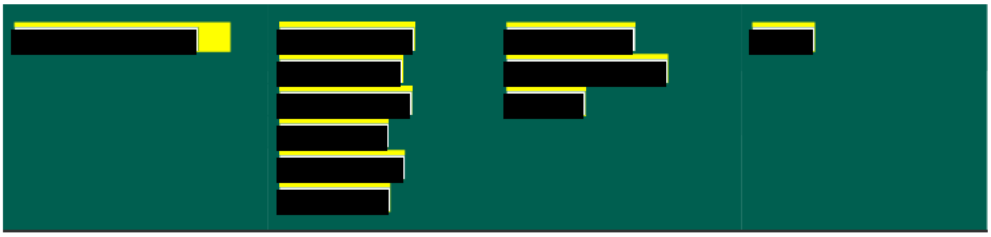
Source: [15, 16]

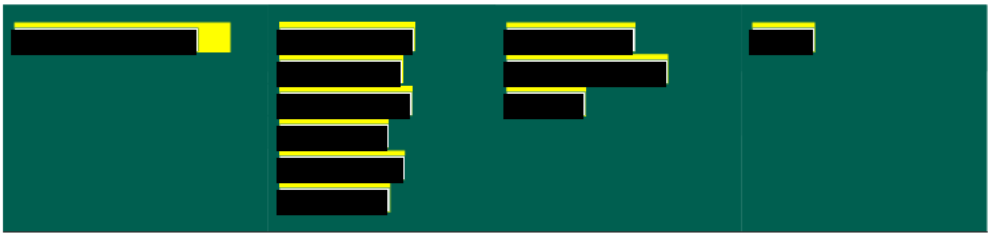
[redacted]

[redacted]

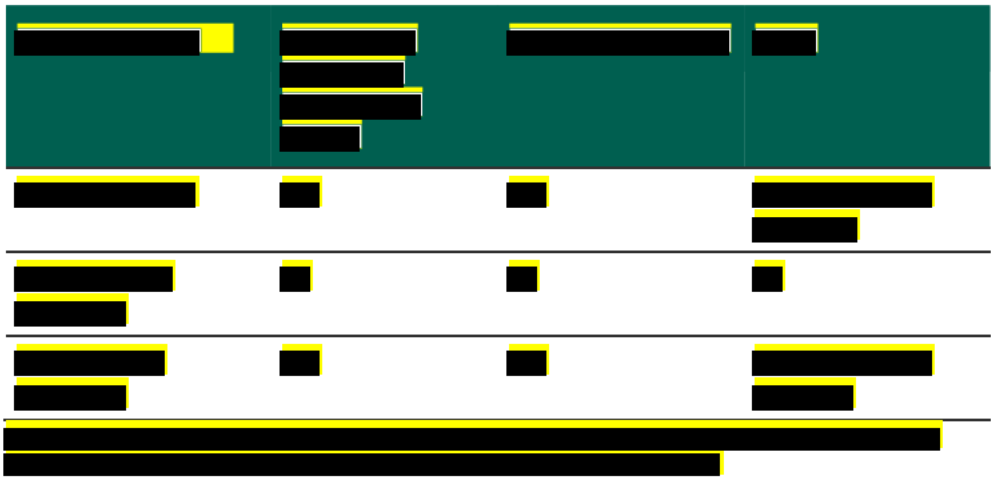
[redacted]

[redacted]

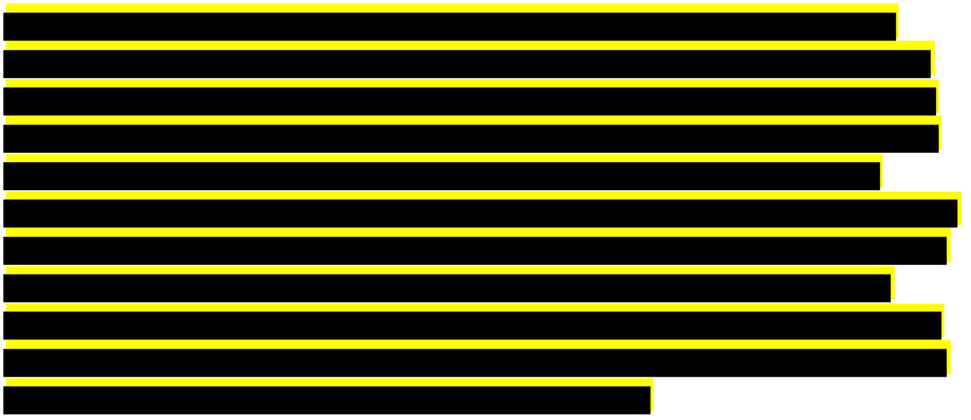




[redacted]



[redacted]



[redacted]

[redacted]

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

Not applicable.

8.1 Presentation of efficacy data from the clinical documentation used in the model

Not applicable.

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 30 Summary of assumptions associated with extrapolation of [effect measure] N/A

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A

Method/approach	Description/assumption
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

Not applicable.

Table 31 Transitions in the health economic model N/A

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N/A	N/A
	Death	N/A	N/A
Recurrence	Death	N/A	N/A
Health state/Transition		N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Not applicable.

Table 32 Estimates in the model N/A

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A

Table 33 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model) N/A

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
[Intervention]	N/A	N/A	N/A
[Comparator]	N/A	N/A	N/A

9. Safety

9.1 Safety data from the clinical documentation

In this section, an overview of safety events for AEGEAN (Table 34 and Table 37), CheckMate 816 (Table 35 and Table 38) and NATCH (Table 36) are presented. The adverse events in AEGEAN are presented for the SAS (safety was assessed in all patients who underwent randomisation and received at least one dose of any trial treatment [i.e., durvalumab or chemotherapy] or placebo) and for the overall period (the neoadjuvant, adjuvant and post-surgical periods not separated). The DCO used was 10th May 2024 (IA2) [16] of AEGEAN and the 4-year update for CheckMate 816 DBL 23rd February 2024 [64] and the 5-year update for CheckMate 816 DBL 23rd January 2025 [83].

In NATCH chemotherapy (preoperative/neoadjuvant and adjuvant), paclitaxel (200 mg/m^2 administered intravenously over 3 hours) was followed immediately by carboplatin (at an area under the curve dose of 6.0 mg/mL/min, administered intravenously over a period of 30 to 60 minutes). Treatment was repeated every three weeks for three cycles. Adverse events were reported for subjects who received at least

one cycle of protocol chemotherapy treatment. The median follow-up time was 51 months. Serious adverse events and adverse events for the surgery-only arm were not reported in the NATCH publication [65].

Table 34 Overview of safety events AEGEAN trial, safety analysis set, DCO 10 May 2024

	Durvalumab + PDC (N = 401)	Placebo + PDC (N = 398)	Difference, % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction ***or dose interruption***, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]	[redacted]

Source: [17]

Table 35 Overview of safety events CheckMate 816, DCO 23 February 2024, follow-up 57.6 months

	Nivolumab + PDC (N=176)	PDC alone (N=176)	Difference, % (95 % CI)
Number of adverse events, n	165 (94)	173 (98)	-5 (-9,0)
Number and proportion of patients with ≥1 adverse events, n (%)	NR	NR	NA
Number of serious adverse events*, n	30 (17)	24 (14)	3 (-4,11)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	NR	NR	NA
Number of CTCAE grade ≥ 3 events, n	76 (43)	79 (45)	-2 (-12,9)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	NR	NR	NA
Number of adverse reactions, n	147 (84)	159 (90)	-7 (-14,0)
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	NA
Number and proportion of patients who had a dose reduction, n (%)	NR	NR	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NR	NR	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	19 (11)	20 (11)	-1 (-7,6)

Source: [64]

Table 36 Overview of safety events NATCH trial, all with at least one cycle of per-protocol of chemotherapy, 51 months follow-up

	Adjuvant (preoperative) chemotherapy (N = 193)	Adjuvant chemotherapy (N = 139)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NA
Number and proportion of patients with ≥1 adverse events, n (%)	NR	NR	NA
Number of serious adverse events*, n	NR	NR	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	NR	NR	NA
Number of CTCAE grade ≥ 3 events, n	NR	NR	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	37 (19)	34 (24)	-5 (-14,4)
Number of adverse reactions, n	NR	NR	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	NA
Number and proportion of patients who had a dose reduction, n (%)	NR	NR	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NR	NR	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	NR	NR	NA

Table 37 lists the number of patients who experienced serious adverse events (SAEs) with frequency of ≥ 5% recorded in the AEGEAN trial, DCO 10th May 2024.

Table 37 Serious adverse events in AEGEAN, safety analysis set, 10 May 2024

Adverse events	Durvalumab + PDC (N = 401)		Placebo + PDC (N = 398)	
	Number (%) of patients with adverse events	Number of adverse events	Number (%) of patients with adverse events	Number of adverse events
Adverse event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
All SAEs (Any SAE including events with outcome of death)	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonias	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). Source: [17]

Table 38 Serious adverse events CheckMate 816, DBL 25 January 2025

Adverse events	Nivolumab+PDC (N=176)		PDC alone (N=176)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	165 (93.8)	NA	173 (98.3)	NA
All SAEs	30 (17.0)	NA	24 (13.6)	NA

Adverse events	Nivolumab+PDC (N=176)		PDC alone (N=176)	
Infections and infestations	4 (2.3)	NA	5 (2.8)	NA
Pneumonias	5 (2.8)	NA	4 (2.3)	NA
Blood and lymphatic system disorders	7 (4.0)	NA	11 (6.3)	NA
Respiratory, thoracic and mediastinal disorders	7 (4.0)	NA	3 (1.7)	NA

*Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 27.1, 1 (except surgery-related adverse events used version 25.0), and were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

†Included are events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose.

‡Most frequent (≥15% of patients in any treatment group).

¶The denominators are based on patients who underwent definitive surgery. Included are events reported up to 90 days after definitive surgery. Grade 5 surgery-related adverse events (defined as events that led to death ≤24 hours after the onset of an adverse event) were reported in two patients in the nivolumab plus chemotherapy group and were deemed by the investigator to be unrelated to the trial drugs (one each due to pulmonary embolism and aortic rupture).

Table 39 Adverse events used in the health economic model N/A

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/A	N/A	N/A
[Add a new row for each adverse event included in the model]	N/A	N/A	N/A	N/A

9.2 Safety data from external literature applied in the health economic model

Not applicable in the 14-week process.

Table 40 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Table 41 below gives an overview of the patient-reported outcome (PRO) from AEGEAN [17] and CheckMate 816 [18].

PRO measures were included as secondary endpoints in the AEGEAN study and assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the lung cancer specific module, Quality of Life Questionnaire - Lung Cancer 13 (QLQ-LC13), in the neoadjuvant period [17]. In addition, patient global Impression of severity (PGIS) and the patient reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) questionnaires were collected as exploratory endpoints. In this assessment, the EORTC QLQ-C30 and QLQ-LC13 are included.

In CheckMate 816, health-related quality of life (HRQoL) was an exploratory endpoint, measured with the EuroQol 5-Dimension 3-Level (EQ-5D-3L) instrument [18]. Changes from baseline in EQ-5D visual analogue scale (VAS; range 0 to 100) and utility index (UI; range −0.594 to 1) scores during the neoadjuvant period (week 4, week 7, and post-neoadjuvant visit 1) was done [18].

In the NATCH trial health related quality of life was not measured [65].

Table 41 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	CheckMate 816	EQ-5D-3L is a generic questionnaire HRQoL. The EQ-5D-3L questionnaire contains a visual analogue scale (EQ-VAS) that provides an aggregate estimate of the patient's self-reported health state on a scale from 0 to 100 (0 and 100 being the worst and best possible health, respectively).
EORTC QLQ-C30	AEGEAN	The EORTC QLQ-C30 is used to evaluate multiple dimensions of cancer patients HRQoL including physical functioning, emotional wellbeing, fatigue, pain, and overall health. It provides a comprehensive profile of

Measuring instrument	Source	Utilization
		functioning and symptom burden across the patient population.
EORTC QLQ-LC13	AEGEAN	The EORTC QLQ-LC13 is a lung cancer-specific instrument used in conjunction with the QLQ-C30. It assesses lung cancer–related symptoms such as coughing, hemoptysis, dyspnoea, and side effects from chemotherapy or radiotherapy, providing disease-specific insights into quality of life.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

10.1.1.1 EORTC QLQ-C30 AEGEAN

The EORTC QLQ-C30 is a core generic questionnaire designed to measure HRQoL in cancer patients. The questionnaire is composed of 30 items. The "core" instrument is combined with disease specific modules, in this case the lung cancer module (QLQ-LC13).

EORTC QLQ-C30 HRQoL data was collected in the AEGEAN study, with change from baseline [17]. Separate analyses of the change from baseline in EORTC QLQ-C30 (which was collected during both neoadjuvant and adjuvant treatment visits), were planned for the neoadjuvant period, in the mITT population, and for the adjuvant period, in the modified resected set [17]. The EORTC QLQ-C30 data were summarised descriptively with respect to change from baseline and clinically relevant changes (≥10 points from baseline) [17].

Mixed models for repeated measures (MMRM) were used to estimate changes from baseline and difference between treatment arms, by visit and on average during the neoadjuvant period and adjuvant period, with covariate adjustment for baseline score [17].

MMRM analyses were conducted for the following five scales/items: Global Health Score/Quality of life (GHS/QoL), physical functioning, role functioning, fatigue and appetite loss (EORTC QLQ-C30) [17]. Time to Treatment Discontinuation (TTD) in EORTC QLQ-C30 symptoms, functioning and GHS/QoL was also calculated from the adjuvant baseline until the first confirmed meaningful deterioration or death, whichever came first, and compared between treatment arms using a stratified log-rank test adjusted for disease stage and PD-L1 expression status at baseline.

Assessment of differences between treatment arms was performed without adjustment made for multiplicity [17].

10.1.1.2 EORTC QLQ-LC13 AEGEAN

The EORTC developed a questionnaire module for the assessment of HRQoL in lung cancer patients, QLQ-LC13, consisting of 13 items to be used in conjunction with the core questionnaire QLQ-C30. The QLQ-LC14 is a valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer patients, when combined with the EORTC QLQ-C30. In the AEGEAN study, HRQoL data were collected with the 13-item lung cancer-specific questionnaire module [17].

The EORTC QLQ-LC13 data were summarised descriptively with respect to change from baseline and clinically relevant changes (≥10 points from baseline). MMRM were used to estimate changes from baseline and differences between treatment arms, by visit and on average during the neoadjuvant period and adjuvant period, with covariate adjustment for baseline score [17].

MMRM analyses were conducted for the following three scales/items: dyspnoea, chest pain and cough in the neoadjuvant period only. Assessment of differences between treatment arms was performed without an adjustment made for multiplicity [17].

10.1.1.3 EQ-5D-3L VAS CheckMate 816

HRQoL was evaluated using EQ-5D-3L. A MMRM analysis evaluated longitudinal changes from baseline in EQ-5D visual analogue scale (VAS; range 0 to 100) and utility index (UI; range −0.594 to 1) scores during the neoadjuvant period (week 4, week 7, and post-neoadjuvant visit 1); higher scores reflect better HRQoL [18].

10.1.2 Data collection

10.1.2.1 EORTC QLQ-C30 AEGEAN

Table 42 and Table 43 present pattern of missing data and completion for durvalumab and placebo for EORTC QLQ-C30

Table 42 Pattern of missing data and completion with EORTC QLQ-C30 for durvalumab, IA2

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IA2: Interims analysis 2

Source: AEGEAN CSR [17]

Table 43 Pattern of missing data and completion with EORTC QLQ-C30 for placebo, IA2

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IA2: Interims analysis 2

Source: AEGEAN CSR [17]

10.1.2.2 EORTC QLQ-LC13 AEGEAN

Table 44 and Table 45 present pattern of missing data and completion for durvalumab and placebo for EORTC QLQ-LC13.

Table 44 Pattern of missing data and completion with EORTC QLQ-LC13 for durvalumab, IA2

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IA2: Interims analysis 2

Source: AEGEAN CSR [17]

Table 45 Pattern of missing data and completion with EORTC QLQ-LC13 for placebo, IA2

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IA2: Interims analysis 2

Source: AEGEAN CSR [17]

10.1.2.3 EQ-5D-3L VAS CheckMate 816

EQ-5D-3L completion rates were > 80% in both treatment arms at baseline and during the neoadjuvant period [18].

10.1.3 HRQoL results

10.1.3.1 EORTC QLQ-C30 AEGEAN

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

10.1.3.2 EORTC QLQ-LC13 AEGEAN

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

10.1.3.3 EQ-5D-3L VAS CheckMate 816

EQ-5D-3L scores during the neoadjuvant period were generally similar to baseline for both treatment arms; there were no clinically meaningful differences between nivolumab+PDC versus PDC alone Table 48 [18].

In both treatment arms, most patients reported "no problems" for individual EQ-5D-3L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline and during treatment [18].

Table 48 HRQoL EQ-5D-5L VAS summary statistics

	Nivolumab + PDC	PDC	Nivolumab +PDC vs. PDC Difference (95% CI)
Baseline			
VAS; MID = 7			
Overall	−0.9 (−2.4, 0.7)	−1.5 (−3.1, 0.1)	0.6 (−1.5, 2.7)
Wk 4	−0.4 (−2.1, 1.4)	−1.7 (−3.5, 0.1)	1.3 (−1.0, 3.7)
Wk 7	−1.3 (−3.2, 0.6)	−0.8 (−2.7, 1.2)	−0.6 (−3.2, 2.0)
Post-neoadjuvant visit 1	−0.8 (−2.9, 1.2)	−2.0 (−4.1, 0.2)	1.1 (−1.7, 3.9)

UI; MID = 0.08			
Overall	−0.003 (−0.024, 0.019)	−0.011 (−0.033, 0.011)	0.008 (−0.020, 0.036)
Wk 4	0.012 (−0.011, 0.036)	0.001 (−0.023, 0.025)	0.011 (−0.021, 0.043)
Wk 7	−0.006 (−0.033, 0.021)	−0.004 (−0.031, 0.023)	−0.002 (−0.038, 0.034)
Post-neoadjuvant visit 1	−0.014 (−0.043, 0.015)	−0.029 (−0.059, 0.001)	0.015 (−0.025, 0.056)

Abbreviations: MID: Minimally Important Difference

10.2 Health state utility values (HSUVs) used in the health economic model

Not applicable.

10.2.1 HSUV calculation

Not applicable

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

Not applicable.

Table 49 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A
...				
[Disutilities]	N/A	N/A	N/A	N/A
...				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 50 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A
...				
[Disutilities]	N/A	N/A	N/A	N/A
...				

Table 51 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A
HSUV B				
...	N/A	N/A	N/A	N/A
[Disutility A]				
...	N/A	N/A	N/A	N/A

11. Resource use and associated costs

Not applicable.

11.1 Medicines - intervention and comparator

Table 52 Medicines used in the model N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A
[Name of the comparator]	N/A	N/A	N/A	N/A

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Not applicable.

Table 53 Administration costs used in the model N/A

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
[E.g. i.v. infusion, subcutaneous infusion]	N/A	N/A	N/A	N/A

11.4 Disease management costs

Not applicable.

Table 54 Disease management costs used in the model N/A

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
[Activity]	N/A			N/A

11.5 Costs associated with management of adverse events

Not applicable.

Table 55 Cost associated with management of adverse events N/A

	DRG code	Unit cost/DRG tariff
[Adverse event]	N/A	N/A
[Adverse event]	N/A	N/A

11.6 Subsequent treatment costs

Not applicable.

Table 56 Medicines of subsequent treatments N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A
[Name of the comparator]	N/A	N/A	N/A	N/A

11.7 Patient costs

Not applicable.

Table 57 Patient costs used in the model N/A

Activity	Time spent [minutes, hours, days]
Activity	N/A

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

Not applicable.

12.1 Base case overview

Not applicable.

Table 58 Base case overview N/A

Feature	Description
Comparator	N/A

Feature	Description
Type of model	N/A
Time horizon	N/A
Treatment line	N/A
Measurement and valuation of health effects	N/A
Costs included	N/A
Dosage of medicine	N/A
Average time on treatment	N/A
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	N/A
Average time in model health state	N/A
Health state 1	
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

Not applicable.

Table 59 Base case results, discounted estimates N/A

	[Intervention]	[Comparator]	Difference
Medicine costs	N/A	N/A	N/A
Medicine costs – co-administration	…	…	…
Administration			
Disease management costs			
Costs associated with management of adverse events			
Subsequent treatment costs			
Patient costs			
Palliative care costs			
Total costs			
Life years gained (health state A)			
Life years gained (health state B)			
Total life years			

	[Intervention]	[Comparator]	Difference
QALYs (state A)			
QALYs (state B)			
QALYs (adverse reactions)			
Total QALYs			
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**N/A**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Not applicable.

Table 60 One-way sensitivity analyses results N/A

Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	N/A	N/A	N/A	N/A
[relevant analysis]	N/A	N/A	N/A	N/A

Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[relevant analysis]	N/A	N/A	N/A	N/A

12.2.2 Probabilistic sensitivity analyses

Not applicable.

13. Budget impact model

Not applicable.

Number of patients (including assumptions of market share)

Table 61 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) N/A

Year 1	Year 2	Year 3	Year 4	Year 5
		Recommendation		

Year 1	Year 2	Year 3	Year 4	Year 5
N/A				
N/A				
		Non-recommendation		
N/A				
N/A				

Budget impact

Table 62 Expected budget impact of recommending the medicine for the indication N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	N/A	N/A	N/A	N/A	N/A
The medicine under consideration is NOT recommended	N/A	N/A	N/A	N/A	N/A
Budget impact of the recommendation	N/A	N/A	N/A	N/A	N/A

14. List of experts

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Appendix A. Main characteristics of studies included

A.1 AEGEAN

Table 37 Main characteristics of studies included

Trial name: AEGEAN	**NCT number: NCT03800134**
Objective	To study the efficacy and safety of perioperative durvalumab + neoadjuvant platinum-based chemotherapy for the treatment of patients with resectable Stage IIA–IIIB(N2) NSCLC.
Publications – title, author, journal, year	Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. Heymach JV, et al., N Engl J Med. 2023
Study type and design	A Phase III, double-blinded, placebo-controlled, multi-center clinical trial. Patients were randomly assigned 1:1, in either the intervention arm (durvalumab) or in the comparator arm (placebo). Crossover was not permitted.
Sample size (n)	mITT population: 740 participants (durvalumab: n=366, placebo: n=374)
Main inclusion criteria	Aged ≥18 years at the time of screening

Trial name: AEGEAN	NCT number: NCT03800134
	Newly diagnosed, previously untreated, histologically or cytologically documented resectable (Stage IIA–Stage IIIB[N2]) NSCLC (according to the AJCC TNM lung cancer staging 8th edition), with mediastinal lymph-node staging performed pathologically at the discretion of the investigator Candidate for lobectomy, sleeve resection, or bilobectomy at screening ECOG PS of 0 or 1 at enrolment and randomisation Provision of sufficient tumour biopsy sample for evaluation and confirmation of EGFR and ALK status Documented tumour PD-L1 status prior to randomisation At least one lesion not previously irradiated that qualifies as a Response Evaluation Criteria in Solid Tumours (RECIST v1.1) target lesion at baseline. Tumour assessment by computed tomography or magnetic resonance imaging (MRI) scan must be performed within 28 days prior to randomization.
Main exclusion criteria	Previous exposure to anti–PD-L1, anti–PD-1, or anti–cytotoxic T-lymphocyte antigen 4 antibodies. Uncontrolled intercurrent illness. Specific active or previously documented autoimmune disorders. Sublobar resections as planned surgery at the time of enrollment.
Intervention	Durvalumab + platinum-based chemotherapy was given as neoadjuvant treatment to 366 patients (mITT). Dosage: should be given at four cycles of platinum-based chemotherapy with durvalumab (1500 mg) IV every three weeks, followed by surgery. Following surgery, durvalumab (1500 mg) IV every four weeks for up to 12 cycles.
Comparator(s)	Placebo (placebo+ platinum-based chemotherapy) was given to 374 patients (mITT), of which 3 did not receive neoadjuvant treatment.

Trial name: AEGEAN	NCT number: NCT03800134
	Dosage: Placebo + platinum-based chemotherapy Q3W for 4 cycles, followed by surgery and placebo Q4W for 12 cycles.
Follow-up time	Median follow-up was 25.9 months (range: 0.0 to 58.6 months).
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	Primary endpoints: • pCR, measured in the mITT population based on a blinded assessment per central pathology review, according to the methods recommended by IASLC 2020 Secondary endpoints: • EFS, measured in the mITT population using BICR assessment, according to the RECIST v1.1 guidelines. • mPR, measured in the mITT population based on a blinded assessment per central pathology review, according to the methods recommended by IASLC 2020. • DFS, measured in the modified resected population using BICR assessment, according to the RECIST v1.1 guidelines • OS, measured in the mITT population. Other endpoints: • HRQoL, assessed by change from baseline (i.e. last pre-neoadjuvant dose. Endpoints used in the application: • EFS primary, supplementary OS and PFS.
Method of analysis	All efficacy analysis was performed on the mITT population. The Kaplan-Meier survival was used to estimate the primary efficacy endpoint in this application, EFS. The hazard ratios and 95% CI were calculated using a Cox proportional hazards model to compare survival outcomes between the two treatment arms. The same strategy was implemented for OS.

Trial name: AEGEAN	NCT number: NCT03800134
	pCR and mPR were calculated using a stratified Miettinen and Nurminen method. P-value was calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary <0.001 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary.
Subgroup analyses	N/A
Other relevant information	N/A

A.2 CheckMate-816

Table 63 Main characteristic of studies included

Trial name: CheckMate 816	NCT number: NCT02998528
Objective	The study aims to evaluate the effectiveness and safety of nivolumab in combination with chemotherapy as a neoadjuvant treatment in patients with resectable non-small cell lung cancer.
Publications – title, author, journal, year	Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung. Forde PM, et al., Cancer. N Engl J Med. 2022. Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. Jonathan Spicer et al., Journal of Clinical Oncology, meeting abstract: 2024 ASCO Annual meeting ll.
Study type and design	A randomized, open label, Phase 3 Trial. Patients were randomly assigned 1:1. Patients were treated with the intervention nivolumab+ chemotherapy or chemotherapy.
Sample size (n)	mITT population: 358 participants (nivolumab+ chemotherapy: n=179, chemotherapy: n=179)
Main inclusion criteria	Early stage IB-IIIA, operable non-small cell lung cancer, confirmed in tissue.

Trial name: CheckMate 816	NCT number: NCT02998528
	Lung function capacity capable of tolerating the proposed lung surgery. ECOG Performance Status of 0-1. Available tissue of primary lung tumour.
Main exclusion criteria	Presence of locally advanced, inoperable or metastatic disease. Participants with active, known or suspected autoimmune disease. Prior treatment with any drug that targets T cell co-stimulations pathways (such as checkpoint inhibitors).
Intervention	Neoadjuvant treatment: Nivolumab (360 mg) + platinum-based chemotherapy every three weeks for three cycles (n=179, whereof 176 received treatment).
Comparator(s)	Neoadjuvant treatment with platinum-based chemotherapy every three weeks for 3 cycles (n=179, whereof 176 received treatment).
Follow-up time	Median 57.6 months at the 4 year follow up
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	Primary endpoints: • EFS, based on BICR assessment per RECIST 1.1. • EFS • pCR, patients not undergoing surgery were included as non-responders for the analysis of pCR, as per EMA guidelines. • pCR

Trial name: CheckMate 816	NCT number: NCT02998528
	Secondary endpoints: • mPR, patients not undergoing surgery were included as non-responders for the analysis of MPR, as per EMA guidelines. • mPR • OS, from randomization to the date of death. • OS • TTDM, defined as the time between the date of randomization and the first date of distant metastasis or the date of death in the absence of distant metastasis. Endpoints included in this application: • EFS, supplementary pCR mPR and OS
Method of analysis	All efficacy analysis was performed on the mITT population. The primary efficacy endpoint, EFS, was estimated using the Kaplan-Meier survival method in this analysis. Survival outcomes between the two treatment arms were compared by calculating the Cox proportional hazard ratios and 95% CI. This same approach was applied to OS.
Subgroup analyses	N/A
Other relevant information	N/A

A.3 NATCH

Table 64 Main characteristic of studies included

Trial name: NATCH	NCT number: NCT00913705
Objective	To compare the effect on disease-free survival of preoperative or adjuvant chemotherapy using paclitaxel-carboplatin with that of observation in patients with early stage NSCLCs. The primary objective of the study was to determine whether preoperative or adjuvant chemotherapy improved disease-free survival in patients with clinically early staged NSCLC. The secondary end points were overall survival and the assessment of chemotherapy adverse events.
Publications – title, author, journal, year	Felip E, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol. 2010 Jul 1;28(19):3138-45. doi: 10.1200/JCO.2009.27.6204. Epub 2010 Jun 1. PMID: 20516435. [65]
Study type and design	Interventional, phase 3, randomised, parallel assignment, open label
Sample size (n)	Randomised N=624 • Surgery alone n=212 • Preoperative chemotherapy n =201 Adjuvant chemotherapy n=211
Main inclusion criteria	• The patients eligible for the study are those with a diagnosis, histologically or cytologically proven, of NSCLC without metastases at stages IB, IIA, IIB and IIIA (not N2) of the disease. Patients with stage IA and tumor size >2cm will be eligible as well. • Patients aged > 18 years. • Tumor considered resectable by the attending surgeon. • The patient must have an ECOG *2 or Karnofsky >60%. • The patients need to have adequate hematological, renal and hepatic function defined as: Absolute neutrophil counts (ANC*) *1.5 x 109/L Platelet counts *100 x 109/L Total bilirubin *1.25 x upper limit of normal distribution Serum creatinine <120 umol/L (<1.5 mg/dl) Creatinine clearance >60 ml/min

Trial name: NATCH	NCT number: NCT00913705
	• ANC = segmented neutrophils + banded neutrophils • The patients should have recovered from any serious surgical sequellae. • Informed consent must be obtained from the patient in accordance with the requirements of the IRB/EC. • If female, the patient must not be pregnant or breast-feeding. Women of child bearing potential need to have a pregnancy test performed and to take appropriate contraceptive action during the period of the study. • Operability criteria: Lung function test will be performed so as to confirm a predictive postoperative value of FEV-1 >-800 ml, i.e. correct homeostasis. A carbon monoxide diffusion test is to be conducted and, when applicable, repeated following the induction treatment while taking into account the sensitivity of post-chemotherapy pulmonary toxicity detection.
Main exclusion criteria	Patients who have previously been treated with chemotherapy and/or radiotherapy. History of significant cardiovascular disease such as non-controlled hypertension, unstable angina or congestive heart failure even if these are controlled by medication. Documented history of acute myocardial infarction in the previous year, ventricular arrhythmias that required medication or 2nd or 3rd atrial-ventricular blocks. Pre-existing sensory or motor neurotoxicity grade >2 based on the WHO criteria. Active infection or other clinical state that could seriously reduce the patient's capacity to tolerate the treatment protocol, including previous allergic reactions to products containing Cremophor (e.g. cyclosporin or vitamin K). Previous or concomitant malignant tumor (with the exception of in situ cervical carcinoma, baso-cellular carcinoma, squamous cell skin carcinoma or urothelial superficial carcinoma) which are considered potentially curable with oncological treatment and have a disease free survival (DFS) greater than 5 years EXCEPTING breast cancer, melanoma and hypernephroma Marked psychoses or senility
Intervention	1. : Neoadjuvant chemotherapy (taxol and carboplatin)

Trial name: NATCH	NCT number: NCT00913705
	Taxol: 200mg/m2 infusion over 3 hours; Carboplatin: AUC= 6 at the end of the Taxol infusion. Administration of 3 cycles at 21-day intervals. Prior to surgery.
Comparator(s)	2. : Adjuvant chemotherapy (taxol and carboplatin) Taxol: 200mg/m2 infusion over 3 hours; Carboplatin: AUC= 6 at the end of the Taxol infusion. Administration of 3 cycles at 21 days interval. Post-surgery 3. Surgery
Follow-up time	5 years, median 51 months in the analysis
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary: • DFS: defined as the length of time from the date of diagnosis to the date of the first documented progression of disease • OS: defined as the length of time from either the date of diagnosis or the start of the treatment that patients diagnosed with the disease are still alive. Secondary • Occurrence and severity of adverse events
Method of analysis	All analyses were performed according to the intention-to-treat principle and included all randomized patients, eligible or not. Disease-free survival and overall survival curves were constructed by the Kaplan-Meier method and compared with the use of the log-rank test and the Cox proportional hazards model. All reported P values are two-sided. Analysis reflects the database as of March 1, 2009.

Trial name: NATCH	NCT number: NCT00913705
	Chemotherapy adverse events were summarized for all patients who received at least one cycle of the assigned chemotherapy treatment. All statistical calculations were performed using STATA(version 10.0; STATA, College Station, TX).
Subgroup analyses	On Age (over 65, 65 and younger), gender (male, female), ECOG PS (0, 1-2,), pretreatment clinical stage (stage I, Stage II-T3N1), surgery (lobectomy/bilobectomy, pneumonectomy)
Other relevant information	NA

Appendix B. Efficacy results per study

B.1 AEGEAN

Table 65 Results per study AEGEAN, modified ITT population

Results of [AEGEAN (NCT03800134)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median EFS mITT	Durvalumab	366	NR (42.3, NR)	NA	NA	NA	HR:0.69	0.53-0.88	NA	The effect of treatment was estimated by the HR together with its corresponding 95% CI, a CI with confidence level adjusted for the relevant alpha level, and p-value. The HR and CI was estimated from the stratified Cox proportional hazards model (Cox 1972) adjusted for IXRS stratification factors disease stage (Stage II vs Stage III) and PD-L1 expression status at	
	Placebo	374	30.0 (20.6, NR)								

Results of [AEGEAN (NCT03800134)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										baseline (TC < 1% vs TC ≥ 1%). The Cox models are fitted using PROC PHREG with the Efron method to control for ties and the CI was calculated using a profile likelihood approach. Kaplan-Meier plots of EFS are presented by treatment arm. Summaries of the number and percentage of patients experiencing an EFS event and the type of event are provided along with median EFS and 95% CI for each treatment.	
EFS rate at 12 months (%) mITT	Durvalumab	366	73.3 (68.1-77.7)	NA	NA	NA	NA	NA	NA	See above EFS	[84]
	Placebo	374	64.1 (58.7-69.0)								[84]

Results of [AEGEAN (NCT03800134)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
EFS rate at 24 months year (%) mITT	Durvalumab	366	65.0 (59.4-70.0)	NA	NA	NA	NA	NA	NA	See above EFS	[84]
	Placebo	374	54.4 (48.7-59.6)								[84]
EFS rate at 36 months IA2 (%) mITT	Durvalumab	366	60.1 (53.9-65.8)	NA	NA	NA	NA	NA	NA	See above EFS	[84]
	Placebo	374	47.9 (41.8-53.8)								[84]
Median OS mITT	Durvalumab	366	NR	NA	NA	NA	HR: 0.89	0.70-1.14	NA	The effect of treatment is estimated by the HR together with its corresponding 95% CI. Kaplan-Meier plots are presented by treatment arm. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent	[84]
	Placebo	374	53.2 (44.3, NR)								

Results of [AEGEAN (NCT03800134)]												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										are provided along with the median OS and 95% CI for each treatment.	
Median EFS, months in PD-L1 ≥1% subgroup	Durvalumab	244	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[84]
	Placebo	249	[redacted]								

B.2 CheckMate 816

Table 66 Results per study CheckMate 816

Results of CheckMate 816 (NCT02998528)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median EFS, months ITT population	Nivolumab+PDC	179	43.8 (30.6–NR)	NA	NA	NA	HR: 0.66	0.49-0.90	NA	Efficacy analyses were performed in patients concurrently randomized to nivolumab+PDC and PDC alone. EFS was compared between treatment groups with a log-rank test stratified by the stratification factors per interactive response technology (PD-L1 [<1%/not evaluable vs. ≥1%], disease stage [IB II vs. IIIA], and sex [male vs. female]). Survival curves and rates were estimated using the Kaplan–Meier method. Hazard ratios and confidence intervals (CIs) were estimated with a stratified Cox	[64]
	PDC alone	179	18.4 (14.0–26.7)								

Results of CheckMate 816 (NCT02998528)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										proportional-hazards model, with treatment group as a single covariate.	
Median EFS, months PD-L1 ≥1% subgroup	Nivolumab+PDC	81	NR (44.42, NR)	NA	NA	NA	HR: 0.49	0.29-0.83	NA	See above EFS	[64]
	PDC	86	26.71 (13.40, NR)								

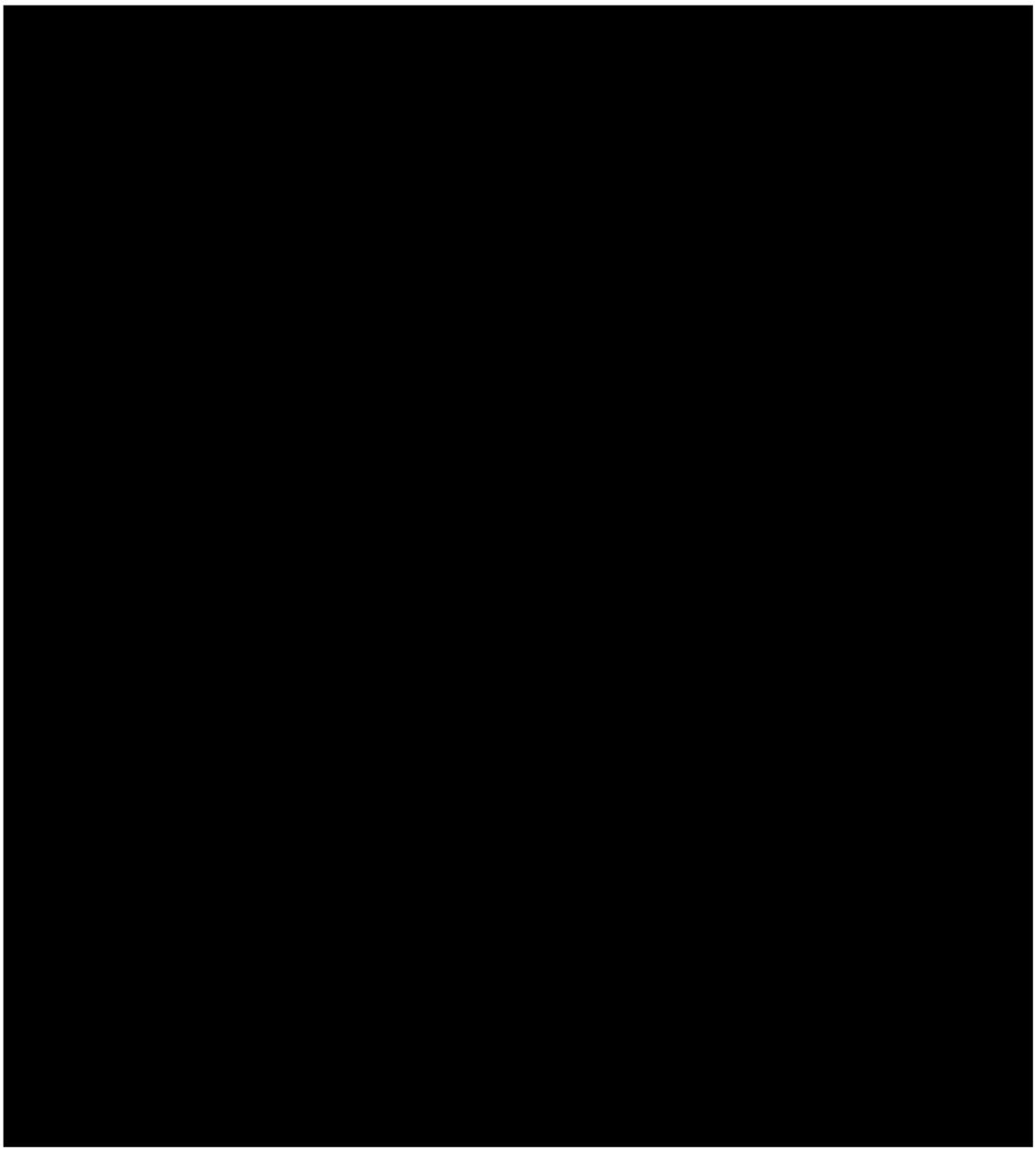
B.3 NATCH

Table 67 Results per NATCH

Results of NATCH (NCT number)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Events DFS	Adjuvant PDC	210	132 (62.9%)	N/A	NA	NA	HR: 0.96	0.75-1.22	0.74	Disease progression or death HR from Cox model comparing adjuvant PDC to surgery	Felip, 2010 [65]
	Surgery	210	125 (59.5%)								

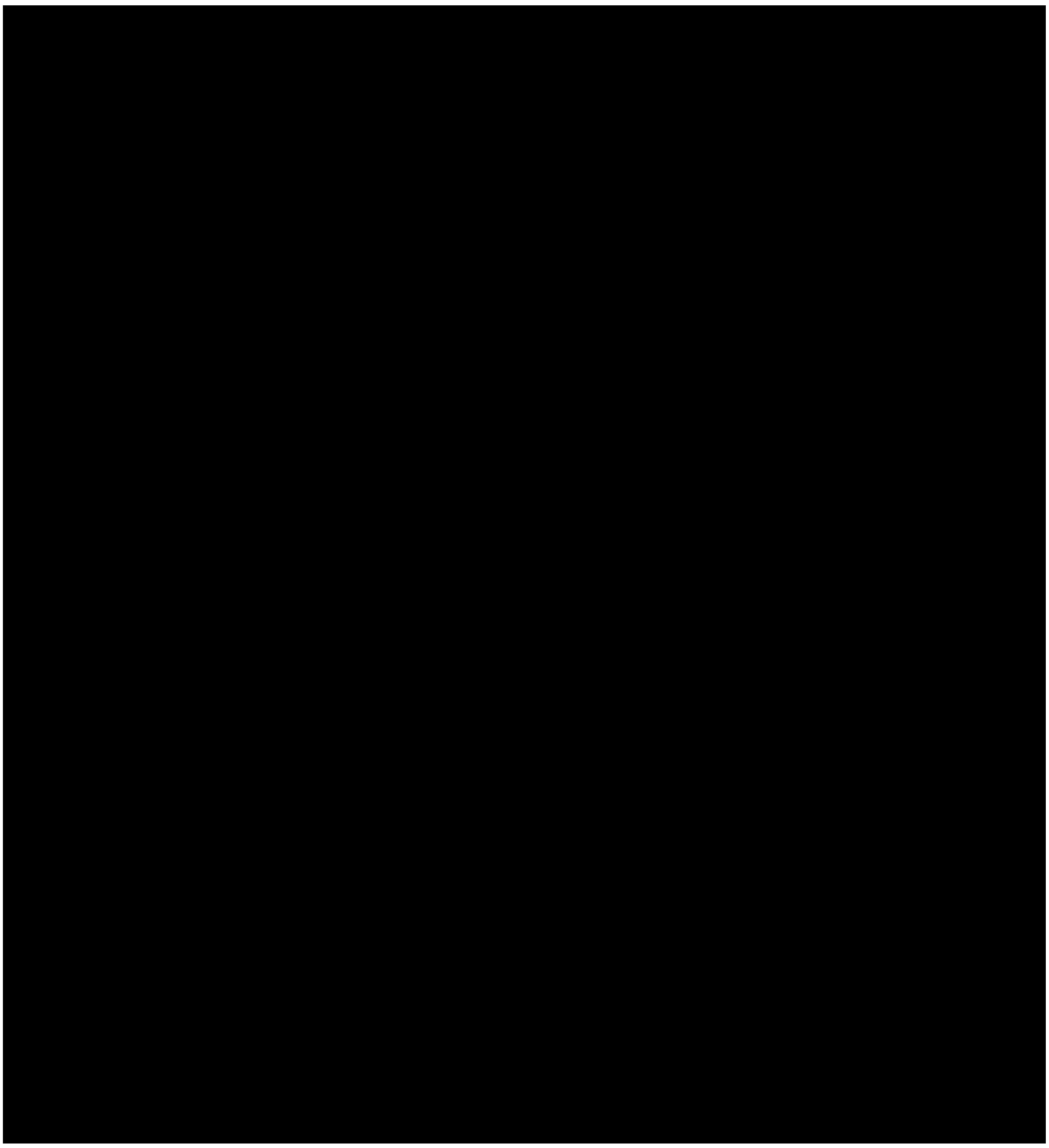
Appendix C. Comparative analysis of efficacy

C.1 Assessment of the proportional hazard assumption



[redacted]

[redacted]



C.2 Matching adjusted indirect comparison

All MAIC analyses were conducted using R version 4.1.0 within the R Studio environment. Packages used included maic (v 0.1.4), survival (v 3.4.0) and survminer (0.4.9).

C.2.1 Matching adjusted indirect comparison versus neoadjuvant novilumab + PDC

The first step in conducting the MAIC involved deriving weights such that the average baseline characteristics in AEGEAN (post-weighting) [16] matched the published aggregate characteristics of the comparator population. For this, a propensity score-type logistic regression equation to estimate weights was used. Specifically, weights were estimated by the odds of being enrolled in the target population (i.e., CheckMate 816) vs AEGEAN, which was calculated as $w_i = exp(\alpha + x_i'\beta)$ where x_i' was the vector of baseline variables that were included for weighting. The β coefficients were determined by the method of moments because only aggregate data for the x_i''s were available for the comparator trial populations, as described in Signorovitch *et al.* [87]. Patients who had missing values for any of the variables included in the MAIC were excluded from the analysis. Once the coefficients were estimated, the equation was applied to the patients from AEGEAN [16] to calculate the individual patient weights.

Next, the distribution of weights was assessed to identify any overly influential observations. The effective sample size (ESS) was calculated by $(\sum w_i)^2/(\sum w_i^2)$. If the populations were perfectly balanced before adjustment, all AEGEAN patients would have $w_i = 1$, and the ESS would equal the original size in AEGEAN's population. Adjustments for population differences assigned patients uneven weights, leading to the inevitable loss of ESS. A low ESS indicates an irregular distribution of weights across patients, meaning that only a small fraction of patients drives the treatment effect in the weighted population [82].

Based on the individual patient weights for the AEGEAN population [16], the (weighted) EFS HRs for perioperative durvalumab + neoadjuvant platinum-based chemotherapy vs perioperative placebo + neoadjuvant platinum-based chemotherapy were derived from weighted Cox PH models. As the weights were derived from the data, robust sandwich estimators were used to compute the standard error (SE) of the weighted logHR in AEGEAN, as recommended in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 [88].

The anchored indirect comparison of perioperative durvalumab vs a comparator treatment X was then calculated on the log-scale, using the weighted AEGEAN EFS HR and the EFS HR reported from the comparator trial (both HRs vs the common comparator), in accordance with Bucher et al.[89]:

$$\log HR_{\text{Peri.D } vs.\text{X}} = \log HR^{AEGEAN}_{\text{Peri.D } vs.\text{PDC}} - \log HR^{Comparator\ trial}_{X\ vs.PDC}$$

$$\text{SE}(\log HR_{\text{Peri.D } vs.\text{X}}) = \sqrt{\left(SE\left(\log HR^{AEGEAN}_{\text{Peri.D } vs.\text{PDC}}\right)\right)^2 + \left(SE\left(\log HR^{Comparator\ trial}_{X\ vs.\ PDC}\right)\right)^2}.$$

The output from the indirect comparisons included the EFS HR and 95% CI for the comparison of perioperative durvalumab vs comparator treatment X. In the MAICs, this HR provided an estimate of the relative effect on EFS of perioperative durvalumab vs comparator treatment X in a population matching the characteristics of the comparator trial population. Anchored indirect comparisons using the unweighted HR from AEGEAN were also conducted.

In accordance with NICE DSU TSD 18 [88], anchored MAICs are considered to be warranted when there are imbalances in baseline characteristics that are considered to be possible EMs. The following characteristics were considered to be possible EMs: disease stage, PD-L1 expression, region (Asia vs non-Asia), sex, histology, smoking status, and planned platinum chemotherapy.

In the base case analysis (Scenario 1), all possible EMs were included in the weighting, regardless of whether imbalances exist between trials in these baseline characteristics, as per recommendation 4 in NICE DSU TSD 18 [88]. An additional analysis (Scenario 2) was also conducted to explore the impact on results of only weighting for those characteristics that were imbalanced (≥5% difference) between trials [82].

The list of characteristics included in the weighting in each scenario for each of the two comparisons is shown in Table 68.

Table 68 Scenarios explored for weighting in the MAIC vs CheckMate (AEGEAN mITT population)

Scenario	Variables for weighting	Rationale
1 Base case	Stage (IIIB vs other) Stage (IIIA vs other) PD-L1 (<50% vs ≥50%) PD-L1(<1% vs ≥1%) Histology (squamous vs non-squamous) Region (Asia vs non-Asia) Sex (male vs female) Smoking status (never vs ever/current) Planned platinum chemotherapy (cisplatin vs carboplatin)	Includes all possible EMs
2	Stage (IIIB vs other) Stage (IIIA vs other) PD-L1 (<50% vs ≥50%) PD-L1(<1% vs ≥1%) Region (Asia vs non-Asia) Planned platinum chemotherapy (cisplatin vs carboplatin)	Includes possible EMs with imbalance (≥5%) between trials at baseline

Source: [82]

The summary of event numbers, and the HRs, for AEGEAN (before weighting) and CheckMate 816 are shown in Table 69 and Table 70, respectively.

Table 69 Trial summaries of EFS in AEGEAN and CheckMate 816

Arm	Trial	N	Events	Maturity
Durvalumab + PDC	AEGEAN	366	124	34%
Placebo + PDC	AEGEAN	374	165	44%
Nivolumab + PDC	CheckMate 816	179	75	42%
PDC	CheckMate 816	179	97	54%

Note: AEGEAN EFS IA2 DCO date: 10th May 2024; CheckMate 816: 4-year update DBL date: 23rd February 2024

Abbreviation: PDC: Platinum based doublet chemotherapy

Source: [16, 64]

Table 70 Pre-weighting EFS HRs (vs PDC ± placebo) from AEGEAN and CheckMate 816 (4-year update)

Arm	HR	LCL (95%)	UCL (95%)	Source
Durvalumab + PDC	0.70	0.56	0.89	AEGEAN EFS IA2 (unstratified Cox regression model) DCO date: 10 May 2024 [16]
Nivolumab + PDC	0.66	0.49	0.90	CheckMate 816 4-year update [64]

Abbreviations: DCO, data cutoff; HR, hazard ratio; LCL, lower confidence limit; PDC, platinum-doublet chemotherapy; UCL, upper confidence limit

A comparison of baseline characteristics between the two studies (overall trial, i.e., both arms) before and after weighting is shown in [redacted] (weighting in Scenario 1) and [redacted] (weighting in Scenario 2).

As described in the imbalances in baseline characteristics between AEGEAN[16] and CheckMate 816, [9, 71-75] including:

- The proportion who received cisplatin at baseline (higher in CheckMate 816 [9, 71-75])
- The proportion with stage IIIA at baseline (higher in CheckMate 816 [9, 71-75])
- The proportion with stage IIIB at baseline (lower in CheckMate 816 [9, 71-75])
- The proportion of patients enrolled in Asia (region) (higher in CheckMate 816 [9, 71-75])
- The proportion with PD-L1 <1% (higher in CheckMate 816[9, 71-75])

Each of these characteristics is considered to be a possible EM.

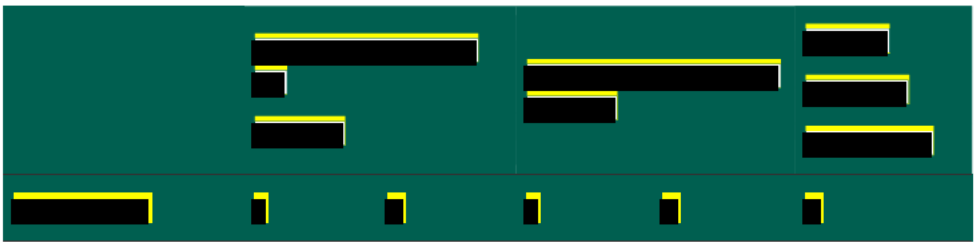
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



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C.3 Network meta analysis

The NMA was conducted in a Bayesian framework, using Monte Carlo Markov Chain simulation methods, and using R version 4.0.2 [88] with the following packages: Rstan (v 2.19.3), multinma (v 0.5.1), and survival (v 3.1.12). The models were run with four chains of 10,000 iterations, of which every second iteration was kept; 5,000 were burn-in iterations (i.e., thinning = 2) to generate the posteriors for the defined parameters. Convergence of the chains was assessed using the Rhat statistic [89].

Since EFS is a time-to-event outcome, the log HRs were analysed using a normal likelihood and identity link (Program 7 of NICE DSU TSD 2) [90].

Non-informative normal (0, 1002) priors were assigned to the treatment effect parameters. Both fixed- and random-effects models were conducted, but there were limited data to estimate between-study heterogeneity for random-effects models, so informative priors based on a log-normal distribution ('subjective outcomes (various)' prior, log-normal ~ (-2.93, 1.582)) were used for random-effects models based on Turner et al [91].

Whereas a fixed-effect model assumes there is a single 'true' effect size underlying the trials informing a treatment comparison (i.e., that differences between studies are purely due to chance variation), random-effects models assume studies informing a treatment comparison are estimating 'similar' effects, but there are differences beyond just chance variation (i.e., total variation = chance differences + between-study heterogeneity). 'Similar' in this case means the effect sizes are coming from a (normal) distribution of effect sizes. Random-effect models are more plausible than fixed-effect models, but there is usually very limited information with which to estimate between-study heterogeneity (as is considered the case here). Given that heterogeneity was identified in the feasibility assessment, the random-effects model was preferred.

When both fixed- and random-effects models were fitted to the data, their deviance information criteria (DIC) were derived. Lower values represent the more parsimonious model, and differences of 3 points were considered meaningful [92]. The model goodness-of-fit was assessed by comparing the posterior mean residual deviance to the number of data points in the network [92]. The number of data points was calculated as the sum of arms across studies reporting arm-level data and the sum of studies reporting contrast-based data. Model fit was considered good if the posterior mean residual deviance was similar to the number of data points [93].

C.3.1 NMA versus adjuvant PDC

EFS HR data were analysed using NMA for the mITT and N2 population of AEGEAN [90, 91]. [redacted] The NMA was conducted in a Bayesian framework, using Monte Carlo Markov Chain simulation methods, and using R version 4.0.2 [92] with the following packages: Rstan (v 2.19.3), multinma (v 0.5.1), and survival (v 3.1.12). The models were run with four chains of 10,000 iterations, of which every second iteration was kept; 5,000 were burn-in iterations (i.e., thinning = 2) to generate the posteriors for the defined parameters. Convergence of the chains was assessed using the Rhat statistic [93].

Since EFS is a time-to-event outcome, the log HRs were analysed using a normal likelihood and identity link (Program 7 of NICE DSU TSD 2) [94].

Non-informative normal $(0, 100^2)$ priors were assigned to the treatment effect parameters. Both fixed- and random-effects models were conducted, but there were limited data to estimate between-study heterogeneity for random-effects models, so informative priors based on a log-normal distribution ('subjective outcomes (various)' prior, log-normal ~ $(-2.93, 1.58^2)$) were used for random-effects models based on Turner et al.[95]

Whereas a fixed-effect model assumes there is a single 'true' effect size underlying the trials informing a treatment comparison (i.e., that differences between studies are purely due to chance variation), random-effects models assume studies informing a treatment comparison are estimating 'similar' effects, but there are differences beyond just chance variation (i.e., total variation = chance differences + between-study heterogeneity). 'Similar' in this case means the effect sizes are coming from a (normal) distribution of effect sizes. Random-effect models are more plausible than fixed-effect models, but there is usually very limited information with which to estimate between-study heterogeneity (as is considered the case here). Given the level of heterogeneity identified in the feasibility assessment, the random-effects model was preferred.

When both fixed- and random-effects models were fitted to the data, their deviance information criteria (DIC) were derived. Lower values represent the more parsimonious model, and differences of 3 points were considered meaningful [96]. The model goodness-of-fit was assessed by comparing the posterior mean residual deviance to the number of data points in the network [96]. The number of data points was calculated as

the sum of arms across studies reporting arm-level data, and the sum of studies reporting contrast-based data. Model fit was considered good if the posterior mean residual deviance was similar to the number of data points.

C.4 Perioperative durvalumab vs adjuvant chemotherapy

C.5 Perioperative durvalumab vs neoadjuvant nivolumab

C.6 Distribution of rescaled weights of AEGEAN (weighted to match CheckMate 816) in Scenarios 1 and 2

Appendix D. Extrapolation N/A

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for switching/cross-over

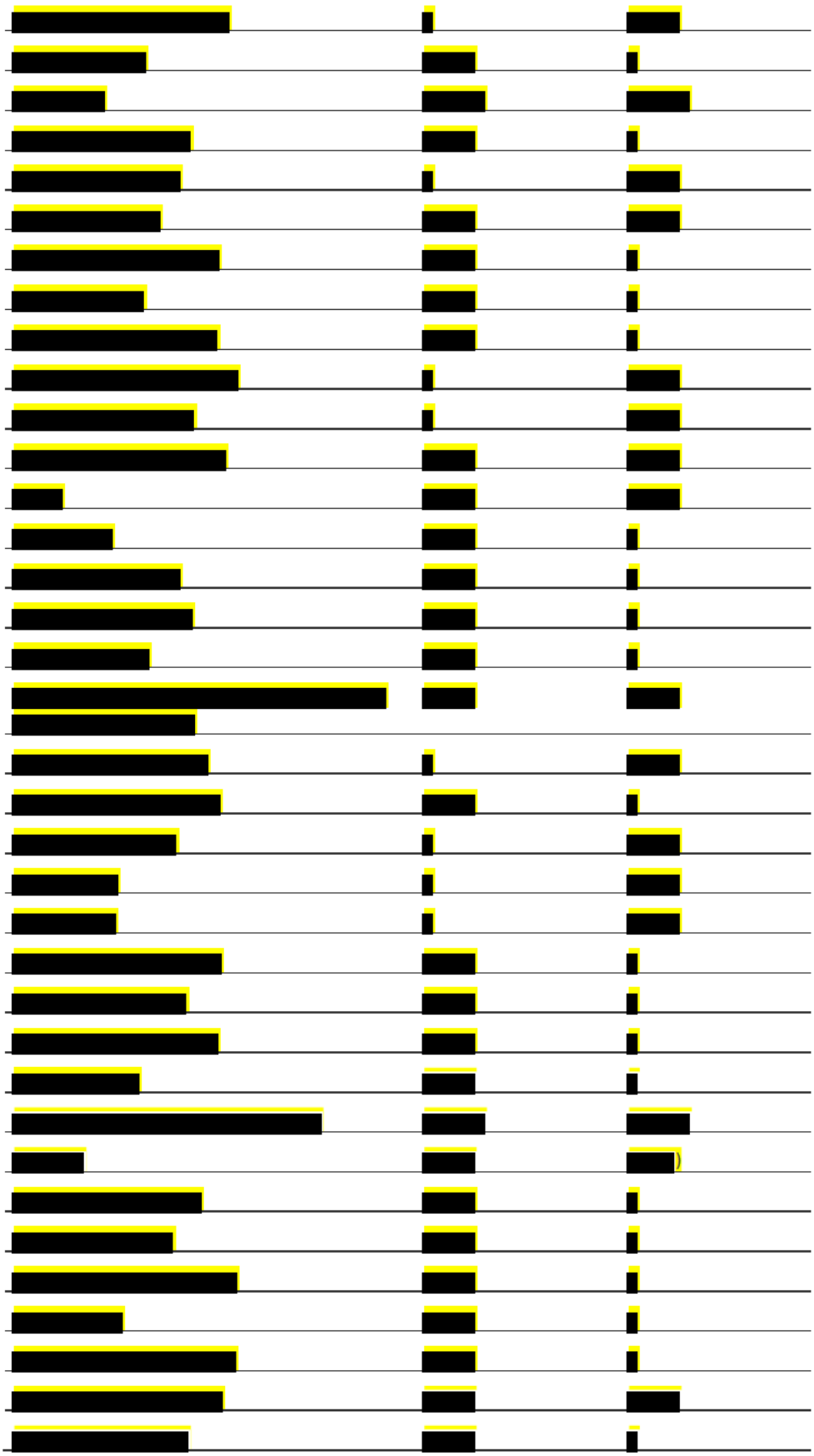
D.1.10 Waning effect

D.1.11 Cure-point

Appendix E. Serious adverse events

Table 76 AEGEAN, number of subjects with serious adverse events, by system organ class and preferred term – overall period (Safety analysis set), DCO 10 May 2024

System organ class / MedDRA Preferred term	Durvalumab + PDC (N=401)	Placebo + PDC (N=398)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



Appendix F. Health-related quality of life N/A

N/A

Appendix G. Probabilistic sensitivity analyses N/A

N/A

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The objective of conducting a *de novo* SLR was to identify the clinical efficacy and safety of durvalumab and relevant comparators for the treatment of stage I–III NSCLC in patients who are candidates for surgical resection.

The SLR was performed in accordance with a pre-specified protocol. This involved searching electronic databases, hand-searching of key conference proceedings from the last two years, and hand-searching of ClinicalTrials.gov, databases, and the bibliographies of any relevant SLRs (network) or meta-analyses ([N]MAs).

The original search for the SLR was conducted in Embase, MEDLINE, and CENTRAL, including Cochrane Database of Systematic Reviews (CDSR) on the 27th of July 2022, later updated on the 30th of October 2023 (Table 67). For the update, no date restrictions were imposed; instead, the results of the updated searches were de-duplicated against those of the original searches. The Database of Abstracts of Reviews of Effects (DARE) via the University of York CRD platform was not updated, as the database had not been updated since 2016.

An additional literature search was conducted on the 25th April 2025 in MEDLINE only using PubMed (Table 77) to capture any major updates compared to the latest update in 2023 using the same search terms.

As the SLR was conducted to explore comparative clinical evidence more broadly, the SLR was subsequently adapted to the Danish context, in line with the DMC guidelines, which require local alignment when a global SLR is used. The following sections present the original and updated SLR methodology and the Danish adaptation to local context and results.

Table 77 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	No restriction	27.07.2022
		No restriction	30.10.2023
MEDLINE	Ovid SP	No restriction	27.07.2022
	Ovid SP	No restriction	30.10.2023
	PubMed	October 14 2023 - April 25 2025	25.04.2025

Database	Platform/source	Relevant period for the search	Date of search completion
CENTRAL	The Cochrane Library, the Wiley Online	No restriction No restriction	27.07.2022 30.10.2023
DARE	York CRD platform	No restriction	27.07.2022

ClinicalTrials.gov and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) were searched (in the original SLR the searches were done on 14th October 2022 and in the updated SLR, on 20th November 2023) using the advanced search function to ensure that all relevant studies were identified. Search terms for each of these sources were devised based on the terms used for the electronic database searches and the specific requirements/format of each search platform. Searches of the ICTRP were date-limited to the 1st of January 2022, and de-duplicated against the results of the original SLR, and searches of ClinicalTrials.gov were date-limited to the date of the search conducted in the original SLR.

Table 78 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	https://clinicaltrials.gov/	Date of registration is between: 01/01/2022 and 17/11/2023 5 searches: (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) and ((neoadjuvant OR neo-adjuvant OR perioperative OR peri-operative) AND ("early stage" OR "Stage I" OR "Stage 1A" OR "Stage IA" OR "Stage 1B" OR "Stage IB" OR "Stage 2" OR "Stage II" OR "Stage 2A" or Stage "IIA" OR "Stage 2B" OR "Stage IIB")) (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) and ((operable OR resectable) AND ("early stage" OR "Stage I" OR "Stage 1A" OR "Stage	14.10.2023

Source name	Location/source	Search strategy	Date of search
		IA" OR "Stage 1B" OR "Stage IB" OR "Stage 2" OR "Stage II" OR "Stage 2A" or Stage "IIA" OR "Stage 2B" OR "Stage IIB"))	
		(NSCLC OR non-small cell lung cancer OR non small cell lung cancer) and ((neoadjuvant OR neo-adjuvant OR perioperative OR peri-operative) AND ("locally advanced" OR "Stage III" OR "Stage 3" OR "Stage IIIA" OR "Stage 3A" OR "Stage IIIB" OR "Stage 3B" OR "Stage 1-II" OR "Stage I-III" OR "Stage IA-IIB" OR "Stage IB-IIIA"))	
		(NSCLC OR non-small cell lung cancer OR non small cell lung cancer) and ((operable OR resectable) AND ("locally advanced" OR "Stage III" OR "Stage 3" OR "Stage IIIA" OR "Stage 3A" OR "Stage IIIB" OR "Stage 3B" OR "Stage 1-II" OR "Stage I-III" OR "Stage IA-IIB" OR "Stage IB-IIIA"))	
		(NSCLC OR non-small cell lung cancer OR non small cell lung cancer) and ((operable OR resectable OR neoadjuvant OR neo-adjuvant OR perioperative OR peri-operative) Limit: 'with results'	
World Health Organization (WHO) International Clinical Trials	https://www.who.int/tools/clinical-trials-registry-platform	Date-limited to the 1st of January 2022 Condition or Disease: NSCLC OR non-small cell	14.10.2023

Source name	Location/source	Search strategy	Date of search
Registry Platform (ICTRP)		lung cancer OR non small cell lung cancer Intervention / treatment: not applied Age group: Adult (18-64), Older Adult (65+) Study type: Interventional (Clinical Trial) Study phase: not applied Status: Enrolling by invitation; Recruiting; Active, Not recruiting; Suspended; Terminated; Completed; Unknown status Search 1: (neoadjuvant OR neo-adjuvant OR perioperative OR peri-operative) AND ("early stage" OR "Stage I" OR "Stage 1A" OR "Stage IA" OR "Stage 1B" OR "Stage IB" OR "Stage 2" OR "Stage II" OR "Stage 2A" or Stage "IIA" OR Stage 2B" OR Stage IIB") Search 2: (operable OR resectable) AND ("early stage" OR "Stage I" OR "Stage 1A" OR "Stage IA" OR "Stage 1B" OR "Stage IB" OR "Stage 2" OR "Stage II" OR "Stage 2A" or Stage "IIA" OR Stage 2B" OR Stage IIB") Search 3: (neoadjuvant OR neo-adjuvant OR perioperative OR peri-operative) AND ("locally advanced" OR "Stage III" OR "Stage 3" OR "Stage IIIA" OR "Stage 3A" OR "Stage IIIB" OR "Stage 3B" OR "Stage 1-II" OR "Stage I-III" OR "Stage	

Source name	Location/source	Search strategy	Date of search
		IA-IIB" OR "Stage IB-IIIA") Search 4: (operable OR resectable) AND ("locally advanced" OR "Stage III" OR "Stage 3" OR "Stage IIIA" OR "Stage 3A" OR "Stage IIIB" OR "Stage 3B" OR "Stage 1-II" OR "Stage I-III" OR "Stage IA-IIB" OR "Stage IB-IIIA")	

Conference proceedings for the last two years (i.e. 2020–2022 in the original SLR and 2023 for the updated SLR from the following congresses were hand-searched to identify any relevant abstracts for inclusion. Where possible, the same search terms and strategy were used for the SLR update as for the original SLR. However, where there were changes in the availability of topics and formatting for some conferences, these strategies were updated as required. ASCO Virtual Plenary Sessions were not available at the time of the original SLR, and so were only searched in the update.

Table 79 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology (ASCO) Annual Meeting 2022, 2021, 2023	https://meetings.asco.org/abstracts-presentations/		(NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND resectable (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND operable (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND neoadjuvant	27.07.2022 30.10.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			(NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND neo-adjuvant (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND adjuvant (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND resected (NSCLC OR non-small cell lung cancer OR non small cell lung cancer) AND surgery	
ASCO Virtual Plenary Sessions	https://meetings.asco.org/abstracts-presentations/search?query=*&q=ASCO%20Plenary%20Series&sortBy=AbstractBrowse&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Plenary%20Series%22%7D%5D%7D	Follow the link and manually search all resources in the 'lung cancer' track, performing title and abstract sift	Covering March 2023–November 2023	30.10.2023
European Society for Medical Oncology (ESMO) Congress 2023, 2022, 2021	https://oncologypro.esmo.org/meeting-resources/esmo-congress	Search with search terms listed, include following topics: Clinical research immunotherapy, non-small cell lung cancer, personalised/precision medicine, surgical	Using the search terms below, search all records: ("NSCLC" OR "non-small cell lung cancer" OR "non small cell lung cancer") AND (“resectable"	27.07.2022 30.10.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
		oncology, translational research. Screen all results for relevance.	or "operable" or "neoadjuvant" or "neo-adjuvant" or "adjuvant" or "resected" or "surgery") AND (“early stage" OR "locally advanced" OR "Stage 1A" OR "Stage IA" OR "Stage 1B" OR "Stage IB" OR "Stage 2" OR "Stage II" OR "Stage 2A" or "Stage IIA" OR "Stage 2B" OR "Stage IIB" OR "Stage 3" OR "Stage IIIA" OR "Stage 3A" OR "Stage IIIB" OR "Stage 3B" OR "Stage I-II" OR "Stage I-III" OR "Stage IA-IIB" OR "Stage IB-IIIA")	
ESMO European Lung Cancer Congress (ELCC) 2022, 2021	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2021	Same as above	Same as above	27.07.2022 30.10.2023
ESMO I-O Congress 2022, 2021, 2020	https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress https://oncologypro.esmo.org/meeting-	Same as above	Same as above	27.07.2022 30.10.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	resources/esmo-immuno-oncology-virtual-congress-2020			
International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC) 2023, 2022, 2021	https://cattendee.abstractsonline.com/meeting/10925/meeting-info?view=appendToCards&initialSearchId=3&searchId=3 https://wclc2022.iaslc.org/wp-content/uploads/2022/07/WCLC2022-Abstract-Book.pdf https://library.iaslc.org/	Search the following tracks and review resources that are posters, ePosters, orals or mini orals: Early-stage Non-small Cell Lung Cancer Local-regional Non-Small Cell Lung Cancer Search the whole 'Plenary' section In the conference book, review the titles of all oral abstract sessions using the following search terms: NSCLC Non small cell lung cancer Non-small cell lung cancer Search the whole 'Plenary Sessions' section Use the Ctrl+F function and click the cog icon and then 'Open Full Acrobat Search' Click 'Show More Options'	EP02.01 EARLY STAGE NON-SMALL CELL LUNG CANCER - BIOMARKERS EP02.02 EARLY STAGE NON-SMALL CELL LUNG CANCER - RADIOTHERAPY EP02.03 EARLY STAGE NON-SMALL CELL LUNG CANCER - SURGERY EP02.04 4 EARLY STAGE NON-SMALL CELL LUNG CANCER - SYSTEMIC THERAPY EP05.01 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - CHEMORADIOTHERAPY AND RADIOTHERAPY EP05.02 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - NEOADJUVANT AND ADJUVANT THERAPY	27.07.2022 30.10.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
		and tick 'Stemming' Under 'Return results containing', select 'Match Any of the words' Type in the following search terms in one line and click search: Non-small NSCLC Non small	EP05.03 LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER - SURGERY"	
IASLC North America Conference on Lung Cancer (NACLC) 2020	https://naclc2020.iaslc.org/wp-content/uploads/2020/10/NACLC2020-Abstract-Book-FINAL.pdf	Use the Ctrl+F function to identify each term in turn: •NSCLC •Non-small cell lung cancer		27.07.2022 30.10.2023
American Association for Cancer Research (AACR) 2023, 2022, 2021	https://www.abstractsonline.com/pp8/#!/10517/presentations AACR Annual Meeting 2021 Online Proceedings and Itinerary Planner | Home (abstractsonline.com)	Search the following terms:	NSCLC + resectable NSCLC + operable NSCLC + neoadjuvant NSCLC + neo-adjuvant NSCLC + adjuvant NSCLC + resected NSCLC + surgery "non small cell lung cancer"	27.07.2022 30.10.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
			"non-small cell lung cancer" + resectable	
			"non-small cell lung cancer" + operable	
			"non-small cell lung cancer" + neoadjuvant	
			"non-small cell lung cancer" + neo-adjuvant	
			"non-small cell lung cancer" + adjuvant	
			"non-small cell lung cancer" + resected	
			"non-small cell lung cancer" + surgery	
ESMO Virtual Plenary Sessions, covering 2020–2022 and July 2022–November 2023	https://www.esmo.org/meeting-calendar/past-meetings?events_filter_form%5Btype%5D%5B%5D=ESMO%20Virtual%20Plenaries	Follow the link and manually search all resources, performing title and abstract sift	Covering 2020–2022 and July 2022–November 2023	27.07.2022 30.10.2023

H.1.1 Search strategies

The following tables describe the search strategies for the original search on 27 July 2022 and the updated search on 30 October 2023 (for MEDLINE, Table 80; Embase, Table 81; CENTRAL, Table 82 and DARE, Table 83.

The additional search in MEDLINE using PubMed conducted on April 25, 2025, used the same search terms, with the publication dates restricted from the end date of the previous search (October 30, 2023) to the present (April 25, 2025) (see search strategy in Table 84)

Table 80 Search strategy table for MEDLINE (searched via the Ovid SP platform)

No.	Query	Results 27.07.2022	Results 30.10.2023

#1	exp carcinoma, non-small-cell lung/	65,988	71,714
#2	NSCLC.ti,ab,kf.	55,433	61,966
#3	1 or 2	82,147	90,524
#4	exp Lung Neoplasms/	264,036	277,449
#5	((lung or pulmonary) adj3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)).ti,ab,kf.	268,284	290,971
#6	4 or 5	357,132	381,810
#7	(non small or nonsmall).ti,ab,kf.	83,028	91,341
#8	6 and 7	82,326	90,590
#9	3 or 8	95,603	104,966
#10	((early* adj2 cancer) or early stage or locally advanc* or stage 1a* or stage Ia* or stage 1b* or stage Ib* or stage 2* or stage II* or stage 3* or stage I-II*).ab,ti,kf.	265,402	288,092
#11	Surgical procedures, operative/	56,765	56,880
#12	(lung* or pulmon* or bronchi* or thora*)	1,749,230	1,839,191
#13	11 and 12	4,110	4,113
#14	Neoadjuvant therapy/ or pulmonary surgical procedures/ or pneumonectomy/	57,945	61,167
#15	(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*).ti,ab,kf.	3,316,560	3,556,724
#16	13 or 14 or 15	3,323,732	3,563,997
#17	9 and 10 and 16	7,652	8,466
#18	Randomized Controlled Trials as Topic/	157,425	164,546
#19	Randomized Controlled Trial/	575,635	601,408
#20	Random Allocation/	106,871	107,032
#21	Double-Blind Method/	172,836	176,377
#22	Single-Blind Method/	32,155	32,987
#23	Placebos/	35,921	35,933

#24	exp Clinical Trials as Topic/	376,634	385,219
#25	Clinical Trial/	535,962	538,884
#26	Clinical Trial, Phase I/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/	78,015	81,854
#27	Controlled Clinical Trial/ or Adaptive Clinical Trial/	95,026	95,461
#28	randomized controlled trial.pt.	575,635	601,408
#29	clinical trial.pt.	535,962	538,884
#30	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	78,015	81,854
#31	(controlled clinical trial or multicenter study).pt.	416,181	430,561
#32	(clinical adj trial*).ti,ab,kf.	457,314	503,782
#33	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).ti,ab,kf.	190,800	200,365
#34	Placebo*.ti,ab,kf.	239,375	251,365
#35	(allocat* adj2 random*).ti,ab,kf.	41,297	44,736
#36	(Randomi?ed adj2 trial*).ti,ab,kf.	397,815	441,437
#37	rct.ti,ab,kf.	30,770	35,316
#38	(single arm adj3 (trial* or stud*)).ti,ab,kf.	8,037	9,764
#39	(open label adj (trial* or stud*)).ti,ab,kf.	12,856	13,682
#40	(non blinded adj (trial* or stud*)).ti,ab,kf.	222	238
#41	(pragmatic trial* or pragmatic stud*).ti,ab,kf.	2,333	2,673
#42	pragmatic clinical trial/	2,137	2,254
#43	or/18-42	1,960,995	2,068,396
#44	exp animals/ not exp humans/	5,040,396	5,163,641
#45	(comment or editorial or case reports or historical article).pt.	4,010,722	4,181,589
#46	(case stud* or case report*).ti.	353,229	391,770
#47	or/44-46	9,041,286	9,340,455
#48	17 and 43	2,014	2,175

#49	48 not 47	1,970	2,121

Note: Database(s): Original SLR: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 26, 2022. SLR update: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to October 27, 2023.

Abbreviations: NSCLC: non-small cell lung cancer; RCT: randomised controlled trial; SLR: systematic literature review.

Table 81 Search strategy table for Embase (searched via the Ovid SP platform)

No.	Query	Results 27.07.2022	Results 30.10.2023
#1	exp non small cell lung cancer/	132,388	156,582
#2	NSCLC.ti,ab,kf.	100,397	112,695
#3	1 or 2	169,720	194,614
#4	exp lung tumor/	437,805	485,529
#5	((lung or pulmonary) adj3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)).ti,ab,kf.	385,155	422,544
#6	4 or 5	537,846	591,145
#7	(non small or nonsmall).ti,ab,kf.	129,949	144,243
#8	6 and 7	128,710	142,923
#9	3 or 8	194,593	220,378
#10	((early* adj2 cancer) or early stage or locally advanc* or stage 1a* or stage Ia* or stage 1b* or stage Ib* or stage 2* or stage II* or stage 3* or stage I-II*).ab,ti,kf.	423,544	464,378
#11	Surgical procedures, operative/	603,394	723,035
#12	(lung* or pulmon* or bronchi* or thora*)	2,618,164	2,835,187
#13	11 and 12	84,474	102,135
#14	lung resection/ or lung surgery/ or neoadjuvant therapy/	57,572	63,066
#15	(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*).ti,ab,kf.	4,268,223	4,618,327

#16	13 or 14 or 15	4,286,150	4,644,251
#17	9 and 10 and 16	15,190	16,986
#18	"randomized controlled trial (topic)"/	232,600	264,210
#19	randomized controlled trial/	719,400	788,248
#20	randomization/	94,466	98,729
#21	double blind procedure/	197,011	211,696
#22	single blind procedure/	46,988	52,126
#23	crossover procedure/	70,998	75,630
#24	placebo/	383,755	403,802
#25	exp "clinical trial (topic)"/	398,961	447,636
#26	clinical trial/	1,039,596	1,072,593
#27	phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	198,592	221,450
#28	controlled clinical trial/ or adaptive clinical trial/ or multicenter study/	734,470	783,636
#29	(clinical adj trial*).ti,ab,kf.	656,580	728,264
#30	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).ti,ab,kf.	266,188	283,068
#31	Placebo*.ti,ab,kf.	347,755	369,739
#32	(allocat* adj2 random*).ti,ab,kf.	50,911	55,447
#33	(Randomi?ed adj2 trial*).ti,ab,kf.	534,259	592,653
#34	rct.ti,ab,kf.	50,933	57,866
#35	(single arm adj3 (trial* or stud*)).ti,ab,kf.	16,405	19,861
#36	(open label adj (trial* or stud*)).ti,ab,kf.	22,746	24,622
#37	(non blinded adj (trial* or stud*)).ti,ab,kf.	325	348
#38	(pragmatic trial* or pragmatic stud*).ti,ab,kf.	3,148	3,694
#39	pragmatic trial/	1,723	2,367

#40	or/18-39	2,756,228	2,984,793
#41	("conference abstract" or "conference review").pt.	4,478,313	4,941,372
#42	limit 41 to yr="1974-2019"	3,827,598	3,864,902
#43	exp animals/ not exp humans/	4,976,023	5,155,468
#44	editorial.pt.	732,301	782,894
#45	editorial/ or case report/	3,460,114	3,672,992
#46	(case stud* or case report*).ti.	428,308	473,718
#47	or/42-46	1,178,7521	1,222,0334
#48	17 and 40	4,075	4,616
#49	48 not 47	2,621	3,118

Note: Database(s): Original SLR: Embase 1974 to 26 July 2022. SLR update: Embase 1974 to 27 October 2023.

Abbreviations: NSCLC: non-small cell lung cancer; RCT: randomised controlled trial; SLR: systematic literature review.

Table 82 Search strategy table CENTRAL in the Cochrane Library databases (searched simultaneously via the Wiley platform)

No.	Query	Results 27.07.2022	Results 30.10.2023
#1	[mh "carcinoma, non-small-cell lung"]	4,828	5,839
#2	NSCLC:ab,ti,kw	10,403	11,377
#3	#1 or #2	12,136	13,457
#4	[mh "Lung Neoplasms"]	8,631	10,548
#5	((lung or pulmonary) NEAR/3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)):ab,ti,kw	25,311	27,754
#6	#4 or #5	25,583	28,062
#7	(non small or nonsmall):ab,ti,kw	30,427	33,237
#8	#6 and #7	15,014	16,314
#9	#3 or #8	15,694	17,036

#10	((early* NEAR/2 cancer) or "early stage" or locally NEXT advanc* or stage NEXT 1a* or stage NEXT Ia* or stage NEXT 1b* or stage NEXT Ib* or stage NEXT 2* or stage NEXT II* or stage NEXT 3* or stage NEXT I-II*):ab,ti,kw	44,926	49,792
#11	[mh ^"Surgical procedures, operative"]	1,079	1,278
#12	(lung* or pulmon* or bronchi* or thora*)	153,153	149,801
#13	#11 and #12	135	138
#14	[mh ^Pneumonectomy] or [mh ^"pulmonary surgical procedures"] or [mh ^"neoadjuvant therapy"]	2,057	3,154
#15	(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*):ab,ti,kw	331,264	374,906
#16	#13 or #14 or #15	331,264	374,906
#17	#9 and #10 and #16	1,969	2,209
#18	[mh ^"Randomized Controlled Trials as Topic"]	1,2812	4,2547
#19	[mh ^"Randomized Controlled Trial"]	118	25732
#20	[mh ^"Random Allocation"]	20,678	23,366
#21	[mh ^"Double-Blind Method"]	147,701	155,271
#22	[mh ^"Single-Blind Method"]	23,070	24,682
#23	[mh ^Placebos]	24,595	25,630
#24	[mh "Clinical Trials as Topic"]	48,709	84,414
#25	[mh ^"Clinical Trial"]	29	19,265
#26	[mh ^"Clinical Trial, Phase I"] or [mh ^"Clinical Trial, Phase II"] or [mh ^"Clinical Trial, Phase III"] or [mh ^"Clinical Trial, Phase IV"]	0	0
#27	[mh ^"Controlled Clinical Trial"] or [mh ^"Adaptive Clinical Trial"]	31	17,160
#28	"randomized controlled trial":pt	556,044	0
#29	"clinical trial":pt	333,860	19,093

#30	("clinical trial, phase i" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv"):pt	35,912	0
#31	("controlled clinical trial" or "multicenter study"):pt	183,921	0
#32	(clinical NEXT trial*):ab,ti,kw	476,796	526,142
#33	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ab,ti,kw	375,874	402,158
#34	Placebo*:ab,ti,kw	346,204	372,468
#35	(allocat* NEAR/2 random*):ab,ti,kw	70,036	78,257
#36	(Randomi?ed NEAR/2 trial*):ab,ti,kw	683,244	756,473
#37	rct:ab,ti,kw	33,999	39,257
#38	("single arm" NEAR/3 (trial* or stud*)):ab,ti,kw	2,609	2,942
#39	("open label" NEXT (trial* or stud*)):ab,ti,kw	11,511	12,479
#40	("non blinded" NEXT (trial* or stud*)):ab,ti,kw	241	267
#41	(pragmatic NEXT trial* or pragmatic NEXT stud*):ab,ti,kw	2,245	2,606
#42	[mh ^"pragmatic clinical trial"]	0	0
#43	#16-#42	1,321,655	1,220,127
#44	#17 and #43	1,302	1,336
#45	#44 in Cochrane Reviews	9	9
#46	#44 in Trials	1,293	1,327

Note: Database(s): Original SLR: Cochrane Database of Systematic Reviews, Issue 7 of 12, July 2022; Cochrane Central Register of Controlled Trials, Issue 7 of 12, July 2022. SLR update: Cochrane Database of Systematic Reviews, Issue 10 of 12, October 2023; Cochrane Central Register of Controlled Trials, Issue 10 of 12, October 2023.

Abbreviations: NSCLC: non-small cell lung cancer; RCT: randomised controlled trial; SLR: systematic literature review

Table 83 Search strategy table for DARE database (searched via the York CRD platform)

No.	Query	Results 27.07.2022
#1	MeSH DESCRIPTOR carcinoma, non-small-cell lung EXPLODE ALL TREES	668
#2	(NSCLC)	257

#3	#1 or #2	732
#4	MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES	1,151
#5	((lung or pulmonary) adj2 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)) or ((cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous) adj2 (lung or pulmonary))	1,451
#6	#4 or #5	1,465
#7	((non small or nonsmall))	821
#8	#6 and #7	819
#9	#3 or #8	833
#10	(early* adj1 cancer) or (cancer adj1 early*)	329
#11	("early stage" or "locally advanc*" or "stage 1a*" or "stage Ia*" or "stage 1b*" or "stage Ib*" or "stage 2*" or "stage II*" or "stage 3*" or "stage I-II*")	1,218
#12	#10 or #11	1,453
#13	MeSH DESCRIPTOR Surgical procedures, operative	243
#14	(lung* or pulmon* or bronchi* or thora*)	6,060
#15	#13 and #14	25
#16	MeSH DESCRIPTOR Pneumonectomy	103
#17	MeSH DESCRIPTOR pulmonary surgical procedures	4
#18	MeSH DESCRIPTOR neoadjuvant therapy	175
#19	(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*)	19,544
#20	#15 or #16 or #17 or #18 or #19	19,544
#21	#9 and #12 and #20	58
#22	#21 in DARE	34

Note: Database(s): Original SLR: Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015. SLR update: DARE was not searched as the database has not been updated since the original SLR.

Abbreviations: DARE: Database of Abstracts of Reviews of Effects; NSCLC: non-small cell lung cancer; SLR: systematic literature review.

Table 84 Search strategy table for MEDLINE (searched via PubMed) – search 25 April 2025

No.	Query	Results 25.04.2025
#1	"Carcinoma, Non-Small-Cell Lung"[MeSH Terms]	78,590
#2	NSCLC[Title/Abstract]	70,651
#3	#1 AND #2	48,522
#4	"Lung Neoplasms"[MeSH Terms]	295,519
#5	((lung[tiab] OR pulmonary[tiab]) AND (cancer*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab] OR malign*[tiab] OR adenocarcinoma*[tiab] OR squamous[tiab]))	437,439
#6	#4 OR #5	509,494
#7	("non small"[Title/Abstract] OR nonsmall[Title/Abstract])	102,264
#8	#6 AND #7	101,901
#9	#3 OR #8	104,298
#10	(("early cancer"[Title/Abstract]) OR "early stage"[Title/Abstract] OR "locally advanced"[Title/Abstract] OR "stage 1a"[Title/Abstract] OR "stage Ia"[Title/Abstract] OR "stage 1b"[Title/Abstract] OR "stage Ib"[Title/Abstract] OR "stage 2"[Title/Abstract] OR "stage II"[Title/Abstract] OR "stage 3"[Title/Abstract] OR "stage I-II"[Title/Abstract])	246,424
#11	"Surgical Procedures, Operative"[MeSH Terms]	3,717,771
#12	(lung[Title/Abstract] OR pulmon*[Title/Abstract] OR bronchi*[Title/Abstract] OR thorac*[Title/Abstract])	1,575,507
#13	#11 AND #12	276,263
#14	("Neoadjuvant Therapy"[MeSH Terms] OR "Pulmonary Surgical Procedures"[MeSH Terms] OR "Pneumonectomy"[MeSH Terms])	115,290
#15	(neoadjuvant*[Title/Abstract] OR neo-adjuvant*[Title/Abstract] OR resect*[Title/Abstract] OR surg*[Title/Abstract] OR lobecto*[Title/Abstract] OR segmentectom*[Title/Abstract] OR pneumonectom*[Title/Abstract] OR	3,868,038

	bilobectom*[Title/Abstract] OR preop*[Title/Abstract] OR pre-op*[Title/Abstract] OR operable*[Title/Abstract] OR operat*[Title/Abstract])	
#16	#13 OR #14 OR #15	4,008,278
#17	#9 AND #10 AND #16	7,222
#18	"Randomized Controlled Trials as Topic"[MeSH Terms]	185,427
#19	Randomized Controlled Trial/	865,502
#20	"Random Allocation"[MeSH Terms]	108,363
#21	"Double-Blind Method"[MeSH Terms]	183,630
#22	"Single-Blind Method"[MeSH Terms]	34,887
#23	"Placebos"[MeSH Terms]	40,372
#24	"Clinical Trials as Topic"[MeSH Terms]	406,685
#25	Clinical Trial/	1,468,156
#26	Clinical Trial, Phase I/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/	140,426
#27	Controlled Clinical Trial/ or Adaptive Clinical Trial/	916,743
#28	"Randomized Controlled Trial"[Publication Type]	637,279
#29	"clinical trial"[Publication Type]	1,020,426
#30	("Clinical Trial, Phase I"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type])	88,596
#31	("Controlled Clinical Trial"[Publication Type] OR "Multicenter Study"[Publication Type])	990,864
#32	(clinical[Title/Abstract] AND trial*[Title/Abstract])	805,074
#33	((single[Title/Abstract] OR double[Title/Abstract] OR triple[Title/Abstract]) AND (blind[Title/Abstract] OR blinded[Title/Abstract] OR masking[Title/Abstract]))	225,404
#34	Placebo*[Title/Abstract]	267,251
#35	(allocat*[Title/Abstract] AND random*[Title/Abstract])	79,587

#36	((Randomized[Title/Abstract] OR Randomised[Title/Abstract]) AND trial*[Title/Abstract])	648,790
#37	rct[Title/Abstract]	41,657
#38	("single arm"[Title/Abstract] AND (trial*[Title/Abstract] OR study[Title/Abstract]))	16,739
#39	("open label"[Title/Abstract] AND (trial*[Title/Abstract] OR study[Title/Abstract]))	61,477
#40	("non blinded"[Title/Abstract] AND (trial*[Title/Abstract] OR study[Title/Abstract]))	1,623
#41	(pragmatic trial*[Title/Abstract] OR pragmatic study[Title/Abstract])	2,983
#42	pragmatic clinical trial/	4,305
#43	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	2,358,996
#44	"Animals"[MeSH Terms] NOT "Humans"[MeSH Terms]	5,329,473
#45	(comment[Publication Type] OR editorial[Publication Type] OR case reports[Publication Type] OR historical article[Publication Type])	4,410,822
#46	(case study[Title] OR case report*[Title])	438,431
#47	#44 OR #45 OR #46	9,738,877
#48	#17 AND #43	2,008
#49	#48 NOT #47	1,959
#50	(#49) AND (("2023/10/14"[Date - Publication] : "3000"[Date - Publication]))	237

H.1.2 Systematic selection of studies

The study eligibility criteria were developed using the population, intervention, comparator, outcomes, study design (PICOs) framework, and are shown in Table 85 for the original SLR and the SLR updates. As the global SLRs did not restrict studies based on intervention or comparator, the relevant PICOs in Denmark of interest were those that might represent potential comparators to perioperative durvalumab in adults with rNSCLC with high risk of recurrence and no EGFR mutations or ALK rearrangements.

In accordance with DMC guidelines, the PICO from the global SLR was adjusted to the reflect the Danish setting, where neoadjuvant nivolumab+PDC is the SoC for patients with PD-L1 ≥1% tumor expression and PDC alone is SoC in the adjuvant setting. In addition, reporting of HR for EFS was important to include for the ITC for relative efficacy estimation (Table 85).

Table 85 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult patients (≥18 years old) with stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC	Patients without NSCLC Patients with stage IV NSCLC or metastatic NSCLC Patients with stage I–III NSCLC who are not candidates for surgical resection of the primary NSCLC (i.e. stage I–III unresectable NSCLC) Children or adolescents (<18 years old)	Adults (≥18 years old) with rNSCLC at high risk of recurrence and no EGFR mutations or ALK re-arrangements
Intervention	Any or no treatment for stage I–III NSCLC prior to surgical resection of the primary NSCLC	No planned surgical resection of primary NSCLC	Perioperative durvalumab and Danish SoC consisting of neoadjuvant nivolumab+PDC and adjuvant PDC
Comparators	Any or none*	Any or none*	Danish SoC consisting of neoadjuvant nivolumab + PDC and adjuvant PDC
Outcomes	Efficacy outcomes: EFS[a], DFS[a], OS, major pathological response, PCr, PFS[a], RFS[a], Recurrence rates and type Safety outcomes HRQoL outcomes	Studies not reporting relevant outcomes Studies reporting relevant outcomes, but in a mixed population (e.g. patients with stage I–III resectable and unresectable NSCLC) where	Reporting of HR for EFS for relative efficacy

		outcomes are not reported separately for the stage I–III resectable NSCLC population	
Study design/publication type	RCTs Non-RCTs† SLR/(N)MAs were considered relevant at the title/abstract review stage and hand searched for relevant primary studies, but were excluded during the full-text review stage unless they themselves present original research.	Non-interventional studies, including: Cohort studies Cross-sectional studies Case-control studies Chart reviews Registries Case reports/studies Non-primary research publications, including: Narrative reviews Editorials Guidelines Commentaries Opinion pieces	RTC
Language restrictions	Human subjects Articles with at least the abstract in the English language	Animal studies Articles not in the English language	English

In the original SLR and SLR update the most stringent record screening process as recommended by Cochrane was followed. The process was as follows:

Each title and abstract were reviewed against the inclusion/exclusion criteria by two independent systematic reviewers. Where the applicability of the inclusion criteria was unclear, the article was included at this stage to ensure that all potentially relevant studies were captured. The independent reviewers then compared their results, and any disagreements were resolved by discussion until a consensus was reached. If necessary, a third independent reviewer was enlisted to arbitrate the final decision.

Each full-text article was then reviewed against the inclusion/exclusion criteria by two independent systematic reviewers, who came to a consensus on the included articles. In

cases where it was unclear whether the article met the inclusion criteria, the article was excluded at this stage to ensure that only relevant articles were ultimately included in the systematic review. The results of the two reviewers were then compared, and any disagreements were resolved by discussion until a consensus was reached. If necessary, a third reviewer was enlisted to arbitrate the final decision.

All publications ultimately included in the SLR were reviewed, and those reporting on the same study were grouped. At subsequent stages of the review (data extraction, quality assessment and write-up), each study was considered as a single unit.

The primary publication for a study was regarded as the earliest journal article which reported outcomes of interest for the study. Secondary publications were considered as any subsequent publications on the study, such as conference abstracts and clinical trial records, which reported outcomes of interest.

A larger-than-anticipated number of records were identified as eligible for inclusion in the review at the time of the original SLR. To manage the scope of the SLR and prioritise the highest-quality and most relevant identified studies, two evidence prioritisation plans were adopted, moving into the extraction phase of the review (for both the original SLR and SLR update). These approaches were as follows:

- Any study design other than an RCT was deprioritised from extraction. This prioritised data from the highest quality study designs
- Studies which compared surgery alone (i.e. had no neoadjuvant or adjuvant treatment) were deprioritised from extraction as being of less relevance to the ITC feasibility assessment. For example, studies were identified that compared different types of surgical resection, which is not considered relevant for the ITC feasibility assessment

Throughout the title/abstract and full-text review stages of the SLR, all identified publications which were deemed relevant for inclusion against the eligibility criteria were formally reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The evidence prioritisation strategy was enacted, moving into the data extraction phase, and therefore only impacted the number of publications which ultimately underwent full data extraction.

Key studies identified in the original SLR and updated reporting on IO therapies (i.e. atezolizumab, pembrolizumab, nivolumab or durvalumab) included four studies examining neoadjuvant IO (CheckMate 816, NeoCOAST, NEOpredict, NEOSTAR) [9, 97-100], two studies examining neoadjuvant and adjuvant IO (Altorki 2021, NADIM II) [101, 102], and two studies examining adjuvant chemotherapy (Chen 2013, NATCH and Peng [65, 103, 104]). CheckMate 816 was the only phase III trial identified in the original SLR assessing an IO regimen and the SLR update identified additional publications for this trial.

The latest updated search from April 25, 2025, yielded 237 results that were screened on title only, of these 14 articles were selected for abstract review. Following this, eight articles were assessed in full-text review, and finally, one of the studies was included to

evaluate the clinical efficacy and safety of durvalumab and potentially relevant comparators.

All studies identified through the original and updated SLRs were assessed against the Danish PICO to identify the publication and trials relevant for assessing the relative efficacy for perioperative durvalumab versus Danish SoC.

The PRISMA diagram outlining the flow of records through the original SLR is presented in Figure 16; the total number of records and unique studies identified across the original SLR. The PRISMA diagram for the SLR update is shown in Figure 17, and lastly the PRISMA diagram from the latest search in Figure 18.

Figure 16 PRISMA flow diagram for studies identified in the original SLR, 27th July 2022, with Danish adaptation

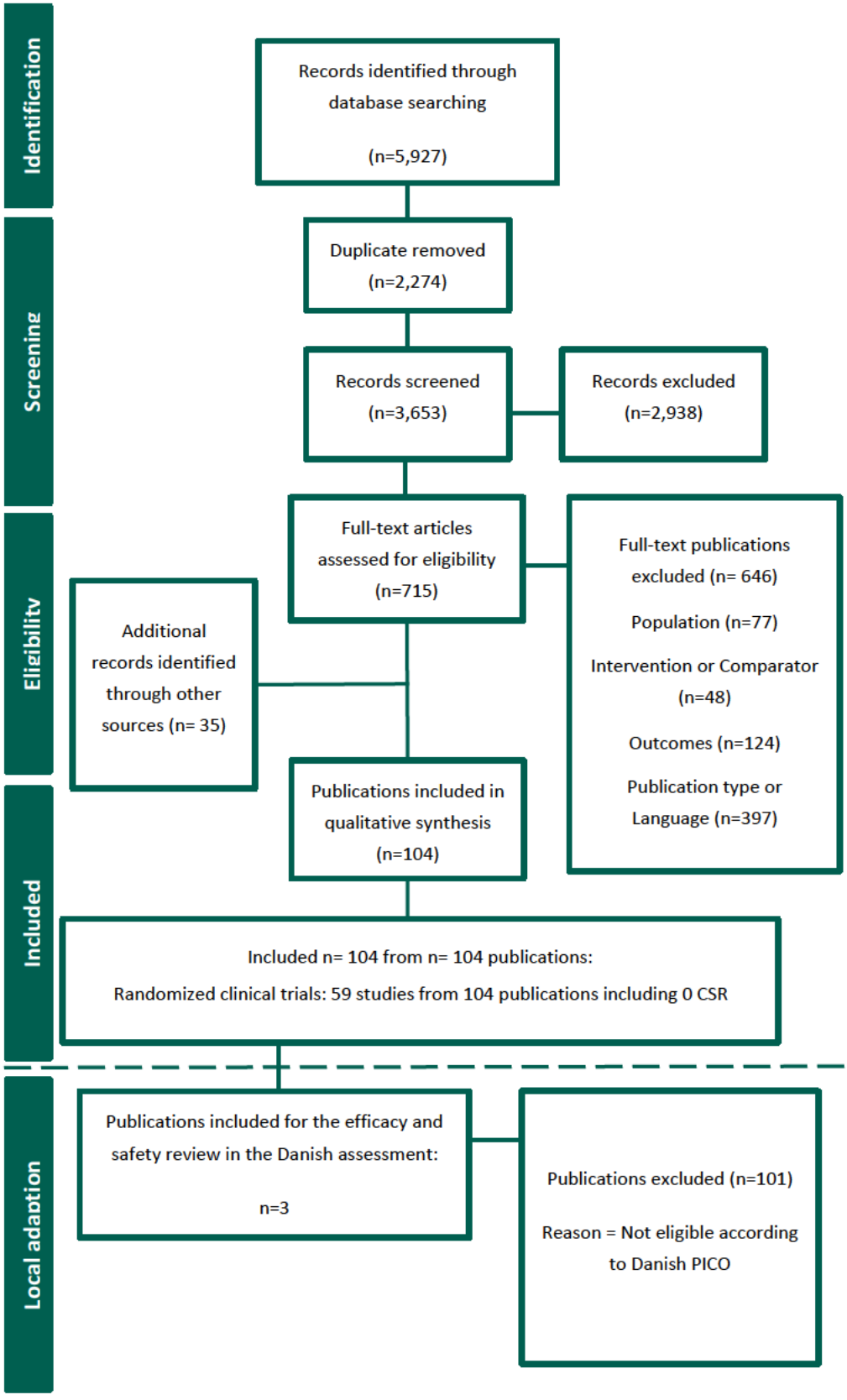


Figure 17 PRISMA flow diagram for studies identified in the updated SLR, 30 October 2023

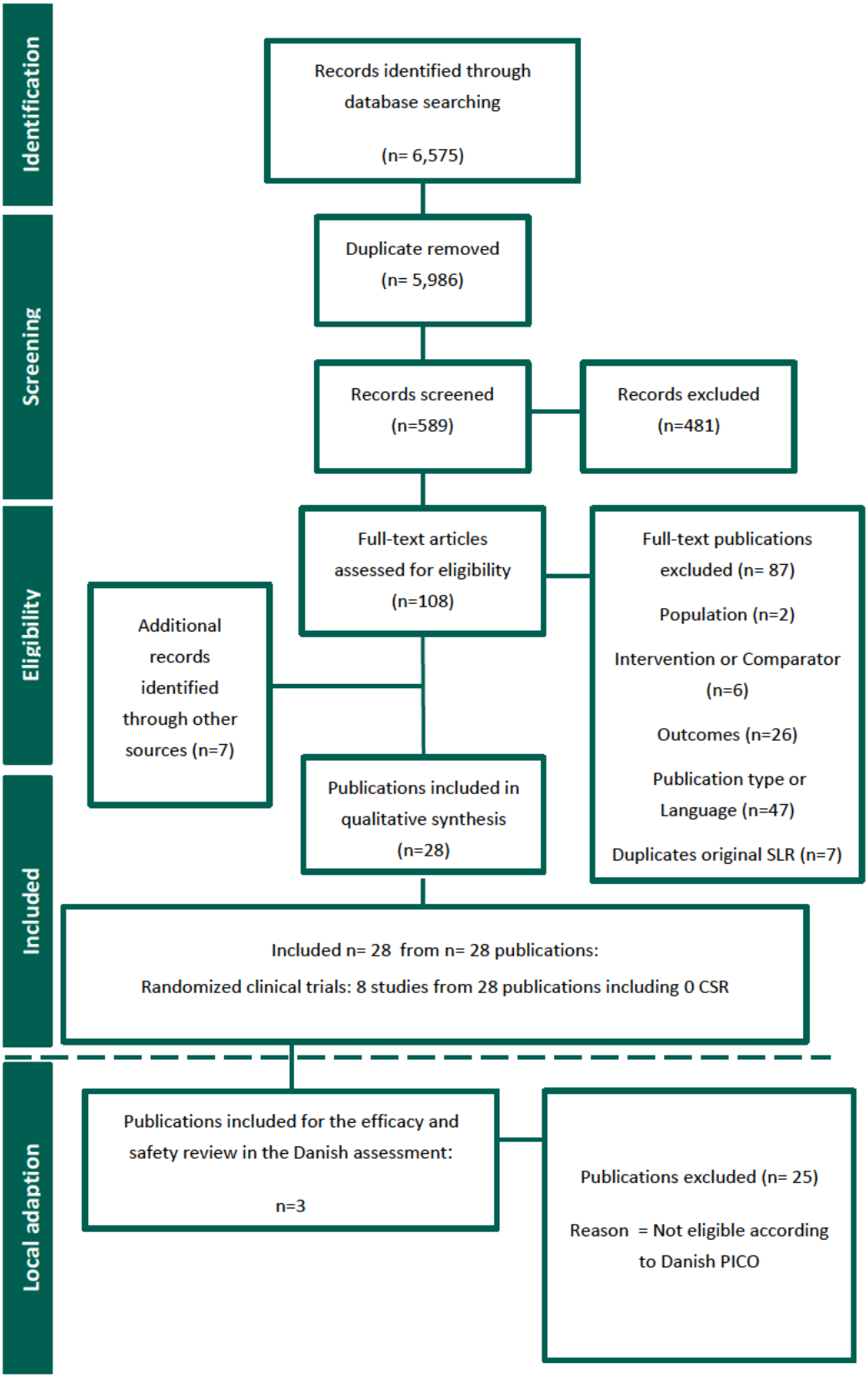
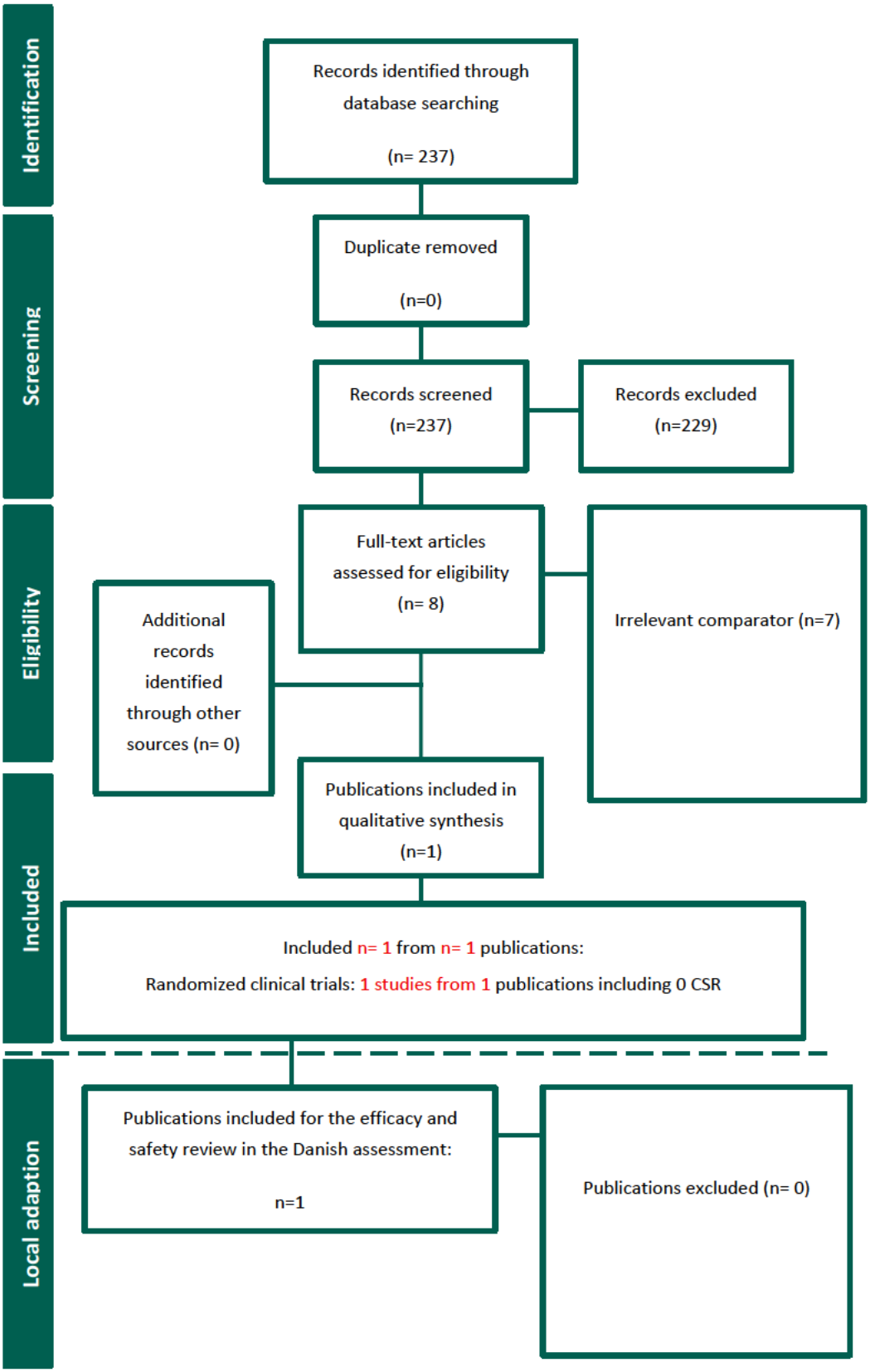


Figure 18 PRISMA flow diagram for studies identified in the updated search, 25 April 2025



Although the original and updated SLRs identified RCTs across various treatment settings (perioperative, neoadjuvant, adjuvant), only two studies were considered relevant for the ITCs based on the adapted Danish PICO and current SoC:

- AEGEAN as the relevant evidence for a comparison versus neoadjuvant PDC
- CheckMate 816 as the relevant evidence for a comparison versus neoadjuvant nivolumab + PDC
- NATCH as the relevant evidence for the comparison versus adjuvant PDC.

The characteristics of these three studies are presented in Table 86.

Table 86 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
AEGEAN	Compare neoadjuvant durvalumab+ PDC platinum-prior to surgery, followed by adjuvant durvalumab monotherapy after surgery, versus neoadjuvant placebo + PDC prior to surgery, followed by adjuvant placebo after surgery in rNSCLC	A Phase III, double-blind, placebo-controlled, multi-centre	Patients with resectable NSCLC (stage II to IIIB [N2 node stage] according to the 8th edition of the AJCC Cancer Staging Manual)	Intervention: Durvalamb +PDC followed by PDC Comparator: Placebo + PDC followed by placebo mITT 740 durvalumab + PDC (n=366) or placebo + PDC (n=374)	EFS (up to 5.5 years after first patient randomized) pCR (up to approximately 15 weeks after randomization)	OS and DFS (up to 5.5 years after randomization) mPR (up to approximately 15 weeks) Subgroup analysis of all above outcomes in PD-L1-TC ≥1% HRQoL (from date of screening to 6 months after last dose)
CheckMate 816	Compare nivolumab +PDC to PDC alone in terms of	A Phase III, randomized, Open label	Patients with stage IB–IIIA (7th edition), resectable	Intervention: Neoadjuvant treatment	EFS (up to a median of 30 months) pCR Rate (up to a	OS, mPR TTDM (up to a median of 30 months)

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	safety and effectiveness in rNSCLC		NSCLC, no known EGFR mutations or ALK alterations, and an ECOG performance score of 0–1	with nivolumab +PDC Comparator: Neoadjuvant treatment with PDC ITT n= 358 nivolumab + PDC (n=179) PDC (n=179)	median of 30 months)	
NATCH/ NCT00913705	Address whether preoperative PDC + surgery or surgery + adjuvant PDC prolongs DFS compared with surgery alone among patients with rNSCLC	A Phase III, randomized, Open label	Patients with stage IA (tumor size 2 cm), IB, II, or T3N1, NSCLC, considered resectable by the multidisciplinary team	Intervention: PDC followed by surgery (n=199), Intervention: Surgery followed by PDC (n=210). Comparator: Surgery alone (n=210) ITT (n=619)	DFS (51 months)	OS, AE's (51 months)

H.1.3 Excluded fulltext references

The following tables includes the excluded studies from the original and updated SLRs.

Table 87 Excluded references from the original SLR 27th July 2022

#	Reference	Reason for exclusion

1	Abbosh C, Frankell A, Garnett A, et al. Phylogenetic tracking and minimalresidual disease detection using ctDNA in early-stageNSCLC: A lung TRACERx study. Cancer Research. Conference: American Association for Cancer Research Annual Meeting, AACR 2020;80.	Irrelevant study design, no human participants or in non-English language
2	Abdel-Rahman O. Impact of current versus former smoking status on the outcomes of non-metastatic non-small cell lung cancer treated with upfront surgery; findings from the National Lung Screening Trial. Expert Review of Respiratory Medicine 2019;13(6):585-591.	Irrelevant intervention
3	Ahern E, Cubitt A, Ballard E, et al. Pharmacodynamics of Pre-Operative PD1 checkpoint blockade and receptor activator of NFkB ligand (RANKL) inhibition in non-small cell lung cancer (NSCLC): Study protocol for a multicentre, open-label, phase 1B/2, translational trial (POPCORN). Trials 2019;20(1) (no pagination).	No relevant outcomes reported
4	Ahern E, Cubitt A, Ives A, et al. Popcorn: Pharmacodynamics of preoperative PD1 checkpoint blockade and rankl inhibition in non-small cell lung cancer (NSCLC): A phase 1b/2 investigator-sponsored trial in progress. Asia-Pacific Journal of Clinical Oncology 2020;16(SUPPL 2):23.	No relevant outcomes reported
5	Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. JSLS : Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons 2007;11(3):368-374.	Irrelevant study design, no human participants or in non-English language
6	Alborelli I, Leonards K, Manzo M, et al. MA09.02 SAKK 16/14 - T-Cell Receptor Repertoire Metrics Predict Response to Neoadjuvant Durvalumab in Patients With Stage IIIA(N2) NSCLC. Journal of Thoracic Oncology 2021;16(10 Supplement):S911.	Irrelevant intervention
7	Alborelli I, Leonards K, Manzo M, et al. SAKK 16/14-T-cell receptor repertoire metrics predict response to neoadjuvant durvalumab in patients with stage IIIA(N2) NSCLC. Oncology Research and Treatment 2021;44(SUPPL 2):4.	No relevant outcomes reported
8	Andre F, Grunenwald D, Pujol JL, et al. Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: Should prophylactic cranial irradiation be reconsidered? Cancer 2001;91(12):2394-2400.	Irrelevant study design, no human participants or in non-English language
9	Anonymous. Preoperative radiochemotherapy no better than postop RT for advanced stage III NSCLC. Oncology Report 2005:110.	Irrelevant study design, no human participants or in non-English language
10	Anonymous. Radical surgery after chemo confers no survival benefit in stage IIIA-N2 NSCLC. Oncology Report 2005:103-104.	Irrelevant study design, no human

		participants or in non-English language
11	Armstrong JG, Martini N, Kris MG, et al. Induction chemotherapy for non-small cell lung cancer with clinically evident mediastinal node metastases: The role of postoperative radiotherapy. International Journal of Radiation Oncology Biology Physics 1992;23(3):605-613.	Irrelevant study design, no human participants or in non-English language
12	Augustin F, Bodner J, Wykypiel H, et al. Initial experience with robotic lung lobectomy: report of two different approaches. Surgical Endoscopy 2011;25:108-13.	Irrelevant study design, no human participants or in non-English language
13	Bahl A, Chander S, Julka PK, et al. Micronuclei evaluation of reduction in neoadjuvant chemotherapy related acute toxicity in locally advanced lung cancer: An Indian experience. Journal of Association of Physicians of India 2006;54(MAR.):191-195.	No relevant outcomes reported
14	Banna GL, Parra HJS, Castaing M, et al. Histology-based Combination Induction Chemotherapy for Elderly Patients with Clinical Stage III Non-small Cell Lung Cancer. Anticancer Research 2017;37:3723-3728.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
15	Beal J, Gomes D, Taranto P, et al. P82.02 Stereotactic Ablative Radiotherapy with Nivolumab for Early-Stage Operable Non-Small Cell Lung Cancer: a phase 2 study. Journal of Thoracic Oncology 2021;16(3 Supplement):S651-S652.	No relevant outcomes reported
16	Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: Results of a meta-analysis of the literature. Lung Cancer 2005;49(1):13-23.	Irrelevant study design, no human participants or in non-English language
17	Billingy NE, Veldhuijzen E, Tromp V, et al. SYMptom monitoring with patient-reported outcomes using a web application among lung cancer patients in the Netherlands (SYMPRO-Lung). Annals of oncology 2020;31:S801-.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
18	Botrel TE, Clark O, Clark L, et al. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and meta-analysis. Lung Cancer 2011;74:89-97.	Irrelevant study design, no human participants or in non-English language
19	Bozcuk H, Abali H, Coskun S, et al. The correlates of benefit from neoadjuvant chemotherapy before surgery in non-small-cell lung cancer: a metaregression analysis. World Journal of Surgical Oncology 2012;10 (no pagination).	No relevant outcomes reported

20	Breathnach OS, Georgiadis MS, Schuler BS, et al. Phase II trial of paclitaxel by 96-hour continuous infusion in combination with cisplatin for patients with advanced non-small cell lung cancer. Clinical Cancer Research 2000;6(7):2670-2676.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
21	Buccheri G, Ferrigno D. Identifying patients at risk of early postoperative recurrence of lung cancer: A new use of the old CEA test. Annals of Thoracic Surgery 2003;75(3):973-980.	Irrelevant study design, no human participants or in non-English language
22	Bund J, Eberhardt K, Hartmann W, et al. Treatment of locally advanced non-small cell lung cancer, stage IIIB with irradiation and interferon beta: Preliminary results of a phase II study. [German]. Strahlentherapie und Onkologie 1998;174(6):300-305.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
23	Burdett S, Pignon Jean P, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews 2015;Issue 3.	Irrelevant study design, no human participants or in non-English language
24	Burdett S, Rydzewska L, Tierney J, et al. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database of Systematic Reviews 2016.	Irrelevant study design, no human participants or in non-English language
25	Burdett S, Stewart L. Postoperative radiotherapy in non-small-cell lung cancer: Update of an individual patient data meta-analysis. Lung Cancer 2005;47(1):81-83.	Irrelevant study design, no human participants or in non-English language
26	Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Journal of Thoracic Oncology 2006;1:611-21.	Irrelevant study design, no human participants or in non-English language
27	Burdett S. Preoperative chemotherapy for non-small-cell lung cancer: A systematic review and meta-analysis of individual participant data. The Lancet 2014;383(9928):1561-1571.	Irrelevant study design, no human participants or in non-English language
28	Cao C, Chandrakumar D, Gupta S, et al. Could less be more?-A systematic review and meta-analysis of sublobar resections versus lobectomy for non-small cell lung cancer according to patient selection. Lung Cancer 2015;89(2):121-132.	Irrelevant study design, no human participants or in non-English language
29	Cao C, Gupta S, Chandrakumar D, et al. Meta-analysis of intentional sublobar resections versus lobectomy for early stage non-small cell lung cancer. Annals of Cardiothoracic Surgery 2014;3:134-141.	Irrelevant study design, no human participants or in non-English language

30	Cao C, Manganas C, Ang SC, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: A meta-analysis of propensity score-matched patients. Interactive Cardiovascular and Thoracic Surgery 2013;16(3):244-249.	Irrelevant study design, no human participants or in non-English language
31	Cao X, Ganti AK, Stinchcombe T, et al. Predicting risk of chemotherapy-induced severe neutropenia: A pooled analysis in individual patients data with advanced lung cancer. Lung Cancer 2020;141:14-20.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
32	Casarrubios M, Nadal E, Cruz-Bermudez A, et al. P60.11 TCR Repertoire Predicts Pathological Response in NSCLC Patients Receiving Neoadjuvant Chemoimmunotherapy from NADIM Trial. Journal of Thoracic Oncology 2021;16(3 Supplement):S545-S546.	No relevant outcomes reported
33	Cascone T, Provencio M, Sepesi B, et al. Checkmate 77T: A phase III trial of neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) followed by adjuvant nivo in resectable early-stage NSCLC. Journal of Clinical Oncology. Conference 2020;38.	No relevant outcomes reported
34	Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. Cochrane Database of Systematic Reviews 2017;2017(6) (no pagination).	Irrelevant study design, no human participants or in non-English language
35	Cerfolio RJ, Bryant AS, Ojha B, et al. Improving the inaccuracies of clinical staging of patients with NSCLC: A prospective trial. Annals of Thoracic Surgery 2005;80(4):1207-1214.	Irrelevant intervention
36	Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. Journal of Thoracic & Cardiovascular Surgery 2006;131:1229-35.	Irrelevant intervention
37	Cesario A, Margaritora S, Galetta D, et al. Correspondence re L. J. Wirth et al., Induction Docetaxel and Carboplatin Followed by Weekly Docetaxel and Carboplatin with Concurrent Radiotherapy, Then Surgery in Stage III Non-Small Cell Lung Cancer: A Phase I Study. Clin Cancer Res 2003;9:1698-704 (multiple letters). Clinical Cancer Research 2004;10(8):2902-2904.	Irrelevant study design, no human participants or in non-English language
38	Ceylan KC, Kaya SO, Samancilar O, et al. The effects of neoadjuvant chemotherapy on pulmonary structures: a quantitative analysis. Thoracic and cardiovascular surgeon 2012;60:111-115.	Irrelevant study design, no human participants or in non-English language
39	Chai T, Zhang P, Lin Y, et al. Postoperative adjuvant therapy for resectable early non-small cell lung cancer: A protocol for a	Irrelevant study design, no human

	systematic review and meta-analysis. Medicine 2019;98:Irrelevant study design, no human participants or in non-English language6468.	participants or in non-English language
40	Chamogeorgakis T, Anagnostopoulos C, Kostopanagiotou G, et al. Does anemia affect outcome after lobectomy or pneumonectomy in early stage lung cancer patients who have not received neo-adjuvant treatment? Thoracic & Cardiovascular Surgeon 2008;56:148-53.	Irrelevant study design, no human participants or in non-English language
41	Chan MV, Huo YR, Cao C, et al. Survival outcomes for surgical resection versus CT-guided percutaneous ablation for stage I non-small cell lung cancer (NSCLC): a systematic review and meta-analysis. European Radiology 2021;31(7):5421-5433.	Irrelevant study design, no human participants or in non-English language
42	Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. The Lancet Oncology 2021;22(10):1448-1457.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
43	Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy in operable stage I NSCLC patients: Long-term results of the expanded STARS clinical trial. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2021;39.	Irrelevant intervention
44	Charlot M, Stein JN, Damone E, et al. Effect of an Antiracism Intervention on Racial Disparities in Time to Lung Cancer Surgery. Journal of clinical oncology 2022;40:1755-1762.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
45	Chen D, Jin Z, Zhang J, et al. Efficacy and Safety of Neoadjuvant Targeted Therapy vs. Neoadjuvant Chemotherapy for Stage IIIA EGFR-Mutant Non-small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Frontiers in Surgery 2021;8:715318.	Irrelevant study design, no human participants or in non-English language
46	Chen E, Wang J, Jia C, et al. Sublobar resection with intraoperative brachytherapy versus sublobar resection alone for early-stage non-small-cell lung cancer: A meta-Analysis. Interactive Cardiovascular and Thoracic Surgery 2021;33(3):377-384.	Irrelevant study design, no human participants or in non-English language
47	Chen FF, Zhang D, Wang YL, et al. Video-Assisted thoracoscopic surgery lobectomy versus open lobectomy in patients with clinical stage , non-small cell lung cancer: A meta-Analysis. European Journal of Surgical Oncology 2013;39(9):957-963.	Irrelevant study design, no human participants or in non-English language
48	Chen GY, Jiang GL, Qian H, et al. Escalated hyperfractionated accelerated radiation therapy for locally advanced non-small cell lung cancer: A clinical phase II trial. Radiotherapy and Oncology 2004;71(2):157-162.	Patients without stage I–III NSCLC who are candidates for surgical

		resection of the primary NSCLC
49	Chen H, Laba JM, Boldt RG, et al. Stereotactic Ablative Radiation Therapy Versus Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score Studies. International Journal of Radiation Oncology Biology Physics 2018;101(1):186-194.	Irrelevant study design, no human participants or in non-English language
50	Chen L, Kurtyka CA, Welsh EA, et al. Early2 factor (E2F) deregulation is a prognostic and predictive biomarker in lung adenocarcinoma. Oncotarget 2016;7:82254-82265.	No relevant outcomes reported
51	Chen Y, Peng X, Zhou Y, et al. Comparing the benefits of chemoradiotherapy and chemotherapy for resectable stage III A/N2 non-small cell lung cancer: A meta-analysis. World Journal of Surgical Oncology 2018;16(1) (no pagination).	Irrelevant study design, no human participants or in non-English language
52	Chen YY, Wang LW, Wang SY, et al. Meta-analysis of postoperative adjuvant chemotherapy without radiotherapy in early stage non-small cell lung cancer. OncoTargets and Therapy 2015;8:2033-2043.	Irrelevant study design, no human participants or in non-English language
53	Cheng C, Wu YL, Gu LJ, et al. [Predicting efficacy of neoadjuvant cheomotherapy on resectable stage IIIA non-small cell lung cancer by multi-gene expressions]. Aizheng 2005;24:846-9.	No relevant outcomes reported
54	Chi CI. A Phase III Randomized Trial of Anatomical Segmentectomy Versus Lobectomy by Minimal Incision for Stage IA Peripheral Non-Small Cell Lung Cancer (<=2cm). https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-15006654 2015.	No relevant outcomes reported
55	Chi CT. A multicenter randomized controlled trial on video-assisted thoracoscopic surgery and axillary thoracotomy for resection of early-stage non-small cell lung cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-TRC-10000750 2010.	No relevant outcomes reported
56	Chi CT. Effect of epidural anesthesia/analgesia on cancer recurrence and metastasis after lung cancer surgery: a single-center, randomized controlled trial. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-TRC-14004136 2014.	No relevant outcomes reported
57	ChiCtr. A multi-center randomized controlled trial of Liu Jiaxiang Qi-Yin Recipe for improving the prognosis of patients with stage IIIA non-small cell lung cancer after radical resection. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000029456 2020.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
58	ChiCtr. A multi-center, prospective, randomized controlled clinical trial for comparison between wedge resection and segmentectomy in the surgical treatment of ground glass	No relevant outcomes reported

	opacity-dominant early stage non-small cell lung cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1800019666 2018.	
59	ChiCtr. A single-center, prospective, randomized controlled clinical trial for comparison between sublobectomy and lobectomy in the surgical treatment of early stage (T1a) invasive adenocarcinoma of the lung. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1900021752 2019.	No relevant outcomes reported
60	ChiCtr. Almonertinib vs. Erlotinib / Chemotherapy for Neo-AdjuVant Treatment of Stage IIIA-N2 EGFR-Mutated NSCLC: a Multicenter, Open-Label, Phase II Randomized Controlled Trial. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000033677 2020.	No relevant outcomes reported
61	ChiCtr. Minimally Invasive of Lobectomy vs Segmentectomy for Stage Ia Lung Adenocarcinoma: a Prospective, Multicenter, Randomized Controlled Trial. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000037065 2020.	No relevant outcomes reported
62	ChiCtr. Robot-assisted thoracic surgery versus video-assisted thoracic surgery in patients with early-stage non-small cell lung cancer: an open-label, multi-center, non-inferiority, randomised controlled trial. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000034737 2020.	No relevant outcomes reported
63	Chu Q, Vincent M, Logan D, et al. Taxanes as first-line therapy for advanced non-small cell lung cancer: a systematic review and practice guideline. Lung Cancer 2005;50:355-374.	Irrelevant study design, no human participants or in non-English language
64	Clark JI, Albain KS. Combined modality therapy for early stage operable and locally advanced potentially resectable non-small cell lung carcinoma. Cancer treatment and research 2001;105:149-170.	Irrelevant study design, no human participants or in non-English language
65	Claude L, Perol D, Ginestet C, et al. A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: Clinical and dosimetric factors analysis. Radiotherapy and Oncology 2004;71(2):175-181.	Irrelevant intervention
66	Cox JD, Azarnia N, Byhardt RW, et al. N<inf>2</inf> (clinical) non-small cell carcinoma of the lung: Prospective trials of radiation therapy with total doses 60 Gy by the Radiation Therapy Oncology Group. International Journal of Radiation Oncology Biology Physics 1991;20(1):7-12.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
67	Ctri. Phase II Randomized controlled trial comparing conventionally fractionated radiation vs hypofractionated radiation in locally advanced non adeno non small cell	Irrelevant intervention

	carcinoma lung. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2013/11/004143 2013.	
68	Ctri. Study in Patients with surgically removable Non-Small Cell Lung Cancer (NSCLC) with Durvalumab plus Chemotherapy before and after surgical removal of tumour versus surgical removal of tumour alone with chemotherapy. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2019/06/019634 2019.	No relevant outcomes reported
69	Ctri. To study the effect of homoeopathy in cancer patients along with chemotherapy and radiotherapy. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2021/10/037391 2021.	No relevant outcomes reported
70	Cykert S, Dilworth-Anderson P, Monroe MH, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. JAMA - Journal of the American Medical Association 2010;303(23):2368-2376.	Irrelevant study design, no human participants or in non-English language
71	Cykert S, Eng E, Walker P, et al. A system-based intervention to reduce Black-White disparities in the treatment of early stage lung cancer: a pragmatic trial at five cancer centers. Cancer medicine 2019;8:1095-1102.	No relevant outcomes reported
72	Dai Y, Han B, Shen J, et al. Preoperative induction chemotherapy for resectable stage IIIA non-small-cell lung cancer: A meta-analysis of 13 double-blind, randomized clinical trials. [Chinese]. Chinese Journal of Lung Cancer 2008;11(3):398-405.	Irrelevant study design, no human participants or in non-English language
73	D'Angelillo RM, Trodella L, Ciresa M, et al. Multimodality treatment of stage III non-small cell lung cancer: Analysis of a phase II trial using preoperative cisplatin and gemcitabine with concurrent radiotherapy. Journal of Thoracic Oncology 2009;4(12):1517-1523.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
74	Darwish S, Minotti V, Crino L, et al. A phase II trial of combined chemotherapy and surgery in stage IIIA non-small cell lung cancer. Lung Cancer 1995;12 Suppl 1:S71-8.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
75	D'Cunha J, Herndon JE, 2nd, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. Lung Cancer 2005;48:241-6.	No relevant outcomes reported
76	de Jong WK, van der Heijden HF, Pruim J, et al. Prognostic value of different metabolic measurements with fluorine-18 fluorodeoxyglucose positron emission tomography in resectable non-small cell lung cancer: a two-center study. Journal of	Irrelevant study design, no human participants or in non-English language

	Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2007;2:1007-12.	
77	De Pauw R, Van Meerbeeck JP. Resection vs radiotherapy following induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: Randomized controlled trial. American Journal of Hematology/ Oncology 2007;6(9):509-512.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
78	De Ruysscher D, Dehing C, Bentzen SM, et al. Can we optimize chemo-radiation and surgery in locally advanced stage III non-small cell lung cancer based on evidence from randomized clinical trials? A hypothesis-generating study. Radiotherapy & Oncology 2009;93:389-95.	Irrelevant study design, no human participants or in non-English language
79	Deng H, Zhao Y, Cai X, et al. PD-L1 expression and Tumor mutation burden as Pathological response biomarkers of Neoadjuvant immunotherapy for Early-stage Non-small cell lung cancer: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology 2022;170 (no pagination).	Irrelevant study design, no human participants or in non-English language
80	Deng HY, Wang YC, Ni PZ, et al. Radiotherapy, lobectomy or sublobar resection? A meta-analysis of the choices for treating stage I non-small-cell lung cancer. European Journal of Cardio-thoracic Surgery 2017;51(2):203-210.	Irrelevant study design, no human participants or in non-English language
81	Dickhoff C, Senan S, Schneiders FL, et al. 119TiP Dual-immunotherapy and short-course medium-dose radiotherapy, followed by surgery for tumor microenvironment modification in early stage NSCLC: The DIRECT-trial. Annals of Oncology 2021;32(Supplement 7):S1427.	No relevant outcomes reported
82	Dickhoff C, Senan S, Schneiders FL, et al. Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable T3-4N0-1 non-small cell lung cancer: The INCREASE trial. BMC Cancer 2020;20(1) (no pagination).	No relevant outcomes reported
83	Dizier B, Callegaro A, Debois M, et al. A Th1/IFNγ Gene Signature Is Prognostic in the Adjuvant Setting of Resectable High-Risk Melanoma but Not in Non-Small Cell Lung Cancer. Clinical cancer research 2020;26:1725-1735.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
84	Dobrodeev A, Zav'ialov AA, Tyzikov SA, et al. [The results of combined treatment for stage III lung cancer including the use of intraoperative radiotherapy]. Voprosy Onkologii 2013;59:606-10.	Irrelevant study design, no human participants or in non-English language
85	Dong ZY, Zhang JT, Liu SY, et al. EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer. OncoImmunology 2017;6(11) (no pagination).	Patients without stage I–III NSCLC who are candidates for surgical

		resection of the primary NSCLC
86	D'Orazio A. Phase II trials of docetaxel/gemcitabine in stage IIIB/IV non-small-cell lunc cancer. Clinical lung cancer 2000;2:173-177.	Irrelevant study design, no human participants or in non-English language
87	Drks. Randomized multicenter trial to compare standard lobectomy versus anatomical segmentectomy each plus radical lymphadenectomy in patients with Non-Small Cell Lung Cancer (NSCLC) pT1a pN0 cM0, Stage IA. https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00004897 2013.	No relevant outcomes reported
88	Drks. SINGLE-PORT VATS vs. 3-PORT-VATS LOBECTOMY/SEGMENTECTOMY FOR NON SMALL CELL LUNG CANCER PATIENTS. A RANDOMISED CLINICAL TRIAL INVESTIGATING PAIN INTENSITY AND POST THORACOTOMY PAIN-SYNDROME. https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00014987 2018.	No relevant outcomes reported
89	Duan H, Wang T, Luo Z, et al. Neoadjuvant programmed cell death protein 1 inhibitors combined with chemotherapy in resectable non-small cell lung cancer: An open-label, multicenter, single-arm study. Translational Lung Cancer Research 2021;10(2):1020-1028.	Irrelevant study design, no human participants or in non-English language
90	Eagan RT. Management of regionally advanced (stage III) non-small cell lung cancer. LCSG 831. Chest 1994;106:340S-343S.	Irrelevant study design, no human participants or in non-English language
91	Eberhardt WE, Gauler TC, Lepechoux C, et al. 10-year long-term survival (LTS) of induction chemotherapy with three cycles cisplatin/paclitaxel followed by concurrent chemoradiation cisplatin/etoposide/45 Gy (1.5 Gy bid) plus surgery in locally advanced non-small-cell lung cancer (NSCLC)-a multicenter phase-II trial (CISTAXOL). Lung Cancer 2013;82:83-9.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
92	Eichhorn F, Klotz LV, Bischoff H, et al. Neoadjuvant anti-programmed Death-1 immunotherapy by Pembrolizumab in resectable nodal positive stage II/IIIa non-small-cell lung cancer (NSCLC): The NEOMUN trial. BMC Cancer 2019;19(1) (no pagination).	No relevant outcomes reported
93	Elayouty HD, Bazaeb AM, Bayazed AM. Radiotherapy with or without concomitant chemotherapy as Pre- or postoperative therapy in Non-small cell lung cancer. Journal of Cancer Science and Therapy 2012;4(4):84-87.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC

94	Ettinger DS. Combined-modality treatment for stage IIIa (N<inf>2</inf>) non-small cell lung cancer: A National Cancer Institute Intergroup study. Cancer Chemotherapy and Pharmacology, Supplement 1998;42:S71-S74.	No relevant outcomes reported
95	Euctr AT. A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Single-agent Tarceva® (erlotinib) Following Complete Tumor Resection and with or without Adjuvant Chemotherapy in Patients with Stage IB-IIIA Non-small Cell Lung Carcinoma who have EGFR-positive Tumors - RADIANT. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2005-001747-29-AT 2006.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
96	Euctr BE. Chemo +/- Pembrolizumab (MK-3475) as Perioperative Therapy for Resectable Stage IIB or IIIA NSCLC. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-001832-21-BE 2017.	No relevant outcomes reported
97	Euctr BG. Multicenter, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard pemetrexed therapy compared to placebo plus standard pemetrexed therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy - BIBF plus Pemetrexed in 2nd line NSCLC patients. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2008-002072-10-BG 2011.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
98	Euctr DE. A Study Evaluating the Efficacy and Safety of Neoadjuvant Treatment with Atezolizumab or Placebo in Combination with Platinum-Based Chemotherapy in Patients with Resectable Stage II, IIIA, or Select IIIB Non-small cell lung cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-002857-12-DE 2018.	No relevant outcomes reported
99	Euctr DE. A Study of Osimertinib with or without Chemotherapy versus Chemotherapy alone as neoadjuvant therapy for Patients with Epidermal Growth Factor Receptor mutation positive resectable Non-Small Cell Lung Cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2020-000058-89-DE 2020.	No relevant outcomes reported
100	Euctr HU. A Study of Neoadjuvant/adjuvant Durvalumab for the Treatment of Patients with Resectable Non-small Cell Lung Cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2018-002997-29-HU 2018.	No relevant outcomes reported
101	Euctr IE. Chemo +/- Pembrolizumab (MK-3475) as Perioperative Therapy for Resectable Stage IIB or IIIA NSCLC.	No relevant outcomes reported

	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-001832-21-IE 2017.	
102	Euctr IT. "Multicenter, prospective, open label study , in patients with non small cell lung cancer (NSCLC), stage IIIB / IV or recurrent, after the failure of first line chemotherapy in which it's possible a treatment that evaluates the effectiveness and the safety of oral BIBF 1120 in combination with standard docetaxel therapy, which can be administered (at the discretion of the referring physician) with tri-weekly or weekly schedule. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2014-005016-42-IT 2015.	No relevant outcomes reported
103	Euctr NL. A Phase 3, Randomized, Double-blind Study of Chemotherapy plus Nivolumab versus Chemotherapy plus Placebo provided before surgery, followed by Nivolumab or Placebo provided after surgery for Participants with Non-small Cell Lung Cancer which can be completely removed by surgery. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019-000262-38-NL 2019.	No relevant outcomes reported
104	Euctr PL. A Study Evaluating the Efficacy and Safety of Neoadjuvant Treatment with Atezolizumab or Placebo in Combination with Platinum-Based Chemotherapy in Patients with Resectable Stage II, IIIA, or Select IIIB Non-small cell lung cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-002857-12-PL 2018.	No relevant outcomes reported
105	Feng J, Wang LF, Han TY, et al. Survival Outcomes of Lobectomy Versus Segmentectomy in Clinical Stage I Non-Small Cell Lung Cancer: A Meta-Analysis. Advances in Therapy 2021;38(7):4130-4137.	Irrelevant study design, no human participants or in non-English language
106	Frontini L, Candido P, Cattaneo MT, et al. Cisplatin-vinorelbine combination chemotherapy in locally advanced non-small cell lung cancer. Tumori 1996;82(1):57-60.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
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109	Furrer K, Weder W, Betticher D, et al. Extended resections for advanced stages T3/T4 NSCLC including N2 disease after	Irrelevant study design, no human

	neoadjuvant treatment: SAKK pooled analysis (16/96, 16/00, 16/01). Respiration 2021;100(7):678-679.	participants or in non-English language
110	Furrer K, Weder W, Eboulet E, et al. P30.01 Extended Resections for Advanced Stages T3/T4 NSCLC After Neoadjuvant Treatment: Conclusions of SAKK Pooled Analysis (16/96, 16/00, 16/01). Journal of Thoracic Oncology 2021;16(10 Supplement):S1051.	Irrelevant study design, no human participants or in non-English language
111	Gambacorta MA, Trodella L, Mantini G, et al. Concomitant radiochemotherapy in locally advanced non-small cell lung cancer. A phase I study. Acta Medica Romana 1999;37(4):510-523.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
112	Garrido P, Pujol JL, Kim ES, et al. Canakinumab with and without pembrolizumab in patients with resectable non-small-cell lung cancer: CANOPY-N study design. Future Oncology 2021;17:1459-1472.	No relevant outcomes reported
113	Giannitto GC, Giuffrida D, Pappalardo A, et al. Paclitaxel, carboplatin and gemcitabine combination as induction chemotherapy for stage IIIA N2 bulky non-small cell lung cancer. Oncology 2005;69:295-300.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
114	Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2012;7:1382-93.	Irrelevant study design, no human participants or in non-English language
115	Group NM-aC. Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-1571.	Irrelevant study design, no human participants or in non-English language
116	Guo SX, Jian Y, Chen YL, et al. Neoadjuvant Chemoradiotherapy vesus Chemotherapy alone Followed by Surgery for Resectable Stage III Non-Small-Cell Lung Cancer: a Meta-Analysis. Scientific Reports 2016;6:34388.	Irrelevant study design, no human participants or in non-English language
117	Hall H, Tocock A, Burdett S, et al. Association between time-to-treatment and outcomes in non-small cell lung cancer: a systematic review. Thorax. 2021;17.	Irrelevant study design, no human participants or in non-English language
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120	Herbst RS. Surgical resection following CT/RT improves PFS in stage IIIA NSCLC. Oncology Report 2005:99.	Irrelevant study design, no human participants or in non-English language
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124	Horita N, Miyazawa N, Morita S, et al. Preoperative chemotherapy is effective for stage III resectable non-small-cell lung cancer: Metaanalysis of 16 trials. Clinical Lung Cancer 2013;14(5):488-494.	Irrelevant study design, no human participants or in non-English language
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127	Huisman C, Giaccone G, Van Groeningen CJ, et al. Combination of gemcitabine and cisplatin for advanced non-small cell lung cancer: A phase II study with emphasis on scheduling. Lung Cancer 2001;33(2-3):267-275.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC

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129	Huynh C, Rayes R, Gaudreau P, et al. P79.05 Phase II Randomized Trial of Neoadjuvant Pembrolizumab +/- Chemotherapy for Operable Stage IA3-IIA Non-Small Cell Lung Cancer. Journal of Thoracic Oncology 2021;16(3 Supplement):S647-S648.	No relevant outcomes reported
130	Iacobelli S, Irtelli L, Sacco R, et al. A phase II study of neoadjuvant chemotherapy with cisplatin, epirubicin and VP-16 for stage III unresectable non-small cell lung cancer. Anticancer Research 1998;18(3 B):2081-2084.	No relevant outcomes reported
131	Imai K, Nakagawa T, Matsuzaki I, et al. Phase II trial of induction chemotherapy with carboplatin and paclitaxel plus bevacizumab in patients with stage IIIA to IV nonsquamous non-small cell lung cancer. Surgery Today 2019;49(8):678-685.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
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133	Iyengar P, Allen BG, Kelsey CR, et al. GRECO-1: Phase 1/2 Study of Stereotactic Body Radiation Therapy (SBRT) With or Without GC4711 for Early Stage, Centrally Located or Large Non-Small Cell Lung Cancer (NSCLC). International journal of radiation oncology, biology, physics 2021;S. 111(3):e471.	Irrelevant intervention
134	Jablonka S, Furmanik F, Jablonka A, et al. Principles of induction chemotherapy for non-small cell lung cancer. Lung Cancer 2001;34(SUPPL. 2):S151-S153.	No relevant outcomes reported
135	JapicCTI J. CheckMate 816: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 816. https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-JapicCTI-173653 2017.	No relevant outcomes reported
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140	Jprn U. Single-port versus conventional three-port video-assisted thoracic surgery (VATS) for early-stage NSCLC: short- and long-term outcomes of a multicentre randomised trial. https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000029906 2018.	No relevant outcomes reported
141	Kaneko K, Kikuchi K, Nakayama M, et al. Combination Chemotherapy of Cisplatin (CDDP), Vinorelbine (VNB), Mitomycin (MMC) in Patients with Advanced Non-small Cell Lung Cancer. [Japanese]. Japanese Journal of Lung Cancer 2003;43(7):878-881.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
142	Kelly K, Awad MM, Saliba T, et al. Neoadjuvant and Adjuvant Capmatinib in Resectable Non-Small Cell Lung Cancer With MET Exon 14 Skipping Mutation or High MET Amplification: GEOMETRY-N Trial. Molecular Cancer Therapeutics. Conference: AACR NCI EORTC International Conference on Molecular Targets and Cancer Therapeutics. Virtual. 2021;20.	No relevant outcomes reported
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144	Kenny PM, King MT, Viney RC, et al. Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. Journal of Clinical Oncology 2008;26:233-41.	Irrelevant intervention
145	Khan TM, Verbus EA, Gandhi S, et al. Osimertinib, Surgery, and Radiation Therapy in Treating Patients with Stage IIIB or IV Non-Small Cell Lung Cancer with EGFR Mutations (NORTHSTAR). Annals of Surgical Oncology 2022;29(8):4688-4689.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
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148	Kiribayashi T, Hata Y, Kishi K, et al. Adherence and feasibility of 2 treatment schedules of s-1 as adjuvant chemotherapy in completely resected lung cancer. Journal of thoracic oncology 2017;12:S1962-S1963.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
149	Kramer GW, Legrand CL, van Schil P, et al. Quality assurance of thoracic radiotherapy in EORTC 08941: a randomised trial of surgery versus thoracic radiotherapy in patients with stage IIIA non-small-cell lung cancer (NSCLC) after response to induction chemotherapy. European journal of cancer (Oxford, England : 1990) 2006;42:1391-1398.	No relevant outcomes reported
150	Langer CJ, Somer R, Litwin S, et al. Phase I study of radical thoracic radiation, weekly irinotecan, and cisplatin in locally advanced non-small cell lung carcinoma. Journal of Thoracic Oncology 2007;2(3):203-209.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
151	Laza Briviesca R, Nadal E, Casarrubios M, et al. FP12.09 Molecular Insight into NADIM Clinical Trial: Potential Immune Biomarkers of Pathological Response for NSCLC Patients. Journal of Thoracic Oncology 2021;16(3 Supplement):S220-S221.	No relevant outcomes reported
152	Lee J, Garrido P, Kim E, et al. MO01.23 Canakinumab or Pembrolizumab as Monotherapy or in Combination as Neoadjuvant Therapy in Patients with Surgically Resected Non-Small Cell Lung Cancer (NSCLC): CANOPY-N Trial. Journal of thoracic oncology 2021;16:S25-S26.	No relevant outcomes reported
153	Lee J, Mok T, Garrido P, et al. Canakinumab or Pembrolizumab as Monotherapy or in Combination as Neoadjuvant Therapy in Patients with Surgically Resected Non-Small Cell Lung Cancer: CANOPY-N Trial. American journal of respiratory and critical care medicine 2021;203.	No relevant outcomes reported
154	Lee J, Tsuboi M, Garrido P, et al. P03.05 CANOPY-N: Neoadjuvant Canakinumab and Pembrolizumab in Patients With Surgically Resectable Non-Small Cell Lung Cancer. Journal of Thoracic Oncology 2021;16(3 Supplement):S260.	No relevant outcomes reported
155	Lee J, Wistuba I, Ngiam C, et al. P03.04 Phase II Study of TKIs as Neo(adjuvant) Therapy in Stage II-III Resectable NSCLC with ALK, ROS1, NTRK or BRAFV600 Alterations. Journal of Thoracic Oncology 2021;16(3 Supplement):S259-S260.	No relevant outcomes reported

156	Lee JM, Garrido P, Kim ES, et al. Randomized phase II study of canakinumab (CAN) or pembrolizumab (PEM) alone or incombination as neoadjuvant therapy in patients (Pts) with surgically resected (Stage IB-IIIA) non-small cell lungcancer (NSCLC): CANOPY-N. Cancer research 2020;80.	No relevant outcomes reported
157	Lee JM, Mok T, Garrido P, et al. Canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in patients with surgically resected non-small cell lung cancer: CANOPY-N trial. Cancer research 2021;81.	No relevant outcomes reported
158	Lee JM, Pujol JL, Garrido P, et al. Canakinumab or Pembrolizumab as Monotherapy or in Combination as Neoadjuvant Therapy in Patients With Resectable Non-Small Cell Lung Cancer: CANOPY-N Trial. Molecular Cancer Therapeutics. Conference: AACR NCI EORTC International Conference on Molecular Targets and Cancer Therapeutics. Virtual. 2021;20.	No relevant outcomes reported
159	Lei T, Li J, Zhong H, et al. Postoperative Radiotherapy for Patients With Resectable Stage III-N2 Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Frontiers in Oncology 2021;11:680615.	Irrelevant study design, no human participants or in non-English language
160	Leonetti A, Minari R, Boni L, et al. Phase II, Open-label, Single-arm, Multicenter Study to Assess the Activity and Safety of Alectinib as Neoadjuvant Treatment in Surgically Resectable Stage III ALK-positive NSCLC: ALNEO Trial. Clinical Lung Cancer 2021;22(5):473-477.	No relevant outcomes reported
161	Li J. P29.07 A Phase Ib Trial of Neoadjuvant Low-Dose Radiation Therapy, Chemotherapy, and Durvalumab for Potentially Resectable Stage III NSCLC. Journal of Thoracic Oncology 2021;16(10 Supplement):S1049-S1050.	No relevant outcomes reported
162	Liao M, Zhao J, Zhou Y. [Multimodality therapy of late stage lung cancer]. Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology] 1995;17:384-6.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
163	Lim E, Batchelor T, Shackcloth M, et al. Study protocol for VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a UK multicentre randomised controlled trial with an internal pilot (the VIOLET study). BMJ Open 2019;9:e029507.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
164	Liu T, Mu Y, Dang J, et al. The role of postoperative radiotherapy for completely resected pIIIA-N2 non-small cell lung cancer patients with different clinicopathological features: A systemic review and meta-analysis. Journal of Cancer 2019;10(17):3941-3949.	Irrelevant study design, no human participants or in non-English language

165	Liu Y, Huang C, Liu H, et al. Sublobectomy versus lobectomy for stage IA (T1a) non-small-cell lung cancer: a meta-analysis study. World Journal of Surgical Oncology 2014;12:138.	Irrelevant study design, no human participants or in non-English language
166	Lokich J, Anderson N, Bern M, et al. Paclitaxel, cisplatin, etoposide combination chemotherapy: A multifractionated bolus dose schedule for non-small cell lung cancer. European Journal of Cancer 1998;34(5):659-663.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
167	Long H, Lin ZC, Lin YB, et al. [Quality of life after lobectomy for early stage non-small cell lung cancer--video-assisted thoracoscopic surgery versus minimal incision thoracotomy]. Aizheng 2007;26:624-8.	Irrelevant study design, no human participants or in non-English language
168	Long H, Lin ZC, Situ DR, et al. [Cytokine responses after lobectomy: a prospective randomized comparison of video-assisted thoracoscopic surgery and minimal incision thoracotomy]. Aizheng 2007;26:991-5.	No relevant outcomes reported
169	Long H, Lin ZC, Situ DR. [Injuries after lobectomy: a prospective randomized comparison of video-assisted thoracoscopic surgery and mini-thoracotomy]. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 2008;46:401-4.	No relevant outcomes reported
170	Lorusso V, Carpagnano F, Di Rienzo G, et al. Accelerated neoadjuvant chemotherapy of non-small cell lung cancer (NSCLC). International Journal of Oncology 1996;8(4):675-680.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
171	Louie AV, Haasbeek CJ, Mokhles S, et al. Predicting Overall Survival After Stereotactic Ablative Radiation Therapy in Early-Stage Lung Cancer: development and External Validation of the Amsterdam Prognostic Model. International journal of radiation oncology, biology, physics 2015;93:82-90.	Irrelevant study design, no human participants or in non-English language
172	Lutz CM, Knap MM, Hoffmann L, et al. Prospectively scored pulmonary toxicities from a non-small cell lung cancer dose escalation trail. Radiotherapy and Oncology 2020;152(Supplement 1):S857-S858.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
173	Mainini C, Rebelo PF, Bardelli R, et al. Perioperative physical exercise interventions for patients undergoing lung cancer surgery: What is the evidence? SAGE Open Medicine 2016;4:2050312116673855.	Irrelevant study design, no human participants or in non-English language
174	Manser R, Wright G, Hart D, et al. Surgery for early stage non-small cell lung cancer. Cochrane database of systematic reviews (Online) 2005:CD004699.	Irrelevant study design, no human

		participants or in non-English language
175	Manser R, Wright G, Hart D, et al. Surgery for local and locally advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews 2005;Issue 1.	Irrelevant study design, no human participants or in non-English language
176	Martin L, Wang X, Patel J, et al. P79.06 CHIO3: ChEmotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage IIIA/B Non-Small Cell Lung Cancer (AFT-46). Journal of Thoracic Oncology 2021;16(3 Supplement):S648.	No relevant outcomes reported
177	Matsuo Y, Nagata Y, Wakabayashi M, et al. Impact of pre-treatment C-reactive protein level and skeletal muscle mass on outcomes after stereotactic body radiotherapy for T1N0M0 non-small cell lung cancer: a supplementary analysis of the Japan Clinical Oncology Group study JCOG0403. Journal of radiation research 2021;62(5):901-909.	Irrelevant intervention
178	Mattson K, Abratt R, Ten GV, et al. Docetaxel as neo-adjuvant therapy for radically treatable stage III non-small cell lung cancer: Early results of an international phase III study. Lung Cancer 2001;34(SUPPL. 4):21-23.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
179	Mattson K. Docetaxel (Taxotere) in the neo-adjuvant setting in non-small-cell lung cancer. Annals of Oncology 1999;10(SUPPL. 5):S69-S72.	No relevant outcomes reported
180	Mattson KV, Abratt RP, ten Velde G, et al. Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: A multinational randomise phase III study. Annals of Oncology 2003;14(1):116-122.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
181	Mauguen A, Pignon JP, Burdett S, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. Lancet Oncology 2013;14:619-26.	Irrelevant study design, no human participants or in non-English language
182	Mayne NR, Elser HC, Darling AJ, et al. Estimating the Impact of Extended Delay to Surgery for Stage I Non-small-cell Lung Cancer on Survival. Annals of surgery 2021;273:850-857.	Irrelevant study design, no human participants or in non-English language
183	Maziak DE, Markman BR, MacKay JA, et al. Photodynamic therapy in nonsmall cell lung cancer: A systematic review. Annals of Thoracic Surgery 2004;77(4):1484-1491.	Irrelevant study design, no human participants or in non-English language

184	Mendogni P, Mazzucco A, Palleschi A, et al. Uniportal and three-portal video-assisted thoracic surgery pulmonary lobectomy for early-stage lung cancer (UNIT trial): study protocol of a single-center randomized trial. Trials 2021;22.	No relevant outcomes reported
185	Meng D, Zhou Z, Wang Y, et al. Lymphadenectomy for clinical early-stage non-small-cell lung cancer: A systematic review and meta-analysis. European Journal of Cardio-thoracic Surgery 2016;50(4):597-604.	Irrelevant study design, no human participants or in non-English language
186	Menna C, Poggi C, Andreetti C, et al. Does the length of uniportal video-assisted thoracoscopic lobectomy affect postoperative pain? Results of a randomized controlled trial. Thoracic cancer 2020;11:1765-1772.	Irrelevant study design, no human participants or in non-English language
187	Meydan D, Cakir S, Ozbek N, et al. Neoadjuvant chemotherapy and concomitant boost radiotherapy in locally advanced non-small cell lung cancer. Turkish Journal of Cancer 2006;36(4):162-168.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
188	Migliorino MR, De Marinis F, Nelli F, et al. A 3-week schedule of gemcitabine plus cisplatin as induction chemotherapy for Stage III non-small cell lung cancer. Lung Cancer 2002;35(3):319-327.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
189	Mignard X, Antoine M, Moro-Sibilot D, et al. IoNESCO trial: Immune neoajuvant therapy in early stage non-small cell lung cancer. Revue des Maladies Respiratoires 2018;35(9):983-988.	No relevant outcomes reported
190	Milroy R, Macbeth F. Neoadjuvant chemotherapy in stage IIIa non-small cell lung cancer. Thorax 1995;50(SUPPL. 1):S25-S30.	Irrelevant study design, no human participants or in non-English language
191	Miyoshi T, Aokage K, Wakabayashi M, et al. Prospective evaluation of watchful waiting for early-stage lung cancer with ground-glass opacity: A single-arm confirmatory multicenter study: Japan Clinical Oncology Group study JCOG1906 (EVERGREEN study). Japanese Journal of Clinical Oncology 2021;51(8):1330-1333.	No relevant outcomes reported
192	Mok TSK, Lopez PG, Kim ES, et al. Randomized phase II study of canakinumab (CAN) or pembrolizumab (PEM) as monotherapy or in combination as neoadjuvant therapy in patients (Pts) with surgically resected (Stage IB-IIIA) non-small cell lung cancer (NSCLC): CANOPY-N. Journal of clinical oncology 2020;38.	No relevant outcomes reported
193	Morgensztern D, Green E, King JC, et al. Role of circulating tumor DNA (ctDNA) from liquid biopsy in early-stage NSCLC resected lung tumor investigation (LIBERTI). Clinical Cancer	No relevant outcomes reported

	Research. Conference: AACR Special Conference on Advances in Liquid Biopsies. Miami, FL United States 2020;26.	
194	Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. British Journal of Radiology 2017;90(1071) (no pagination).	Irrelevant study design, no human participants or in non-English language
195	Nakajima EC, Leal JP, Fu W, et al. CT and PET radiomic features associated with major pathologic response to neoadjuvant immunotherapy in early-stage non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. Conference 2020;38.	Irrelevant study design, no human participants or in non-English language
196	Nakamura H, Kawasaki N, Taguchi M, et al. Role of preoperative chemotherapy for non-small-cell lung cancer: A meta-analysis. Lung Cancer 2006;54(3):325-329.	Irrelevant study design, no human participants or in non-English language
197	Nath TS, Mohamed N, Gill PK, et al. A Comparative Analysis of Video-Assisted Thoracoscopic Surgery and Thoracotomy in Non-Small-Cell Lung Cancer in Terms of Their Oncological Efficacy in Resection: A Systematic Review. Cureus 2022;14:e25443.	Irrelevant study design, no human participants or in non-English language
198	Navani N, Fisher DJ, Tierney JF, et al. The Accuracy of Clinical Staging of Stage I-IIIa Non-Small Cell Lung Cancer: An Analysis Based on Individual Participant Data. Chest 2019;155:502-509.	Irrelevant study design, no human participants or in non-English language
199	Nct. 3D Reconstruction in Video-assisted Thoracoscopic Surgery (VATS) Segmentectomy. https://clinicaltrials.gov/show/NCT04004494 2019.	No relevant outcomes reported
200	Nct. A Study of Neoadjuvant Atezolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Patients With Resectable Stage II, IIIA, or Select IIIB Non-Small Cell Lung Cancer (IMpower030). https://clinicaltrials.gov/show/NCT03456063 2018.	No relevant outcomes reported
201	Nct. A Study of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed by Surgical Removal and Adjuvant Treatment With Nivolumab or Placebo for Participants With Surgically Removable Early Stage Non-small Cell Lung Cancer. https://clinicaltrials.gov/show/NCT04025879 2019.	No relevant outcomes reported
202	Nct. A Study of Toripalimab or Placebo Plus Chemotherapy as Treatment in Early Stage NSCLC. https://clinicaltrials.gov/show/NCT04158440 2019.	No relevant outcomes reported
203	Nct. A Trial of SHR-1316/Placebo in Combination With Chemotherapy in Patients With Resectable NSCLC. https://clinicaltrials.gov/show/NCT04316364 2020.	No relevant outcomes reported

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283	Sierra-Rodero B, Garitaonaindia Y, Martinez-Cutillas M, et al. Predictive molecular parameters of pneumonitis development in stage IIIa NSCLC patients treated with neo-adjuvant chemo-immunotherapy from NADIM clinical trial. Journal of Thoracic Oncology 2021;16(4 Supplement):S740.	No relevant outcomes reported
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293	Stamatis G, Eberhardt W, Stuben G, et al. Preoperative chemoradiotherapy and surgery for selected non-small cell lung cancer IIIB subgroups: Long-term results. Annals of Thoracic Surgery 1999;68(4):1144-1149.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
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309	Tochner ZA, Pass HI, Sindelar WF, et al. Long term tolerance of thoracic organs to intraoperative radiotherapy. International Journal of Radiation Oncology, Biology, Physics 1992;22:65-9.	Irrelevant study design, no human participants or in non-English language
310	Togashi K, Sugawara M, Miyamura H, et al. [Effect of preoperative chemotherapy for bulky N2 non-small-cell lung cancer]. Kyobu Geka - Japanese Journal of Thoracic Surgery 1999;52:915-9.	Irrelevant study design, no human participants or in non-English language
311	Tong S, Qin Z, Wan M, et al. Induction chemoradiotherapy versus induction chemotherapy for potentially resectable stage IIIA (N2) non-small cell lung cancer: A systematic review and	Irrelevant study design, no human

	meta-analysis. Journal of Thoracic Disease 2018;10(4):2428-2436.	participants or in non-English language
312	Trinkaus ME, Blum R, Rischin D, et al. Imaging of hypoxia with ¹⁸F-FAZA PET in patients with locally advanced non-small cell lung cancer treated with definitive chemoradiotherapy. Journal of Medical Imaging and Radiation Oncology 2013;57(4):475-481.	Irrelevant intervention
313	Trodella L, Cellini N, Picciocchi A, et al. Phase I-II trial of concomitant continuous carboplatin (CBDCA) infusion and radiotherapy in advanced nonsmall cell lung cancer with evaluation for surgery: Final report. International Journal of Radiation Oncology Biology Physics 1997;37(1):93-101.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
314	Troschel FM, Jin Q, Eichhorn F, et al. Sarcopenia on preoperative chest computed tomography predicts cancer-specific and all-cause mortality following pneumonectomy for lung cancer: A multicenter analysis. Cancer Medicine 2021;10:6677-6686.	Irrelevant study design, no human participants or in non-English language
315	Tsakiridis T, Pond G, Wright J, et al. Randomized Phase II Trial of Metformin in Combination with Chemoradiotherapy (CRT) in Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC); the OCOG-ALMERA trial (NCT02115464). International journal of radiation oncology biology physics 2020;108:S104-.	Irrelevant intervention
316	Tsuboi M, Luft A, Ursol G, et al. Perioperative pembrolizumab + platinum-based chemotherapy for resectable locally advanced non-small cell lung cancer: the phase III KEYNOTE-671 study. Annals of oncology 2020;31:S801-S802.	No relevant outcomes reported
317	Tsuboi M, Weder W, Escriu C, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. Future Oncology 2021;17(31):4045-4055.	No relevant outcomes reported
318	Tsuboi M, Weder W, Escriu C, et al. P03.02 Neoadjuvant Osimertinib with/without Chemotherapy vs Chemotherapy for EGFR Mutated Resectable NSCLC: NeoADAURA. Journal of Thoracic Oncology 2021;16(3 Supplement):S258.	No relevant outcomes reported
319	Tsutani Y, Miyata Y, Nakayama H, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: A multicenter study. Journal of Thoracic and Cardiovascular Surgery.	Irrelevant study design, no human participants or in non-English language
320	Tsutani Y, Nakayama H, Ito H, et al. Long-Term Outcomes After Sublobar Resection Versus Lobectomy in Patients With Clinical Stage IA Lung Adenocarcinoma Meeting the Node-Negative Criteria Defined by High-Resolution Computed Tomography and	Irrelevant study design, no human participants or in non-English language

	[¹⁸F]-Fluoro-2-Deoxy-d-Glucose Positron Emission Tomography. Clinical Lung Cancer 2021;22:e431-e437.	
321	Ung YC, Maziak DE, Vanderveen JA, et al. ¹⁸Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: A systematic review. Journal of the National Cancer Institute 2007;99(23):1753-1767.	Irrelevant study design, no human participants or in non-English language
322	van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. Journal of the National Cancer Institute 2007;99:442-450.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
323	Van Schil P, Van Meerbeeck J, Kramer G, et al. Morbidity and mortality in the surgery arm of EORTC 08941 trial. European Respiratory Journal 2005;26(2):192-197.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
324	Vansteenkiste J, Betticher D, Eberhardt W, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. Journal of thoracic oncology 2007;2:684-685.	Irrelevant study design, no human participants or in non-English language
325	Vel'sher LZ, Gabuniia ZR, Grishina TI, et al. [Galavit-induced change of immunologic parameters in patients with non-small lung cancer]. Voprosy Onkologii 2009;55:51-5.	No relevant outcomes reported
326	Vera P, Mezzani-Saillard S, Edet-Sanson A, et al. FDG PET during radiochemotherapy is predictive of outcome at 1 year in non-small-cell lung cancer patients: A prospective multicentre study (RTEP2). European Journal of Nuclear Medicine and Molecular Imaging 2014;41(6):1057-1065.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
327	Veronesi G, Solli PG, Leo F, et al. Low morbidity of bronchoplastic procedures after chemotherapy for lung cancer. Lung Cancer 2002;36:91-7.	No relevant outcomes reported
328	Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Practical Radiation Oncology 2017;7(5):295-301.	Irrelevant study design, no human participants or in non-English language
329	Vokes EE, Mauer AM, Haraf DJ, et al. Phase I study of docetaxel and concomitant chest radiation. Oncology 1997;11(7 SUPPL.):23-26.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
330	Voorn MJJ, Beukers K, Trepels CMM, et al. Associations between pretreatment nutritional assessments and treatment	Irrelevant study design, no human

	complications in patients with stage I-III non-small cell lung cancer: A systematic review. Clinical Nutrition ESPEN 2022;47:152-162.	participants or in non-English language
331	Vuong D, Bogowicz M, Unkelbach J, et al. New voxel-based approach to study the relation of tumor location and survival in NSCLC (SAKK-16/00). Radiotherapy and Oncology 2020;152(Supplement 1):S846-S847.	Irrelevant study design, no human participants or in non-English language
332	Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. European Journal of Cardio-Thoracic Surgery 2004;26:173-82.	No relevant outcomes reported
333	Wang C, Wang M, Yu B. 1169TiP Penpulimab-based combination neoadjuvant/adjuvant therapy for patients with resectable locally advanced non-small cell lung cancer: a phase II clinical study (ALTER-L043). Annals of oncology 2021;32:S938-.	No relevant outcomes reported
334	Wang C, Wang R, Ma Y, et al. TiP Neoadjuvant tislelizumab or placebo + platinum-based chemotherapy followed by adjuvant tislelizumab or placebo in patients with resectable non-small cell lung cancer (NSCLC): A phase III trial in progress. Journal of Thoracic Oncology 2021;16(4 Supplement):S746.	No relevant outcomes reported
335	Wang P, Wang S, Liu Z, et al. Segmentectomy and Wedge Resection for Elderly Patients with Stage I Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine 2022;11(2) (no pagination).	Irrelevant study design, no human participants or in non-English language
336	Wang S, Mao Y. Progress in neoadjuvant immunotherapies for resectable non-small cell lung cancer. [Chinese]. Chinese Journal of Lung Cancer 2020;23(5):371-380.	Irrelevant study design, no human participants or in non-English language
337	Wang S, Meng C, Jiang Z, et al. Self-made thoracic needled suspending device with a snare: an excellent aid for uniportal video-assisted thoracic lobectomy and segmentectomy for lung cancer. Oncology letters 2019;17:3671-3676.	Irrelevant study design, no human participants or in non-English language
338	Wang S, Wang C, Zhang J, et al. 40P Evolutionary trajectories and clonal migration underlying tumor progression and lymph node metastasis in resectable lung cancer. Annals of Oncology 2021;32(Supplement 5):S373.	Irrelevant intervention
339	Wang W, Kong F, Hu C, et al. MA13.01 A Validation Study on DNA Repair Gene Variant for Lung Cancer Survival Prediction after Chemoradiation: a Secondary Analysis for RTOG-0617 Study. Journal of thoracic oncology 2021;16:S181-.	Irrelevant study design, no human participants or in non-English language
340	Wang W, Wu L, Lu S, et al. A randomized double-blind placebo-controlled phase iii study evaluating perioperative toripalimab combined with platinum-based doublet chemotherapy in	No relevant outcomes reported

	resectable stage iii NSCLC. Journal for ImmunoTherapy of Cancer 2020;8(SUPPL 3):A223-A224.	
341	Wang Z, Qi Z, Cheng D, et al. Lobe-Specific Node Dissection Can Be a Suitable Alternative to Systematic Lymph Node Dissection in Highly Selective Early-Stage Non-Small-Cell Lung Cancer Patients: A Meta-Analysis. Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia 2021;27(3):143-150.	Irrelevant study design, no human participants or in non-English language
342	Wang Z, Zhu XX, Song Y. Phase II clinical study of toripalimab in combination with stereotactic radiotherapy as a neoadjuvant therapy for the treatment of resectable (N1-N2) non-small cell lung cancer. Journal for ImmunoTherapy of Cancer 2021;9(SUPPL 2):A496.	No relevant outcomes reported
343	Watanabe Y, Iwa T. Clinical value of immunotherapy with the streptococcal preparation OK-432 in non-small cell lung cancer. Journal of Biological Response Modifiers 1987;6:169-80.	Irrelevant intervention
344	Watanabe Y, Shimizu J, Yoshida Y, et al. [Immunotherapy for lung cancer by streptococcal preparation OK-432]. Nippon Geka Gakkai Zasshi. Journal of Japan Surgical Society 1989;90:1432-5.	Irrelevant intervention
345	Watanabe Y, Yamada T, Ichihashi T, et al. [Surgery and adjuvant therapy of non-small cell lung cancer]. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 1986;13:1534-46.	Irrelevant intervention
346	Weiden PL, Piantadosi S. Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small cell lung cancer: A phase 2 study of the LCSG. Chest 1994;106(6 SUPPL.):344S-347S.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
347	Weiden PL, Piantadosi S. Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small-cell lung cancer: a phase II study of the Lung Cancer Study Group. Journal of the National Cancer Institute 1991;83(4):266-273.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
348	Wen SW, Han L, Lv HL, et al. A Propensity-Matched Analysis of Outcomes of Patients with Clinical Stage I Non-Small Cell Lung Cancer Treated surgically or with stereotactic radiotherapy: A Meta-Analysis. Journal of Investigative Surgery 2019;32(1):27-34.	Irrelevant study design, no human participants or in non-English language
349	Whitson BA, Groth SS, Duval SJ, et al. Surgery for Early-Stage Non-Small Cell Lung Cancer: A Systematic Review of the Video-Assisted Thoracoscopic Surgery Versus Thoracotomy Approaches to Lobectomy. Annals of Thoracic Surgery 2008;86(6):2008-2018.	Irrelevant study design, no human participants or in non-English language

350	Widesott L, Amichetti M, Schwarz M. Proton therapy in lung cancer: Clinical outcomes and technical issues. A systematic review. Radiotherapy and Oncology 2008;86(2):154-164.	Irrelevant study design, no human participants or in non-English language
351	Wink KCJ, van Baardwijk A, Troost EGC, et al. Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors. Cancer Treatment Reviews 2017;56:8-15.	Irrelevant study design, no human participants or in non-English language
352	Witlox WJA, Ramaekers BLT, Zindler JD, et al. The Prevention of Brain Metastases in Non-Small Cell Lung Cancer by Prophylactic Cranial Irradiation. Frontiers in Oncology 2018;8:241.	Irrelevant study design, no human participants or in non-English language
353	Wright G, Manser RL, Byrnes G, et al. Surgery for non-small cell lung cancer: Systematic review and meta-analysis of randomised controlled trials. Thorax 2006;61(7):597-603.	Irrelevant study design, no human participants or in non-English language
354	Wu KL, Jiang GL, Liao Y, et al. Three-dimensional conformal radiation therapy for non-small-cell lung cancer: A Phase I/II dose escalation clinical trial. International Journal of Radiation Oncology Biology Physics 2003;57(5):1336-1344.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
355	Wu Q, Gao W, Zhu J, et al. Efficacy of stereotactic body radiotherapy versus surgery for the treatment of early non-small cell lung cancer: A meta-analysis. [Chinese]. Chinese Journal of Lung Cancer 2020;23(12):1066-1072.	Irrelevant study design, no human participants or in non-English language
356	Wu YL, Chen K, Xing W, et al. 84P SHR-1316 vs placebo in combination with chemotherapy as perioperative treatment in patients with resectable stage II-III NSCLC: a randomized, double-blind, multicenter, phase Ib/III trial. Annals of oncology 2022;33:S72-.	Irrelevant intervention
357	Wurstbauer K, Deutschmann H, Dagn K, et al. DART-bid (Dose-differentiated accelerated radiation therapy, 1.8 Gy twice daily)-a novel approach for non-resected NSCLC: Final results of a prospective study, correlating radiation dose to tumor volume. Radiation Oncology 2013;8(1) (no pagination).	Irrelevant intervention
358	Xiong L, Lou Y, Bai H, et al. Efficacy of erlotinib as neoadjuvant regimen in EGFR-mutant locally advanced non-small cell lung cancer patients. Journal of International Medical Research 2019;48.	Irrelevant study design, no human participants or in non-English language
359	Xu G, Rong T, Lin P. Adjuvant chemotherapy following radical surgery for non-small-cell lung cancer: A randomized study on 70 patients. Chinese Medical Journal 2000;113(7):617-620.	Irrelevant intervention

360	Xu XL, Dan L, Chen W, et al. Neoadjuvant chemoradiotherapy or chemotherapy followed by surgery is superior to that followed by definitive chemoradiation or radiotherapy in stage IIIA (N2) nonsmall-cell lung cancer: A meta-analysis and system review. OncoTargets and Therapy 2016;9:845-853.	Irrelevant study design, no human participants or in non-English language
361	Xu YP, Li B, Xu XL, et al. Is There a Survival Benefit in Patients with Stage IIIA (N2) Non-small Cell Lung Cancer Receiving Neoadjuvant Chemotherapy and/or Radiotherapy Prior to Surgical Resection: A Systematic Review and Meta-analysis. Medicine (United States) 2015;94(23):e879.	Irrelevant study design, no human participants or in non-English language
362	Xue C, Dong H, Chen Y, et al. Neoadjuvant Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer. Journal of the College of Physicians and Surgeons Pakistan 2022;32(6):779-788.	Irrelevant study design, no human participants or in non-English language
363	Xue W, Duan G, Zhang X, et al. Meta-analysis of segmentectomy versus wedge resection in stage IA non-small-cell lung cancer. OncoTargets and therapy 2018;11:3369-3375.	Irrelevant study design, no human participants or in non-English language
364	Yan TD, Black D, Bannon PG, et al. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. Journal of Clinical Oncology 2009;27(15):2553-2562.	Irrelevant study design, no human participants or in non-English language
365	Yang CH, Tsai CM, Wang LS, et al. Gemcitabine and cisplatin in a multimodality treatment for locally advanced non-small cell lung cancer. British Journal of Cancer 2002;86(2):190-195.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
366	Yang DM, Palma DA, Kwan K, et al. Predicting pathological complete response (pCR) after stereotactic ablative radiation therapy (SABR) of lung cancer using quantitative dynamic [¹⁸F]FDG PET and CT perfusion: a prospective exploratory clinical study. Radiation Oncology 2021;16(1) (no pagination).	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
367	Yang F, Sui X, Chen X, et al. Sublobar resection versus lobectomy in Surgical Treatment of Elderly Patients with early-stage non-small cell lung cancer (STEPS): Study protocol for a randomized controlled trial. Trials 2016;17(1) (no pagination).	No relevant outcomes reported
368	Yang KL, Chang YC, Ko HL, et al. Optimizing Survival of Patients With Marginally Operable Stage IIIA Non-Small-Cell Lung Cancer Receiving Chemoradiotherapy With or Without Surgery. Clinical Lung Cancer 2016;17:550-557.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC

369	Yang W, An Y, Li Q, et al. Co-ablation versus cryoablation for the treatment of stage III–IV non-small cell lung cancer: a prospective, noninferiority, randomized, controlled trial (RCT). Thoracic cancer 2021;12:475-483.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
370	Yi JS, Ready N, Healy P, et al. Immune activation in early-stage non-small cell lung cancer patients receiving neoadjuvant chemotherapy plus ipilimumab. Clinical Cancer Research 2017;23(24):7474-7482.	No relevant outcomes reported
371	Yoshino I, Yamaguchi M, Yamazaki K, et al. Surgical outcome of an anatomical resection of clinical stage IA non-small cell lung cancer assisted with a video-thoracoscopy. Surgery Today 2010;40(8):719-724.	Irrelevant study design, no human participants or in non-English language
372	Yoshioka H, Shimokawa M, Seto T, et al. Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer. Annals of oncology : official journal of the european society for medical oncology 2019;30:1978-1984.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
373	Yu Y, Lu S. Perioperative chemotherapy of stage III N2 non-small cell lung cancer. Chinese-German Journal of Clinical Oncology 2009;8(4):185-189.	Irrelevant study design, no human participants or in non-English language
374	Zeng H, Hendriks L, Witlox W, et al. Risk factors for cognitive impairment in NSCLC: Secondary findings of the NVALT-11 study. Radiotherapy and Oncology 2021;161(Supplement 1):S107-S108.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
375	Zhan P, Wang J, Lv XJ, et al. Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: A systematic review with meta-analysis. Journal of Thoracic Oncology 2009;4(9):1094-1103.	Irrelevant study design, no human participants or in non-English language
376	Zhang B, Zhu F, Ma X, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: A systematic review and meta-analysis. Radiotherapy and Oncology 2014;112(2):250-255.	Irrelevant study design, no human participants or in non-English language
377	Zhang C, Hong HZ, Fan JH, et al. Comparison between immunotherapy and chemotherapy as neoadjuvant setting in resectable non-small cell lung cancer: A systematic review and meta-analysis of prospective trials. Annals of Oncology 2020;31(Supplement 6):S1378-S1379.	Irrelevant study design, no human participants or in non-English language

378	Zhang H, Zhang DX, Ju T, et al. The effect of postoperative radiotherapy on the survival of patients with resectable stage III-N2 non-small-cell lung cancer: A systematic review and meta-analysis. Neoplasma 2019;66(5):717-726.	Irrelevant study design, no human participants or in non-English language
379	Zhang J, Mao T, Gu Z, et al. Comparison of complete and minimal mediastinal lymph node dissection for non-small cell lung cancer: Results of a prospective randomized trial. Thoracic Cancer 2013;4(4):416-421.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
380	Zhang L, Li M, Yin R, et al. Comparison of the oncologic outcomes of anatomic segmentectomy and lobectomy for early-stage non-small cell lung cancer. Annals of Thoracic Surgery 2015;99(2):728-737.	Irrelevant study design, no human participants or in non-English language
381	Zhang T, Guo Q, Zhang Y, et al. Meta-analysis of adjuvant chemotherapy versus surgery alone in T2aN0 stage IB non-small cell lung cancer. Journal of Cancer Research and Therapeutics 2018;14(1):139-144.	Irrelevant study design, no human participants or in non-English language
382	Zhang Z, Liu D, Feng H, et al. Is video-assisted thoracic surgery lobectomy better than thoracotomy for early-stage non-small-cell lung cancer? A systematic review and meta-analysis. European Journal of Cardio-Thoracic Surgery 2013;44:407-414.	Irrelevant study design, no human participants or in non-English language
383	Zhao JL, Nie YQ, Yang P, et al. Effect of selective lymph node dissection on immune function in patients with T1 stage non-small cell lung cancer: A randomized controlled trial. Translational Cancer Research 2021;10(6):2918-2931.	No relevant outcomes reported
384	Zhao X, Wen X, Wei W, et al. Predictors for the efficacy of Endostar combined with neoadjuvant chemotherapy for stage IIIA (N2) NSCLC. Cancer biomarkers 2017;21:169-177.	No relevant outcomes reported
385	Zhao Y, Wang W, Liang H, et al. The Optimal Treatment for Stage IIIA-N2 Non-Small Cell Lung Cancer: A Network Meta-Analysis. Annals of Thoracic Surgery 2019;107(6):1866-1875.	Irrelevant study design, no human participants or in non-English language
386	Zheng YZ, Zhai WY, Zhao J, et al. Oncologic outcomes of lobectomy vs. segmentectomy in non-small cell lung cancer with clinical T1N0M0 stage: A literature review and meta-analysis. Journal of Thoracic Disease 2020;12(6):3178-3187.	Irrelevant study design, no human participants or in non-English language
387	Zhong W, Yang X, Bai J, et al. Complete mediastinal lymphadenectomy: the core component of the multidisciplinary therapy in resectable non-small cell lung cancer. European Journal of Cardio-thoracic Surgery 2008;34(1):187-195.	Irrelevant study design, no human participants or in non-English language
388	Zhou H, Lin L, Qin T, et al. Neoadjuvant camrelizumab, nab-paclitaxel, and carboplatin in patients with stage IB-IIIA non-small cell lung cancer (NANE-LC): A study protocol of	No relevant outcomes reported

prospective, single-arm, multicenter, phase II study. Journal of Thoracic Disease 2021;13(11):6468-6475.

Table 88 Excluded references from the updated SLR, 30th October 2023

#	Reference	Reason for exclusion
1	Abogunrin S, Lorenzi M, Cadarette S, et al. Disease-Free Survival as a Potential Surrogate Endpoint for Overall Survival in Patients With Early-Stage Non-Small Cell Lung Cancer: A Systematic Literature Review and Meta-Analyses. Value in Health 2022;25(12 Supplement):S3-S4.	Irrelevant study design, no human participants or in non-English language
2	Aiman W, Ashar Ali M, Yar Khan N, et al. Survival Outcomes of Lobectomy Vs Sublobar Resection in Small-Sized Peripheral Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Rcts. Chest 2023;164(4 Supplement):A4215.	Irrelevant study design, no human participants or in non-English language
3	Barlesi F, Mercier O, Lowczak A, et al. 1290TiP A phase II multicenter, open label, non-randomized study of neoadjuvant and adjuvant treatment with IPH5201 and durvalumab in patients with resectable, early-stage (II to IIIA) non-small cell lung cancer (MATISSE). Annals of Oncology 2023;34(Supplement 2):S744.	No relevant outcomes
4	Cascone T, Garcia-Campelo R, Spicer J, et al. NeoCOAST: open-label, randomized, phase 2, multidrug platform study of neoadjuvant durvalumab alone or combined with novel agents in patients (pts) with resectable, early-stage non-small-cell lung cancer (NSCLC). Cancer research 2022;82.	Duplicate with the original SLR conference searches
5	Chen Y, Qin J, Wu Y, et al. Does major pathological response after neoadjuvant Immunotherapy in resectable nonsmall-cell lung cancers predict prognosis? A systematic review and meta-analysis. International Journal Of Surgery 2023;109:2794-2807.	Irrelevant study design, no human participants or in non-English language
6	ChiCtr. A Multi-center Prospective Clinical Trial Exploring Surgical Strategies For Peripheral Early-Stage Non-Small Cell Lung Cancer (NSCLC). https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2200062165 2022.	No relevant outcomes
7	ChiCtr. Comparison of Segmentectomy Versus Lobectomy for Early-Stage Non-Small Cell Lung Cancer <= 2 cm in the Middle 1/3 of Lung Field: a Prospective and Multi-Center RCT Study. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2100047249 2021.	No relevant outcomes
8	ChiCtr. Efficacy of neoadjuvant hypofractionated radiotherapy versus chemotherapy combined with Camrelizumab in stage III non-small cell lung cancer: a prospective, regional, multi-center, Phase II clinical trial.	No relevant outcomes

	https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2200061624 2022.	
9	ChiCtr. Efficacy of neoadjuvant versus adjuvant immunotherapy in Stage II-IIIA resectable non-small cell lung cancer. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2200067160 2022.	No relevant outcomes
10	ChiCtr. Phase II Clinical Trial of Adjuvant Anlotinib in Patients with Stage IA Non-Small Cell Lung Cancer at High Risk of Recurrence. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000037398 2020.	Irrelevant intervention
11	ChiCtr. To evaluate the efficacy and safety of endoscopic surgical system assisted thoracoscopic radical resection of lung cancer in clinical trials. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2300069475 2023.	No relevant outcomes
12	Dacoregio MI, Castro CEDR, Michelon IF, et al. 1288P Neoadjuvant therapy with anti-PD-1/PD-L1 plus platinum-base chemotherapy for resectable stage II-III non-small cell lung cancer: A systematic review and meta-analysis of randomized clinical trials. Annals of Oncology 2023;34(Supplement 2):S743.	Irrelevant study design, no human participants or in non-English language
13	Evison M, Maconachie R, Mercer T, et al. What is the optimal management of potentially resectable stage III-N2 NSCLC? Results of a fixed-effects network meta-analysis and economic modelling. Erj Open Research 2023;9.	Irrelevant study design, no human participants or in non-English language
14	Felip E, Wang C, Ciuleanu TE, et al. 932MO Nivolumab (NIVO) plus platinum-doublet chemotherapy (chemo) versus chemo as neoadjuvant treatment for resectable non-small cell lung cancer (NSCLC): health-related quality of life (HRQoL) outcomes from CheckMate 816. Annals of oncology 2022;33:S973-S974.	Duplicate with the original SLR conference searches
15	Fong KY, Chan YH, Chia CML, et al. Sublobar resection versus lobectomy for stage IA non-small-cell lung cancer <= 2 cm: a systematic review and patient-level meta-analysis. Updates in Surgery 2023;10:10.	Irrelevant study design, no human participants or in non-English language
16	Girard N, Spicer J, Provencio M, et al. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer (NSCLC): event-free survival (EFS) results from the phase 3 CheckMate 816 trial. Cancer research 2022;82.	Duplicate with the original SLR conference searches
17	Han B, Fang V, Yao F, et al. 948TiP Efficacy and safety of almonertinib in the adjuvant treatment of resectable stage I non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-sensitizing mutations in solid and/or micropapillary components. Annals of Oncology 2022;33(Supplement 7):S981.	No relevant outcomes

18	Heymach JV, Mitsudomi T, Harpole D, et al. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: the AEGEAN Trial. Clinical lung cancer 2022;23:e247-e251.	No relevant outcomes
19	Huang W, Deng HY, Ren ZZ, et al. LobE-Specific lymph node diSsectiON for clinical early-stage non-small cell lung cancer: protocol for a randomised controlled trial (the LESSON trial). BMJ Open 2022;12:e056043.	No relevant outcomes
20	jRCT J. AEGEAN. https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-jRCT2080224587 2019.	No relevant outcomes
21	Leonetti A, Minari R, Boni L, et al. EP02.04-001 Alectinib as Neoadjuvant Treatment in Surgically Resectable Stage III ALK-Positive NSCLC: ALNEO Phase II Trial (GOIRC-01-2020). Journal of Thoracic Oncology 2022;17(9 Supplement):S231.	No relevant outcomes
22	Li H, Wang Y, Chen Y, et al. Ground glass opacity resection extent assessment trial (GREAT): A study protocol of multi-institutional, prospective, open-label, randomized phase III trial of minimally invasive segmentectomy versus lobectomy for ground glass opacity (GGO)-containing early-stage invasive lung adenocarcinoma. Frontiers in Oncology 2023;13 (no pagination).	No relevant outcomes
23	Liang W, Xu E, Zhao J, et al. EP05.02-009 Aumolertinib Versus Erlotinib/Chemotherapy for Neoadjuvant Treatment of Stage IIIA EGFR-mutant NSCLC (ANSWER). Journal of Thoracic Oncology 2022;17(9 Supplement):S285-S286.	No relevant outcomes
24	Lu FL, Lv C, Zhuo ML, et al. EP05.02-008 Phase II Trial of Neoadjuvant Icotinib Plus Chemotherapy for Stage II-IIIB EGFR-mutant Non-small-Cell Lung Cancer. Journal of Thoracic Oncology 2022;17(9 Supplement):S285.	Irrelevant intervention
25	Marinelli D, Gallina FT, Pannunzio S, et al. Surgical and survival outcomes with perioperative or neoadjuvant immune-checkpoint inhibitors combined with platinum-based chemotherapy in resectable NSCLC: a systematic review and meta-analysis of randomised clinical trials. Critical Reviews in Oncology-Hematology 2023:104190.	Irrelevant study design, no human participants or in non-English language
26	Meldola PF, Toth OAS, Schnorrenberger E, et al. Sublobar resection versus lobectomy for stage IA non-small-cell lung cancer: A systematic review and meta-analysis of randomized controlled trials. Surgical Oncology 2023;51 (no pagination).	Irrelevant study design, no human participants or in non-English language
27	Nct. Comparison of Segmentectomy and Lobectomy in Small (2 cm or Less 0.5<CTR<1) Non-small Cell Lung Cancer: a Prospective,	No relevant outcomes

	Multicenter Randomized Controlled Study. https://clinicaltrials.gov/ct2/show/NCT06028412 2023.	
28	Nct. Neoadjuvant KRAS G12C Directed Therapy With Adagrasib (MRTX849) With or Without Nivolumab. https://clinicaltrials.gov/show/NCT05472623 2022.	No relevant outcomes
29	Nct. Neoadjuvant Therapy With Toripalimab and JS004 Combined With Platinum-based Doublet Chemotherapy for Resectable or Potentially Resectable Stage III Non-small Cell Lung Cancer: a Randomised Controlled, Open-label, Phase 2 Trial. https://clinicaltrials.gov/show/NCT05891080 2023.	No relevant outcomes
30	Nct. The Effect of Toripalimab Plus Radiotherapy in Patients With Operable Stage II-IIIA (N+) Non Small Cell Lung Cancer. https://clinicaltrials.gov/show/NCT05798845 2023.	No relevant outcomes
31	Ostoros G, Hettle R, Georgoulia N, et al. Association between event-free survival and overall survival after neoadjuvant treatment for non-small cell lung cancer: a systematic review and meta-analysis. Expert Review of Anticancer Therapy 2023:1-9.	Irrelevant study design, no human participants or in non-English language
32	Pass H, Kim AW, Felip E, et al. 970TiP SKYSCRAPER-05: Phase II study of neoadjuvant atezolizumab (Atezo) + tiragolumab (Tira) with or without platinum-based chemotherapy (CT) in patients (Pts) with locally advanced resectable stage II-IIIB NSCLC. Annals of Oncology 2022;33(Supplement 7):S990-S991.	No relevant outcomes
33	Provencio M, Serna R, Nadal E, et al. PL03.12 Progression Free Survival and Overall Survival in NADIM II Study. Journal of thoracic oncology 2022;17:S2-S3.	Duplicate with the original SLR conference searches
34	Provencio-Pulla M, Nadal E, Larriba JLG, et al. Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial. Journal of clinical oncology 2022;40.	Duplicate with the original SLR conference searches
35	Qiu F, Fan J, Shao M, et al. Two cycles versus three cycles of neoadjuvant sintilimab plus platinum-doublet chemotherapy in patients with resectable non-small-cell lung cancer (neoSCORE): a randomized, single center, two-arm phase II trial. Journal of clinical oncology 2022;40.	Duplicate with the original SLR conference searches
36	Rajaram R, Sholl LM, Dacic S, et al. LIBRETTO-001 cohort 7: A single-arm, phase 2 study of neoadjuvant selpercatinib in patients with resectable stage IB-IIIA RET fusion-positive NSCLC. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2022;40.	No relevant outcomes
37	Schuler MHH, Cuppens K, Ploenes T, et al. LBA37 A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small cell	Duplicate with the original SLR conference searches

	lung cancer (NEOpredict-Lung). Annals of oncology 2022;33:S1404.	
38	Scott SC, Hu C, Smith K, et al. EP02.04-007 Phase 2 Trial of Neoadjuvant KRASG12C Directed Therapy with Adagrasib (MRTX849) With or Without Nivolumab in Resectable NSCLC (Neo-KAN). Journal of Thoracic Oncology 2022;17(9 Supplement):S235.	No relevant outcomes
39	Sobottka-Brillout AB, Tochtermann G, Trueb M, et al. Oncology Research and Treatment 2022;45(Supplement 2):58-59.	No relevant outcomes
40	Spicer J, Cascone T, Kar G, et al. 929MO Platform study of neoadjuvant durvalumab (D) alone or combined with novel agents in patients (pts) with resectable, early-stage non-small cell lung cancer (NSCLC): pharmacodynamic correlates and circulating tumor DNA (ctDNA) dynamics in the NeoCOAST study. Annals of oncology 2022;33:S971.	No relevant outcomes
41	Syaj S, Akhdar M, Ababneh O, et al. EP02.04-008 Efficacy and Safety of Neoadjuvant Chemoimmunotherapy in Resectable Non-small Cell Lung Cancer (NSCLC): a systematic review and meta-analysis. Journal of Thoracic Oncology 2022;17(9 Supplement):S235-S236.	Irrelevant study design, no human participants or in non-English language
42	Syaj S, Akhdar M, Ababneh OE, et al. Pathological response to neoadjuvant chemoimmunotherapy in resectable non-small cell lung cancer (NSCLC): A systematic review and meta-analysis. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO 2022;40.	Irrelevant study design, no human participants or in non-English language
43	Takada K, Takamori S, Brunetti L, et al. Impact of Neoadjuvant Immune Checkpoint Inhibitors on Surgery and Perioperative Complications in Patients With Non-small-cell Lung Cancer: A Systematic Review. Clinical Lung Cancer 2023;03:03.	Irrelevant study design, no human participants or in non-English language
44	Taylor S, Tsim S, Navani N, et al. Impact on quality of life from multi-modality treatment for lung cancer: a randomised controlled feasibility trial of surgery versus no surgery as part of multi-modality treatment in potentially resectable stage III-N2 NSCLC (the PIONEER trial). Lung Cancer 2022;165(Supplement 1):S69.	No relevant outcomes
45	Tian S, Kozono DE, Ohri N, et al. NAUTIKA1: A Multicenter Phase II Study with a PD-L1+ Cohort of Patients Receiving Atezolizumab (Atezo) with Low-Dose Stereotactic Body Radiation Therapy (SBRT) as Neoadjuvant Therapy for Resectable Stage IB-III NSCLC. International Journal of Radiation Oncology Biology Physics 2022;114(3 Supplement):e392-e393.	No relevant outcomes
46	Wang Y, Li C, Wang Z, et al. Comparison between immunotherapy efficacy in early non-small cell lung cancer and advanced non-small cell lung cancer: a systematic review. BMC Medicine 2022;20:426.	Irrelevant study design, no human participants or in non-English language

47	Wang Y, Zhai H, Wang J, et al. Study protocol of an open-label prospective phase II umbrella study of precise neoadjuvant therapy for patients with stage II-IIIB resectable non-small cell lung cancer (PURPOSE). Frontiers in Oncology 2022;12:1052774.	No relevant outcomes
48	Xu L, Shi M, Wang S, et al. Immunotherapy for bilateral multiple ground glass opacities: An exploratory study for synchronous multiple primary lung cancer. Frontiers in Immunology 2022;13 (no pagination).	Irrelevant intervention
49	Zaraca F, Kirschbaum A, Pipitone MD, et al. Prospective randomized study on the efficacy of three-dimensional reconstructions of bronchovascular structures on preoperative chest CT scan in patients who are candidates for pulmonary segmentectomy surgery: the PATCHES (Prospective rAndomized sTudy efficaCy of tHree-dimensional rEconstructions Segmentecomy) study protocol. Trials [Electronic Resource] 2023;24:594.	No relevant outcomes
50	Zeng H, Hendriks LEL, Witlox WJA, et al. Risk factors for cognitive impairment in radically treated stage III NSCLC: Secondary findings of the NVALT-11 study. Radiotherapy & Oncology 2023;183:109627.	Patients without stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC
51	Zhang W, Chen S, Lin X, et al. Lobectomy versus segmentectomy for stage IA3 (T1cN0M0) non-small cell lung cancer: a meta-analysis and systematic review. Frontiers in Oncology 2023;13 (no pagination).	Irrelevant study design, no human participants or in non-English language

Table 89 Excluded references from the updated search, 25 April 2025

#	Reference	Reason for exclusion
1	Awad MM, Forde PM, Girard N, Spicer J, Wang C, Lu S, et al. Neoadjuvant Nivolumab Plus Ipilimumab Versus Chemotherapy in Resectable Lung Cancer, J Clin Oncol 2025 Vol. 43 Issue 12 Pages 1453-1462	Irrelevant comparator
2	Lu S, Zhang W, Wu L, Wang W, Zhang P, Fang W, et al. Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non-Small Cell Lung Cancer: The Neotorch Randomized Clinical Trial, Jama 2024 Vol. 331 Issue 3 Pages 201-211	Irrelevant comparator
3	Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised,	Irrelevant comparator

	double-blind, placebo-controlled, phase 3 trial, Lancet 2024 Vol. 404 Issue 10459 Pages 1240-1252	
4	Sun C, Wang X, Xu Y, Shao G, Chen X, Liu Y, et al. Efficiency and safety of neoadjuvant PD-1 inhibitor (sintilimab) combined with chemotherapy in potentially resectable stage IIIA/IIIB non-small cell lung cancer: Neo-Pre-IC, a single-arm phase 2 trial, EClinicalMedicine 2024 Vol. 68 Pages 102422	Irrelevant comparator
5	Yu X, Huang C, Du L, Wang C, Yang Y, Yu X, et al. Efficacy and safety of perioperative sintilimab plus platinum-based chemotherapy for potentially resectable stage IIIB non-small cell lung cancer (periSCOPE): an open-label, single-arm, phase II trial, EClinicalMedicine 2025 Vol. 79 Pages 102997	Irrelevant comparator
6	Yue D, Wang W, Liu H, Chen Q, Chen C, Liu L, et al. Perioperative tislelizumab plus neoadjuvant chemotherapy for patients with resectable non-small-cell lung cancer (RATIONALE-315): an interim analysis of a randomised clinical trial, Lancet Respir Med 2025 Vol. 13 Issue 2 Pages 119-129	Irrelevant comparator
7	Zhou B, Zhang F, Guo W, Wang S, Li N, Qiu B, et al. Five-year follow-up of neoadjuvant PD-1 inhibitor (sintilimab) in non-small cell lung cancer, J Immunother Cancer 2024 Vol. 12 Issue 8	Irrelevant comparator

H.1.4 Quality assessment

The quality of all included RCTs was assessed using the quality assessment tool developed by the University of York's CRD [105]. The quality assessment was completed by one individual and verified by a second independent reviewer.

The quality of non-RCTs and observational studies was to be assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [106]. While non-RCTs were included in the abstract and full-text stage of the review, these were deprioritised moving into the data extraction phase.

As such, quality assessments were not performed for non-RCTs.

H.1.5 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A

Table 90 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A
	N/A	N/A	N/A
	N/A	N/A	N/A

Abbreviations:

Table 91 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A			
N/A			

Table 92 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

I.1.1 Search strategies

N/A

Table 93 Search strategy for [name of database]

No.	Query	Results
N/A		N/A

No.	Query	Results

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A

J.1.1 Example: Systematic search for [...]

N/A

Table 94 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

N/A

Table 95 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A			

Abbreviations:

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