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# Perioperative immunotherapy strategies for resectable non-small cell lung cancer (Protocol)

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[Intervention Protocol]

# Perioperative immunotherapy strategies for resectable non-small cell lung cancer

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

1. To compare, via a network meta-analysis, the effectiveness and safety of different immunotherapy agents that are administered in a perioperative setting to people with resectable non small-cell lung cancer
2. To perform indirect comparisons in order to generate a clinically meaningful hierarchy of perioperative strategies of immunotherapy administration for overall survival in operable people with resectable non small-cell lung cancer

# BACKGROUND

## Description of the condition

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for 18% of total cancer deaths in 2020. Smoking is the number one risk factor for lung cancer; it is responsible for 80% to 85% of lung cancer cases worldwide (GLOBOCAN 2020; Hung 2020). Moreover, smoking is an important factor associated with a poorer response to NSCLC treatment (Li 2020). Other environmental or occupational factors are recognized as carcinogenic to the lungs, for example, asbestos, diesel engine exhaust, radon, polycyclic aromatic hydrocarbons, certain ionizing radiation, silica, and cadmium (Leiter 2023). Lung cancer is predominantly a disease of older adults. In most cytotoxic chemotherapy studies, advanced age alone does not predict a lack of therapeutic benefit, but it predicts a higher risk of toxicities (Veluswamy 2016).

Lung cancers represent a group of heterogeneous entities both in terms of histology and molecular profile (Herbst 2008). Histologically, they are categorized into two types: non-small cell lung cancer (NSCLC) and small cell lung carcinoma (SCLC). NSCLCs are typically subdivided into adenocarcinoma, squamous cell carcinoma (SqCC), and large-cell carcinoma. Non-small cell lung cancer is the most common type of lung cancer, accounting for 80 to 85% of all lung cancers (Herbst 2008). Both NSCLC and SCLC have very low survival rates.

The tumor-node-metastasis (TNM) classification describes the anatomic extent of a cancer. TNM classification has three components: the features/extent of the primary tumor (T), regional lymph node(s) involvement (N), and distant metastases (M). The classification of these three categories makes it possible to define four stages. Outcomes differ according to the stage at diagnosis, with a 24-month survival rate of 87% to 97% for stage I NSCLC and of 10 to 23% for stage IV. Stage I to IIIA NSCLC (classified as 'early stages' in the TNM classification, eighth edition (Goldstraw 2016)) account for 40% to 45% of all cases of lung cancer (Goldstraw 2016). This number is likely to grow with the increased use of low-dose computed tomography screening, leading to increased identification of early-stage NSCLC. As the TNM classification has evolved over years, we will mention the version used for each of the studies reported in this review.

Prognosis and therapeutic options are also guided by the general condition of the person as defined by the ECOG (Eastern Cooperative Oncology Group) Performance Status Scale (Oken 1982).

The treatment cornerstone for early-stage lung cancer is surgery, with or without perioperative (i.e. around the time of surgery) chemotherapy (Ettinger 2022). Chemotherapy in the perioperative setting is recommended when there is a lymph node involvement or tumors are larger than 4 cm, or both (Ettinger 2022). People diagnosed at metastatic stages of NSCLC (stage IV in the TNM classification, eighth edition (Goldstraw 2016)) are not eligible for surgery. For NSCLC at stages I to III, a Multidisciplinary Tumor Board (MTB) assessment of resectability needs to be performed prior to initiating surgical treatment. The definition of resectability is based on the assessment of whether an R0 (complete surgical resection using IASLC criteria) can be achieved (Detterbeck 2024). For stages I to II, the resectability criteria are agreed upon by the MTB. For stages III (TNM classification, ninth edition (Detterbeck 2024)), resectability criteria are more detailed and are discussed because the treatment of stage III N2 NSCLC (TNM classification, ninth edition (Detterbeck 2024)) is multimodal. The description of a single station (N2a) and the infiltration of many stations (N2b) were added as new sub-descriptors of the N2 status (Huang 2024).

Outcomes have improved in recent years, which might be linked to better participant selection, preoperative and postoperative optimization, as well as enhanced surgical methods that promote quicker and more effective recovery. Some people have also benefited from the development of new perioperative treatments, such as immunotherapy.

## History of therapies in the perioperative setting

Perioperative chemotherapy is intended to lower mortality by decreasing the likelihood of recurrence of the cancer. For decades, people with resectable stage II to III disease (TNM classification, eighth edition, Goldstraw 2016) were treated with platinum-based chemotherapy administrated after surgery (adjuvant). However, the benefits for survival were rather limited, with an approximate 5% increase in overall survival (OS) (Lim 2009; Pignon 2008). Attempts to enhance outcomes by adding antiangiogenic drugs (e.g. bevacizumab) or adjuvant postoperative radiation therapy did not increase the likelihood of survival (Le Pechoux 2022; Wakelee 2017).

In recent years, first-line immunotherapy and chemoimmunotherapy have transformed the therapeutic landscape, improving the prognosis of patients with lung cancer (Capella 2024). Programmed cell death 1 (PD1)/programmed cell death ligand 1 (PD-L1) is often used by tumors to evade the immune system, rendering it ineffective in eliminating tumor cells that often express the PD-L1 ligand on their surface. PD-1/PD-L1 blockade immunotherapy is an immune checkpoint inhibitor (ICI) that allows the immune system to recognize cancer cells again and thus destroy them. PD-1/PD-L1 blockade immunotherapy has achieved robust clinical responses in people with advanced NSCLC and has recently been included in neoadjuvant (preoperative), adjuvant (postoperative), and perioperative (preoperative and postoperative) regimens, based on studies that show improvements in event-free survival (EFS) and disease-free survival (DFS), respectively, for early-stage resectable NSCLC without a driver mutation (Aredo 2024; Banna 2024; Desai 2023; Dunne 2024). Currently, it is established that PD-1/PD-L1 blockade immunotherapy is less effective in people who have lung cancer with EGFR mutation or ALK rearrangement (actionable oncogene drivers) that can be treated with targeted therapy (Ng 2019). Immunotherapy is prescribed for six months to one year in studies, if it maintains its efficacy and is well tolerated (Aredo 2024).

## Clinical endpoints in the perioperative setting

The clinical endpoints commonly used for the evaluation of perioperative strategies are:

- event-free survival (EFS), defined as the time after primary treatment for a cancer ends that the patient remains free of certain complications or events that the treatment was intended to prevent or delay;

- disease-free survival (DFS), corresponding to the time of occurrence of disease-free state or attainment of a complete remission to disease recurrence or death; and
- overall survival, defined as the time from randomization into a study until death from any cause.

Because of the time required for these endpoints, surrogate endpoints such as pathologic response were developed, for example, major pathologic response (MPR; defined as ≤ 10% residual viable tumor cells on the surgically removed specimen) and complete pathologic response (pCR; defined as the absence of viable tumor cells on the surgically removed specimen).

### Contribution of immune checkpoint inhibitors (ICIs) in the perioperative setting

In individuals presenting positive protein PD-L1 in tumor cells, stage II to IIIA NSCLC (according to the 7th version of the TNM classification (Edge 2010)), IMpower010 was the first phase III trial to show a DFS benefit with immunotherapy after full surgical resection, adjuvant platinum-doublet chemotherapy (cisplatin + either vinorelbine, docetaxel or gemcitabine and pemetrexed for non-squamous NSCLC), and then up to a year with adjuvant atezolizumab (Felip 2021), leading the US Food & Drug Administration (FDA) to authorize atezolizumab for use in this group. A noteworthy finding of the trial was that, while participants with PD-L1-positive stage II-IIIA showed a benefit for DFS (stratified hazard ratio (HR) 0.66, 95% CI 0.50 to 0.88), according to a post hoc analysis, most of the advantage was driven by those with tumor PD-L1 expression ≥ 50%. For people with PD-L1 1% to 49%, the hazard ratio was 0.87, and for ≥ 50%, it was 0.43. Atezolizumab has only been approved by the European Commission for people with PD-L1 ≥ 50% due to the lack of evidence of benefit for PD-L1 of 1% to 49%.

The KEYNOTE-091 (PEARLS) trial, which has FDA approval regardless of PD-L1 expression, similarly showed improvement in DFS for people with stage IB (≥ 4 cm) to IIIA NSCLC (according to the seventh version of the TNM classification (Edge 2010)) who received adjuvant pembrolizumab for up to a year. However, PD-L1 expression did not correlate with higher or lower efficacy in the KEYNOTE-091 study: the HR for DFS with PD-L1 > 50% was 0.82 (0.57 to 1.18) versus 0.76 (0.63 to 0.91) in the trial group as a whole (O'Brien 2022). None of the arms of that trial received treatment other than pembrolizumab or placebo, in contrast to the IMpower010 trial where best supportive care was provided in the comparator group.

For people with resectable stage IB to IIIA NSCLC (according to the seventh version of the TNM classification (Edge 2010)), the CheckMate-816 study showed an improvement in EFS with three cycles of nivolumab plus platinum-doublet chemotherapy (carboplatin + paclitacel, gemcitabine + cisplatin, or pemetrexed + cisplatin and adjuvant vinorelbine + cisplatin or docetaxel + cisplatin) in four cycles, when compared with chemotherapy alone in the neoadjuvant setting (Forde 2022). This combination has also been approved by the European Commission and the FDA. The HR for EFS in CheckMate-816 was 0.85 (0.54 to 1.32), 0.58 (0.30 to 1.12), and 0.24 (0.10 to 0.61) for participants with PD-L1 expression < 1%, 1% to 49%, and ≥ 50%, respectively. Improved EFS in the chemotherapy/nivolumab group was highly associated with the achievement of a pathologic complete response (pCR) (HR 0.13, versus no pCR).

In the perioperative setting, the AGEAN trial, which has FDA approval, was a phase III trial that evaluated the efficacy of durvalumab and platinum-doublet chemotherapy (carboplatin + paclitaxel, cisplatin + gemcitabine, carboplatin + gemcitabine or pemetrexed + either cisplatin or carboplatin) given in four cycles before surgery in comparison to placebo and platinum-doublet chemotherapy for individuals with resectable early-stage (IIIA-IIIB) NSCLC according to the eighth version of the TNM classification. The durvalumab-based regimen arm's median EFS was not attained after a follow-up of 11.7 months, while the chemotherapy-alone arm's median EFS was 25.9 months. Compared to individuals in the chemotherapy-alone arm, those in the durvalumab-based regimen arm exhibited a 32% lower chance of 'disease progression preventing decisive surgery', disease recurrence, or death (Heymach 2023; Wakelee 2023)

The phase 3 CheckMate 77T trial showed statistically significant improvement in EFS for neoadjuvant treatment with nivolumab plus chemotherapy (participants with squamous tumor histology received either cisplatin plus docetaxel or carboplatin plus paclitaxel, and people with nonsquamous tumor histology received either cisplatin plus pemetrexed, carboplatin plus pemetrexed, or carboplatin plus paclitaxel) followed by surgery and adjuvant nivolumab versus placebo plus chemotherapy, in people with previously untreated resectable stage II to IIIB non-small cell lung cancer (NSCLC) (Cascone 2024).

### How the intervention might work

Most people with advanced NSCLC will not be cured, so, to reduce mortality from NSCLC, it is important to effectively treat early-stage disease.

A clinical trial by Conroy 2023 suggests that the incorporation of neoadjuvant immunotherapy into treatment may lead to:

- tumor regression and long-lasting anti-tumor immune responses in people with resectable NSCLC;
- early eradication of micrometastases;
- a higher treatment initiation rate, as well as a higher rate of adherence to treatment;
- the possibility of surgical downstaging (defined as changing the TNM stage after neoadjuvant or induction treatment from a higher stage (indicating more extensive disease) to a lower stage (indicating less extensive disease));
- a potential decrease in the need for more extensive procedures (such as pneumonectomy or open thoracotomy);
- the ability to assess pathologic responses, which may serve as a predictor of survival and inform decisions about future immunotherapy treatment.

A review by Peng 2023 reported that adjuvant immunotherapy can "eliminate undetectable residual "micrometastatic" tumor cells that may exist in lymph nodes, blood vessels, or lymphatic vessels, delaying or reducing postoperative recurrence and metastasis, prolonging PFS and OS, and improving patient quality of life".

In research with mice to inform preclinical models of resectable NSCLC, neoadjuvant immunotherapy was shown to be superior to adjuvant immunotherapy for prolonging survival, reducing distal recurrence, and inducing anti-tumor immunity (Cascone 2018).

In other histological types of cancer, results show some benefit from a neoadjuvant strategy. For example, in a phase 2 randomized trial involving patients with resectable melanoma, event-free survival at two years was 23 percentage points higher among those who received neoadjuvant immunotherapy (pembrolizumab) followed by adjuvant pembrolizumab than among those who received adjuvant immunotherapy (pembrolizumab) alone (Patel 2023).

### Why it is important to do this review

There are currently several perioperative treatment strategies available that use immunotherapy: different immunotherapy agents, immunotherapy added to chemotherapy, different timings of administration (neoadjuvant, adjuvant). Therefore, in the absence of head-to-head RCTs comparing the different perioperative strategies, uncertainty remains as to the best option for operable people with resectable NSCLC.

Many questions remain unanswered about the use of immunotherapy in the perioperative setting.

- Which people could benefit most from immunotherapy? Evidence regarding the therapeutic benefit of immunotherapy as a perioperative treatment for early-stage NSCLC (stage I to II) is limited. Biomarkers, such as PD-1/PD-L1, T cell infiltration, tumor mutation burden (TMB), and others, are helpful for the selection of non-operable people who benefit most from immunotherapy (Herath 2022). However, studies examining immunotherapy as perioperative treatment usually do not use biomarkers for participant selection. The necessity of taking PD-1/PD-L1 expression into account when applying immunotherapy as perioperative treatment is debated. Some clinical characteristics, imaging data, liquid biopsies, and other alternative biomarkers may be able to predict the effectiveness of neoadjuvant immunotherapy, as is the case in the adjuvant setting. Another factor for consideration is age: a gap remains in knowledge of the effects of perioperative immunotherapy in the elderly. We know that perioperative chemotherapy is not effective above the age of 75 (Früh 2008), but is this also the case for immunotherapy?
- What is the optimal duration of perioperative immunotherapy? Various treatment durations have been proposed, but clinical studies have not compared them to establish which one is most effective.
- What is the best timing and sequence of immunotherapy when used with other systemic therapies? The timing of immunotherapy (adjuvant, neoadjuvant, or both prescriptions) has not been compared in clinical studies, making it impossible to recommend any strategy.

Stakeholders (patients, practitioners) need relevant, accessible, up-to-date, and reliable syntheses of high-quality evidence to inform their NSCLC treatment decisions. Many randomized controlled trials (RCTs) have been registered on the use of immunotherapy in the perioperative setting, and their results will be published gradually over the coming years. However, almost all of these trials are using placebo as a comparator, which may be because the pharmaceutical industry, which is the main sponsor of large RCTs, does not want to take the risk of a comparison that would not be in favor of their product and potentially block the approval process (Lathyris 2010). Clinical studies directly comparing one perioperative immunotherapy strategy versus another for the population of interest have not been conducted; hence, a network meta-analysis (a method for the synthesis of indirect evidence) would be useful to explore the evidence that is available.

## OBJECTIVES

1. To compare, via a network meta-analysis, the effectiveness and safety of different immunotherapy agents that are administered in a perioperative setting to people with resectable non small-cell lung cancer
2. To perform indirect comparisons in order to generate a clinically meaningful hierarchy of perioperative strategies of immunotherapy administration for overall survival in operable people with resectable non small-cell lung cancer

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include parallel-group randomized controlled trials (RCTs). We will exclude cross-over and cluster-randomized trials, as these study designs are not relevant for this topic.

#### Types of participants

People aged 18 years or older, with pathologically confirmed NSCLC (any histology) of stage I to IIIA according to the IASLC Lung Cancer Staging classification (eighth edition, Goldstraw 2016), with an indication for resection or operation. If participants younger than 18 years of age are involved in a study, we will only include the data related to the participants who are 18 years or older, when possible. Participants must not have any contraindication to immunotherapy or standard of care (chemotherapy). When possible, participants who have an NSCLC with an EGFR mutation or an ALK translocation will be excluded.

As changes in TNM classifications do not alter the inclusion criteria in studies of perioperative treatments, we assume that the participants in the included studies would be equally eligible to be randomized to any of the interventions listed below.

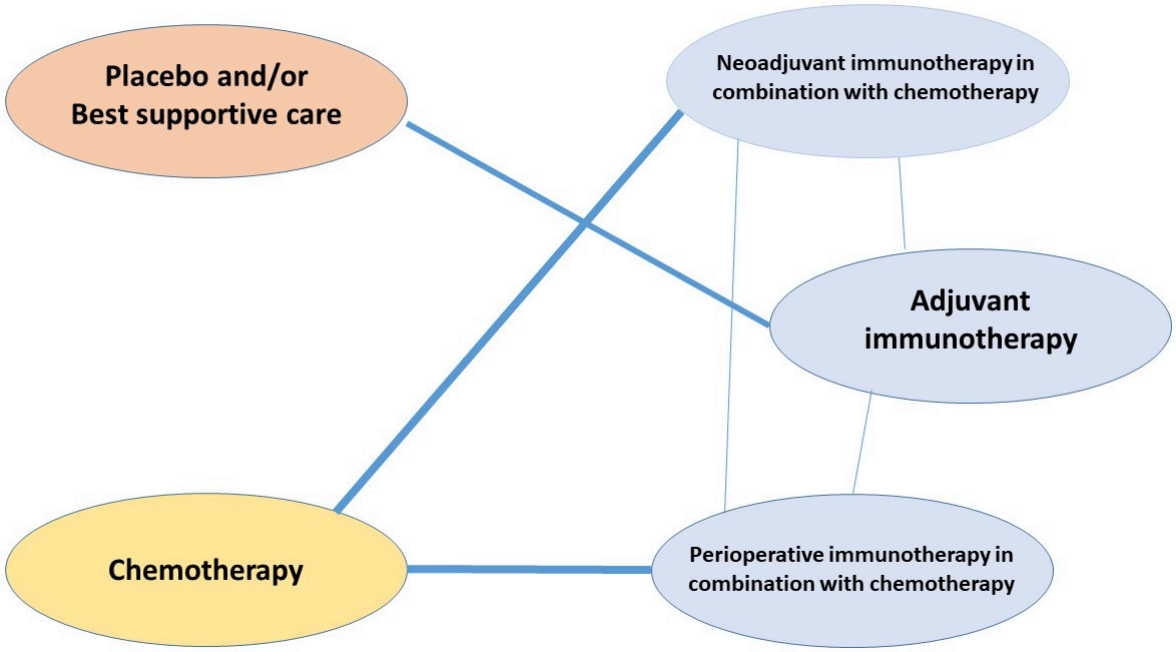
#### Types of interventions

We will include perioperative immunotherapy strategies (neoadjuvant, adjuvant, both (named as perioperative)), with or without chemotherapy (irrespective of the chemotherapy protocol).

Chemotherapy regimens are usually composed of doublet platine, such as docetaxel, etoposide, paclitaxel, pemetrexed, vinorelbine, whether neoadjuvant, adjuvant, or both, and with no limit on the number of cycles.

For immunotherapy, we will consider the following six comparisons (see the network graph in Figure 1). Interventions can be given at any dose and frequency and for any duration.

**Figure 1. Network graph**




1. Neoadjuvant immunotherapy in combination with chemotherapy versus chemotherapy alone
2. Adjuvant immunotherapy after chemotherapy versus chemotherapy plus placebo or best supportive care
3. Perioperative immunotherapy in combination with chemotherapy versus chemotherapy plus placebo or best supportive care
4. Neoadjuvant immunotherapy in combination with chemotherapy versus adjuvant immunotherapy
5. Neoadjuvant immunotherapy in combination with chemotherapy versus perioperative immunotherapy in combination with chemotherapy
6. Perioperative immunotherapy in combination with chemotherapy versus adjuvant immunotherapy

Currently, the most commonly used immunotherapy drugs are atezolizumab, cemiplimab, durvalumab, nivolumab, pembrolizumab, sintilimab, and other PD-1 and PD-L1 inhibitors.

We will exclude double immunotherapy interventions because these are not currently approved. To our knowledge, there is no RCT on the topic yet.

### Types of outcome measures

#### *Primary outcomes*

Overall survival (OS) from randomization or allocation to death or last follow-up, at 2 and 5 years

#### *Secondary outcomes*

- Disease-free survival (DFS) from randomization or allocation to the first sign or symptom of cancer or death, at 2 and 5 years
- Event-free survival (EFS) from randomization or allocation to an event that may include disease progression, discontinuation of the treatment for any reason, or death, at 2 and 5 years
- Pathologic response assessed on the surgical specimens, defined as major pathologic response (MPR; defined as ≤ 10% residual viable tumor cells on the surgically removed specimen) and complete pathologic response (pCR; defined as the absence of viable tumor cells on the surgically removed specimen)
- Harms, toxicity profile, assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (guidelines (CTCAE V4 2009)
- Health-related quality of life, evaluated with QLQ-C30 (Aaronson 1993) or QLQ-LC13 (Bergman 1994) at baseline and 3 months after surgery

## Search methods for identification of studies

We will perform a comprehensive search with no restrictions on language or publication status.

### Electronic searches

We will search the following electronic databases to identify all relevant published RCTs.

- MEDLINE (accessed via Pubmed)
- Embase via Elsevier
- Cochrane Central Register of Controlled Trials (CENTRAL)

We will search from 2018 onwards as the first trial of immunotherapy for lung cancer was published in 2018 (Forde 2018). We will perform the electronic searches according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2025). Our search strategy will

combine relevant medical subject headings (MeSH) and keywords. The search strategies for MEDLINE via PubMed, Embase, and CENTRAL were designed with the help of the Lung Cancer Group Information Specialist (FC); they are shown in Appendix 1.

We will also conduct searches in the following clinical trial registries to identify unpublished and ongoing trials.

- US National Institutes of Health Ongoing Trials Register - ClinicalTrials.gov (www.clinicaltrials.gov/)
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/)

#### Searching other resources

We will search the following key conference proceedings from 2023 onwards.

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- American Association for Cancer Research (AACR)
- World Conference on Lung Cancer (WCLC)

We will contact corresponding authors of ongoing studies as we identify them. We will ask them to alert us when study results are available or to share early or unpublished data with us.

We will manually search the reference lists of all newly included studies to check for any relevant studies we may have missed.

### Data collection and analysis

#### Selection of studies

Two review authors (CM, FC) will independently review titles and abstracts retrieved by the searches to determine which records should be assessed further; they will use Covidence to do this screening. The same two review authors will independently investigate all potentially relevant records as full-text articles, and will classify studies as included, excluded, awaiting classification, or ongoing, following the criteria for each provided in chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2025). We will resolve any discrepancies through consensus or by consulting a third review author (GE).

There may be multiple reports of a primary study, or companion documents. We will gather all publications relating to unique studies and compile all available data to maximize the yield of information. We will use the most complete data set aggregated across all publications. If in doubt, we will give priority to the publication reporting the longest follow-up of our primary or secondary outcomes.

#### Data extraction and management

We will develop a dedicated data extraction form using an Excel spreadsheet (Microsoft Excel), which we will pilot-test in advance. For studies that fulfill our inclusion criteria, two review authors (from GE, CM, RM) will independently extract data. In case of disagreement, we will consult another study author (RM or VW).

We will conduct data management and analysis according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2025).

We will contact the authors of the included studies to obtain key missing data as needed.

#### Outcome data

For each included study, we will extract data relevant to all experimental interventions (type of immunotherapy + type of chemotherapy; chronology and duration of administration) and comparator interventions (type of chemotherapy or placebo or best supportive care; chronology and duration of administration).

We will extract information on relevant outcomes, including definitions and timing of measurement. We will extract all relevant outcome data (e.g. time to events, number of events), in addition to extracting all relevant subgroup data (e.g. based on age, TNM stage, node stage, smoking status, performance status). For dichotomous outcomes, we will obtain numbers of events and totals for populations, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will obtain the means and standard deviations or data necessary to calculate this information.

#### Data on potential effect modifiers

We will extract all possible potential modifiers from each included study, such as inclusion criteria, participant characteristics (e.g. age, race, sex, smoking status, performance status, TNM stage, distribution of PD-L1 scores), and features of the interventions and comparisons.

#### Other data

We will extract information relevant to the study design, trial identifiers, study dates, study locations and settings, study funding sources, and declarations of interest by primary investigators.

#### Assessment of risk of bias in included studies

Two review authors (from GE, CM, RM) will independently apply version 2 of the Cochrane risk of bias tool for randomized trials (RoB 2), which is described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*, to assess potential biases in and across the included studies (Higgins 2019).

We will use the RoB 2 Excel tool available at https://www.riskofbias.info/ to implement RoB 2.

We will rate each domain of the tool as having low risk of bias, high risk of bias, or some concerns at study level, and for each outcome and each outcome measure where possible. We will use signaling questions/tool algorithms. We will provide support for our judgment of each domain with a brief description. We will reach a judgment on the overall risk of bias for each outcome within a study by considering all domains relevant to the outcome (i.e. both study-level entries, such as allocation sequence concealment, and outcome-specific entries, such as blinding).

We will provide different tables to summarize the risk of bias for each outcome, outcome measure, and time point.

We will resolve disagreements by consensus or by consultation with another review author (RM or VW).

Using RoB 2, we will consider the following domains:

- bias arising from the randomization process;

- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

For bias due to deviations from intended interventions, we will use the effect of assignment to the interventions at baseline (regardless of whether the interventions were received as intended: the intention-to-treat effect), as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

### Relative treatment effects

For overall survival, disease-free survival, and event-free survival outcomes, we will use the hazard ratio (HR) and 95% CI to combine data.

For dichotomous outcomes, such as adverse events, we will use a risk ratio (RR) with a 95% CI as a measure of an estimated effect.

For continuous data, such as health-related quality of life measures, we will use the mean difference (MD) to combine data across studies using the same measures; we will use the standardized mean difference (SMD) when studies use different scales to measure the same outcome.

### Relative treatment ranking

We will estimate the ranking probabilities for each of the immunotherapy treatments. We will use the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness and safety of each treatment (Salanti 2011). SUCRA accounts for both effect size magnitude and uncertainty around the underlying effect size. A SUCRA value of 100% indicates that the treatment is the most effective one, while a value of 0% indicates the least effective treatment in the network. We will display results (network plot, SUCRA plots, and league table) using the 'netmeta packages' in R (Chaimani 2017; R 2021).

### Unit of analysis issues

The participant will be the primary unit of analysis.

#### *Studies with multiple treatment groups*

Studies with multiple comparison groups that compare two or more intervention groups versus the same control group will be included in both pairwise and network meta-analysis. In order to avoid a unit of analysis error, we will treat multi-arm studies as multiple independent two-arm studies for the pair-wise analysis. We will do this by, for example, combining groups to create a single pair-wise comparison or dividing the control group.

For the network meta-analysis, we will calculate within-study correlation as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions (*Deeks 2024).

### Dealing with missing data

We will try to obtain any missing data relevant to the risk of bias assessment and the review outcomes from study authors. We will perform intention-to-treat analysis if data are available. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals) and critically appraise issues of missing data. We will classify the studies as having a high risk of bias if they have employed single imputation procedures (e.g. latest observation carried forward, mean imputation). In these situations, we will apply a 'pattern mixture model' (i.e. a method of handling missing data) to conduct a sensitivity analysis (Mavridis 2015; White 2008), which will allow us to assess the degree of robustness of the findings and deviations from the 'missing at random' assumption.

### Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of clinical heterogeneity, we will generate descriptive statistics for trial and study population characteristics (potential effect modifiers such as type of chemotherapy, dose, frequency, and duration of treatment) across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pair-wise comparison by comparing these characteristics. We will assess the impact of these relevant modifiers by performing subgroup analysis and sensitivity analysis.

### Assessment of the transitivity assumption

The validity of the consistency assumption, or the statistical agreement between direct and indirect evidence, may be threatened by a lack of transitivity in a network (Caldwell 2005; Franco 2021; Lu 2004). The foundation of network meta-analysis is the transitivity assumption, which means that effect modifiers in a network have a similar distribution across treatment comparisons (Cipriani 2013; Jansen 2013). To check the transitivity assumption, we will conduct sensitivity, subgroup, and meta-regression analysis, when possible, to ensure the robustness of the findings. When the effect of modifiers such as age, type of chemotherapy, dose, frequency, and duration of treatment before surgery are imbalanced across comparisons, we will not proceed with any further statistical analysis for that outcome.

In this context, we expect that the transitivity assumption will hold, assuming that:

- the common treatment used to compare different strategies indirectly is similar when it appears in different trials (chemotherapy product in standard of care is administered in a similar way); and
- all pair-wise comparisons do not differ with respect to the distribution of effect modifiers (the design and study characteristics of neoadjuvant versus chemotherapy alone trials are similar to adjuvant immunotherapy versus chemotherapy alone).

### Assessment of statistical heterogeneity

If possible, we will investigate whether treatment effects for our primary outcomes are robust in subgroup analyses and network meta-regression.

We will assess the presence of heterogeneity within each pair-wise comparison using the $I^2$ statistic (percentage of variability that is due to differences in the underlying effects across studies) and $\tau 2$ statistics.

We will base the assessment of statistical heterogeneity in the entire network on the magnitude of $\tau 2$ estimated from the network meta-analysis models. For dichotomous outcomes, we will

compare the magnitude of the heterogeneity variance with the empirical distribution (Turner 2012).

### Assessment of statistical consistency

In network meta-analysis, results can be misleading in the presence of inconsistency. We will assess whether there is inconsistency at a local level (within a network) or global level (the entire network). We will evaluate each network locally using the loop-specific method by generating an inconsistency factor along with a 95% CI for each closed-loop (Veroniki 2013). We will then investigate this further and determine which piece of evidence is causing the inconsistency. Additionally, we will use the design-by-treatment interaction model to perform an overall assessment for consistency in each network (White 2012). It has been demonstrated that inconsistency tests are not very effective at identifying actual inconsistencies (Song 2003; Veroniki 2013). Therefore, even if there is no evidence of inconsistency, we will evaluate transitivity. If inconsistency is found, we will follow the guidance provided in the *Cochrane Handbook for Systematic reviews of interventions* (Chaimani 2019).

### Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting. We will use comparison-adjusted funnel plots to assess small-study effects. There are different possible explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We will, therefore, interpret these results carefully. When there is visual asymmetry of a funnel plot, we will perform an exploratory analysis for dichotomous data, such as using contour-enhanced funnel plots and trim-and-fill sensitivity analysis.

### Methods for direct treatment comparisons

We will estimate the pair-wise relative treatment effects of the competing interventions, using the random-effects model to calculate the pooled hazard ratio with 95% confidence intervals for survival outcomes, and relative effect sizes (mean differences or risk ratio) with the corresponding 95% confidence intervals for the other outcomes. We will perform our analysis according to recommendations provided in Chapter 9 of the *Cochrane Handbook* (McKenzie 2019), and use Cochrane's statistical software, Review Manager (RevMan 2025).

### Methods for indirect and mixed comparisons

We will structure a network diagram to assess whether network meta-analysis is possible (Figure 1). We will conduct the analysis using a Frequentist framework for each review outcome, applying the random-effects model in R using the netmeta packages (R 2021). The Frequentist approach is based on the principle of objective probability, where probability is defined as the frequency with which an event reoccurs through repeated experiments.

When meta-analysis either by pair-wise or network meta-analysis is not possible, we will summarize the individual study results narratively.

### Subgroup analysis and investigation of heterogeneity

For the standard pair-wise analysis, we will investigate heterogeneity by visually inspecting the forest plots, $Chi^2$, and calculating the $I^2$ statistic (Deeks 2024). For network meta-analysis, we will assess heterogeneity by assessing the statistical heterogeneity in the whole network based on the magnitude of heterogeneity across the parameters (Rhodes 2015; Turner 2012). We will assess any statistical disagreement between direct and indirect comparisons (incoherence) with local and global approaches (Higgins 2013). For the local approach, we will calculate the difference between direct and indirect estimated effects across all the closed loops in the network (Veroniki 2013). Globally, we will apply the 'design by-treatment' approach (Higgins 2013).

Whenever we find important heterogeneity or inconsistency, we will explore possible sources for our primary outcome (OS). When sufficient studies are available, we will perform subgroup analysis by using the following potential effect modifiers as possible sources of inconsistency or heterogeneity.

- Participant age (younger than 65 years versus 65 years and older)
- TNM stage (≤ II versus IIIA versus IIIB)
- Node stage (N0 versus N1 versus N2; N2a versus N2b)
- Performance status (0 versus 1)
- Smoking status (current smokers versus never smokers)

We chose these variables because they have been shown to impact prognosis after the resection of localised lung cancer (Wei 2011).

We will assess the difference between subgroups by comparing the network diagram for each subgroup. We will also compare the estimated effects of pair-wise and network meta-analysis for each subgroup.

### Sensitivity analysis

We plan to perform sensitivity analysis for our primary outcome (OS) to explore the influence of the following factors (when applicable) on effect size.

- Restricting the analysis to RCTs with overall low risk of bias
- Restricting the analysis to RCTs with less than 20% missing data on any of the review outcomes.

We will investigate any differences in the results when applying the sensitivity analysis, by assessing the changes of estimated effects and the assessment of model fit.

### Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for each outcome listed below.

- OS at 2 and 5 years
- DFS at 5 years
- EFS at 5 years
- Harms, toxicity profile

Each table will include the certainty of the evidence for direct analysis, indirect analysis, and network meta-analysis using the Confidence in Network Meta-analysis (CINeMA) framework and software (Chaimani 2021; CINeMA 2020; Salanti 2014). To evaluate our confidence in the results of the pair-wise comparisons for the four key outcomes, we will use the GRADE approach (Schünemann 2023).

We will first assess the certainty of available direct evidence for each outcome and rate the evidence using the standard GRADE approach. We will conduct the assessment based on consideration of the following aspects.

1. Study design limitations (risk of bias)
2. Inconsistency
3. Imprecision
4. Indirectness
5. Publication bias

After grading the certainty of the evidence, we will use CINeMA to assess biases in the network meta-analysis (CINeMA 2020), looking at the following domains.

1. Within-study bias
2. Reporting bias
3. Indirectness
4. Imprecision
5. Heterogeneity
6. Incoherence

This tool will provide a matrix to show the proportion of each study's contribution to the evidence from the NMA. The summary of findings table will show the network geometry, relative effect estimates for the highest certainty of the evidence, baseline risk information, certainty of the evidence, and ranking of the treatments (Yepes-Nuñez 2019).

We will use CINeMA to judge the evidence as no concerns, some concerns, or major concerns, for each of the six domains.

At each stage, two review authors (from RM, CM, GE) will independently evaluate the certainty rating for the evidence (direct and indirect). We will resolve disagreements through discussion and, when necessary, through consultation with a third review author (VW).

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### Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Toby Lasserson, Acting Editor-in-Chief, Cochrane Library
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# APPENDICES

## Appendix 1. Search strategies

### MEDLINE search strategy accessed via PubMed

1 Carcinoma, Non-Small-Cell Lung[MeSH Terms]
2 NSCLC[Title/Abstract]
3 "lung cancer*"[Title/Abstract]
4 "lung carcinom*"[Title/Abstract]
5 "lung neoplasm*"[Title/Abstract]
6 "lung tumor*"[Title/Abstract]
7 "lung tumour*"[Title/Abstract]
8 "non small cell*"[Title/Abstract]
9 "nonsmall cell*"[Title/Abstract]
10 (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)
11 #1 OR #2 OR #10
12 ((Pulmonary Surgical Procedures[MeSH Terms]) OR (pneumonectomy[MeSH Terms])) OR (thoracotomy[MeSH Terms])
13 ((((((((((((((lobectomy[Title/Abstract]) OR ("Lymph node sampl*"[Title/Abstract])) OR (operable[Title/Abstract])) OR (perioperat*[Title/Abstract])) OR (peri-operat*[Title/Abstract])) OR (postoperat*[Title/Abstract])) OR (post-operat*[Title/Abstract])) OR (preoperat*[Title/Abstract])) OR (pre-operat*[Title/Abstract])) OR (resectable[Title/Abstract])) OR (resection*[Title/Abstract])) OR (segmentectomy[Title/Abstract])) OR (surgery[Title/Abstract])) OR (surgical*[Title/Abstract])) OR (thoracotomy[Title/Abstract])
14 (((Immunotherapy[MeSH Terms]) OR (Antineoplastic Agents, Immunological[Pharmacological Action])) OR (Immune Checkpoint Inhibitors[MeSH Terms])) OR (Immune Checkpoint Inhibitors[Pharmacological Action])

15 ((((("Immune Checkpoint Inhibitor*") OR ("PD L1 Inhibitor*")) OR ("PD 1 Inhibitor*")) OR ("CTLA 4 Inhibitor*")) OR (Immunotherap*)
16 (((((((nivolumab[MeSH Terms]) OR (nivolumab[Title/Abstract])) OR (Opdivo[Title/Abstract])) OR ("ONO 4538"[Title/Abstract])) OR (ONO4538[Title/Abstract])) OR ("MDX 1106"[Title/Abstract])) OR (MDX1106[Title/Abstract])) OR (BMS 936558[Title/Abstract])) OR (BMS936558[Title/Abstract])
17 (((((pembrolizumab[Supplementary Concept]) OR (pembrolizumab[Title/Abstract])) OR (lambrolizumab[Title/Abstract])) OR (Keytruda[Title/Abstract])) OR (SCH-900475[Title/Abstract])) OR (MK-3475[Title/Abstract])
18 ((((durvalumab[Supplementary Concept]) OR (durvalumab[Title/Abstract])) OR (Imfinzi[Title/Abstract])) OR (MEDI-4736[Title/Abstract])) OR (MEDI4736[Title/Abstract])
19 (((((atezolizumab[Supplementary Concept]) OR (atezolizumab[Title/Abstract])) OR (Tecentriq[Title/Abstract])) OR (anti-PDL1[Title/Abstract])) OR (MPDL3280A[Title/Abstract])) OR (MPDL-3280A[Title/Abstract])
20 (((((avelumab[Supplementary Concept]) OR (avelumab[Title/Abstract])) OR (bavencio[Title/Abstract])) OR ("MSB 0010682"[Title/Abstract])) OR (MSB0010682[Title/Abstract])) OR (MSB0010718C[Title/Abstract])
21 #12 OR #13
22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
23 #11 AND #21 AND #22
24 randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy[MeSH Subheading] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]
25 animals[MeSH Terms] NOT humans[MeSH Terms]
26 #24 NOT #25
27 #23 AND #26

**Embase search strategy accessed via Elsevier**

| |
|---|
| 'non small cell lung cancer'/exp |
| NSCLC:ti,ab |
| "lung cancer*":ti,ab |
| "lung carcinom*":ti,ab |
| "lung neoplasm*":ti,ab |
| "lung tumor*":ti,ab |
| "lung tumour*":ti,ab |
| "non small cell*":ti,ab |
| "nonsmall cell*":ti,ab |
| (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9) |
| #1 OR #2 OR #10 |
| 'lung surgery'/exp OR 'thoracotomy'/exp |
| (lobectomy OR "Lymph node sampl*" OR operable OR perioperat* OR perioperat* OR postoperat* OR preoperat* OR resectable OR resection* OR segmentectomy OR surgery OR surgical* OR thoracotomy):ti,ab |
| 'immunotherapy'/exp OR 'immunological antineoplastic agent'/exp OR 'immune checkpoint inhibitor'/exp |
| ("Immune Checkpoint Inhibitor*" OR "PD L1 Inhibitor*" OR "PD 1 Inhibitor*" OR "CTLA 4 Inhibitor*"):ti,ab |
| 'nivolumab'/exp OR (nivolumab OR Opdivo OR "ONO 4538" OR ONO4538 OR "MDX 1106" OR MDX1106 OR "BMS 936558" OR BMS936558):ti,ab |

*(Continued)*

| |
|---|
| 'pembrolizumab'/exp OR (pembrolizumab OR lambrolizumab OR Keytruda OR "SCH-900475" OR "MK-3475"):ti,ab |
| 'durvalumab'/exp OR (durvalumab OR Imfinzi OR "MEDI-4736" OR MEDI4736):ti,ab |
| 'atezolizumab'/exp OR (atezolizumab OR Tecentriq OR "anti-PDL1" OR MPDL3280A OR "MPDL-3280A"):ti,ab |
| 'avelumab'/exp OR (avelumab OR bavencio OR "MSB 0010682" OR MSB0010682 OR MSB0010718C):ti,ab |
| #12 OR #13 |
| #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 |
| #11 AND #21 AND #22 |
| 'randomized controlled trial'/exp OR (randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups):ti,ab |
| 'animal'/exp NOT 'human'/exp |
| #24 NOT #25 |
| #23 AND #26 |

**CENTRAL search strategy**

#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees 4896
#2 nsclc 11095
#3 "lung cancer*" 23446
#4 "lung carcinom*" 51
#5 "lung neoplasm*" 76
#6 "lung tumor*" 672
#7 "lung tumour*" 672
#8 "non small cell*" 15374
#9 "nonsmall cell*" 10462
#10 (#3 or #4 or #5 or #6 or #7) and (#8 or #9) 14841
#11 MeSH descriptor: [Pulmonary Surgical Procedures] explode all trees 1633
#12 MeSH descriptor: [Pneumonectomy] explode all trees 607
#13 MeSH descriptor: [Thoracotomy] explode all trees 616
#14 lobectomy OR "Lymph node sampl*" OR operable OR perioperat* OR perioperat* OR postoperat* OR preoperat* OR resectable OR resection* OR segmentectomy OR surgery OR surgical* OR thoracotomy 357817
#15 #11 OR #12 OR #13 OR #14 358434
#16 MeSH descriptor: [Immunotherapy] explode all trees 8819
#17 MeSH descriptor: [Antineoplastic Agents, Immunological] explode all trees 538
#18 MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees 95
#19 "Immune Checkpoint Inhibitor*" OR "PD L1 Inhibitor*" OR "PD 1 Inhibitor*" OR "CTLA 4 Inhibitor*" 974
#20 MeSH descriptor: [Nivolumab] explode all trees 618
#21 nivolumab OR Opdivo OR "ONO 4538" OR ONO4538 OR "MDX 1106" OR MDX1106 OR "BMS 936558" OR BMS936558 2655
#22 pembrolizumab OR lambrolizumab OR Keytruda OR SCH-900475 OR MK-3475 2658
#23 durvalumab OR Imfinzi OR MEDI-4736 OR MEDI4736 996
#24 atezolizumab OR Tecentriq OR anti-PDL1 OR MPDL3280A OR MPDL-3280A 1296
#25 avelumab OR bavencio OR "MSB 0010682" OR MSB0010682 OR MSB0010718C 356
#26 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 372451
#27 #10 AND #15 AND #26 3209

## CONTRIBUTIONS OF AUTHORS

Writing of the protocol: CM, GE, MC, FC, VW, RM

Design of the search strategies: FC

## DECLARATIONS OF INTEREST

Corynne Marchal declares that she has no conflict of interest. She is Managing Editor for the Cochrane Lung Cancer Group but was not involved in the editorial process for this protocol.

Guillaume Eberst reports having received consultancy fees from Amgen, AstraZeneca, Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, and Pfizer Cananda Inc.

François Calais declares that he has no conflict of interest. He is Information Specialist for the Cochrane Lung Cancer Group but was not involved in the editorial process for this protocol.

"Virginie Westeel reports 'relationship/activity' leading to personal payments with AMGEN" (speaker bureau, consultancy fees, scientific committee, scientific advisory board, and travel expenses); AstraZeneca (scientific advisory board, scientific committee, speaker bureau, and travel expenses); Bristol-Myers-Squibb (speaker bureau and travel expenses); IPSEN Biopharmaceuticals Inc (board of experts); Janssen pharmaceuticals (travel expenses); Merck Sharp and Dohme (speaker bureau, scientific committee, travel expenses); Roche (scientific committee, speaker bureau, and travel expenses); Sanofi (speaker bureau, travel expenses). VW is Co-ordinating Editor for the Cochrane Lung Cancer Group but was not involved in the editorial process for this review.

Reem Malouf declares that she has no conflict of interest.

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