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Immunotherapy for advanced and recurrent malignant pleural mesothelioma (Protocol)

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Immunotherapy for advanced and recurrent malignant pleural mesothelioma

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ABSTRACT

Objectives

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

To assess the effects of immune checkpoint inhibitors (single-agent or combination therapy) in people with advanced malignant pleural mesothelioma in a first-line or salvage setting.

BACKGROUND

Description of the condition

Malignant pleural mesothelioma (MPM) is a rare but aggressive form of cancer of the lining around the lungs, called the pleura. MPM's age-standardised incidence rate is 0.44 /100,000 persons, corresponding to 30,870 registered cases worldwide in 2020 (Sung 2020; Zhai 2021). Most cases are caused by previous asbestos exposure (Carbone 2019). There is a latency period of approximately 40 years between exposure and disease presentation (Bibby 2016; Kato 2018). Due to this latency, the incidence of MPM varies between countries due to different times of asbestos ban regulations. While the incidence of MPM has peaked in many regions, it continues to increase in resource-limited regions (Zhai 2021; Zhu 2023).

The prognosis of MPM is poor, with reported median survival ranging from eight to 14 months from diagnosis, and a five-year overall survival rate of 8.5% (Beckett 2015). Most people with MPM have locally advanced or metastatic disease at diagnosis. There are three main histological subtypes: epithelioid, sarcomatoid, and biphasic/mixed. Median survival time varies between subtypes, from a median survival of 4.0 months for sarcomatoid MPM to 13.1 months for epithelioid MPM (Beckett 2015). There are no diagnostic biomarkers for MPM (i.e. tumour markers that detect or confirm the presence of the disease). However, there is a test to measure the amount of a small molecule called mesothelin-related peptides (SMRP) in the blood. These peptides emanate from proteins in the membranes lining the cavities around the lungs (and other organs). People with MPM often have large amounts of SMRP in their blood, and the SMRP level is thought to be related to the extent of the disease. Programmed death-ligand 1 (PD-L1) is expressed in 20% to 40% of people with MPM, and the levels of expression correlate with poor prognosis (Brosseau 2019; Cedrés 2015; Hassan 2019; Jin 2020; Mansfield 2014; Sobhani 2019). Additionally, there are no biomarkers yet available to guide treatment decisions in MPM (Scherpereel 2018; Yang 2020).

Current treatment options for first-line treatment of MPM are combinations of surgery (for limited stages only), chemotherapy, immune checkpoint inhibitors (ICIs), vascular endothelial growth factor (VEGF) inhibitors, and radiotherapy (NCCN 2024). Randomised controlled trials (RCTs) have shown no benefit of surgery in MPM (Bibby 2016, Hiddinga 2013; Lim 2024; Yanagawa 2013). ICIs are the most widespread type of immunotherapy, and are defined as the administration of monoclonal antibodies directed against regulatory immune checkpoint molecules that inhibit T cell activation. This review focusses specifically on the use of single- or double-agent ICIs of any type.

Description of the intervention

Immune checkpoint inhibitors (ICIs)

Cancer immunotherapy is an approach to combating cancer that generates or augments an immune response against cancer cells. Two types of immunotherapy have proven particularly effective: ICIs and the administration of anti-tumour immune cells via adoptive cell therapy (ACT). Treatment with ICIs is the most widespread type of immunotherapy, and is defined as the administration of monoclonal antibodies directed against regulatory immune checkpoint molecules that inhibit T cell activation. ICIs stop proteins on the cancer cells from stopping/switching off T cells, which are the cells that would normally recognise and attack cancer cells. In other words, ICIs aid the restoration of normal immune system functioning, so that T cells are able to find and attack the cancer cells. The main targets for ICIs are the checkpoint molecules cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death-ligand 1 (PD-L1) (Ferrara 2021). The first FDA-approved ICI treatment in 2011 was ipilimumab, a CTLA-4 antagonist approved for the treatment of metastatic melanoma.

CTLA-4 and PD-1/PD-L1 inhibitors can be used alone or in combination. For a range of solid cancers, the advent of ICIs in the past decade represents a major treatment breakthrough, including for advanced non-small cell lung cancer (NSCLC), for which it has changed the first-line treatment (Buchbinder 2016; Ferrara 2021; Garon 2015).

Nivolumab with/without ipilimumab was added to the NCCN MPM guidelines in 2018 as salvage therapy; that is, treatment given after the cancer has not responded to other first-line treatments (NCCN 2024). In November 2020, the US Food and Drug Administration (FDA) approved nivolumab in combination with ipilimumab for the first-line treatment of adults with unresectable MPM (Baas 2020; Baas 2021; NCCN 2024; Wright 2020). In April 2021, the European Medicines Agency (EMA) approved the combination therapy nivolumab and ipilimumab as first-line treatment of adults with unresectable MPM (EMA 2021).

The level of PD-L1 expression in tumour cells is a prognostic marker for a range of solid tumours. For some types of cancers, including NSCLC, the level of PD-L1 expression might predict response to ICI therapy (Garon 2015). Studies of PD-L1 expression in MPM in relation to survival have shown inconsistent results. A recent meta-analysis found that PD-L1 overexpression was associated with poor overall survival but not progression-free survival (PFS) and correlated with the sarcomatoid and biphasic types of MPM (Jin 2020).

This review focusses specifically on the use of single- or double-agent ICIs of any type. Other treatment options for MPM are antifolates and chemotherapy, vascular endothelial growth factor (VEGF) inhibitors, and radiotherapy (NCCN 2024). As trials assessing ICIs may have used combinations of these options as comparators, they are mentioned below for context.

Antifolates and chemotherapy

Antifolates are a class of drugs that antagonise (i.e. block) the actions of folic acid. Antifolates were one of the first modern anticancer drugs. In advanced disease, or as part of a multimodal regimen for people with operable MPM, the use of antifolates (i.e. pemetrexed and raltitrexed) in combination with a platinum-based chemotherapy regimen (i.e. cisplatin or carboplatin) has been the standard of care for roughly the past six decades. This regimen has response rates of around 25%, resulting in a survival benefit of a few months and improved health-related quality of life (HRQoL) with less dyspnoea (i.e. breathlessness) and pain (Arnold 2015; NCCN 2024; Santoro 2008; Vogelzang 2003). In 2003, Vogelzang and colleagues defined pemetrexed and a platin (i.e. a platinum-based drug) as standard therapy for MPM (Vogelzang 2003). However, this study was widely criticised for lacking equipoise, as the combination used was compared to platinum alone, which, at the

time of the study, was not a standard therapy for mesothelioma (Goudar 2008).

Targeted therapy

Targeted therapies are a type of cancer therapy aimed at specific molecular targets responsible for tumour growth; for example, proteins promoting the formation of blood vessels or cell division. The use of targeted therapies in MPM has been less beneficial than in other cancers (Yang 2020). However, in 2016, the Mesothelioma Avastin Cisplatin Pemetrexed (MAPS) study found that the addition of the VEGF inhibitor bevacizumab to chemotherapy was associated with longer median overall survival than chemotherapy alone (Zalcman 2016). Bevacizumab is an anti-angiogenesis drug, which means that it impedes the development of blood supply to a tumour. The MAPS study results led to the National Comprehensive Cancer Network (NCCN) panel recommending a first-line pemetrexed, cisplatin, and bevacizumab regimen followed by maintenance bevacizumab for eligible patients. While there was initial concern about toxicity related to the addition of bevacizumab, in a later publication from the MAPS study, no negative impact on HRQoL was found (Eberst 2019). Other acceptable first-line chemotherapeutic options include single-agent treatment with pemetrexed or vinorelbine.

Radiotherapy

The use of radiotherapy (RT) in MPM has no confirmed survival benefit but is used as part of a multimodal regimen or as palliative treatment for chest pain, bronchial or oesophageal obstruction, and other mesothelioma-related symptoms. The combination of immunotherapy and radiotherapy is currently being investigated by a number of clinical phase I trials (Hanna 2021).

Limited data are available to guide second-line chemotherapy and beyond (NCCN 2024). Response rates are generally low, and no standard second-line option is available. Key questions regarding chemotherapeutic treatment of MPM remain unanswered, including the effectiveness of delayed versus immediate chemotherapy, the optimal number of cycles of chemotherapy, the usefulness of pemetrexed maintenance therapy, and the optimum choice of second-line treatment (Bibby 2016).

How the intervention might work

The process by which cancer evades the surveillance of the immune system can be described by "its three component phases" (Mittal 2014): elimination, in which tumour cells are cleared by the host immune system; equilibrium, which is a state of tumour control; and escape, in which the tumour evolves to overcome host immunity (Mittal 2014). Immunotherapy works by interfering with the development of immunotolerance, and thereby aiding elimination of tumour cells by the host immune system.

Upregulation of inhibitory immune checkpoint ligands is one of the mechanisms through which tumour cells evade immune surveillance. Blocking these ligands allows cytotoxic T cells to proliferate, resume their functions of immune surveillance and anti-tumour activity, or both. Available ICIs represent distinct but complementary mechanisms of action (Wei 2018). CTLA-4 is expressed by T cells and, after binding to CD80/CD86, activates an inhibitory downstream signal in human lymphocytes suppressing activation and proliferation. CTLA-4 inhibition induces T-cell proliferation and de-novo anti-tumour T-cell responses, including in memory T cells. Nivolumab and pembrolizumab bind PD-1 on immune cells, blocking their interaction with PD-L1 and PD-L2 expressed by tumour cells. Atezolizumab, durvalumab, and avelumab bind PD-L1 on tumour cells, preventing interaction with PD-1. Both classes of drugs counteract PD-1 mediated inhibition of T-cell activation, restoring the function of existing anti-tumour T cells.

In normal immune-homeostasis, immune checkpoints serve to prevent an excessive and uncontrolled immune response. The significant systemic adverse effects related to ICIs are thus comprised of a diverse spectrum of immune-mediated injury to non-cancer tissues (immune-related adverse events). In a meta-analysis, the overall incidence of immune-related adverse events of grades 3 to 5 were 17.9% and 46.3%, for single-agent ICI and combination therapy, respectively (Liu 2020). The most frequently affected organs are the lungs, skin, gastrointestinal tract, liver, endocrine, pulmonary and cardiovascular systems, but virtually any organ system can be affected. In general, immune-related adverse events of grade 3 to 5 are managed by the administration of systemic corticosteroids, counteracting both the adverse immune response and, to some extent, the anti-cancer immune-response. Immune-related adverse events are associated with significant morbidity, mortality, and impaired quality of life. In a recent Cochrane review of single or combined ICIs compared to first-line platinum-based chemotherapy for people with advanced NSCLC, no difference was observed in grade 3 to 5 adverse events between combined ICIs and platinum-based chemotherapy (Ferrara 2021).

Why it is important to do this review

MPM is a rare and aggressive type of cancer with a poor prognosis, limited treatment options, and with no formally approved targeted therapy or second-line agents. There are several literature reviews of immunotherapy in MPM, but none with a systematic approach (Bibby 2016; De Gooijer 2020; Dozier 2017; Scherpereel 2018; Tartarone 2018; Thomas 2017; Uprety 2021; Zhou 2021). Questions remain about the comparative effectiveness of ICIs versus other treatment options for MPM. The addition of ICIs to the NCCN MPM guidelines will increase the number of people treated outside randomised trials, adding to the significance of a systematic approach to emerging evidence.

As most people with MPM are diagnosed with an advanced stage of disease and thus are not candidates for surgery with curative intent, most receive palliative systemic antitumour therapy. The clinical settings of adjuvant versus palliative treatment differ significantly. For these reasons, this review focusses only on people with advanced unresectable or recurrent MPM.

OBJECTIVES

To assess the effects of immune checkpoint inhibitors (single-agent or combination therapy) in people with advanced malignant pleural mesothelioma in a first-line or salvage setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel randomised trials, and variants on randomised trials, such as multi-arm or factorial trials. In parallel trials, participants are randomised to an experimental intervention or a standard treatment (e.g. immunotherapy versus placebo). In multi-arm trials, participants may be randomised to two (or more) experimental interventions or a standard treatment (e.g. immunotherapy versus chemotherapy versus placebo). In factorial designs, participants may be randomised to one of various intervention combinations (e.g. immunotherapy plus chemotherapy; immunotherapy alone; chemotherapy alone; no immunotherapy and no chemotherapy). Since MPM is a progressive disease, we will not consider cross-over trials. We will not include cluster-randomised trials, as we expect there to be important variation in terms of treatment standards and participant populations between geographical settings.

Types of participants

We will include studies in adults (18 years or older) with histologically-confirmed, advanced MPM, who are treatment-naïve to immunotherapy. Advanced MPM is defined as histologically confirmed, unresectable MPM, not amenable to curative therapy (surgery with or without chemotherapy). As evidence for surgical intervention is lacking, we will accept any definition of unresectable mesothelioma used in the included studies, including if this is determined by the investigators at the individual sites based on local standards (Scherpereel 2020).

Types of interventions

We will consider for inclusion studies that test one or more of the following comparisons.

- Single-agent PD-1/PD-L1 inhibitor (such as pembrolizumab, nivolumab, durvalumab) therapy versus:
  - chemotherapy;
  - chemotherapy and immune checkpoint inhibitor combination therapy;
  - combination therapy with PD-1/PD-L1 inhibitors (such as pembrolizumab, nivolumab, durvalumab) and CTLA-4 inhibitor (such as ipilimumab);
  - placebo or best supportive care (defined by investigators as the best palliative care, but excluding antineoplastic agents (Zafar 2008)).
- Combination therapy with PD-1/PD-L1 inhibitors (such as pembrolizumab, nivolumab, durvalumab) and CTLA-4 inhibitor (such as ipilimumab) versus:
  - chemotherapy;
  - chemotherapy and immune checkpoint inhibitor combination therapy;
  - placebo or best supportive care (defined by investigators as the best palliative care, but excluding antineoplastic agents (Zafar 2008/11)).

The use of non-curative surgical procedures or radiotherapy is not an exclusion criterion.

Types of outcome measures

A core outcome set for malignant pleural mesothelioma is being developed but is unavailable at the time of writing this protocol (Caruana 2024). Our choice of primary outcomes is guided by a standard set of patient-centred outcomes for lung cancer (Mak 2016).

Primary outcomes

- Overall survival. The interval between the date of randomisation and the date of death from any cause (any time point).
- Serious adverse events (SAEs) (any time point). Defined as Grade 3, 4, or 5 adverse events by the National Cancer Institute – Common Terminology Criteria for Adverse Events (National Cancer Institute 2024) (any time point). In summary, these are adverse events requiring hospitalisation or prolongation of hospitalisation; adverse events limiting self-care activities of daily life; life-threatening adverse events; and deaths related to adverse events.
- Heath-related quality of life (HRQoL) (any time point). Measured by condition-specific instruments (i.e. the Lung Cancer Symptom Scale (LCSS) and LCSS-Meso; European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and LC13 questionnaires; MD Anderson Symptom Inventory for malignant pleural mesothelioma (MDASI-MPM)). If included studies do not use condition-specific tools, we will accept any generic instruments used (i.e. EuroQoL five-dimension questionnaire (EQ-5D), the Health Utilities Index (HUI) or the family of Short Form health profiles – the SF-36 or the SF-12, etc.).

Secondary outcomes

- Objective response rate (ORR) (any time point). Defined according to any version of the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (Eisenhauer 2009; Therasse 2000), immune-modified response criteria (imRECIST; Hodi 2018), immune-related response criteria (Nishino 2013; Wolchok 2009), or immunotherapy response criteria (iRECIST; Seymour 2017).
- Progression-free survival (PFS) (any time point). Time from randomisation to either death or disease progression, whichever occurred first. Disease progression is defined according to either RECIST version 1.0 (Therasse 2000), RECIST version 1.1 (Eisenhauer 2009), or the other immune-specific response criteria identified above; that is, disease progression is defined as at least a 20% increase in the sum of the longest diameter of target lesions, or as at least 20% increase in the nadir.

Search methods for identification of studies

We will include eligible published and unpublished studies regardless of language of publication.

Electronic searches

The Cochrane Lung Cancer Group Information Specialists developed the search strategies, and will search the following databases for us:

- Cochrane Central Register of Controlled Trials (CENTRAL; from 2010, Issue 1) (Appendix 1);

- MEDLINE (accessed viaPubMed) from 01 January 2010 to date of search (Appendix 2);
- Embase (accessed via Elsevier) from 01 January 2010 to date of search (Appendix 3).

Searches will start from 01 January 2010 because the interventions of interest were not available prior to this date.

The MEDLINE search was designed using the Cochrane Highly Sensitive Search Strategy, sensitivity and precision-maximising version (2008 version) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 6.4.11.1 and detailed in Box 4.4.b) (Higgins 2023).

We will apply no restrictions on the language of publication.

Searching other resources

We will check the reference lists of all identified relevant reviews and included studies. We will contact authors of identified trials, experts in the field, and manufacturers of relevant therapies to identify other published and unpublished studies.

We will check for potentially eligible trials in the abstracts of studies submitted to relevant conferences from 2021 onwards:

- American Society of Clinical Oncology (ASCO);
- European Society of Medical Oncology (ESMO);
- European Lung Cancer Congress (ELCC);
- International Association for the Study of Lung Cancer (IASLC);
- World Lung Cancer Conference;
- International Symposium on Malignant Mesothelioma; and
- International Mesothelioma Interest Group International Meeting.

We will search in clinical trial registries (ClinicalTrials.gov; EU Clinical Trials Register; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)) to identify ongoing studies.

We will search for clinical study reports in the European Medicines Agency Portal for Clinical Data and the WHO ICTRP, and we will apply for access to clinical study reports involving PD-1/PD-L1 interventions through Canada's Drug Agency (previously known as the Canadian Agency for Drugs and Technologies in Health (CADTH)).

Data collection and analysis

Selection of studies

We will perform study selection using Covidence (Covidence.org). Two review authors (AKH, AVY) will independently conduct initial screenings of titles and abstracts from our electronic search results. Subsequently, AKH and AVY will independently assess the full texts of studies preliminarily identified as 'eligible', 'potentially eligible', or those with 'unclear' eligibility, to determine their final inclusion in the review.

Two review authors (AKH, AVY) will independently search the conference proceedings, the clinical trial registries, and the European Medicines Agency Portal for Clinical Data. We will resolve any disagreements through discussion, involving a third author (BH) when necessary.

Two review authors (AKH, AVY) will independently search reference lists, and one review author (AKH) will use citation tracking (Scopus) on included articles.

We will capture the screening process and article/study flow in a PRISMA flow diagram.

Data extraction and management

Two review authors (AKH, AVY) will independently extract data from the included studies, using a data extraction form in Covidence (Covidence.org) that we have pilot-tested on at least one study. We will collect data from all reports of a single study in a single form. We will resolve any disagreements through discussion, involving a third author (BH) when necessary. We will contact trial authors whenever relevant information is missing from the retrieved reports. If we cannot contact trial authors or receive no response to requests for information, we will try to extract effect estimates from P values, t statistics, ANOVA (analysis of variance) tables, or other statistics as appropriate.

We will extract the following data.

- Study methods
  - Trial design (i.e. parallel, multi-arm, factorial)
  - Study timing (enrolment dates, run-in period, follow-up period, total duration)
  - Number of study centres and locations (countries)
  - Inclusion and exclusion criteria
  - Method of randomisation (simple randomisation, stratified randomisation, stratification, allocation ratio)
  - Methods of allocation concealment
  - Blinding (participants, clinicians, outcome assessors)
  - Number of withdrawals per arm
  - Early stopping of trial (and reason for stopping)
- Participants
  - Number per arm
  - Age range
  - Gender distribution
  - Histological subtype (epithelioid, sarcomatoid, and biphasic/mixed)
  - Severity of the condition (stage)
  - Diagnostic criteria
  - Performance status
  - PD-L1 expression
- Interventions
  - Intervention (dose, route, frequency)
  - Comparison (dose, route, frequency)
  - Allowed supplementary treatments
  - Excluded treatments
- Outcomes
  - Primary and secondary outcomes, as specified and collected, in each included study.
  - Specific data will vary according to the type of outcome:
    - Binary outcomes (serious adverse events; objective response rate): raw data (n/N) per trial arm. Risk ratio, odds ratio, and respective confidence interval if no raw data are provided; time point at which outcome was assessed.

- Time-to-event outcomes (overall survival; progression-free survival): events and person time per trial arm. Hazard ratio (HR) with confidence interval, covariates if only model-based estimates are provided; time point at which outcome was assessed.
- Continuous outcomes (HRQoL): measurement instrument, specific metrics reported (preferably post-intervention measurement, but when only a change from baseline is reported, we will collect that metric), means, standard deviations, number of participants; time point at which outcome was assessed.
- Serious adverse events: collected systematically or non-systematically; time point at which outcome was assessed.

- Other
  - Funding for trial and material support
  - Notable conflicts of interest of trial authors. For USA-based physicians, we will check the Open Payments Database.

Assessment of risk of bias in included studies

Two review authors (AKH, AVY) will assess the risk of bias in each randomised study using the Cochrane risk of bias 2 tool (RoB 2, Sterne 2019), focusing on the assessment of assignment to the intervention (the intention-to-treat effect). The RoB 2 tool assesses five domains:

- bias arising from the randomisation 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.

We will assess the randomisation process domain at the trial level. We will assess the other risk of bias domains separately for each outcome within each trial. Our risk of bias judgements will be based on the RoB 2 algorithm, and we will document any deviation from the algorithm. We will resolve any disagreements in the assessment of the risk of bias (for each signalling question and the overall rating) through discussion, involving a third review author if necessary. For the primary outcomes, we will use the Risk of Bias due to Missing Evidence (ROB-ME) tool (Page 2023).

Measures of treatment effect

We will analyse the outcomes based on the intention-to-treat (ITT) principle, where data are available.

- Binary outcomes (serious adverse events; objective response rate): we will present risk ratios.
- Time-to-event outcomes (overall survival; progression-free survival): we will present hazard ratios.
- Continuous outcomes (HRQoL): we will present standardised mean differences if included studies measure this outcome using different instruments; otherwise, we will calculate mean differences.

For all measures, we will calculate the corresponding 95% confidence intervals.

Unit of analysis issues

The unit of analysis for this review will be the individual participant. Cluster-randomised trials and cross-over trials, which can lead to unit of analysis issues, do not meet the eligibility criteria for this systematic review.

For HRQoL outcomes, there may be issues with repeated observations of participants. To address this, we will focus on the longest follow-up reported from each study.

If studies have multiple arms, we will only include the arms assessing the interventions listed in Types of interventions. Possible comparisons we anticipate finding in eligible studies include the examples listed below, where we describe how we would handle these studies.

- If a multi-arm trial assesses two doses of a single intervention (e.g. pembrolizumab 200 mg monotherapy once every three weeks, pembrolizumab 400 mg monotherapy once every six weeks, or best supportive care), we will combine the two arms (checkpoint inhibitor monotherapy versus best supportive care).
- If a multi-arm trial assesses two different checkpoint inhibitors with similar targets and a comparator (e.g. pembrolizumab 200 mg monotherapy once every three weeks, nivolumab 360 mg monotherapy once every three weeks, or best supportive care), we will combine the two checkpoint inhibitor arms (checkpoint inhibitor monotherapy versus best supportive care).
- If a multi-arm trial assesses three relevant interventions (e.g. pembrolizumab 200 mg monotherapy once every three weeks, pemetrexed combined with cisplatin every three weeks, pembrolizumab 200 mg combined with pemetrexed and cisplatin every three weeks), we will include all relevant comparisons in separate meta-analyses (e.g. analysis 1: checkpoint inhibitor monotherapy versus chemotherapy; analysis 2: checkpoint inhibitor monotherapy versus combined checkpoint inhibitor and chemotherapy; analysis 3: combined checkpoint inhibitor and chemotherapy versus chemotherapy). As the same trial will not be included twice in any of the pairwise comparisons, we will not split arms.

Dealing with missing data

Whenever possible, we will use clinical study reports. When trial data are only available in journal articles or conference abstracts, if needed, we will contact investigators and study sponsors to obtain data on key trial characteristics and any missing outcome data. If we do not receive a response after three contact attempts, we will state this information in the Results section of the review, and consider to what extent this decreases our confidence in the systematic review results.

Our main analysis will be an available-case analysis. We will conduct sensitivity analyses under extreme assumptions to explore to what extent any missing outcome data impact confidence in our estimates (see Sensitivity analysis).

Assessment of heterogeneity

We will identify heterogeneity by visual inspection of the forest plots and by considering the I^2 statistic. We will interpret the I^2 statistic as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023), as follows:

- 0% to 40%: may not be important;
- 30% to 60%: represents moderate heterogeneity;
- 50% to 90%: represents substantial heterogeneity;
- 75% to 100%: represents considerable heterogeneity.

If there is at least substantial heterogeneity (I^2 statistic ≥ 50%), we will attempt to determine possible reasons for the heterogeneity by examining individual studies and subgroup characteristics. If there is inconsistency in the direction of effect, we will not perform meta-analysis, and we will summarise the data in tabular form instead.

Assessment of reporting biases

To detect and manage reporting bias, we will:

- search for sources other than published reports (i.e. trial registries and clinical study reports; see Searching other resources);
- contact study authors if we suspect double publication has occurred;
- compare findings of eligible studies with published protocols when available, or contact study authors to request the study protocol in order to assess selective outcome reporting;
- examine how much of the sample size across all eligible trials has missing results;
- generate funnel plots and visually examine their symmetry;
- test for symmetry (Egger's test) if there are at least 10 studies reporting the outcome.

We will assess the impact of missing results using the Risk of Bias due to Missing Evidence (ROB-ME) tool (Page 2023).

Data synthesis

We will use RevMan for the analyses (RevMan 2024).

- Binary outcomes (serious adverse events; objective response rate): we plan to use the DerSimonian and Laird inverse-variance method (random-effects model) (DerSimonian 1986), as we anticipate at least some clinical heterogeneity between studies, and as such, we assume each study measures a different underlying true effect. However, we will use Peto's method (fixed-effect model) (Yusuf 1985), if there are fewer than five studies per comparison and no significant heterogeneity (Tufanaru 2015), or if there are rare (< 1%) events (Deeks 2023).
- Time-to-event outcomes (overall survival and progression-free survival): we will use generic inverse-variance methods (random-effects model) calculating the log hazard ratios and standard errors from the results of Cox proportional-hazards regression models.
- Continuous outcomes (HRQoL):
  - If the studies use different instruments to assess HRQoL, we will calculate standardised mean differences (SMD) if we judge that the instruments measure effects that can meaningfully be combined. Whenever possible, we will use post-intervention values. If we have a mixture of change-from-baseline and post-intervention SMD values, we will place them in different subgroups, and we will not pool the two subgroups together. This is because the standard deviation (SD) of SMD depends on between- and within-person variability, while the SD of mean difference (MD) only depends on between-person variability.
  - If all studies report the same instrument, we will calculate mean differences (MDs). Whenever possible, we will use post-intervention values. If we have a mixture of change-from-baseline and post-intervention MD values, we will place them in different subgroups, and we will pool the two subgroups together (Deeks 2023). We will impute the SD of mean differences, if necessary (Higgins 2023).

Subgroup analysis and investigation of heterogeneity

We will not perform subgroup analyses or meta-regression, as we anticipate very few trials. For possible future updates, we will consider subgroup analysis of high risk versus low risk of bias trials, first-line versus salvage therapy, with expression versus without expression of predictive biomarkers (including, but not limited to, epithelioid versus sarcomatoid histology or PD-L1 status), industry-funded versus publicly-funded studies, and generic versus condition-specific HRQoL questionnaires.

Sensitivity analysis

If possible, we will perform the following sensitivity analyses to explore the robustness of the findings of the primary analysis.

- We will restrict the analysis to studies with clinical study reports (to explore how the data source may influence our confidence in the estimates).
- For health-related quality of life, we will use a series of four progressively more stringent imputation strategies for missing outcome data (Ebrahim 2013):
  - we will impute missing outcome data in the intervention and control groups by using the mean score from the control arm of the same trial;
  - we will impute missing outcome data in the intervention group using the worst mean score amongst the intervention arms of the included trials, and we will impute missing outcome data in the control group using the best mean score amongst the control arms of the included trials;
  - we will impute missing outcome data in the intervention group using the worst mean score amongst the control arms of the included trials, and we will impute missing outcome data in the control group using the best mean score amongst the control arms of the included trials;
  - we will impute missing outcome data in the intervention group using the worst mean score amongst the control arms of the included trials, and we will impute missing outcome data in the control group using the best mean score amongst the intervention arms of the included trials.
- For serious adverse events (grades 3 to 4), we will perform an "all had the event" sensitivity analysis, in which we assume that all participants in the intervention and control arms who withdrew or were lost to follow-up experienced an adverse event (Akl 2013). This scenario assumes that participants in either study arm may withdraw if they experience adverse events. It is more relevant for pairwise comparisons involving an active comparator.
- We will perform a "worst case scenario" sensitivity analysis, in which we assume that all participants in the intervention group who withdrew or were lost to follow-up experienced an adverse event (Akl 2013). For the control group, we will only consider participants with complete outcome data. This scenario assumes that participants may withdraw if they

experience adverse events with the experimental intervention. It is more relevant for pairwise comparisons involving a placebo or best supportive care comparator.

Summary of findings and assessment of the certainty of the evidence

We will prepare the summary of findings tables using GRADEpro software and standard Cochrane methods (GRADEpro GDT; Schünemann 2023). The summary of findings tables will present the overall certainty of the body of evidence for the main review outcomes: overall survival; serious adverse events; health-related quality of life; objective response rate; and progression-free survival.

We will assess the certainty of the evidence using the five GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness, and publication bias. Two review authors (AKH, AVY), working independently, will perform a GRADE assessment of the overall certainty of the body of evidence for each outcome, based on the five GRADE dimensions (overall risk of bias judgement, consistency of effect, imprecision, indirectness, and publication bias). We will resolve any disagreements through discussion or by asking a third review author (BH) to arbitrate. We will justify our decisions to downgrade or upgrade the certainty of the evidence, and incorporate these judgements into the reporting of results for each outcome. We will use the overall RoB 2 judgement to feed into the GRADE assessments.

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APPENDICES

Appendix 1. CENTRAL search strategy

ID Search Hits
#1 MeSH descriptor: [Mesothelioma, Malignant] explode all trees 42
#2 mesothelioma* or MPM 908
#3 MeSH descriptor: [Pleural Neoplasms] explode all trees 268
#4 pleural neoplasm* OR pleural cancer* 1531
#5 #1 OR #2 OR #3 OR #4 2057
#6 MeSH descriptor: [Immunotherapy] explode all trees 8300
#7 immunotherap* 12279
#8 MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees 26
#9 Checkpoint OR PD L1 Inhibitor*OR CTLA 4 Inhibitor* OR PD 1 Inhibitor* 7894
#10 MeSH descriptor: [Antineoplastic Agents, Immunological] explode all trees 374
#11 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees 9788
#12 MeSH descriptor: [Ipilimumab] explode all trees 214
#13 Ipilimumab OR Yervoy OR MDX 010 OR MDX010 OR MDX CTLA 4 1372
#14 pembrolizumab OR SCH-900475 OR Keytruda OR MK-3475 OR lambrolizumab 1970
#15 MeSH descriptor: [Nivolumab] explode all trees 509
#16 Nivolumab OR Opdivo OR ONO 4538 OR ONO4538 OR MDX 1106 OR MDX1106 OR BMS 936558 OR BMS936558 2070
#17 durvalumab OR MEDI4736 OR MEDI-4736 OR Imfinzi 724
#18 avelumab OR MSB-0010682 OR MSB0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB-0010718C 256
#19 atezolizumab OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446 978
#20 tremelimumab OR ticilimumab OR CP 675 OR CP675 OR CP 675206 OR CP675206 379
#21 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 31132
#22 #5 AND #21 255

Appendix 2. MEDLINE search strategy (accessed via PubMed)

Search number Query
1 Mesothelioma, Malignant[MeSH Terms] OR mesothelioma* OR MPM OR pleural neoplasm* OR pleural cancer*
2 immunotherapy[MeSH Terms] OR Immunotherap* OR "immune checkpoint inhibitors"[MeSH Terms] OR Immune Checkpoint Inhibitors[Pharmacological Action] OR Checkpoint OR PD L1 Inhibitor* OR CTLA 4 Inhibitor* OR PD 1 Inhibitor* OR Antineoplastic Agents, Immunological[Pharmacological Action] OR Antibodies, Monoclonal, Humanized[MeSH Terms]
3 "ipilimumab"[MeSH Terms] OR Ipilimumab OR Yervoy OR MDX 010 OR MDX010 OR MDX CTLA 4
4 pembrolizumab[Supplementary Concept] OR pembrolizumab OR SCH-900475 OR Keytruda OR MK-3475 OR lambrolizumab

5 Nivolumab[MeSH Terms] OR Nivolumab OR Opdivo OR ONO 4538 OR ONO4538 OR MDX 1106 OR MDX1106 OR BMS 936558 OR BMS936558
6 durvalumab[Supplementary Concept] OR durvalumab OR MEDI4736 OR MEDI-4736 OR Imfinzi
7 avelumab[Supplementary Concept] OR avelumab OR MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB-0010718C
8 atezolizumab[Supplementary Concept] OR atezolizumab OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446
9 tremelimumab[Supplementary Concept] OR tremelimumab OR ticilimumab OR CP 675 OR CP675 OR CP 675206 OR CP675206
10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11 #1 AND #10
12 randomized controlled trial[Publication Type] OR controlled clinical 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]
13 animals[MeSH Terms] NOT humans[MeSH Terms]
14 #12 NOT #13
15 #11 AND #14

Appendix 3. Embase search strategy (accessed via Elsevier)

#1 'pleura mesothelioma'/exp OR 'pleural mesotheliom*' OR 'mpm'
#2 'immunotherapy'/exp OR 'immunotherap*' OR 'immune checkpoint inhibitor'/exp OR 'immune checkpoint inhibitor*' OR 'checkpoint' OR 'programmed death 1 receptor'/exp OR 'pd 1' OR 'pd l1' OR 'cytotoxic t lymphocyte antigen 4'/exp OR 'clta 4'
#3 'ipilimumab'/exp OR 'ipilimumab' OR 'strentarga' OR 'yervoy' OR 'bms 734016' OR 'bms734016' OR 'mdx 010' OR 'mdx010' OR 'mdx 101' OR 'mdx101'
#4 'pembrolizumab'/exp OR 'pembrolizumab' OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'sch 900475' OR 'sch900475'
#5 'nivolumab'/exp OR 'nivolumab' OR 'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'ono 4538' OR 'ono4538' OR 'opdivo'
#6 'durvalumab'/exp OR 'durvalumab' OR 'bavencio' OR 'msb 0010682' OR 'msb 0010718c' OR 'msb 10682' OR 'msb 10718c' OR 'msb0010682' OR 'msb0010718c' OR 'msb10682' OR 'msb10718c' OR 'pf 06834635' OR 'pf 6834635' OR 'pf06834635' OR 'pf6834635'
#7 'atezolizumab'/exp OR 'atezolizumab' OR 'tecentriq' OR 'tecntriq' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446'
#8 'avelumab'/exp OR 'avelumab' OR 'bavencio' OR 'msb 0010682' OR 'msb 0010718c' OR 'msb 10682' OR 'msb 10718c' OR 'msb0010682' OR 'msb0010718c' OR 'msb10682' OR 'msb10718c' OR 'pf 06834635' OR 'pf 6834635' OR 'pf06834635' OR 'pf6834635'
#9 'ticilimumab'/exp OR 'ticilimumab' OR 'tremelimumab' OR 'cp 675 206' OR 'cp 675, 206' OR 'cp 675206' OR 'cp675 206' OR 'cp675, 206' OR 'cp675206'
#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 #1 AND #10
#12 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp OR random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR (doubl* NEAR/1 blind*) OR (singl* NEAR/1 blind*) OR assign* OR allocat* OR volunteer*
#13 #11 AND #12

CONTRIBUTIONS OF AUTHORS

Conception and writing of the protocol: all review authors (AKH, AVY, RSC, ARJM, KJJ, BH)

DECLARATIONS OF INTEREST

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Rita Saúde Conde: declares travel payments from AstraZeneca and Merck.

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