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TABLE OF CONTENTS

[Intervention Protocol]

Immune checkpoint inhibitors (anti PD-1 or anti PD-L1) plus platinum-etoposide versus platinum-etoposide alone for first-line treatment of extensive small cell lung cancer

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ABSTRACT

Objectives

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

To evaluate the efficacy and safety of immune checkpoint inhibitors (anti PD-1 or anti PD-L1) plus platinum-etoposide compared with platinum-etoposide alone for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC).

BACKGROUND

Description of the condition

Worldwide, lung cancer is still the most commonly diagnosed cancer and the leading cause of cancer death, accounting for 11.6% of total cancer cases and 18.4% of total cancer deaths (Bray 2018). Lung cancer can be divided into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) according to histological classification. According to the World Health Organization (WHO) classification (Travis 2015), SCLC is defined as a high-grade (fast spreading) neuroendocrine tumour with scant cytoplasm; poorly defined cell borders; a finely dispersed, granular, nuclear chromatin; and absent or inconspicuous nucleoli. Mitoses (cell divisions) are numerous, with an average of 80 mitoses per 2 mm^2, and necrosis (cell death) is extensive (Travis 2015). For a small number of people with SCLC, the tumor may be a mixture of SCLC and NSCLC, and this may not be obvious from small biopsies or cytological samples. SCLC is an aggressive neuroendocrine cancer with different clinical characteristics from NSCLC, and its incidence - at approximately 15% - is lower than that of NSCLC - at approximately 85% (Govindan 2006).

The main cause of SCLC is smoking, and more than 95% of patients are current or former smokers (Kalemkerian 2017). Limited-stage SCLC is defined as a disease that is limited to one side of the chest and regional nodes, that can be encompassed in a safe radiotherapy field. In contrast, extensive-stage SCLC (ES-SCLC) is disease that has spread beyond the boundaries of limited-stage disease, and includes distant metastasis (new tumors), malignant pericardial or pleural effusions (collection of fluid around heart or in lungs), and involvement of contralateral supraclavicular and contralateral hilar lymph nodes (Micke 2002). Approximately 30% of patients with SCLC are diagnosed when the disease is at the limited stage, but the remaining 70% have an initial diagnosis where there has been extensive spread of the cancer, usually accompanied by the appearance of metastases in both lungs and distant organs (Kalemkerian 2013; van Meerbeeck 2011). The combination of this strong invasiveness, rapid progression, tendency to metastasize, and a resistance to anti-cancer medicines, results in high levels of mortality. ES-SCLC has a natural disease course of two to four months and a two-year overall survival (OS) rate of 1.5% to 6% (Govindan 2006; Oronsky 2017).

While limited-stage SCLC is curable, ES-SCLC is incurable (Kalemkerian 2017). Surgery has little effect on the treatment of SCLC unless patients are diagnosed early (Amini 2014). Today, chemoradiotherapy is the standard of care for both SCLC and ES-SCLC (Levy 2021). The commonly used first-line treatment method for ES-SCLC is platinum-based chemotherapy (four to six cycles of etoposide plus either cisplatin or carboplatin) (Früh 2013; Farago 2018). However, due to the high aggressiveness of SCLC, the median overall survival is about 10 months (Früh 2013). Recently, immune checkpoint inhibitors (a type of immune checkpoint drugs, used to block immune checkpoint proteins), for example, durvalumab, and atezolizumab, have been used to treat ES-SCLC and have shown potential value (Horn 2018; Paz-Ares 2019).

Description of the intervention

Immunotherapy is currently revolutionizing all fields of oncology, and the recent development of immune checkpoint inhibitors has changed the treatment landscape of many cancer types (Finn 2018). Immune checkpoints are a normal part of the immune system. Their role is to prevent an immune response from being so strong that it destroys healthy cells in the body (Marin-Acevedo 2021). Immune checkpoint inhibitors work by preventing the checkpoint protein from binding to its partner protein, programmed cell death ligand 1 (PD-L1), allowing T cells to kill cancer cells (Marin-Acevedo 2021). Immune checkpoint inhibitors can stimulate lymphocytes (white blood cells) against tumour cells and are better tolerated than chemotherapy, which is toxic to cells (Chen 2017).

The immune checkpoint inhibitors anti-PD-1 and anti-PD-L1 have been studied most In the treatment of lung cancer. The immune checkpoint receptor PD-1 (also known as CD279) is encoded for by the PDCD1 gene, which is expressed on a variety of cells including: B cells, dendritic cells, activated CD4+ T cells and CD8+ T cells (Ribas 2018; Topalian 2020). When PD-1 binds to one of its ligands (binding sites), PD-L1 (B7-H1, CD274) or PD-L2 (B7-DC, CD273), T-cell activation is reduced, which weakens the body's ability to eliminate tumor cells (Ribas 2018; Topalian 2020). The immune checkpoint inhibitor, ipilimumab, was the first to be tried for first-line treatment of SCLC and was first to be approved for use. A multicenter, phase II clinical trial compared the efficacy of ipilimumab plus etoposide and platinum-based chemotherapy (cisplatin or carboplatin) versus placebo plus etoposide and platinum-based chemotherapy in the first-line treatment of patients with advanced SCLC (Reck 2013). The results showed that ipilimumab plus chemotherapy significantly improved immune-related progression-free survival (irPFS, i.e. the time from randomization of participants to immune-related progressive disease or death) compared with chemotherapy alone. However, there was no clinically significant improvement in OS, and the incidence of adverse events in the ipilimumab group was higher than that in the group that received chemotherapy alone. This trial was followed by an exploration of the efficacy of ipilimumab combined with etoposide and cisplatin (chemotherapy medicines) in the treatment of SCLC in a phase III clinical study (Reck 2016). The results of the Reck 2016 study showed no benefits in terms of PFS and OS for those in the triple-combination group (ipilimumab plus etoposide and cisplatin) compared with those in the etoposide plus cisplatin group, and the incidence of adverse events, treatment-related discontinuation rates, and mortality in the triple-combination group were higher than those in the etoposide plus cisplatin group.

Recently, a double-blind, placebo-controlled, phase III trial evaluated atezolizumab (a PD-L1 inhibitor) plus carboplatin and etoposide in patients with ES-SCLC (Horn 2018). The results indicated the median OS of the atezolizumab group was 12.3 months and that of the placebo group was 10.3 months; the corresponding median PFS times were 5.2 months and 4.3 months, respectively. This suggests that the addition of atezolizumab to chemotherapy in first-line treatment of ES-SCLC results in significantly longer OS and PFS than chemotherapy alone. Another randomized controlled trial compared the efficacy and safety of durvalumab (a PD-L1 inhibitor) plus platinum-etoposide versus platinum-etoposide alone for first-line treatment of people with ES-SCLC (Paz-Ares 2019). This found that the durvalumab plus platinum-etoposide combination was associated with a significant improvement in OS (median OS: 13.0 months versus 10.3 months), and no differences were found in the incidence of adverse events or mortality between the two groups.

Common adverse events for immune checkpoint inhibitors (PD-1 or PD-L1 inhibitors) occur mainly in the skin, endocrine, hepatic, and pulmonary systems, and the gastrointestinal tract (Xu 2018). Common immune-related adverse events include pneumonitis (inflammation of lung tissue), colitis (inflammation of the colon), and endocrinopathies (hormone-related problems) (Khoja 2017). The deaths of patients receiving PD-1 or PD-L1 inhibitors are mainly attributed to pneumonia, hepatitis, and neurotoxic (nerve-damaging) effects (Martins 2019; Xu 2018). However, the incidence of fatal adverse events associated with immune checkpoint inhibitors is lower than that associated with conventional treatments, such as platinum-doublet chemotherapy and targeted therapies (Martins 2019).

How the intervention might work

Theoretically, PD-1 inhibitors (e.g. nivolumab and pembrolizumab) and PD-L1 inhibitors (e.g. atezolizumab, avelumab, and durvalumab) have the same effect in the immune system as active lymphocytes have against tumor cells. A better understanding of the immune microenvironment is necessary to elucidate the roles of PD-1 and PD-L1 inhibitors in SCLC. Indeed, the immunosuppressive tumor environment observed in SCLC may inhibit the efficacy of immunotherapy. The immunosuppressive pattern in the stroma, the limited PD-L1 expression and the lack of antigen presentation suggest that SCLC has a weak immunogenic T-cell profile, which may have negative impacts on the immune response (Carvajal-Hausdorf 2019; He 2017; Parra 2016; Remon 2021; Yu 2017). According to preclinical evidence, chemotherapeutic agents and targeted therapies may synergize with immune checkpoint inhibitors by increasing the immunogenicity of cancer cells, suppressing immunosuppressive signaling pathways, and increasing the sensitivity of cancer cells to CD8 T-cell-dependent immunosurveillance and rejection (Galluzzi 2015; Spigel 2013).

Mechanisms through which chemotherapy may enhance the activity of immune checkpoint inhibitors include:

- increasing the mutation load in cancer cells (Szikriszt 2016), which causes new binding sites (neo-epitopes) for anti-tumor antibodies. New antigens (molecules that initiate the production of these antibodies) can drive productive anti-tumour immunity (McGranahan 2016; Pardoll 2012; Rizvi 2015; Snyder 2014; Syn 2017);
- inducing immunogenic cell death of cancer cells through exposure to calreticulin (a protein that promotes anti-cancer activity of white blood cells (macrophages)), allied with increased presentation of neoepitopes on antigen-presenting cells (APCs) (Galluzzi 2015; Pfirschke 2016);
- inactivation of STAT6 (a protein involved in signalling within the immune system) in the tumor cells by platinum-containing drugs (e.g. cisplatin, carboplatin, and oxaliplatin), which leads to decreased PD-L2 expression, and results in enhanced recognition and killing by the tumor-specific T cells (Hato 2014);
- regulation of the immune environment by depleting or reducing the unhelpful activity of myeloid-derived cell subsets and immunosuppressive regulatory T-cells, and allowing the reactivation of exhausted antigen-specific CD8 T-cells (Bagchi 2021; Galluzzi 2015; Riaz 2017; Kodumudi 2010; Zitvogel 2008);
- promotion of major histocompatibility complex class I expression and presentation of components of the antigen machinery in cancer cells (i.e. improved presentation of antigens to anti-cancer lymphocytes) (de Biasi 2014; Galluzzi 2012);
- normalizing tumor blood vessels through anti-angiogenic effects (Missiaen 2018), thus allowing for larger CD8 T-cell infiltration.

Why it is important to do this review

Since SCLC has a very high mortality rate, an effective medicine with few serious side effects would be a very helpful treatment option for ES-SCLC. In recent years, immune checkpoint inhibitors have become the most promising new treatment for cancers. Some studies of combinations of chemotherapy and immune checkpoint inhibitors in the treatment of ES-SCLC have reported survival rates that are significantly higher than for treatment with chemotherapy or immune checkpoint inhibitors alone. At present, it is unclear whether treatment effects and adverse events depend upon the population (e.g. age, sex), or the type of treatment agents (e.g. nivolumab, embroil, atezolizumab, or durvalumab), or both.

This review hopes to address these questions in order to enable physicians to make evidence-based decisions when treating patients with ES-SCLC.

OBJECTIVES

To evaluate the efficacy and safety of immune checkpoint inhibitors (anti PD-1 or anti PD-L1) plus platinum-etoposide compared with platinum-etoposide alone for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs). To limit publication bias, we will also incorporate unpublished online data and meeting abstracts if they provide sufficient data for analysis and assessment of possible bias. We will not consider cluster-randomized or quasi-randomized trials.

Types of participants

We will include adults (18 years or more) with histologically or cytologically confirmed SCLC and clinical evidence of extensive stage disease according to a standardized diagnostic system, such as the Veterans Administration Lung Study Group staging system; measurable ES-SCLC according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1; or other well-recognized classifications (Horn 2018). We will apply no restrictions on gender or ethnicity of patients.

Types of interventions

The experimental intervention will be anti PD-1 (for example, nivolumab, pembrolizumab/lambrolizumab, pidilizumab, or tislelizumab) or anti PD-L1 (for example, atezolizumab, avelumab, or durvalumab) plus platinum-etoposide used for the first-line treatment of ES-SCLC.

Since our review focuses on anti PD-1 and anti PD-L1, we will exclude the following interventions:

- anti-CTLA-4 plus platinum-etoposide, and
- anti PD-1/anti PD-L1 plus anti-CTLA-4 plus platinum-etoposide.

The control will be platinum-etoposide alone or platinum-etoposide plus placebo. The platinum-containing part of the combination can be cisplatin, carboplatin, or oxaliplatin.

The eligible comparisons will be:

- anti PD-1 or anti PD-L1 plus platinum-etoposide versus platinum-etoposide; and
- anti PD-1 or anti PD-L1 plus platinum-etoposide versus platinum-etoposide plus placebo.

Types of outcome measures

Primary outcomes

- Overall survival (OS): time from randomization to death from any cause
- Overall rates of any adverse events and serious adverse events (SAEs): severity graded assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (NCI-CTCAE 2010), including the percentage of treatment-related deaths. We define serious adverse events as an adverse event that results in: death; is life-threatening; requires inpatient hospitalization or extends a current hospital stay; results in an ongoing or significant incapacity or interferes substantially with normal life functions; or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.

Secondary outcomes

- Progression-free survival (PFS): time from randomization to the date of disease progression or death from any cause
- Objective response rate (ORR): according to Response Evaluation Criteria in Solid Tumours (RECIST) (Eisenhauer 2009), or immune-related RECIST (Wolchok 2009)
- Health-related quality of life (HRQoL), measured by a validated scale
- Duration of response: time from the first occurrence of a documented, objective, confirmed response to treatment to the time of disease progression as determined by the investigator (according to RECIST) (Eisenhauer 2009), or death from any cause, whichever occurs first.

Search methods for identification of studies

Electronic searches

The Cochrane Lung Cancer Group Information Specialists will search for randomized controlled trials from 2005 onwards. Searching will commence at 2005, as immune checkpoint inhibitors were not available - even in clinical trials - before 2005. The following databases will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1);
- MEDLINE (via PubMed) (Appendix 2);
- Embase (Appendix 3).

We will perform the MEDLINE search using the Cochrane highly sensitive search strategy, sensitivity and precision-maximizing version (2008 version) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 4.4, Box 4.4.f) (Higgins 2011).

The review authors (YG, JHT) will search the following clinical trial registries to identify unpublished and ongoing trials:

- International Clinical Trials Registry Platform (ICTRP) (who.int/ictrp);
- ClinicalTrials.gov (clinicaltrials.gov);
- ISRCTN - metaRegister of Controlled Trials (isrctn.com/page/mrct).

For databases other than MEDLINE, Embase, and CENTRAL, we will adapt the search strategies accordingly. If ongoing trials that have not been published are identified through these searches, we will contact the authors to obtain relevant data.

Searching other resources

We will check reference lists of included studies and previous systematic reviews and contact experts in the field to identify further studies and ongoing clinical trials. We will also handsearch the reports of conferences (from 2017 to date of search) from the following sources:

- American Society of Clinical Oncology (ASCO);
- European Society of Medical Oncology (ESMO);
- European Lung Cancer Conference (ELCC);
- International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC);
- European Society for Medical Oncology Immuno-Oncology congress (ESMO IO);
- American Association of Cancer Research (AACR).

Data collection and analysis

Selection of studies

We will use a reference management software (Covidence) to manage the retrieved records and remove duplicates. Independently, two review authors (YG, SZS) will screen the titles and abstracts of all records to exclude studies that clearly do not meet the inclusion criteria. We will retrieve the full-text of potentially relevant references and the same two review authors (YG, SZS) will assess the full-texts independently to determine their final eligibility according to the inclusion and exclusion criteria. We will resolve any disagreement through discussion or, if required, we will consult a third reviewer (FJS or JHT). We will document reasons for study exclusion. We will identify and exclude duplicate reports and collate multiple reports of the same study. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (YG, SZS) will extract data from the included studies and a third author (ML) will check the data. We will resolve disagreements by consensus, or by involving a third reviewer (JHT). The data extraction form will include the following items:

- methods: study design, randomization protocol, number of study centres and location, duration of study, duration of follow-up period, study setting, withdrawals, date of study;
- participants: sample size (total and by arm), age, gender, stage, severity of condition, diagnostic criteria, smoking history, co-morbidities, previous treatments, inclusion and exclusion criteria;
- interventions: detail of intervention, e.g. choice and dosing schedule of immune checkpoint inhibitors and chemotherapies;
- outcomes: OS, overall rates of any adverse events and serious adverse events, PFS, ORR, HRQoL, duration of response, and treatment-related adverse events, and:
  * for each outcome: outcome definition, unit of measurement (if relevant);
  * results: number of participants allocated to each intervention group, the total number analyzed for each outcome, and the missing participants.

We will extract results as follows:

- for time to event data (e.g. OS, PFS), we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its standard error using the methods of Parmar 1998 and Tierney 2007.
- for dichotomous outcomes (e.g. ORR, adverse events or deaths, if it is not possible to use a HR) we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- for continuous outcomes (e.g. HRQoL measures, duration of response), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and the standard error.

We will extract both unadjusted and adjusted statistics (if reported). Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants will be analyzed in the groups to which they were randomized.

Assessment of risk of bias in included studies

Independently, two review authors (YG, ML) will assess the methodological risk of bias of included studies using the Cochrane risk of bias tool (Higgins 2011). We will resolve disagreements by discussion with a third review author (JHT). We will assess the risk of bias according to the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other potential bias

We will judge each item as being at high, low or unclear risk of bias. We will report results in both a risk of bias graph and a risk of bias summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For time to event data, we will use the HR, if possible.
- For dichotomous outcomes, we will analyze data based on the number of events and the number of participants included in the intervention and comparison groups. We will use these to calculate the RR and 95% confidence interval (CI).
- For continuous outcomes, we will analyze data based on the mean, standard deviation (SD) and number of participants assessed for both the intervention and comparison groups to calculate mean differences (MD) (if trials measured outcomes on the same scale) or standardized mean differences (SMD) (if trials measured outcomes on different scales) between treatment arms with a 95% CI.

If multiple comparisons are reported in a single trial, we will include the relevant arms only. We will conduct meta-analyses only where this is meaningful, that is, if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

Unit of analysis issues

For studies with multiple intervention arms, if clinically meaningful, we will combine groups to create a single pairwise comparison. For example, for a clinical trial of three arms (arm A: immunotherapy plus chemotherapy; arm B: chemotherapy regimen 1; arm C: chemotherapy regimen 2), we will combine the results of arms B + C and compare arm A against the combined results of arm B + C.

Dealing with missing data

We will contact the original study authors to obtain missing data (participant, outcome, or summary data), if possible. If a trial does not report HRs and further data cannot be obtained by contacting authors, we will estimate the HR from log-rank Chi^2 or P values, ratios of median time-to-events, observed-to-expected event ratios, and survival rates at given time points using the methods of Parmar 1998 and Tierney 2007, or read from the Kaplan-Meier survival curves, if provided. We will investigate the effects of any imputed data on pooled effect estimates using sensitivity analyses.

Assessment of heterogeneity

For each meta-analysis, we will evaluate the heterogeneity between studies using the Chi^2 test with I^2statistic and P value. We will consider I^2 values greater than 50% or P values lower than 0.10 in the Chi^2 test as indicative of substantial heterogeneity (Higgins 2019). If we identify substantial heterogeneity, we will perform subgroup and sensitivity analyses to explore it. If we cannot find a reason for the heterogeneity, we will not perform a meta-analysis, but will provide a narrative description of the results of each study.

Assessment of reporting biases

If we identify 10 or more studies that investigate a particular outcome, we will construct and evaluate funnel plots (Sterne 2011) corresponding to meta-analysis of the outcome to assess the potential for small study effects such as publication bias. We

will assess funnel plot symmetry visually, and if asymmetry is suggested, we will perform exploratory analyses to investigate it.

Data synthesis

If the treatments, participants, and clinical question are similar enough for pooling to be appropriate, we will perform meta-analyses. We will use the fixed-effect model to pool trial results into a meta-analysis if the statistical heterogeneity is sufficiently low (I^2 < 50%). If statistical heterogeneity is substantial (I^2 ≥ 50%), we will use the random-effects model with inverse variance for meta-analysis (DerSimonian 1986).

- For time-to-event data, we will pool HRs using the generic inverse variance method.
- For dichotomous outcomes, we will calculate RR for each study and then pool these.
- For continuous outcomes, we will pool the MD between the treatment arms at the end of follow-up if all trials measured the outcome using the same scale, otherwise, we will use SMD.

We will perform statistical analysis according to guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will perform meta-analyses using Review Manager 5.4 software (RevMan 2020). If we are unable to pool data statistically using meta-analysis, we will perform a narrative synthesis of results. We will present the major outcomes and results, organized by intervention categories according to the major types, or aims of the identified interventions, or both.

Subgroup analysis and investigation of heterogeneity

When possible (i.e. when data are available), we will consider the following factors for subgroup analysis:

- anti PD-1 versus anti PD-L1;
- age < 65 years versus ≥ 65 years;
- men versus women.

Sensitivity analysis

We will perform sensitivity analyses defined a priori to assess the robustness of our conclusions. We will conduct sensitivity analysis by excluding:

- studies with a high risk of bias (those classified as high risk in at least one of these criteria: randomization and allocation concealment);
- unpublished studies;
- studies using imputed values for meta-analysis.

Summary of findings and assessment of the certainty of the evidence

We will use the five GRADE criteria (risk of bias, inconsistency, imprecision, indirectness, and publication bias) to rate the overall certainty of the evidence for each outcome. We will generate a summary of findings table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* to present the certainty of evidence of main findings using GRADEpro software (GRADEpro GDT 2015; Higgins 2019). We will justify decisions to downgrade the certainty of the evidence using footnotes, and we will make comments to explain our reasons for doing this.

We will include the following outcomes in the summary of findings table:

- overall survival;
- overall rates of serious adverse events;
- progression-free survival;
- objective response rate;
- HRQoL;
- duration of response.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1. MeSH descriptor: [Small Cell Lung Carcinoma] explode all trees

#2. SCLC

#3. small cell

#4. oat cell

#5. lung cancer*

#6. lung carcinom*

#7. lung neoplasm*

#8. lung tumo*

#9. lung malignan*

#10. #1 or #2

#11. (#3 or #4) and (#5 or #6 or #7 or #8 or #9)

#12. #10 or #11

#13. MeSH descriptor: [Immunotherapy] explode all trees

#14. Immunotherap*

#15. MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees

#16. Immune Checkpoint OR PD-1 Inhibitor* OR PD-L1 Inhibitor* OR Programmed Cell Death Protein 1 Inhibitor* OR Programmed Death-Ligand 1 Inhibitor*

#17. Nivolumab

#18. Nivolumab OR BMS-936558 OR MDX-1106 OR ONO-4538 OR Opdivo

#19. pembrolizumab OR SCH-900475 OR Keytruda OR MK-3475 OR lambrolizumab

#20. pidilizumab OR CT 011

#21. tislelizumab

#22. atezolizumab OR MPDL3280A OR MPDL 3280A OR Tecentriq OR RG7446 OR RG 7446

#23. avelumab OR MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB 0010718C

#24. durvalumab OR MEDI4736 OR MEDI 4736 OR Imfinzi

#25. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#26. MeSH descriptor: [Drug Therapy] explode all trees

#27. MeSH descriptor: [Antineoplastic Agents] explode all trees

#28. Drug Therap* OR Chemotherap* OR Pharmacotherap* OR Antineoplastic* OR Antitumo* OR Anticancer*

#29. MeSH descriptor: [Cisplatin] explode all trees

#30. Cisplatin OR Diamminodichlor* OR Dichlorodiammineplatinum OR NSC 119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam

#31. MeSH descriptor: [Carboplatin] explode all trees

#32. carboplatin OR cis-Diammine* OR CBDCA OR Paraplatin* OR Platinwas OR Ribocarbo OR Carboplat OR Neocarbo OR Carbosin OR Carbotec OR Ercar OR JM 8 OR JM8 OR Nealorin OR NSC 241240 OR NSC241240 OR Blastocarb

#33. MeSH descriptor: [Oxaliplatin] explode all trees710

#34. Oxaliplatin* OR L-OHP Cpd OR Eloxatin* OR ACT 078 OR ACT078

#35. MeSH descriptor: [Etoposide] explode all trees

#36. Etoposide OR Eposide OR Eto GRY OR Exitop OR Lastet OR NSC 141540 OR NSC141540 OR Onkoposid OR Riboposid OR Toposar OR Vepesid OR VP 16 213 OR VP 16213 OR VP 16 OR VP16 OR Vépéside OR Celltop OR Etopos OR Etomedac OR Eposin

#37. (#29 OR #30 OR #31 OR #32 OR #33 OR #34) AND (#35 OR #36)

#38. #28 OR #37

#39. #12 AND #25 AND #38

Appendix 2. PubMed search strategy

#1. small cell lung carcinoma[MeSH Terms]

#2. SCLC

#3. small cell

#4. oat cell

#5. lung cancer*

#6. lung carcinom*

#7. lung neoplasm*

#8. lung tumo*

#9. lung malignan*

#10. #1 OR #2

#11. #3 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9)

#12. #10 OR #11

#13. immunotherapy[MeSH Terms] OR Immunotherap*

#14. Immune Checkpoint Inhibitors[MeSH Terms] OR Immune Checkpoint Inhibitors[Pharmacological Action] OR Immune Checkpoint OR PD-1 Inhibitor* OR PD-L1 Inhibitor* OR Programmed Cell Death Protein 1 Inhibitor* OR Programmed Death-Ligand 1 Inhibitor*

#15. Nivolumab[MeSH Terms] OR Nivolumab OR BMS-936558 OR MDX-1106 OR ONO-4538 OR Opdivo

#16. pembrolizumab[Supplementary Concept] OR pembrolizumab OR SCH-900475 OR Keytruda OR MK-3475 OR lambrolizumab

#17. pidilizumab[Supplementary Concept] OR pidilizumab OR CT 011

#18. tislelizumab[Supplementary Concept] OR tislelizumab

#19. atezolizumab[Supplementary Concept] OR atezolizumab OR MPDL3280A OR MPDL 3280A OR Tecentriq OR RG7446 OR RG 7446

#20. avelumab[Supplementary Concept] OR avelumab OR MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB 0010718C

#21. durvalumab[Supplementary Concept] OR durvalumab OR MEDI4736 OR MEDI 4736 OR Imfinzi

#22. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#23. Drug Therapy[MeSH Terms] OR Drug Therap* OR Chemotherap* OR Pharmacotherap* OR Antineoplastic Agents[MeSH Terms] OR Antineoplastic* OR Antitumo* OR Anticancer*

#24. Cisplatin[MeSH Terms] OR Cisplatin OR Diamminodichlor* OR Dichlorodiammineplatinum OR NSC 119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam

#25. carboplatin[MeSH Terms] OR carboplatin OR cis-Diammine* OR CBDCA OR Paraplatin* OR Platinwas OR Ribocarbo OR Carboplat OR Neocarbo OR Carbosin OR Carbotec OR Ercar OR JM 8 OR JM8 OR Nealorin OR NSC 241240 OR NSC241240 OR Blastocarb

#26. Oxaliplatin[MeSH Terms] OR Oxaliplatin* OR L-OHP Cpd OR Eloxatin* OR ACT 078 OR ACT078

#27. Etoposide[MeSH Terms] OR Etoposide OR Eposide OR Eto GRY OR Exitop OR Lastet OR NSC 141540 OR NSC141540 OR Onkoposid OR Riboposid OR Toposar OR Vepesid OR VP 16 213 OR VP 16213 OR VP 16 OR VP16 OR Vépéside OR Celltop OR Etopos OR Etomedac OR Eposin

#28. #23 OR ((#24 OR 25 OR #26) AND #27)

#29. #12 AND #22 AND #28

#30. 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]

#31. animals[MeSH Terms] NOT humans[MeSH Terms]

#32. #30 NOT #31

#33. #29 AND #32

Appendix 3. Embase search strategy

#1. exp small cell lung cancer/

#2. SCLC.ti,ab,kw.

#3. small cell.ti,ab,kw.

#4. oat cell.ti,ab,kw.

#5. lung cancer*.ti,ab,kw.

#6. lung carcinom*.ti,ab,kw.

#7. lung neoplasm*.ti,ab,kw.

#8. lung tumo*.ti,ab,kw.

#9. lung malignan*.ti,ab,kw.

#10. #1 OR #2

#11. #4 OR #5 OR #6 OR #7 OR #8 OR #9

#12. #3 AND #11

#13. #10 OR #12

#14. exp immunotherapy/

#15. Immunotherap*.ti,ab,kw.

#16. #14 OR #15

#17. 'immune checkpoint inhibitor*'.mp.

#18. (Immune Checkpoint OR PD-1 Inhibitor* OR PD-L1 Inhibitor* OR Programmed Cell Death Protein 1 Inhibitor* OR Programmed Death-Ligand 1 Inhibitor*).ti,ab,kw.

#19. exp nivolumab/

#20. (Nivolumab OR BMS-936558 OR MDX-1106 OR ONO-4538 OR Opdivo).ti,ab,kw.

#21. pembrolizumab.ti,ab,hw,tn,mf,kw.

#22. (SCH-900475 OR Keytruda OR MK-3475 OR lambrolizumab).ti,ab,kw.

#23. pidilizumab.ti,ab,hw,tn,mf,kw.

#24. "CT 011".ti,ab,kw.

#25. tislelizumab.ti,ab,hw,tn,mf,kw.

#26. atezolizumab.ti,ab,hw,tn,mf,kw.

#27. (MPDL3280A OR MPDL 3280A OR Tecentriq OR RG7446 OR RG 7446).ti,ab,kw.

#28. avelumab.ti,ab,hw,tn,mf,kw.

#29. (MSB-0010682 OR MSB0010682 OR bavencio OR MSB0010718C OR MSB 0010718C).ti,ab,kw.

#30. durvalumab.ti,ab,hw,tn,mf,kw.

#31. (MEDI4736 OR MEDI 4736 OR Imfinzi).ti,ab,kw.

#32. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31

#33. exp drug therapy/

#34. exp antineoplastic agent/

#35. (Drug Therap* OR Chemotherap* OR Pharmacotherap* OR Antineoplastic* OR Antitumo* OR Anticancer*).ti,ab,kw.

#36. exp cisplatin/

#37. (Cisplatin OR Diamminodichlor* OR Dichlorodiammineplatinum OR NSC 119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam).ti,ab,kw.

#38. exp carboplatin/

#39. (carboplatin OR cis-Diammine* OR CBDCA OR Paraplatin* OR Platinwas OR Ribocarbo OR Carboplat OR Neocarbo OR Carbosin OR Carbotec OR Ercar OR JM 8 OR JM8 OR Nealorin OR NSC 241240 OR NSC241240 OR Blastocarb).ti,ab,kw.

#40. exp oxaliplatin/

#41. (Oxaliplatin* OR L-OHP Cpd OR Eloxatin* OR "ACT 078" OR ACT078).ti,ab,kw.

#42. exp etoposide/

#43. (Etoposide OR Eposide OR Exitop OR Lastet OR NSC 141540 OR NSC141540 OR Onkoposid OR Riboposid OR Toposar OR Vepesid).ti,ab,kw.

#44. VP 16213.ti,ab,kw.

#45. VP 16.ti,ab,kw.

#46. VP16.ti,ab,kw.

#47. (Vepeside OR Celltop OR Etopos OR Etomedac OR Eposin).ti,ab,kw.

#48. #36 OR #37 OR #38 OR #39 OR #40 OR #41

#49. #42 OR #43 OR #44 OR #45 OR #46 OR #47

#50. #48 AND #49

#51. #33 OR #34 OR #35

#52. #50 OR #51

#53. #13 AND #32 AND #52

#54. crossover procedure/

#55. double-blind procedure/

#56. randomized controlled trial/

#57. single-blind procedure/

#58. random*.mp.

#59. factorial*.mp.

#60. (crossover* OR cross over* OR cross-over*).mp.

#61. placebo*.mp.

#62. (double* adj blind*).mp.

#63. (singl* adj blind*).mp.

#64. assign*.mp.

#65. allocat*.mp.

#66. volunteer*.mp.

#67. #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66

#68. #53 AND #67

#69. (animals NOT humans).mp.

#70. #68 NOT #69

CONTRIBUTIONS OF AUTHORS

YG, SZS,and JHT designed and drafted the protocol.

All authors approved the final version of the protocol.

DECLARATIONS OF INTEREST

Ya Gao: none known

Shuzhen Shi: none known

Ming Liu: none known

Fanqi Wu: none known

Junhua Zhang: none known

Fujian Song: none known

Jinhui Tian: none known

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