Cochrane Library

Cochrane Database of Systematic Reviews

Immune checkpoint inhibitors (anti PD-1 or anti PD-L1) versus chemotherapy for second- or third-line treatment of metastatic non-small cell lung cancer (Protocol)

Moraes FY, Perry LA, Penny-Dimri JC, Ramson D, de Castria TB, Bowman RV, Santos FN, Fong KM, Riera R

Moraes FY, Perry LA, Penny-Dimri JC, Ramson D, de Castria TB, Bowman RV, Santos FN, Fong KM, Riera R.
Immune checkpoint inhibitors (anti PD-1 or anti PD-L1) versus chemotherapy for second- or third-line treatment of metastatic non-small cell lung cancer.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012644.
DOI: 10.1002/14651858.CD012644.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Immune checkpoint inhibitors (anti PD-1 or anti PD-L1) versus chemotherapy for second- or third-line treatment of metastatic non-small cell lung cancer

Fabio Y Moraes[1,2], Luke A Perry[3], Jahan C Penny-Dimri[3], Dhruvesh Ramson[3], Tiago B de Castria[4], Rayleen V Bowman[5], Fábio N Santos[6], Kwun M Fong[5], Rachel Riera[7]

[1]Department of Radiation Oncology, Hospital Sirio Libanes, Sao Paulo, SP, Brazil. [2]Radiation Medical Program, Princess Margaret Cancer Centre, Toronto, Canada. [3]Monash University, Melbourne, Australia. [4]Clinical Oncology, Instituto do Câncer do Estado de São Paulo (ICESP/FMUSP), São Paulo, Brazil. [5]Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, Australia. [6]Medical Oncology, AC Camargo Cancer Center, São Paulo, Brazil. [7]Cochrane Brazil, Centro de Estudos de Saúde Baseada em Evidências e Avaliação Tecnológica em Saúde, São Paulo, Brazil

Contact address: Fabio Y Moraes, Department of Radiation Oncology, Hospital Sirio Libanes, Rua Dona Adma Jafet, 91 Bela Vista, Sao Paulo, SP, 01308-050, Brazil. fymoraes@gmail.com, fabio.ymoraes@hsl.org.br.

Editorial group: Cochrane Lung Cancer Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Moraes FY, Perry LA, Penny-Dimri JC, Ramson D, de Castria TB, Bowman RV, Santos FN, Fong KM, Riera R. Immune checkpoint inhibitors (anti PD-1 or anti PD-L1) versus chemotherapy for second- or third-line treatment of metastatic non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012644. DOI: 10.1002/14651858.CD012644.

ABSTRACT

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

To evaluate the effectiveness and safety of immune checkpoint inhibitors (anti PD-1 or anti PD-L1) compared with standard chemotherapy for second- or third-line treatment of metastatic non-small cell lung cancer (NSCLC).

BACKGROUND

Description of the condition

Lung cancer is the most common malignancy worldwide with more than 1.8 million new cases diagnosed in 2012 (Ferlay 2012). The incidence among men has decreased in the last three decades, while the incidence among women has risen (Ferlay 2012). Nonetheless, lung cancer is still more common among men than women (76.4 cases per 100,000 men in the USA versus 52.7 cases per 100,000 women in the USA) (SEER 2015). Lung cancer incidence rates show substantial variation internationally, with rates highest in Eastern Asia, Eastern Europe and the USA (Ferlay 2012). The most important risk factor for lung cancer remains smoking and its reduction can partially explain the trends observed in lung cancer incidence over recent decades (SEER 2015).

Lung cancer has a significant economic burden. Its cost represents approximately 10% of US cancer care expenditure, which in 2010 was more than 12 billion dollars (Mariotto 2011). Despite these high costs, lung cancer continues to be the most important cause of cancer-related death worldwide, accounting for more than 1.5 million deaths during 2012 (Ferlay 2012).

Lung cancer is classified into two main groups based on tumour histology: small cell lung cancer (15%), and non-small cell lung

cancer (85%) (SEER 2015). Non-small cell lung cancer (NSCLC) is further divided into adenocarcinoma (48%), squamous cell carcinoma (SCC) (25%), and other (27%) (SEER 2015).

In the past, the outcome of advanced NSCLC was poor, with a median survival of 4 to 5 months and 1-year survival rate of 10% (Bunn 1998). Platinum-based therapies as well as non-platinum based single agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan have improved the median survival to 7 to 9 months and 1-year survival rate to over 35% (Carney 1998). Thereafter, trials comparing single-agent cisplatin with cisplatin in combination with newer agents showed significant improvement in survival results with combination therapy (Sandler 2000; Wozniak 1998). Nonetheless, no combination therapy proved superior to the others (Schiller 2002). Other agents such as pemetrexed and bevacizumab combined with platinum-based therapies have shown improved survival results (Sandler 2006; Scagliotti 2008).

Standard first-line treatment for fit patients without an epidermal growth factor receptor (EGFR)-sensitizing mutation or Anaplastic Lymphona Kinase (ALK) gene rearrangement is platinum-based doublets chemotherapy (Masters 2015). Patients with performance status 2 and who are more than 70 years of age may also benefit from single agent or carboplatin-based doublets chemotherapy (Masters 2015).

In the last decade, there have been improvements in understanding of the molecular pathways implicated in the development of targeted therapies and improvements in personalised medicine for NSCLC patients. Mutation of the EGFR gene is present in 10% to 60% of NSCLC, and is associated with the squamous cell carcinoma histology, Asian ethnicity, female gender, and absence of smoking (Sequist 2013). Treatment with EGFR tyrosine kinase inhibitors led to a tumour response rate of over 50% and an almost 100% increase in median progression-free survival (Ferlay 2012; Sequist 2013). ALK rearrangement is less common than EGFR mutations (around 1%); however, ALK-inhibitors achieve results superior to chemotherapy for mutated patients and are now indicated for the first-line treatment of patients with ALK-rearranged tumours (Solomon 2014).

After progression at first-line platinum-based combination therapy or targeted agents there are few treatment options, especially for SCC. Each year, 300,000 people with lung cancer have disease progression during or after first-line chemotherapy (Ferlay 2012). Docetaxel was approved for the second-line treatment of NSCLC based on a randomized clinical trial (RCT) that compared docetaxel 75 mg/m^2 in the first day of a three-week cycle with best supportive care. One hundred and four patients were enrolled in this study and docetaxel improved the time to progression from 6.7 months to 10.6 months ($P < 0.001$), and the median overall survival from 4.6 months to 7.0 months ($P = 0.047$) (Shepherd 2000). The tumour response rate was under 10% in this study and the toxicity of docetaxel in the second-line setting was not negligible (three deaths were observed because of the treatment) (Shepherd 2000). Docetaxel is a semi-synthetic taxane anti-cancer agent. It binds to beta-tubulin molecule and acts against microtubule depolymerization. As a result, docetaxel stabilizes microtubules and reduces their functions during the cell division. This cytotoxic agent can lead to adverse events such as bone marrow suppression, asthenia, alopecia, and peripheral neuropathy (Shepherd 2000).

In 2004, pemetrexed showed similar efficacy results (median survival time was 8.3 versus 7.9 months for pemetrexed and docetaxel, respectively) with significantly less toxicity, however, this treatment is not approved for SCC (Hanna 2004). Erlotinib is an oral tyrosine kynase inhibitor (TKI) that targets the intracellular domain of EGFR. This drug was studied in an RCT that assigned 731 patients in a 2:1 ratio to erlotinib or placebo (Shepherd 2005). The patients were eligible if they had previously failed to one or two chemotherapy-lines. Erlotinib achieved a 30% reduction in the risk of death and became an option for the second- or third-line treatment setting regardless of tumour histology or EGFR mutation status (Shepherd 2005).

Nevertheless, the efficacy of erlotinib for patients without EGFR mutation was denied after a phase III trial that randomized patients after first-line chemotherapy progression to erlotinib or docetaxel (Garassino 2013). All patients' tumours were EGFR wild-type. In this trial, docetaxel achieved a 27% reduction in the risk of death (the median overall survival was 8.2 months versus 5.4 months) (Garassino 2013).

Description of the intervention

Tumour cells acquire several mutations during their development. These mutations may lead to tumour cell immortality and aberrant proliferation. Some of these mutations can produce aberrant proteins that can serve as neo-epitopes that are recognized by the immune system (Chen 2012). Not all tumours have the same burden of mutations, and it is believed that the higher tumour burden leads to high immunogenicity (Chen 2012). Squamous and non-squamous NSCLCs, as well as melanoma, have the highest burden of mutations, and they were studied early with immunotherapy (Lawrence 2013). The immune system is able to recognize and destroy tumour cells as well as pathogenic agents.

Nevertheless, one of the hallmarks of cancer is its ability to avoid the immune system (Hanahan 2011). There are many complex interactions between antigen presenting cells (APC), lymphocytes and tumour cells. The first event is the antigen recognition and preparation by APC. The antigen is presented to the T-cell receptor (TCR) bound to the Major Histocompatibility Complex (MHC). T-cell activation is triggered by the B7-1 or B7-2 present on the APC surface after binding with the CD28 lymphocyte receptor. After activation, T-cell lymphocytes start to produce several cytokines and express several surface receptors in order to regulate the immune system activation and prevent immune exacerbation. These receptors are known as immune checkpoints (Chen 2012).

There are several checkpoints that act as co-stimulators or co-inhibitors of T-cell activity. The most studied is the link between the lymphocytes' membrane receptor, Program Cell Death 1 (PD-1), and its ligand 1 or 2 (PD-L1 or PD-L2), which are expressed by cells from different tissues as well as some tumour cells. This interaction inhibits the immune system and causes lymphocytes to apoptosis (Chen 2012).

Immune checkpoint inhibitors have emerged as agents which may stimulate lymphocytes against tumour cells and might be better tolerated than cytotoxic chemotherapy. There are several monoclonal antibodies against immune checkpoints other than PD-1 or PD-L1 (e.g. CTLA-4, TIM-3, 4-1BBL, OX-40), however, for the treatment of lung cancer the most studied are anti PD-1 or anti PD-L1. These immune checkpoint inhibitors have been evaluated in recent phase III trials (Borghaei 2015; Brahmer 2015; Herbst 2015; Rittmeyer 2017) comparing these new drugs with standard second- or third-line chemotherapy (frequently docetaxel).

Although immune checkpoint inhibitors showed promising results, these drugs are very expensive and the treatment might have a significant social impact. Moreover, despite the relative low incidence of adverse events with immune checkpoint inhibitors compared with docetaxel, these adverse events can be severe and sometimes life-threatening. There is therefore a need for biomarkers and clinical features that can help predict a response to treatment leading to the individualization of care.

How the intervention might work

The majority of immune checkpoint inhibitors studied in the second-line setting for the treatment of NSCLC act on the PD-1/PD-L1 pathway. There are two groups of agents: anti PD-1 (e.g. nivolumab and pembrolizumab) and anti PD-L1 (e.g. atezolizumab, avelumab and durvalumab). Theoretically, the two targets may have the same efficacy in the immune system. It was believed that anti PD-1 agents that bind the lymphocyte receptor and block PD-L1 and PD-L2 binding could be more active, but could lead to more adverse events than anti-PD-L1 agents; however, this has not been shown in recent trials (Pilotto 2015). Consequently, we know that all immune checkpoint inhibitors activate lymphocytes against tumour cells. Although they have a reasonable safety profile, these compounds can produce several auto-immune adverse reactions such as pneumonitis, endocrinopathies, and colitis (Borghaei 2015; Brahmer 2015; Herbst 2015).

In recent years, many studies assessed a predictive biomarker for the efficacy of immune checkpoint inhibitors. Although tumour PD-L1 expression was the most frequently evaluated biomarker because of its direct relationship with the immune checkpoint inhibitors' mechanism of action, there is no consensus yet as to whether PD-L1 should be used as a predictive biomarker and the standard way to assess it (Pilotto 2015).

Why it is important to do this review

The Food and Drug Administration (FDA) has approved nivolumab for the second-line treatment of NSCLC based upon the results of RCTs. These trials raised some controversy regarding progression-free survival (PFS) and the potential role of tumour PD-L1 expression as a predictive biomarker.

The search for a reliable biomarker (e.g. PD-L1 expression) or patient clinical features (e.g. smoking status and tumour histology) that are related to treatment benefit is essential because of the elevated costs of these innovative therapies.

Furthermore, despite apparent superiority against docetaxel, questions remain regarding the optimal time to use these agents (second-line or beyond), disparities between squamous cell cancer and non-squamous cell cancer outcomes, the role of tumour PD-L1 expression as a predictive biomarker, and its most reliable assessment method as well as its cutoff value.

A systematic review could answer the question of whether these agents are really better than chemotherapy in these advanced lines of treatment, analyse the role of tumour PD-L1 expression as a predictive biomarker, and help physicians to make an evidence-based decision when treating the individual with NSCLC.

OBJECTIVES

To evaluate the effectiveness and safety of immune checkpoint inhibitors (anti PD-1 or anti PD-L1) compared with standard chemotherapy for second- or third-line treatment of metastatic non-small cell lung cancer (NSCLC).

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomized controlled trials (RCTs) with or without blinding, including those reported as full text, those published as abstract only, and unpublished data. We will include both superiority or non-inferiority trials.

We will exclude cluster-randomized or cross-over design studies as this design can introduce dependence (or clustering) reducing their statistical power. Moreover we consider that cluster-randomized trials are an uncommon RCT design for NSCLC intervention trials.

Types of participants

We will consider studies that enrolled patients 18 years of age or older with pathologically confirmed NSCLC, squamous as well as non-squamous histology, with radiologically confirmed metastatic disease (Edge 2010). Presence or absence of tumoral PD-L1 expression will be allowed. Advanced disease can be at the time of diagnosis or due to progression.

Additionally, the participants must have been previously treated and failed with at least one platinum-based chemotherapy regimen or targeted therapy (for EGFR-mutated, EML-ALK translocated, and ROS1-mutated population).

Types of interventions

Intervention: anti PD-1 (nivolumab or pembrolizumab) or anti PD-L1 (atezolizumab, avelumab or durvalumab)

Control: chemotherapy

Types of outcome measures

Primary outcomes

- Overall survival (OS) on intention-to-treat analysis.
- Frequency of participants with at least one adverse event. The frequency will be considered separately for each grade of toxicity (I or II, and III or IV) in accordance with the National Cancer Institute Common Toxicity Criteria - CTCAE version 4 (NCI 2009).

Secondary outcomes

- Overall survival considering one-, two-, three-, four-, and five-year survival rates.
- Progression-free survival (PFS) (defined as the time from randomization to the first disease progression according to the investigator's or central assessment of the Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) (Therasse 2000) on intention-to-treat analysis.
- Response rate (according to the investigator's or central assessment of the RECIST version 1.1 [Therasse 2000) and/or the immune-related response criteria [Wolchok 2009)).
- Role of PD-L1 expression, its degree and its significance as a predictive biomarker.
- Quality of life, regardless of the assessment tool.

Search methods for identification of studies

We will implement electronic search strategies according to recommendations of the Cochrane Lung Cancer Review Group. The search strategies are based on the search strategy developed for MEDLINE, revised for each database. It uses a combination of controlled vocabulary and free-text terms and is linked with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Electronic searches

We will conduct a literature search to identify published and unpublished randomized controlled trials. No data or language restrictions will be applied. When necessary, we will translate the non-English language papers and fully assess them for potential inclusion in the review. We will search the following electronic databases (Appendix 1).

- Cochrane Central Register of Controlled Trials (CENTRAL, current edition).
- MEDLINE (1966 to present).
- Embase (1988 to present).
- LILACS (1990 to present).

Searching other resources

We will check reference lists of primary studies and review articles for additional references. We will contact experts on the topic and ask them to identify other published and unpublished studies presented at international conferences. We will also contact the pharmaceutical industry for additional studies.

Grey literature databases

We will search the following databases.

- Health Management Information Consortium (HMIC) database www.ovid.com/site/catalog/DataBase/99.jsp.
- National Technical Information Service (NTIS) database www.ntis.gov/products/ntisdb.aspx.
- OpenGrey www.opengrey.eu/.

Clinical trials registers/trial result registers

We will also search at the following clinical trials registers.

- AstraZeneca Clnical Trials.
- Bristol-Myers Squibb Clinical Trial Registry.
- Clinical Trials.gov.
- ISRCTN Registry:
  - archived registers www.isrctn.com/search?q=&filters=conditionCategory%3ACancer%2CtrialStatus%3ACompleted&searchType=basic-search;
  - active registers www.isrctn.com/search?q=&filters=conditionCategory%3ACancer%2CtrialStatus%3AOngoing&searchType=basic-search.
- Eli Lilly and Company Clinical Trial Registry:
  - www.lillytrials.com;
  - www.lillytrials.com/initiated/initiated.html.

- EU Clinical Trials Register.
- GlaxoSmithKline Clinical Study Register.
- International Clinical Trials Registry Platform Search Portal.
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Clinical Trials Portal.
- Roche Clinical Trials Results Database.

Proceedings of meetings

- American Society of Clinical Oncology (ASCO) (from 2013 to present).
- International Association for the Study of Lung Cancer (IASLC) World Lung Cancer Conference (from 2013 to present).
- Proceedings of the European Society of Medical Oncology (ESMO) (from 2013 to present).
- Proceedings of the European Cancer Conference Organization (ECCO) (from 2013 to present).

Data collection and analysis

Selection of studies

Three review authors (FYM, TBC and FNS) will independently screen titles and abstracts for potential inclusion. Studies will be classified as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text study reports/publication and three review authors (FYM, TBC and FNS) will independently assess the full text and identify studies for inclusion or exclusion, and also record reasons for exclusion. We will solve any disagreement through discussion or, if required, we will consult a additional review author (RR). We will identify and exclude duplicates and gather multiple reports (ancillary references) of the same study (since each study rather than each report is the unit of interest in the review).

We will correspond with investigators, where appropriate, to clarify study eligibility (it may be appropriate to request further information, such as missing results, at the same time).

We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

We will use a standard form to handle methodological characteristics and outcome data from included studies. Three review authors (PA, TBC and FNS) will extract the following information.

1. Methods: study design, duration of study, duration of follow-up period, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: sample size, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria, previous treatments.
3. Interventions: intervention, comparison, concomitant medications, excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

One review author (PA) will copy across the data from the data collection form into the Review Manager file (Review Manager 2014). We will double check that the data are entered correctly by comparing the included trial reports with how the data are presented in the systematic review. A second review author (TBC or FNS) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (FYM, TBC and FNS) will independently evaluate the risk of bias for each study using the criteria recommended in the 'Risk of bias' (RoB) tool described in Chapter 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement will be solved by an additional review author (RR). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of outcome assessment.
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Other bias.

The domain from the RoB tool called 'Blinding of participants and personnel' will not be evaluated because of intrinsic difficulties associated with blinding of patients and healthcare providers included in a trial with novel therapies such as immune checkpoints inhibitors that can lead to different toxicity profiles, which are easily manageable when detected early. For a similar reason, we will not judge the domain 'Blinding of outcome assessment' for the outcome 'Frequency of participants with at least one adverse event'.

We will classify each domain as high, low or unclear risk and provide a justification for our judgment in the 'Risk of bias' table (for details, see Table 8.5c of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). We will summarise the risk of bias across different studies for almost all domains with only one entry per study. We will consider the domains 'Blinding of outcome assessment' (except for the outcome 'Frequency of participants with at least one adverse event') and 'Incomplete outcome data' separately for different outcomes (i.e. for unblinded outcome assessment, risk of bias for all-cause mortality may be

different than for a patient-reported quality of life scale).

Measures of treatment effect

We will assess dichotomous data as risk ratio and continuous data as mean difference or standardised mean difference. We will confirm that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction and report if the directions were reversed when it was required.

The results for time-to-event outcomes (such as OS and PFS) will be presented as hazard ratio (HR) and 95% confidence intervals (CI). HR for each individual trial will be extracted either directly from published data, whenever available, or indirectly estimated using reported summary statistics or Kaplan-Meier curves according to the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011; Parmar 1998; Tierney 2007).

We will carry out meta-analyses only when this is meaningful; in other words, only when the treatments, participants and clinical question are similar enough for pooling to be appropriate.

When multiple trial arms are reported in a unique study, we will include only the relevant arms. If two comparisons (e.g. intervention drug 1 dose X versus control drug and intervention drug 1 dose Y versus control drug) must be inserted into the same meta-analysis, we will halve the control group to avoid double counting.

Unit of analysis issues

We will analyse each eligible trial for potential unit of analysis errors such as using non-standard trial design or reporting multiple observations for the same outcome. We anticipate that these errors will be rare in our systematic review; however, if a trial reports multiple observations for the same outcome it will be excluded from the meta-analysis. We will assess all trials with potential unit of analysis errors according to the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We will contact authors and/or study sponsors in order to verify additional study characteristics and obtain missing outcome data when possible (i.e. when a study is published as abstract only).

Assessment of heterogeneity

We will apply the I^2 statistic (Higgins 2003) to measure heterogeneity among the trials in each meta-analysis. If we identify substantial heterogeneity we will explore it by prespecified subgroup analysis. Statistical diversity will be investigated by estimates of treatment effect through forest plots produced using Review Manager 5 software (Review Manager 2014). An I^2 value higher than 50% will be considered as substantial heterogeneity (Higgins 2011). In this case, we will use the random-effects model rather than the fixed-effect model.

Assessment of reporting biases

We will contact study authors for missing outcome data. When this is not possible, and the missing data are thought to lead serious bias, the impact of including such studies in the overall assessment of results will be investigated by a sensitivity analysis**.**

If it is possible to pool more than ten trials, we will create and investigate a funnel plot to explore publication biases.

Data synthesis

We will carry out meta-analyses only when the treatments, participants and clinical question are similar enough for pooling to be appropriate.

We will generate a 'Summary of findings' table using the following outcomes: response rate, adverse events rate, hazard ratios (HR) estimated for progression-free survival and overall survival, and survival rates at one, two, three, and five years. We will use the five GRADE criteria (study limitations, consistency of effect, imprecision, indirectness and publication bias) to evaluate the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for each prespecified outcome. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook* (Higgins 2011) and use GRADEpro software (GRADEpro GDT 2015). We will justify all decisions to down- or upgrade the quality of evidence using footnotes and make comments to facilitate the readers' comprehension.

The default analysis will be using the fixed-effect model unless there is moderate to substantial heterogeneity, where random-effects modeling will be used.

Subgroup analysis and investigation of heterogeneity

When possible (data available), the following will be considered for subgroup analysis.

- Squamous cell NSCLC or non-squamous cell NSCLC.
- Anti PD-1 or anti PD-L1.
- EGFR mutant or wild type.
- Prior lines of therapy: 1 or more.
- Prior TKI or non-prior TKI.
- ECOG 0 or 1 or 2 (if included).
- Presence or absence of tumoral PD-L1 over expression (defined by the studies' authors or established according to the most frequent value among all studies).

Sensitivity analysis

We will conduct predefined sensitivity analysis to assess the robustness of the conclusions considering studies with high risk of bias (those classified as high risk in at least one of these criteria: randomization, allocation concealment and blinding) versus studies with low risk of bias.

ACKNOWLEDGEMENTS

We acknowledge the help and support of the Lung Cancer Review Group, including the Information Specialists François Calais and Giorgio Maria Agazzi for designing search strategies The authors also thank the following editors and peer referees who provided comments to improve the protocol: Corynne Marchal (Managing Editor), Mia Schmidt-Hansen (Editor), Elisabeth Quoix (Editor), Marta Roqué (Editor), Fergus Macbeth (Editor of the Lung Cancer Group), Virginie Westeel (Editor of the Lung Cancer Group and Sign-off Editor) (Sophie Paget-Bailly (Statistician), Ian Stubbing (Consumer).

We acknowledge the support and oncological expertise of Pedro Aguiar Jr in writing and peer reviewing this protocol.

REFERENCES

Additional references

Borghaei 2015
Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New England Journal of Medicine* 2015;**373**:1627–39.

Brahmer 2015
Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *New England Journal of Medicine* 2015;**373**:123–35.

Bunn 1998
Bunn PA Jr, Vokes EE, Langer CJ, Schiller JH. An update on North American randomized studies in non-small cell lung cancer. *Seminars in Oncology* 1998;**25**:2–10.

Carney 1998
Carney DN. New agents in the management of advanced non-small cell lung cancer. *Seminars in Oncology* 1998;**25**: 83–8.

Chen 2012
Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clinical Cancer Research* 2012;**18**:6580–7.

Edge 2010
Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Manual*. 7th Edition. New York (NY): Springer-Verlag, 2010.

Ferlay 2012
Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. International Agency for Research on Cancer 2014; Vol. 1.1.

Garassino 2013
Garassino MG, Martellix O, Broggini M, Farina G, Veronese S, Rulli E, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncology* 2013;**14**(10): 981–8.

GRADEpro GDT 2015 [Computer program]
GRADE Working Group, McMaster University. GRADEpro. https://gradepro.org/ (accessed 12 December 2016). Hamilton (ON): GRADE Working Group, McMaster University, 2015.

Hanahan 2011
Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646–74.

Hanna 2004
Hanna N, Shepherd FA, Fossella FV, Pereira JR, de Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *Journal of Clinical Oncology* 2004;**22**:1589–97.

Herbst 2015
Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Hanx JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2015;**387**(10027):1540–50.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration.

Lawrence 2013
Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer

and the search for new cancer-associated genes. *Nature* 2013;**499**:214–8.

Liberati 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology* 2009;**62**(10):e1–34.

Mariotto 2011
Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *Journal of the National Cancer Institute* 2011; **103**(2):117–28.

Masters 2015
Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, et al. Systemic therapy for stage IV non-small-cell lung cancer update. *Journal of Clinical Oncology* 2015; **33**(30):3488–515.

NCI 2009
National Cancer Institute. Common Terminology Criteria for Adverse Events. 2009; Vol. v 4.0.

Parmar 1998
Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival end-points. *Statistics in Medicine* 1998;**17**(24): 2815–34.

Pilotto 2015
Pilotto S, Kinspergher S, Peretti U, Calio A, Carbognin L, Ferrara R, et al. Immune checkpoint inhibitors for non-small-cell lung cancer: does that represent a 'new frontier'? . *Anticancer Agents in Medicinal Chemistry* 2015;**15**(3): 307–13.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre: The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre: The Cochrane Collaboration, 2014.

Rittmeyer 2017
Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;**389**(10066):255-65.

Sandler 2000
Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. *Journal of Clinical Oncology* 2000;**18**:122–30.

Sandler 2006
Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *New England Journal of Medicine* 2006;**355**:2542–50.

Scagliotti 2008
Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *Journal of Clinical Oncology* 2008; **26**:3543–51.

Schiller 2002
Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *New England Journal of Medicine* 2002;**346**:92–8.

SEER 2015
SEER Cancer Statistics Factsheets: Lung and Bronchus Cancer. National Cancer Institute 2015 (accessed 12 December 2016).

Sequist 2013
Sequist LV, Yang JCH, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *Journal of Clinical Oncology* 2013; **31**:3327–34.

Shepherd 2000
Shepherd F, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. *Journal of Clinical Oncology* 2000;**18**: 2095–103.

Shepherd 2005
Shepherd FA, Pereira JR, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *New England Journal of Medicine* 2005;**353**:123–32.

Solomon 2014
Solomon BJ, Mok T, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *New England Journal of Medicine* 2014;**371**:2167–77.

Therasse 2000
Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. *Journal of the National Cancer Institute* 2000;**92**:205–16.

Tierney 2007
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.

Wolchok 2009
Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clinical Cancer Research* 2009;**15**:7412–20.

Wozniak 1998
Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, et al. Randomized phase

III trial of cisplatin (CDDP) vs. CDDP plus navelbine (NVB) in treatment of advanced non-small cell lung cancer (NSCLC): an update of a Southwest Oncology Group study (SWOG-9308). Proceedings of the American Society of Clinical Oncology (Abstract #1744). 1998; Vol. 17:453a.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Embase

#1 'lung cancer'/exp
#2 'non small cell lung cancer'/exp
#3 'non-small cell':tn,lnk,ab,ti
#4 'nonsmall cell':tn,lnk,ab,ti
#5 'lung tumor'/exp
#6 'lung carcinoma'/exp
#7 'lung neoplasm':tn,lnk,ab,ti
#8 'nsclc':tn,lnk,ab,ti
#9 'lung carcinom*':tn,lnk,ab,ti
#10 'lung neoplasm*':tn,lnk,ab,ti
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12 'immune checkpoint inhibitor*':tn,lnk,ab,ti
#13 'nivolumab':tn,lnk,ab,ti
#14 'pembrolizumab':tn,lnk,ab,ti
#15 'atezolizumab':tn,lnk,ab,ti
#16 'avelumab':tn,lnk,ab,ti
#17 'durvalumab':tn,lnk,ab,ti
#18 'immunotherapy'/exp
#19 'immunotherap*':tn,lnk,ab,ti
#20 'anti pd-1':tn,lnk,ab,ti
#21 'anti pd-l1':tn,lnk,ab,ti
#22 'pd-1 inhibitor*':tn,lnk,ab,ti
#23 'pd-l1 inhibitor*':tn,lnk,ab,ti
#24 'pd-1 block*':tn,lnk,ab,ti
#25 'pd-l1 block*':tn,lnk,ab,ti
#26 'target* pd-1':tn,lnk,ab,ti
#27 'target* pd-l1':tn,lnk,ab,ti
#28 'programmed death 1':tn,lnk,ab,ti
#29 'programmed death ligand':tn,lnk,ab,ti
#30 'anti programmed death':tn,lnk,ab,ti
#31 'programmed death 1 ligand 1'/exp
#32 'programmed death 1 receptor'/exp
#33 'biomarker*':tn,lnk,ab,ti
#34 #12 OR #13 OR #14 OR #15 OR #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 OR #32 OR #33

#35 #11 AND #34
#36 random*
#37 factorial*
#38 placebo*
#39 doubl* NEAR/2 blind*
#40 singl* NEAR/2 blind*
#41 assign*
#42 allocat*
#43 volunteer*
#44 'double-blind procedure'/exp
#45 'randomized controlled trial'/exp
#46 'single-blind procedure'/exp
#47 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48 #35 AND #47

MEDLINE

#1,"Search Carcinoma, Non-Small-Cell Lung[MeSH Terms]"
#2,"Search nsclc[Title/Abstract]"
#3,"Search lung cancer*[Title/Abstract]"
#4,"Search lung carcinoma*[Title/Abstract]"
#5,"Search lung neoplasm*[Title/Abstract]"
#6,"Search lung tumor*[Title/Abstract]"
#7,"Search lung tumour*[Title/Abstract]"
#8,"Search non-small cell*[Title/Abstract]"
#9,"Search nonsmall cell*[Title/Abstract]"
#10,"Search (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)"
#11,"Search #1 OR #2 OR #10",50583,05:53:21
#12,"Search checkpoint inhibit*[Title/Abstract]"
#13,"Search antibodies, monoclonal[MeSH Terms]"
#14,"Search antibodies, monoclonal, humanized[MeSH Terms]"
#15,"Search nivolumab[Title/Abstract]"
#16,"Search pembrolizumab[Title/Abstract]"
#17,"Search atezolizumab[Title/Abstract]"
#18,"Search avelumab[Title/Abstract]"
#19,"Search durvalumab[Title/Abstract]"
#20,"Search Antigens, CD274[MeSH Terms]"
#21,"Search anti pd-1[Title/Abstract]"
#22,"Search anti pd-l1[Title/Abstract]"
#23,"Search pd-1[Title/Abstract]"
#24,"Search pd-l1[Title/Abstract]"
#25,"Search pd-l1"
#26,"Search programmed death 1[Title/Abstract]"
#27,"Search programmed death ligand[Title/Abstract]"
#28,"Search programmed cell death 1 receptor[MeSH Terms]"
#29,"Search biomarker*[Title/Abstract]"
#30,"Search #12 OR #13 OR #14 OR #15 OR #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 #39"
#31,"Search #11 AND #30"
#32,"Search randomized controlled trial[Publication Type]"
#33,"Search controlled clinical trial[Publication Type]"
#34,"Search randomized[Title/Abstract]"
#35,"Search placebo[Title/Abstract]"

#36,"Search drug therapy[MeSH Subheading]"
#37,"Search randomly[Title/Abstract]"
#38,"Search trial[Title/Abstract]"
#39,"Search groups[Title/Abstract]"
#40,"Search #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39"
#41,"Search animals [MeSH Terms] NOT humans [MeSH Terms]"
#42,"Search #40 NOT #41"
#43,"Search #31 AND #42"

Cochrane Central Register of Controlled Trials (CENTRAL)

#1(lung cancer*):TI,AB,KY
#2(non-small cell*):TI,AB,KY
#3(non small cell*):TI,AB,KY
#4(nonsmall cell*):TI,AB,KY
#5MESH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES
#6MESH DESCRIPTOR Carcinoma, Non-Small-Cell Lung EXPLODE ALL TREES
#7nsclc:TI,AB,KY
#8#1 or #2 or #3 or #4 or #5 or #6 or #7
#9(checkpoint inhibit*):TI,AB,KY
#10MESH DESCRIPTOR antibodies, monoclonal EXPLODE ALL TREES
#11MESH DESCRIPTOR antibodies, monoclonal, humanized EXPLODE ALL TREES
#12nivolumab:TI,AB,KY
#13pembrolizumab:TI,AB,KY
#14atezolizumab:TI,AB,KY
#15avelumab:TI,AB,KY
#16durvalumab:TI,AB,KY
#17MESH DESCRIPTOR Antigens, CD274 EXPLODE ALL TREES
#18(anti pd-1):TI,AB,KY
#19(anti pd-l1):TI,AB,KY
#20pd-1:TI,AB,KY
#21pd-l1:TI,AB,KY
#22(programmed death 1):TI,AB,KY
#23(programmed death ligand):TI,AB,KY
#24(programmed cell death 1 receptor):TI,AB,KY
#25biomarker*:TI,AB,KY
#26#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27#8 AND #26

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: FYM, RR, FNS, TBC

Designing the protocol: FYM, RR, FNS, TBC

Coordinating the protocol: FYM, RR

Designing search strategies: FC, GMA - IS Lung Cancer Group

Writing the protocol: FYM, RR, LAP, JPD, DMR, KF, RB

Providing general advice on the protocol: LAP, JPD, DMR, KF, RB

Performing previous work that was the foundation of the current study: PA

DECLARATIONS OF INTEREST

Fabio Y Moraes: none known

Luke A Perry: none known

Jahan C Penny-Dimri: none known

Dhruvesh Ramson: none known

Tiago B de Castria: none known

Rayleen V Bowman: received partial reimbursement for travel and accommodation as Honorarium for chairing and discussant activities at World Lung Cancer Conference - Sydney 2013. The Prince Charles Hospital Foundation: RVB is holding this grant as principal investigator, and several others (NHMRC, and other competitive funding bodies as co-investigator or associate investigator). Asgard: RVB has a managed share portfolio tied to superannuation.

Fábio N Santos: certifies to have no affiliations with or involvement in any organization or entity with any financial interest in the work for publication or non-financial interest in the subject matter or materials discussed in this manuscript. However, he has received relevant financial activities outside the submitted work for lectures from Merck-Sharp & Dome, Bristol-Meyers Squibb and Roche and for meeting expenses from Pfizer, Merck-Sharp Dome and Bayer.

Kwun M Fong: is Secretary-General of the Asian Pacific Society of Respirology (APSR). He has recieved travel costs reimbursed for official APSR meetings. NHMRC, Hospital Foundation, Cancer Australia, Cancer Council Qld, ACRF: Conference support for speaking/facilitating at various educational meetings from organisers of meetings which include not-for-profits and industry - only travel expenses reimbursed. Attendance and participation at educational meetings including industry and professional colleges/societies - meals and travel provided/reimbursed when needed.

Chair, Lung Foundation Australia Lung Cancer Consultative Group - travel expenses reimbursed. Other work-related meetings, eg. Cancer Australia - travel expenses reimbursed.

Reimbursed for time/travel as reviewer for grant applications for research/cancer organisations/agencies, and honoraria for time to mark higher degree theses.

Rachel Riera: none known