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[Intervention Protocol]

Adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) for the treatment of people with resected stage I to III non-small-cell lung cancer and EGFR mutation

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ABSTRACT

Objectives

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

To assess the effectiveness and safety of adjuvant EGFR tyrosine kinase inhibitors (TKIs) in patients with resected stage I to III non-small-cell lung cancer (NSCLC) harbouring an activating EGFR mutation.

BACKGROUND

Description of the condition

Lung cancer causes the most deaths from cancer worldwide, and non-small-cell lung cancer (NSCLC) accounts for 85% of all cases (Sung 2021). Most people with NSCLC are diagnosed when the disease is already advanced, with only one-third presenting with resectable disease and thus being eligible for surgery (Ganti 2021). Nevertheless, despite the curative intent of the treatment, prognosis remains limited for the common relapses. With a five-year median follow-up, the percentage of people who have disease recurrence or who die after surgery ranges from 45% among patients with stage IB disease to 76% among those with stage III disease, regardless of the use of postoperative chemotherapy (Pignon 2008; Burdett 2015).

About half of NSCLCs, especially adenocarcinomas, harbour at least one oncogenic driver mutation that can potentially be targeted, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS-1), Kirsten rat sarcoma virus (KRAS), v-Raf murine sarcoma viral oncogene homolog B (BRAF), human epidermal growth factor receptor 2 (HER2), mesenchymal-epithelial transition (MET), rearranged during transfection (RET), and neurotrophic tyrosine receptor kinase (NTRK) gene alterations (Jordan 2017). Somatic mutations of EGFR responsible for its aberrant constitutive activation are found in about 50% of Asian patients and 10% to 15% of European patients with adenocarcinoma (Zhang 2016). The most common conferring sensitivity to EGFR tyrosine kinase inhibitors (TKIs) are in-frame deletions occurring in exon 19 (Del19) and point mutations in codon 858 (exon 21) (Lynch 2004). These mutations are more commonly observed in adenocarcinomas arising in those who have never smoked, females, and young patients (Pao 2004).

Description of the intervention

Currently, cisplatin-based adjuvant chemotherapy represents the standard of care in people with completely resected stage II to IIIA NSCLC, whether or not they harbour mutation (Postmus 2017). Postoperative treatment may also be considered in selected cases of people with stage IB disease and high-risk features (Strauss 2008). However, two meta analyses showed that adjuvant chemotherapy is associated with a relatively small overall survival absolute benefit at five years, ranging from 4% to 5.4% (Pignon 2008; Burdett 2015).

The most commonly used regimen in the adjuvant setting is the combination of cisplatin and vinorelbine, but toxicities of this doublet are non-negligible and compliance suboptimal. Age, performance status, pre-existing comorbidities and recovery from surgery must be taken into account for eligibility to treatment (Postmus 2017). Neutropenia, anaemia and febrile neutropenia are the most common haematological grade 3 to 4 adverse events. Other common non-haematological toxic effects include nausea/vomiting, asthenia, anorexia, and infections (Winton 2005; Douillard 2006).

In October 2021 atezolizumab, an anti-programmed death-ligand 1 (PDL1) drug, was approved by the Food and Drug Administration (FDA) for postoperative treatment following resection and platinum-based chemotherapy in people with stage II to IIIA NSCLC whose tumours have PD-L1 expression on 1% or more of tumour cells. The approval was based on the positive results of a randomised phase-3 trial showing that atezolizumab met its primary end point of increasing disease-free survival over best supportive care in this population. The trial included people with EGFR mutations and a certain benefit was seen in people whose PD-L1 expression was 1% or more of tumour cells, although these data need to be carefully interpreted and confirmed, due to the small number of people included with these mutations (Felip 2021).

The effectiveness of EGFR TKIs in advanced NSCLC with activating EGFR mutations has led to the investigation of their use as adjuvant treatment for resectable disease. Gefitinib, erlotinib and icotinib are first-generation EGFR TKIs that selectively and reversibly inhibit the EGFR tyrosine kinase domain. Gefitinib and erlotinib are approved worldwide for treating people with EGFR-mutant advanced NSCLC, while icotinib is only approved in China. They have shown benefits in terms of response, progression-free survival, and health-related quality of life over platinum-based chemotherapy in metastatic EGFR-mutant NSCLC. They were the standard first-line treatment in this setting for many years before the advent of osimertinib (Pao 2010).

The second generation of EGFR TKIs includes irreversible inhibitors afatinib, shown to be superior to platinum-based chemotherapy in untreated patients (Yang 2015), and dacomitinib, which has been shown to achieve better PFS than the first-generation EGFR TKI gefitinib (Yi-Long Wu 2017). Thus they represent another FDA-approved treatment option in front-line EGFR-mutant metastatic NSCLC.

Unfortunately, resistance to first- and second-generation inhibitors inevitably appears after nine to 14 months of treatment, in about half of cases driven by the acquisition of a T790M EGFR resistance mutation (Sequist 2011). Osimertinib is a third-generation oral EGFR-TKI that potently and selectively inhibits both EGFR sensitizing mutations and the resistant exon 20 EGFR T790M mutation, and has clinical activity against central nervous system metastases. Osimertinib is approved in people with the T790M mutation at the time of progression on first/second-generation EGFR TKIs (Cross 2014). Moreover, upfront osimertinib is the preferred choice in the first-line treatment of people with NSCLC and sensitizing EGFR mutations, since it has been shown to significantly improve progression-free survival and overall survival compared to gefitinib or erlotinib in this setting (Ramalingam 2020).

Although EGFR TKIs demonstrate a different toxicity profile compared to cytotoxic agents, the inhibition of the non-mutant form of EGFR in the skin and gastrointestinal tract is responsible for their side effects, such as rash, dry skin, stomatitis, and diarrhoea (Ding 2017). However, adverse events are usually mild or moderate, manageable, and responsible for rather low discontinuation rates.

In December 2020, the FDA approved osimertinib as adjuvant treatment of EGFR mutant early-stage NSCLC after tumour resection, based on the improvement in disease-free survival shown in the ADAURA trial (Wu 2020). The recommended dose is 80 mg orally once daily until disease recurrence or for up to three years. Previous data suggested that adjuvant first-generation EGFR TKIs can provide clinical benefit in people with EGFR mutant NSCLC. However, adjuvant phase-3 trials of first-generation EGFR-TKIs were not practice-changing.

How the intervention might work

Many people with resectable lung cancer eventually relapse with distant metastases, indicating that an occult tumour cell dissemination might already be present at the time of primary surgery (Demicheli 2012). The aim of adjuvant treatment is to prevent recurrence and improve survival after curative-intent surgery, through eradication of micrometastatic disease. Many agents demonstrating a survival advantage in metastatic disease have been afterwards investigated as adjuvant treatment. After resection of oncogene-addicted NSCLC, targeted therapies, as EGFR TKIs, could act effectively to eliminate the micrometastatic disease, thus improving the efficacy of their cytotoxic counterpart, with a possibly better profile of toxicity (Marks 2008).

Epidermal growth factor receptor is a transmembranous protein tyrosine kinase member of the ErbB receptor family, also known as ErbB1 or HER1. Following binding of its ligands, such as epidermal growth factor (EGF) or transforming growth factor α (TGFα), it can form homodimers or heterodimers with other members of the receptor family, such as ErbB2 (HER2), ErbB3 (HER3), or ErbB4 (HER4), further activating receptor autophosphorylation (Roskoski 2014). This phosphorylation triggers activation of intracellular pathways, such as MAPK/ERK and PI3K/Akt, which control cell growth, adhesion, survival, migration, proliferation, and differentiation. Therefore, aberrant activation of EGFR is closely associated with dysregulated cell proliferation, invasiveness, metastases, angiogenesis, and chemoresistance in a variety of cancers, including NSCLC (Salomon 1995).

Tumours with EGFR-activating mutations depend on EGFR activity to maintain their malignant properties (known as "oncogene addiction"), thus providing a strong rationale for molecular targeted therapy. EGFR TKIs compete with adenosine triphosphate (ATP) to bind the intracellular catalytic domain of the receptor, inhibiting the autophosphorylation process and downstream signalling, ultimately exerting an antiproliferative effect (Arteaga 2003).

First-generation EGFR TKIs were designed as reversible inhibitors containing quinazoline structure (Hidalgo 2001). Acquired resistance to these compounds has prompted the development of second-generation EGFR inhibitors. Most of them retained the 4-aminoquinazoline structure, and introduced acrylamide unsaturated groups, forming irreversible, covalent attachments to cysteine 797 (Cys797) at the ATP binding site. They act as potent and irreversible inhibitors and exhibit additional activity against other members of the EGFR receptors family (Barf 2012). However, as monotherapy, they failed to overcome T790M-mediated resistance (Katakami 2013).

Core structures of third-generation EGFR TKIs were converted from 4-aminoquinazoline to 2-aminopyrimidine, thus sparing the inhibition of wild-type receptor. Osimertinib is one of the third-generation inhibitors designed to target both EGFR-TKIs sensitizing mutations and T790M-resistant mutation (Cross 2014).

Why it is important to do this review

Epidermal growth factor receptor-activating mutations are the first and most common targetable alterations described in people with NSCLC. Subsequently, advances in knowledge of the biology of NSCLC have led to the approval of several targeted agents for the treatment of oncogene-addicted advanced disease (Planchard 2018). Nevertheless, the paradigm of precision medicine has not been applied yet in the early stage of disease. Resectable NSCLC represents a largely unmet need due to the risk of relapse and small impact on survival of available adjuvant treatments.

The publication of the first results of the ADAURA trial (Wu 2020), and the subsequent FDA approval of osimertinib in the adjuvant setting, has led to a considerable discussion. Could targeted therapies eliminate the risk of relapse after resection by suppressing micrometastatic disease, or might they only delay recurrence, before the development of acquired resistance? Given the lack of evidence supporting disease-free survival as a validated surrogate end point, overall survival remains the most clinically meaningful endpoint in the adjuvant setting. Further uncertainties include the optimal duration of treatment, safety profile, and the effectiveness in people with different stages of disease, previous adjuvant chemotherapy, or type of EGFR sensitizing mutation.

OBJECTIVES

To assess the effectiveness and safety of adjuvant EGFR tyrosine kinase inhibitors (TKIs) in patients with resected stage I to III non-small-cell lung cancer (NSCLC) harbouring an activating EGFR mutation.

METHODS

Criteria for considering studies for this review

Types of studies

This review will include randomised controlled trials (RCTs) reporting on the clinical effectiveness and safety of EGFR TKIs in people with completely resected NSCLC and EGFR-activating mutations.

We will apply no restrictions on language or publication status. If sufficient data are available, we will include meeting abstracts and unpublished online data. For such data we will perform a sensitivity analysis of the results.

Types of participants

We will include people aged 18 years or over, of either sex, diagnosed with completely resected stage I to III NSCLC and a proven activating EGFR mutation.

Types of interventions

We will consider for inclusion studies reporting the following comparisons.

- First-, second-, and/or third-generation EGFR TKIs versus standard platinum-based adjuvant chemotherapy.
- First-, second-, and/or third-generation EGFR TKIs versus placebo or best supportive care only.
- Second-and/or third-generation EGFR TKIs versus first- and/or second-generation EGFR TKIs.

Types of outcome measures

Primary outcomes

- Overall survival (OS): defined as time from randomisation to death from any cause (www.cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival)
- Disease-free survival (DFS): defined as the time from randomisation to disease recurrence (determined by radiological or pathological disease assessment, or both) or death from any cause (www.cancer.gov/publications/dictionaries/cancer-terms/def/disease-free-survival)
- Adverse events (AEs): any AEs as reported by the included trials individually. We will investigate the incidence of grade 3 events (severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living) and grade 4 events (life-threatening consequences; urgent intervention indicated) based on the Common Terminology Criteria for Adverse Events (CTCAE) and Patient-Reported Outcomes CTCAE (PRO-CTCAE) (Kluetz 2016). We will also check the included trials for incidence of grade 5 AEs (deaths related to adverse events). Second primary tumours considered as second primary tumours of the same cancer as the primary tumour and any unrelated malignant tumour will be considered as events.

Secondary outcomes

- Health-related quality of life (HRQoL): measured via validated generic or disease-specific questionnaires, or validated items

Search methods for identification of studies

Electronic searches

We will search the following electronic databases.

- Cochrane Lung Cancer Group Trial Register.
- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue).
- MEDLINE, accessed via PubMed (from 1946 to present).
- Embase (from 1980 to present).

The search strategies for CENTRAL, MEDLINE, and Embase are shown in Appendix 1, Appendix 2, and Appendix 3, respectively. We will search all databases using both controlled vocabulary (namely medical subject headings (MeSH) in MEDLINE and EMTREE in Embase) and a wide range of free-text terms. We will perform the MEDLINE search using the Cochrane Highly Sensitive Search Strategy and precision-maximising version, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021).

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

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

Searching other resources

We will handsearch the references of eligible studies to identify additional studies for inclusion. We will search the meeting abstracts of conferences at the following sources from 2019 onwards.

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

We will also retrieve clinical study reports about the EGFR TKI from the European Medicines Agency (EMA) website.

Data collection and analysis

Selection of studies

We will select studies for inclusion according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Three review authors (MO, MI, CM) will independently screen all titles and abstracts retrieved by the electronic searches using Covidence. The same review authors will obtain the full texts for all relevant studies and will independently check each study against the review eligibility criteria. Any disagreements will be resolved by discussion or by involving another review author (GV) when necessary. We will report the results of the study selection process using a PRISMA flow diagram (Moher 2009). We will record the reasons for exclusion of studies after full-text assessment and report this information in the 'Characteristics of excluded studies' table.

Data extraction and management

We will develop a data extraction form. Two review authors (MO, GV) will independently extract relevant data and perform a cross-check. We will involve a third review author to reach consensus when necessary (RF). We will not be blinded to the names of study authors or to the institutions where studies were conducted and funded. When we encounter multiple publications for the same study, we will choose the first publication dealing with the primary end point in this review as a study identifier (study ID).

We will extract the following details from each included study.

- Source: citation, study name (if applicable), and contact details.
- Geographical location of the study.
- Methods: study design, total duration of study, number of study centres and locations, study setting, date of study.
- Participants: number (N), age, gender, pathological stage, smoking history, type of EGFR mutation, ethnicity, adjuvant chemotherapy, inclusion and exclusion criteria.
- Interventions: type of treatment, duration of treatment.
- Outcomes: primary and secondary outcomes, with definitions and time points.
- Results: number of people included in each arm, estimates of effect with confidence interval and P value, and subgroup analysis.
- Notes: notable conflicts of interest of trial authors.
- Miscellaneous: funding source.

Assessment of risk of bias in included studies

Two review authors (GV, VS) will independently apply the Cochrane risk of bias tool, according to Chapter 8 of the 2011 version of

the *Cochrane Handbook for Systematic Reviews of Interventions,* in order to assess quality and potential biases across included studies (Higgins 2011). We will rate each domain of the tool as being at 'low', 'high', or 'unclear' risk of bias at the study level and for each outcome, if possible, and we will support the rating of each domain with a brief description. We will summarise risk of bias for each outcome within a study by considering all domains relevant to the outcome (i.e. both study-level entries, such as allocation sequence concealment, and outcome-specific entries, such as blinding). We will provide a figure to summarise the risk of bias. If the two review authors cannot reach consensus, a third review author (RF) will be consulted.

Using the Cochrane risk of bias tool, we will consider the following domains.

- Selection bias: random sequence generation.
- Selection bias: allocation concealment.
- Performance bias: blinding of participants and personnel.
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data for outcomes related to efficacy and safety.
- Reporting bias: selective reporting of outcomes.
- Other bias, such as inclusion of participants discordant to prespecified number of participants needed for calculation, unplanned interim analyses, and unbalanced baseline characteristics across study arms.

Measures of treatment effect

For time-to-event outcomes (DFS and OS), we will use hazard ratios (HRs) to measure treatment effects. We will report each HR along with the 95% confidence interval (CI). We will extract the HR from the included studies when this information is available. When it is not reported in the included study, we will try to calculate the HR by using Kaplan-Meier survival curves and the dedicated methods of Parmar and Tierney (Parmar 1998; Tierney 2007).

For dichotomous outcomes (AEs), we will use risk ratios (RRs) and 95% CIs if possible. For continuous outcomes (HRQoL), we will use mean differences (MDs) between treatment arms when a similar scale is implemented to measure outcomes, and standardised mean differences (SMDs) when different scales are used to measure the same outcome. We will report each MD and SMD with their relative 95% CI. We will confirm that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction of effect, and report if directions were reversed.

Unit of analysis issues

The primary unit of analysis is the participant. For studies with multiple comparison groups that compare two or more intervention groups with the same control group, we will, as first choice, combine groups to create a single pair-wise comparison. If this is not possible, the analysis will be carried out including each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparisons. More specifically: for dichotomous outcomes, both the number of events and the total number of patients will be divided up; for continuous outcomes, only the total number of participants will be divided up and the means and standard deviations left unchanged.

Dealing with missing data

In the case of missing or unclear individual data, we will contact the study authors directly. We will follow Cochrane recommendations when dealing with such data details, as provided in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). If we are unable to obtain the missing data from the study authors, we will perform analysis using only the available data and will discuss them in the context of study findings. In the assessment of the continuous outcome we expect to be able to perform an imputation by missing date in the case of missing standard deviation information. We will use the method proposed by Marinho and colleagues (Marinho 2003) that implemented a linear regression model between log(standard deviation) and log(mean).

Assessment of heterogeneity

We will follow Cochrane recommendations for assessment of heterogeneity (Deeks 2021). We will visually investigate heterogeneity by using forest plots generated via Review Manager 5.4 (Review Manager 2020) and look if CIs of individual studies have poor overlap. In addition, we will use the Chi^2 test to assess the presence of heterogeneity and, to overcome the possible presence of low statistical power due to studies with small sample size, we will use a P value of 0.1, rather than conventional level of 0.05, to determine statistical significance.

We will assess statistical heterogeneity of treatment effects between pooled trials for each considered outcome using the I^2 statistic to quantify heterogeneity (Higgins 2002), considering the following guidelines for interpretation.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: significant heterogeneity.

If I^2 is higher than 75%, we will consider not pooling the data. For moderate heterogeneity, we will explore sources of clinical and statistical heterogeneity, including clinically significant subgroup analysis.2

Assessment of reporting biases

We plan to generate funnel plots and to perform Egger's linear regression tests to investigate reporting biases for considered outcomes when a sufficient number of trials is included in a single meta-analysis (at least 10 trials). We will follow the recommendations in Chapter 10 of the 2011 version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

We will enter data into Review Manager 5.4 (Review Manager 2020). One review author (GV) will enter the data, and a second review author (GF) will double-check the data for accuracy. If sufficient clinically similar studies are available (at least two), we will perform meta-analyses, according to recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

We will apply the generic inverse-variance method and random-effects model for all types of outcomes. For dichotomous

outcomes, we will apply both Mantel-Haenszel method than DerSimonian and Laird inverse variance method (DerSimonian 1986). We will undertake both a fixed-effect and a random-effects meta-analysis, with an intention to present the random-effects result if there is no indication of funnel plot asymmetry. In the case of an indication of funnel plot asymmetry, we will present both analyses and perform a sensitivity analysis in which small studies are excluded. We will consider rates of AE separately for each type, and AE combined according to their grades.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will investigate potential heterogeneous results by conducting subgroup analysis, according to the following variables.

- Type of EGFR activating mutation (ex19del or L858R mutation).
- Ethnicity.
- Geographical location of the study.
- Previous adjuvant chemotherapy.
- Stage according to TNM 8th edition (Brierley 2016).
- Gender.
- Age.
- Smoking status.

Sensitivity analysis

We will investigate the robustness of the review by performing the following sensitivity analyses, when appropriate.

- Undertaking the analysis using the fixed-effect model for selected outcomes.
- Including only outcomes with low risk of bias, according to the summary assessment of risk of bias.
- Including or not including results from studies with incomplete data.
- Including or not including abstracts and unpublished studies.
- Including or not including results from studies with imputed data (continuous outcome).
- We will perform leave-one-out analyses to show difference in results driven by one single study.
- We will evaluate, in the presence of funnel plot asymmetry, the effect of excluding small studies.

Summary of findings and assessment of the certainty of the evidence

We will create two summary of findings tables using GRADEpro GDT software. One table will display the evidence on EGFR TKIs versus placebo or best supportive care, and a second table will display the evidence on EGFR TKIs versus platinum-based chemotherapy. In each table, we will include the following outcomes.

- Disease-free survival.
- Overall survival.
- Adverse events: grades 3, 4, 5.
- Health-related quality of life.

We will apply the GRADE approach when creating the summary of findings tables, as suggested in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021). We will assess the quality of evidence using the five GRADE considerations: risk of bias, imprecision, inconsistency, indirectness, and publication bias. We will justify any decisions to downgrade or upgrade the certainty of the evidence using footnotes, and where necessary, we will make comments to aid the reader's understanding of the review.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2 nsclc
#3 lung cancer*
#4 lung carcinom*
#5 lung neoplasm*
#6 lung tumor*
#7 lung tumour*
#8 non small cell*
#9 nonsmall cell*
#10 (#3 or #4 or #5 or #6 or #7) and (#8 or #9)
#11 MeSH descriptor: [Pneumonectomy] explode all trees
#12 Pneumonectom* OR Resection* OR lobectom* OR surger* OR surgical OR postoperati*
#13 #11 OR #12
#14 MeSH descriptor: [Protein Kinase Inhibitors] explode all trees
#15 Tyrosine Kinase Inhibitor* OR TKI OR TKIs
#16 MeSH descriptor: [Gefitinib] explode all trees
#17 Gefitinib OR Iressa OR ZD1839 OR ZD 1839
#18 MeSH descriptor: [Erlotinib Hydrochloride] explode all trees
#19 Erlotinib OR Tarceva OR OSI 774 OR OSI774 OR CP 358774 OR CP358774
#20 MeSH descriptor: [Afatinib] explode all trees
#21 Afatinib OR Gilotrif OR BIBW 2992 MA2 OR BIBW 2992MA2 OR BIBW2992 MA2
#22 Dacomitinib OR Vizimpro OR PF 00299804 OR PF00299804
#23 Osimertinib OR Tagrisso OR AZD9291
#24 Icotinib OR BPI-2009H OR Conmana
#25 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26 #10 AND #13 AND #25

Appendix 2. MEDLINE search strategy

1 Carcinoma, Non-Small-Cell Lung[MeSH Terms]
2 nsclc
3 lung cancer*
4 lung carcinom*
5 lung neoplasm*
6 lung tumor*
7 lung tumour*
8 non small cell*
9 nonsmall cell*
10 (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)
11 #1 OR #2 OR #10
12 pneumonectomy[MeSH Terms]
13 Pneumonectom* OR Resection* OR lobectom* OR surger* OR surgical OR postoperati*
14 #12 OR #13
16 (protein kinase inhibitors[MeSH Terms]) OR (Protein Kinase Inhibitors[Pharmacological Action]) OR TKI OR TKIs
17 ((((Gefitinib[MeSH Terms]) OR (Gefitinib)) OR (Iressa)) OR (ZD1839)) OR (ZD 1839)
18 ((((((Erlotinib[MeSH Terms]) OR (Erlotinib)) OR (Tarceva)) OR (OSI 774)) OR (OSI774)) OR (CP 358774)) OR (CP358774)
19 (((((Afatinib[MeSH Terms]) OR (Afatinib)) OR (Gilotrif)) OR (BIBW 2992 MA2)) OR (BIBW 2992MA2)) OR (BIBW2992 MA2)
20 ((((Dacomitinib[Supplementary Concept]) OR (Dacomitinib)) OR (Vizimpro)) OR (PF 00299804)) OR (PF00299804)
21 (((Osimertinib[Supplementary Concept]) OR (Osimertinib)) OR (Tagrisso)) OR (AZD9291)
22 ((((Icotinib[Supplementary Concept])) OR (Icotinib)) OR (BPI-2009H)) OR (Conmana)
23 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24 #11 AND #14 AND #23
25 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]
26 animals[MeSH Terms] NOT humans[MeSH Terms]
27 #25 NOT #26
28 #24 AND #27

Appendix 3. Embase search strategy

#1 'non small cell lung cancer'/exp
#2 nsclc:ti,ab,kw
#3 'lung cancer*':ti,ab,kw
#4 'lung carcinom*':ti,ab,kw
#5 'lung neoplasm*':ti,ab,kw
#6 'lung tumor*':ti,ab,kw
#7 'lung tumour*':ti,ab,kw
#8 'non small cell*':ti,ab,kw
#9 'nonsmall cell*':ti,ab,kw
#10 #3 OR #4 OR #5 OR #6 OR #7
#11 #8 OR #9
#12 #10 AND #11
#13 #1 OR #2 OR #12
#14 'lung resection'/exp OR 'lung lobectomy'/exp OR lobectom*:ti,ab,kw OR pneumolobectom*:ti,ab,kw OR pneumonectom*:ti,ab,kw OR resection*:ti,ab,kw OR surger*:ti,ab,kw OR surgical:ti,ab,kw OR postoperati*:ti,ab,kw
#15 'protein tyrosine kinase inhibitor'/exp OR 'tyrosine kinase inhibitor*':ti,ab,kw OR tki:ti,ab,kw OR tkis:ti,ab,kw
#16 'gefitinib'/exp OR gefitinib:ti,ab,kw OR geftinat:ti,ab,kw OR iressa:ti,ab,kw OR zd1839:ti,ab,kw
#17 'erlotinib'/exp OR erlotinib:ti,ab,kw OR tarceva:ti,ab,kw OR 'osi 774':ti,ab,kw OR osi774:ti,ab,kw OR 'cp 358774':ti,ab,kw OR cp358774:ti,ab,kw OR 'nsc 718781':ti,ab,kw OR nsc718781:ti,ab,kw
#18 'afatinib'/exp OR afatinib:ti,ab,kw OR gilotrif:ti,ab,kw OR 'bibw 2992':ti,ab,kw OR bibw2992:ti,ab,kw
#19 'dacomitinib'/exp OR vizimpro:ti,ab,kw OR 'pf 00299804':ti,ab,kw OR 'pf 299*':ti,ab,kw OR pf299*:ti,ab,kw OR 'pf 804':ti,ab,kw OR pf804:ti,ab,kw
#20 'osimertinib'/exp OR osimertinib:ti,ab,kw OR mereletinib:ti,ab,kw OR 'azd 9291':ti,ab,kw OR azd9291:ti,ab,kw OR tagrisso:ti,ab,kw
#21 'icotinib'/exp OR icotinib:ti,ab,kw OR conmana:ti,ab,kw OR 'bpi 2009*':ti,ab,kw OR bpi2009*:ti,ab,kw
#22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #13 AND #14 AND #22
#24 '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*

#25 #23 AND #24

CONTRIBUTIONS OF AUTHORS

All authors contributed to writing the protocol. MO, RF, MI and GV worked on the medical content; and VS, GF, CM and NS worked on the statistics and methods.

DECLARATIONS OF INTEREST

Mario Occhipinti: none known

Roberto Ferrara has received payment for advisory board membership from Merck Sharp & Dohme, and from BeiGene Switzerland GmbH

Martina Imbimbo is Principal Investigator for phase-1 clinical trials from Bristol Myers Squibb, AstraZeneca and Immatics

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NOTES

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