Guideline 7-22 BEING UPDATED

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer

S. Kulkarni, E. Vella, N. Coakley, S. Cheng, R. Gregg, Y.C. Ung, P.M. Ellis, and the Lung DSG

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Guideline 7-22 is currently BEING UPDATED. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal a standardized process to ensure the currency of each document. (PEBC Assessment & Review Protocol)

Guideline 7-22 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/831

For information about this document, please contact Dr. S Kulkarni, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline 7-22: Section 1

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer: Recommendations Summary

GUIDELINE OBJECTIVES

To make recommendations in the maintenance setting regarding the use of systemic treatment in the care of patients with non-small cell lung cancer (NSCLC).

TARGET POPULATION

Advanced, stage IIIB/IV patients who have NSCLC who have not progressed (i.e., complete response, partial response or stable disease) following four to six cycles of platinum-based chemotherapy and maintained an Eastern Cooperative Oncology Group performance status of 0 to 2.

INTENDED USERS

Oncologists involved in the care of patients with NSCLC who require maintenance systemic treatment.

RECOMMENDATION

Maintenance therapy is recommended as an option for therapy as described below:

- **Maintenance therapy with pemetrexed should be considered an option for patients with non-squamous NSCLC. Maintenance therapy with pemetrexed is not recommended for patients with squamous NSCLC.**
- **Maintenance therapy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) may be considered an option. No recommendation can be made with respect to the choice of gefitinib or erlotinib. Any decision should be made in conjunction with discussion with the patient.**
- **There is insufficient evidence to recommend docetaxel or gemcitabine as maintenance chemotherapies.**
- **In patients who elect to have a break following first-line therapy, second-line therapy should be considered at the time of progression. Please refer to the Program in Evidence-Based Care guidelines on the use of second-line therapies in NSCLC [1,2].**

Qualifying statements

- **These recommendations apply both to patients who previously received pemetrexed or non-pemetrexed-containing platinum-doublet chemotherapy.**
- **Trials have evaluated both erlotinib and gefitinib, but no trials directly compared these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, although the overall survival advantage was modest for both agents.**
- **The recommendation for EGFR TKIs applies to both EGFR mutation-positive and wild-type patients.**
- **In patients receiving maintenenance bevacizumab, it is unclear whether the addition of maintenance pemetrexed improves overall survival.**

Guideline 7-22: Section 2

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer: Guideline

GUIDELINE OBJECTIVES

To make recommendations in the maintenance setting regarding the use of systemic treatment in the care of patients with non-small cell lung cancer (NSCLC).

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Advanced, stage IIIB/IV patients who have NSCLC who have not progressed (i.e., complete response, partial response or stable disease) following four to six cycles of platinum-based chemotherapy and maintained an Eastern Cooperative Oncology Group performance status of 0 to 2.

INTENDED USERS

Oncologists involved in the care of patients with NSCLC who require maintenance systemic treatment.

RECOMMENDATION, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

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- **The recommendation for EGFR TKIs applies to both EGFR mutation-positive and wild-type patients.**
- **In patients receiving maintenenance bevacizumab, it is unclear whether the**

addition of maintenance pemetrexed improves overall survival (OS).

Key Evidence

- For pemetrexed maintenance therapy, the overall certainty of the estimate of effects from phase III randomized controlled trials (RCTs) was considered to be moderate due to the indirectness of the comparison groups. Specifically, the trials did not compare immediate versus delayed treatment, but maintenance treatment versus placebo. Various second-line therapies were chosen at the discretion of the physician. Meta-analysis of three RCTs found that patients randomized to pemetrexed as maintenance therapy had longer overall survival compared with those who did not receive maintenance pemetrexed therapy (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.69 to 0.89; p=0.0003, I^2=0%) [3-5]. At a baseline risk of 51% at 12 months, there would be 8% (83 per 1000) fewer deaths at 12 months (95% CI from 40 fewer to 121 fewer) for patients who received pemetrexed maintenance therapy. Three RCTs reported on quality of life and found either no difference in the majority of scores or significant delays in symptom deterioration in favour of patients who received pemetrexed maintenance treatment [3,6,7]. A significant interaction was observed between histology (squamous versus non-squamous carcinoma) and treatment for progression-free survival (PFS) and OS in Ciuleanu 2009 [3]. The two other RCTs included only patients with non-squamous histology [5,6]. Meta-analysis with these two RCTs, plus the data from patients with non-squamous carcinoma from Ciuleanu 2009, found that patients with non-squamous cell histology who received pemetrexed as maintenance therapy had longer OS (HR, 0.74; 95% CI, 0.64 to 0.86; p<0.0001) and PFS (HR, 0.51; 95% CI, 0.41 to 0.63; p<0.00001) compared with those who did not receive pemetrexed as maintenance therapy.
- For EGFR TKI maintenance therapy, the overall certainty of the estimate of effects from phase III RCTs was considered to be moderate, again due to the indirectness of the comparison groups. Meta-analysis of four RCTs found that OS was better in patients who received EGFR TKIs as maintenance therapy compared with those who did not receive maintenance EGFR TKI therapy (HR, 0.84; 95% CI, 0.75 to 0.94, p=0.002) [8-11]. At a baseline risk of 51% at 12 months, there would be 6% (59 fewer per 1000) fewer deaths at 12 months (95% CI from 21 fewer to 96 fewer per 1000) for patients who received EGFR TKI maintenance therapy. Two RCTs found improvements in quality of life for patients who received EGFR TKI maintenance therapy [9,10]. A significant interaction was found between EGFR mutation status and treatment for PFS, with a larger improvement in PFS for patients with EGFR mutations (EGFR positive: HR, 0.22; 95% CI, 0.10 to 0.46; EGFR wild-type: HR, 0.82; 95% CI, 0.71 to 0.96; p=0.0007); however no such interaction was found for OS (EGFR positive: HR, 0.59; 95% CI, 0.33 to 1.05; EGFR wild-type: HR, 0.87; 95% CI, 0.70 to 1.08; p=0.22).
- For gemcitabine maintenance therapy, the overall certainty of the estimate of effects from phase III RCTs was considered to be low owing to the indirectness of the comparison groups, the inclusion of an abstract, and the small number of included studies. Meta-analysis of two RCTs found no difference in OS between patients who received gemcitabine as maintenance therapy compared with those who did not receive gemcitabine as maintenance therapy [8,12]. Only one RCT reported on quality of life and found no difference between treatment arms [13]. No significant interactions were found for gemcitabine.
- For docetaxel maintenance therapy, the overall certainty of the estimate of effects from phase III RCTs was considered to be moderate due to the inclusion of abstracts and the small number of studies found. Two RCTs found no difference in OS between patients who received docetaxel as maintenance therapy compared with those who did not receive docetaxel as maintenance therapy [14,15]. Only one RCT reported on quality of life and

found no difference between treatment arms [14]. No significant interactions were found for docetaxel.

Interpretation of Evidence

- There was strong agreement among the members of the Working Group that OS and quality of life were critical outcomes for recommendation development. PFS and adverse effects were considered to be important outcomes of interest.
- For pemetrexed and EGFR TKI maintenance therapies, the Working Group believed the desirable effects to be modest but clinically meaningful and the undesirable effects to be small. They believed the trade-offs between desirable and undesirable effects to be large in selected populations (such as offering pemetrexed in patients with non-squamous cell carcinoma) and dependent on discussions between the oncologist and the patient.
- While these data demonstrate a similar reduction in the hazard ratio for OS for maintenance pemetrexed and EGFR TKIs, the consensus of the members of the Lung Cancer Disease Site Group favoured the use of pemetrexed in patients with non-squamous histology over EGFR TKIs (pemetrexed non-squamous: HR, 0.74; 95% CI, 0.64 to 0.86; EGFR TKIs all patients: HR, 0.84; 95% CI, 0.75 to 0.94).
- Since a significant interaction favouring non-squamous over squamous cell carcinoma for OS in patients receiving pemetrexed maintenance therapy was found in one RCT and the remaining two RCTs included only patients with non-squamous cell carcinoma, the Working Group recommended pemetrexed in this subgroup of patients with the strongest evidence [3,5,6]. The Ciuleanu 2009 trial was not powered to detect treatment effects within subgroups [3]. Therefore, the absence of a significant improvement in OS in patients with squamous cell histology could be due to lack of power to show an effect. However, trials evaluating pemetrexed in combination with a platinum agent in first-line treatment, or compared with docetaxel in second-line therapy also demonstrated a significant interaction between histology and treatment [16,17]. As a consequence of these interactions, the product information for pemetrexed in many jurisdictions now limits its use to patients with non-squamous histology.
- No significant interaction was found for OS between EGFR mutation status and EGFR TKI maintenance therapy; therefore, the use of EGFR mutation status is not recommended to predict which patients might benefit from maintenance EGFR TKI therapy.
- Three studies examined the effects of erlotinib maintenance therapy [8,10,11], whereas only one study used gefitinib maintenance therapy [9]. There were no trials that compared these two agents with each other. However, the strongest data would support the use of erlotinib in this setting, although the OS advantage is modest for both agents.
- One RCT randomized patients to maintenance bevacizumab plus pemetrexed compared with maintenance bevacizumab alone but was not powered for OS and the number of OS events was small in the most recent publication [5]. Therefore, no recommendation can be made with respect to adding maintenance pemetrexed to maintenance bevacizumab.
- For gemcitabine and docetaxel maintenance therapies, the Working Group believed the trade-offs between desirable and undesirable effects were uncertain due to insufficient evidence.
- The Working Group recommended that patients who do not receive maintenance systemic therapy should be considered for second-line therapy at the time of progression because this is an alternate standard of care.
- The main objective was to evaluate the efficacy of specific drugs rather than the particular maintenance strategy (switch versus continuous) and, therefore, these recommendations were written with this purpose.

IMPLEMENTATION CONSIDERATIONS

The Working Group considered these recommendations to be the current standard of care and thus would be feasible to implement and would not affect current health inequities. These recommendations would validate what providers are currently implementing. If EGFR TKIs became funded as a result of this guideline, then this would result in a change in cost to the health care system but only to a minority of patients. They believed the outcomes valued in this guideline would align with patient values and patients would view these recommendations as acceptable.

RELATED GUIDELINES

Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC; Lung Disease Site Group. Use of the epidermal growth factor receptor inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib in the treatment of non–small-cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario; 2014 Apr 23. Program in Evidence-Based Care Evidence-based Series No.: 7-9 Version 2 [1].

UPDATING

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at:
https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true

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CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix A.

Contact Information

For information about this document, please contact Swati Kulkarni, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer: Guideline Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) [18]. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [18]. PEBC guidelines include an evidence review (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

Focus

The primary focus of this guideline is on the clinical evidence. Other features related to the implementation of recommendations such as costs, human resources, unique requirements for special or disadvantaged populations, development and measurement of quality indicators are addressed by other divisions at CCO. The perspective of the Maintenance Systemic Treatment in NSCLC Guideline Group on these issues is described in Section 2 under “Implementation Considerations”.

Guideline Developers

This guideline was undertaken by the Maintenance Systemic Treatment in Non-small cell Lung Cancer (NSCLC) Guideline Group, a group organized by the PEBC at the request of the Lung Cancer Disease Site Group (DSG). The group was comprised of 14 medical oncologists, 10 radiation oncologists, six surgeons, one specialist in bioethics, and two methodologists (see Appendix A for membership). The project was led by a small working committee of the group, referred to as the Working Group from this point forward, whose members were responsible for creating the evidence base, drafting the first version of the recommendations and leading the response to the external review. The Working Group members are noted in Appendix A. All members contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Competing interests in the areas of receiving financial support as a consultant or principal investigator from a relevant business entity were declared; Appendix A provides further detail. Individuals with competing interests were not allowed to participate as a member of the Working Group unless otherwise stated.

Guideline Methods

The PEBC uses the AGREE II as its organizational methodological framework. Beginning with a project plan, systematic methods of evidence synthesis (see section 4) and/or adaptation, consensus of interpretation of evidence, drafting and contextualization of recommendations, and internal and external review (see section 5) of the draft guideline define key steps in the process. The PEBC's processes and methods are described in more detail in the PEBC Handbook (https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=50876) and the PEBC Methods Handbook (http://pebctoolkit.mcmaster.ca/doku.php?id=projectdev:pebc_methods_handbook).

A search for existing guidelines for adaptation or endorsement was conducted and no comprehensive guidelines that covered all types of systemic treatments for maintenance were found. A search of the primary literature was required (see section 4).

ACKNOWLEDGEMENTS AND AUTHORSHIP

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- Melissa Brouwers, Charles Butts, Craig Earle, Desiree Hao, Sheila McNair, Hans Messersmith, Shail Verma, Morzycki Wojciech for providing feedback on draft versions.
- Elizabeth Chan for conducting a data audit.
- Sara Miller for copyediting.

Guideline 7-22: Section 4

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer: Evidence Review

INTRODUCTION

Lung cancer has the highest incidence of all the cancers and is the leading cause of cancer-related death in Canada, with an estimated 26,100 new cases and 20,500 deaths from lung cancer in 2014 [19]. Non-small cell lung cancer (NSCLC) accounts for most cases of lung cancer and is often diagnosed at later stages when treatment options are limited. Platinum-based chemotherapy is the standard of care for first-line therapy. Many patients who receive a minimum of four cycles of first-line platinum-based chemotherapy experience rapid disease progression. Second-line therapies are indicated for those patients at the time of disease progression, but only two-thirds of patients receive second-line therapy [20,21]. Rapid deterioration can make patients ineligible for second-line therapy and creates a lost opportunity to receive effective treatment. Maintenance therapy can increase the proportion of patients who receive additional therapy beyond first-line platinum-doublet treatment.

There are two types of maintenance therapies. Continuous maintenance therapy involves continuation with the same first-line therapy, whereas switch maintenance therapy involves changing to an alternate drug for maintenance treatment. A previous PEBC guideline has examined the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as maintenance therapy in patients with advanced, stage IIIB/IV NSCLC who have not progressed (i.e., complete response, partial response, or stable disease) following first-line platinum-based chemotherapy [1]. This review will update this evidence as well as include evidence for maintenance chemotherapy. Additionally, this systematic review will address the question of whether special populations, defined by clinical characteristics (such as Asian ethnicity, female sex, histology, age or smoking status), or molecular characteristics (such as the presence of activating mutations of the *EGFR* gene), should influence the recommendations concerning the use of maintenance therapies.

This evidentiary base will be used to develop recommendations on the use of systemic treatment in the maintenance of patients with NSCLC. Based on this guideline objective, the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. In patients with advanced NSCLC who have received initial first-line platinum-based chemotherapy for a minimum of four cycles, does maintenance systemic therapy improve overall survival (OS), progression-free survival (PFS), or quality of life in comparison with either placebo or second line therapy at the time of progression?

2. In patients with advanced NSCLC who have received initial first-line platinum-based chemotherapy for a minimum of four cycles, does any systemic therapy agent improve OS, PFS or quality of life in comparison with other systemic therapies?

3. In patients with advanced NSCLC, are there any clinical or molecular characteristics that identify subgroups of patients who derive greater benefit from maintenance systemic therapy?

METHODS

This evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews were identified that addressed the research questions and were of reasonable quality, then those systematic reviews formed the core of the evidentiary base.
2. Systematic review of the primary literature: This focused on those areas not covered by any existing reviews.

The Program in Evidence-Based Care (PEBC) is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Search for Existing Systematic Reviews

The MEDLINE (1985 to January 14, 2014), EMBASE (1985 to January 14, 2014), and Cochrane Library (January 2014) databases were searched for published systematic reviews. The Canadian Medical Association Infobase (http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm), the National Guidelines Clearinghouse (http://www.guideline.gov/), and other websites were searched for guidelines with systematic reviews. Search terms indicative of non–small-cell lung cancer, maintenance systemic treatment and systematic reviews were used. The full search strategy is available in Appendix B.

Any identified systematic reviews that addressed the research questions were assessed using the AMSTAR tool [22]. The results of the AMSTAR assessment were used to determine whether any existing review could be incorporated as part of the evidentiary base.

Primary Literature Systematic Review

In the absence of finding systematic reviews, the following methods were used to search for primary literature.

Literature Search Strategy

The MEDLINE (1985 to September 30, 2014), EMBASE (1985 to September 30, 2014), and Cochrane Library (June 2014) databases were searched for randomized controlled trials (RCTs). Reference lists of papers and review articles were scanned for additional citations. The American Society of Clinical Oncology Conference proceedings were searched from 2009 to 2013. Search terms indicative of non–small-cell lung cancer, maintenance systemic treatment and randomized clinical trials were used. The full search strategy is available in Appendix B.

Study Selection Criteria and Protocol

Inclusion Criteria

1) Phase III RCTs comparing maintenance systemic treatment against another systemic treatment or placebo; and
2) Four prior cycles of platinum-based chemotherapy; and
3) Stage IIIB or IV NSCLC; and
4) Studies that include 50 or more patients; and
5) Fully published papers or published abstracts of trials in any language that reported at least one of the following outcomes by treatment group: symptom control, quality of life, tumour response rate, survival or toxicity. Data from slide presentations associated

with abstract trial reports were also included if the presentations were publicly available on meeting websites and they provided additional data.

Exclusion Criteria

1) Pilot trials, interim analyses, dose-escalation trials, or case series (including expanded access programs) studies.
2) Letters and editorials that reported clinical trial outcomes.
3) Conference abstracts before 2009.

A review of the titles and abstracts that resulted from the search was done by one (NC) reviewer independently. For those items that warranted full text review, one (NC) reviewer reviewed each item in collaboration with four others (SK, PE, RG, EV).

Data Extraction and Assessment of Study Quality

Data extraction was done independently by either reviewer NC or EV.

Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating improved efficacy for the experimental arm and a HR > 1.0 indicating improved efficacy for the control arm. All extracted data and information were audited by an independent auditor.

Important features, such as treatment, study inclusion criteria, response rate, PFS, OS, quality of life and adverse effects, for each study were extracted. Quality features for each study were also extracted. These included funding, methods of randomization, allocation concealment, patient stratification, power reported, and intention-to-treat analyses (ITT).

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.2) provided by the Cochrane Collaboration [23]. For time-to-event outcomes, hazard ratios (HR), rather than the number of events at a certain time point, was the preferred statistic for meta-analysis, and was used if reported. If the HR and/or its standard error were not reported, they were derived from other information reported in the study, if possible, using the methods described by Parmar et al or individual investigators were contacted [24]. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in review manager were used. Test for subgroup differences was used to determine whether interactions of treatment and any clinical or molecular characteristics for time-to-event outcomes were significant. To assess the credibility of any significant subgroup interactions, the Working Group answered a list of questions developed by Guyatt 2011 [25]. Interactions where more criteria were met were considered to be more convincing and less spurious.

Statistical heterogeneity was calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

The GRADE method for assessing the quality of aggregate evidence was used for each comparison using the GRADEpro Guideline Development Tool [26,27]. The outcomes were rated for their importance for decision-making by the Working Group members. Only those outcomes that were considered critical or important were included in the GRADE evidence tables. Five factors were assessed for each outcome in each comparison. These included the risk of bias, inconsistency, indirectness, imprecision, and publication bias. The median OS and PFS were estimated by visual inspection from the Kaplan-Meier curves from each of the studies at 12 months for OS and at six months for PFS.

RESULTS

Search for Existing Systematic Reviews

A total of 124 English and foreign-language studies were identified. Eighteen of those were selected for full-text review. No relevant published systematic reviews were identified. They either did not answer our research questions or did not adhere to our study eligibility criteria.

Primary Literature Systematic Review

Literature Search Results

A total of 1776 English and foreign-language studies were identified. Two hundred and fifty nine were selected for full-text review. Of those, eighteen met the pre-defined eligibility criteria for this systematic review [3-15,28-32]. The search flow diagram is available in Appendix C.

Study Design and Quality

Fourteen phase III RCTs with 22 publications were identified. Of those, 17 were fully published reports [3-11,13,14,28,31,33-36], and five were in abstract form [12,15,29,30,32]. Twelve of the studies were from four RCTs [4-7,10,15,28,30,33-36]. The characteristics and outcomes of the included studies can be found in Tables 1 to 3 and the quality assessment of the studies can be found in Table 4. For the fully published papers, the randomization method was either unclear or not reported in three studies [5,13,31]. Blinding was either open label or not reported in four studies [5,13,14,31]. Losses to follow-up were not reported in four studies [10,11,13,31] and the role of the funder was unclear in five studies [5,11,13,14,31]. Two studies randomized before first-line therapy and not before maintenance therapy; therefore, no statistical comparisons between maintenance arms could be applied [29,31]. These two studies have not been included in the statistical comparisons below. Different strategies of maintenance therapy have been evaluated, including continuation of the same drug (continuation maintenance) or switching to an alternate drug (switch maintenance). A priori, the main objective was to evaluate the efficacy of specific drugs in the maintenance setting, rather than the particular maintenance strategy and therefore continuous and switch maintenance were combined in some meta-analyses.

Table 1. Studies selected for inclusion.

Reference	Treatment	Type of maintenance	Inclusion criteria	N	Median follow-up (months)
EGFR TKIs					
Cappuzzo 2010 and Brugger 2011 [10,28] SATURN phase 3	Erlotinib 150 mg/day Placebo Second-line at discretion of investigators	Switch	Stage IIIB/IV PS 0-1 Completion of 4 cycles of standard platinum chemotherapy without disease progression	438 451	11.4 11.5
Johnson 2013 [11] ATLAS Phase 3	Bevacizumab 15 mg/kg + Erlotinib 150 mg/day Bevacizumab 15 mg/kg + placebo Second-line at discretion of investigators	Partial continuous	Stage IIIB/IV PS 0-1 4 cycles of platinum-based chemotherapy + bevacizumab	370 373	8.5 8.3
Perol 2012 [8] IFCT-GFPC 0502 Phase 3	Gemcitabine 1250 mg/m^2 Erlotinib 150 mg/day Observation group Second-line treatment: Pemetrexed 500 mg/m^2 every 21 days	Switch and continuous	Stage IIIB/IV PS 0-2 Had 4 cycles of cisplatin plus gemcitabine	154 155 155	All patients 25.6
Zhang 2012 [9] INFORM: C-TONG 0804 Phase 3 East Asian population	Gefitinib 250 mg/day Placebo Second-line at discretion of investigators	Switch	Stage IIIB/IV PS 0-2 Had 4 cycles of platinum-based doublet chemotherapy without disease progression	148 148	All patients 15.9
Pemetrexed					
Barlesi 2013 [5] Rittmeyer 2013 [7] AVAPERL Phase3	Bevacizumab 7.5 mg/kg Bevacizumab 7.5 mg/kg + pemetrexed 500 mg/m^2	Continuous Results from randomization	Stage IIIB non-squamous No previous treatment Induction phase with bevacizumab + cisplatin + pemetrexed	125 128	All patients 8.1

	Second-line at discretion of investigators				
Ciuleanu 2009 [3] H3E-MC-JMEN Phase 3	Pemetrexed 500 mg/m^2 + BSC Placebo + BSC Second-line at discretion of investigators	Switch Results from randomization	Stage IIIB/IV PS 0-1 Had 4 cycles of platinum-based doublet chemo without disease progression No previous pemetrexed	441 222	11.2 10.1
Paz-Ares 2012/13 [4,6] PARAMOUNT Phase 3	Pemetrexed 500 mg/m^2 + BSC Placebo + BSC Second-line at discretion of investigators	Continuous	Stage IIIB/IV PS 0-1 4 cycles of pemetrexed + cisplatin with radiographical evidence of PR, CR or SD	359 180	All patients 12.5
Gemcitabine					
Belani 2010 [12] Phase 3 Abstract 7506	Gemcitabine 1000 mg/m^2 + BSC BSC	Continuous	Stage IIIB/IV Gemcitabine and carboplatin for 4 cycles	128 127	NR
Brodowicz 2006 [13] Phase 3	Gemcitabine 1000 mg/m^2 + BSC BSC Second-line at discretion of investigators	Continuous Results from randomization	Stage IIIB/IV Karnofsky PS>70 No previous chemotherapy except run in with 3 cycles of gemcitabine and cisplatin	138 68	20.5 17.0
Nagy 2014 [32] Abstract 115P	Gemcitabine 250 mg/m^2 Supportive care	Continuous	Advanced and metastatic 4 cycles of gemcitabine/cisplatin	120 total	NR
Docetaxel					
Fidias 2009 [14] Phase 3	Immediate docetaxel 75 mg/m^2 Delayed docetaxel 75 mg/m^2	Switch	Stage IIIB/IV PS 0-1 4-6 cycles of gemcitabine + carboplatin	153 156	NR
Zhang 2013, Lu 2013 [15,30] TFINE study, C-TONG 0904 Abstr Phase 4	Docetaxel 60 mg/m^2 BSC	Continuous	Stage IIIB/IV PS 0-1 No prior chemotherapy Induction phase 4 cycles with	123 (118 for OS) 61	NR

NCT01038661 Asian population			cisplatin + docetaxel		
Other					
Patel 2013 [31] Pointbreak Phase 3	Pemetrexed 500 mg/m^2 + Bevacizumab 15 mg/kg bevacizumab 15 mg/kg Second-line at discretion of investigators	Partial Continuous Randomization occurred before first-line treatment only	Stage IIIB/IV non-squamous PS 0-1 4 cycles of induction therapy of pemetrexed + carboplatin + bevacizumab or paclitaxel, carboplatin and bevcizumab	292 298	11.7 11.9
Zinner 2013 [29] ASCO abstract LBA8003	Pemetrexed 500 mg/m^2 Bevacizumab 15 mg/kg	Partial continuous Results from induction phase Randomization occurred before first-line treatment only	Stage IV non-squamous PS 0-1 4 cycles of induction chemotherapy pemetrexed + carboplatin or paclitaxel, carboplatin and bevcizumab	182 179	NR

Abbreviations: BSC, best supportive care; CR, complete response; EGFR, epidermal growth factor receptor; NR, not reported; OS, overall survival; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor

Table 2. Response rates, progression-free survival, overall survival and adverse effects.

Reference	Treatment	Response rate, CR + PR	Median progression-free survival	Median overall survival	Adverse effects
EGFR TKIs					
Cappuzzo 2010 and Brugger 2011 [10,28] SATURN phase 3	Erlotinib 150 mg day Placebo	11.9% 5.4% p=0.0006	12.3 weeks 6 months 25% (95% CI 21-29%) 11.1 weeks HR 0.71 (95% CI 0.62-0.82); P<0.0001 6 months 15% (95% CI 12-19%)	12 months 11 months HR 0.81 (95% CI 0.70-0.95) p=0.0088	**Grade 3&4 (%)** / E / P Rash / 37(9) / 0 Pruritus / 1 / 0 Diarrhea / 7(2) / 0
Johnson 2013 [11] ATLAS Phase 3	Bevacizumab 15 mg/kg + Erlotinib 150 mg/day Bevacizumab 15 mg/kg + placebo	NR	4.8 months 3.7 months HR 0.708 (95% CI 0.580-0.864) p<0.001	14.4 months 13.3 months HR 0.917 (95% CI 0.698-1.205) p<0.5341	Grades 3&4 (%) / Bev + ER / Bev + Pla Rash / 25(6.8) / 2(0.5) Diarrhea / 36(9.8) / 7(1.9) Hypertension / 23(6.3) / 22(6.0)
Perol 2012 [8] IFCT-GFPC 0502 Phase 3	Gemcitabine 1250 mg/m^2 Erlotinib 150 mg/day Observation group	NS	Gemcitabine vs observation 3.8 vs 1.9 months HR 0.56 (95% CI 0.44-0.72) p<0.001 Erlotinib vs observation 2.9 vs 1.9 months HR 0.69 (95% CI 0.54-0.88) p=0.003	Gemcitabine vs observation 12.1 vs 10.8 months HR 0.89 (95% CI 0.69-1.15) p=0.3867 Erlotinib vs observation 11.4 vs 10.8 months HR 0.87 (95% CI 0.68-1.13) p=0.3043	Grades 3&4 (%) / Gem / E / Observe Anemia / 4(2.6) / 2(1.3) / 1 (0.6) Neutropenia / 32(20.8) / 1(0.6) / 1 (0.6) Rash / 0 / 14(9.0) / 0 Diarrhea / 1(0.6) / 1(0.6) / 0
Zhang 2012 [9] INFORM: C-TONG 0804	Gefitinib 250 mg/day	NS	4.8 months (95% CI 3.2-8.5)	18.7 months (95% CI 15.6-22.2)	Grades 3&4 (%) / Gefitinib / Placebo Rash / 0 / 0

Phase 3 East Asian population	Placebo		2.6 months (95% CI 1.6-2.8) HR 0.42 (95% CI 0.33-0.55) p<0.0001	16.9 months (95% CI 14.5-19.0) HR 0.84 (95% CI 0.62-1.14) p=0.26	Diarrhea 0 0 Cough 0 0 Dyspnea 0 0 WBC decreased 0 0
Pemetrexed					
Barlesi 2013 [5] Rittmeyer 2013 [7] AVAPERL Phase3	Bevacizumab 7.5 mg/kg Bevacizumab 7.5 mg/kg + pemetrexed 500 mg/m^2	50.0% (95%CI 40.9-59.1) 55.5% (95%CI 46.4-64.3)	3.7 months 7.4 months HR 0.48 (95% CI 0.35-0.66); p<0.001	12.8 months Not yet reached HR 0.75 (95% CI 0.47-1.19); p=0.219	Grades 3&4 (%) Bev Bev + Pem Neutropenia 0 7(5.6) Anemia 0 4(3.2) Fatigue 2(1.7) 3(2.4)
Ciuleanu 2009 [3] Phase 3	Pemetrexed 500 mg/m^2 + BSC Placebo + BSC	6.8% 1.8%	4.3 months (95% CI 4.1-4.7) 2.6 months 95CI; 1.7-2.8 HR 0.50 (95% CI 0.42-0.61); p<0.0001	13.4 months (95% CI 11.9-15.9) 10.6 months (95% CI 8.7-12.0) HR 0.79 (95% CI 0.65-0.95); p=0.012	Grades 3&4 (%) Pemetrexed Placebo Neutropenia 13(3) 0 Anemia 12(3) 1(<1) Fatigue 22(5) 1(<1) Diarrhea 2(<1) 0 Vomiting 1(<1) 0 Rash 1(<1) 0
Paz-Ares 2012/13 [4,6] PARAMOUNT Phase 3	Pemetrexed 500 mg/m^2 + BSC Placebo + BSC	3% 0.6%	4.4 months (95% CI, 4.1-5.7) 2.8 months (95% CI, 2.6-3.0) HR 0.60 (95% CI 0.50-0.73); p<0.001	13.9 months (95% CI 12.8-16.0 months) 11 months (95% CI 10.0-12.5 months) HR 0.78 (95% CI 0.64-0.96); p=0.0195	Grades 3&4 (%) Pem Placebo Anemia 6.4 0.6 Neutropenia 5.8 0 Fatigue 4.7 1.1 Vomiting 0.3 0 Diarrhea 0.3 0
Gemcitabine					
Belani 2010 [12] Phase 3 Abstract 7506	Gemcitabine 1000 mg/m^2 + BSC BSC	NR	3.9 months (95% CI 3.3-3.5) 3.8 months (95% CI 2.6-5.5	8.0 months (95% CI 6.0-10.2) 9.3 months (95% CI 7.7-12.7) HR 0.97 (95% CI 0.72-1.30);	Grades 3&4 % Gem BSC Anemia 9.4 2.4 Neutropenia 13.3 1.6 Fatigue 3.9 1.6

				p=0.84	
Brodowicz 2006 [13] Phase 3	Gemcitabine 1250 mg/m^2 + BSC BSC	NR	TTP 3.2months (95% CI 2.8-4.1) 2.0 months (95% CI 1.6-2.6) p<0.001	10.2 months (95% CI 8.0-13.4) 8.1 months (95% CI 6.6-11.1) p=0.172	Grades 3&4 %) / Gemcitabine Neutropenia / 14.9 Anemia / 2.6 Nausea/Vomiting / 0.8
Nagy 2014 [32] Abstract 115P	Gemcitabine 250 mg/m^2 Supportive care	NR	TTP 6.1 months (95% CI 5.3-6.6) 5.8 months (95% CI 5.2-6.4) p=0.454	9 months (95% CI 7.9-10.0) 8 months (95% CI 8.5-9.4) p=0.994	No grade 3 or 4 toxicity in either arm Significant grade 2 anemia in 8 patients in maintenance arm
Docetaxel					
Fidias 2009 [14] Phase 3	Immediate docetaxel 75 mg/m^2 Delayed docetaxel 75 mg/m^2	35.9% 11.2%	5.7 months (95% CI 4.4-6.9 months) 2.7 months (95% CI 2.6-2.9 months) p=0.0001	12.3 months (95% CI 10.4-15.2 months) 9.7 months (95% CI 8.4-12.5 months) p=0.0853	Grades 3&4 (%) / Immediate docetaxel / Delayed docetaxel Neutropenia / 40(27) / 28 (28) Anemia / 1(0.7) / 0 Fatigue / 14(9) / 4(4) Dyspnea / 4(2) / 4(4) Vomiting / 0 / 1(1) Diarrhea / 1(0.7) / 5(5)
Zhang 2013, Lu 2013 [15,30] TFINE study, C-TONG 0904 Abstr Phase 4 NCT01038661 Asian population	Docetaxel 60 mg/m^2 BSC	NR	5.4 months (95% CI 2.8-7.0) 2.8 months (95% CI 1.8-3.1 p=0.002	12.3 months (95% CI 11.2-14.1 months) 13.7 months (95% CI 12.0-15.7 months) p=0.77	NR
Other					
Patel 2013 [31] Pointbreak Phase 3	pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg bevacizumab 15 mg/kg	NR	8.6 months (95% CI 7.4-9.5) 6.9 months (95% CI 6.2-7.3)	17.7 months (95% CI 16.6-20.5) 15.7 months (95% CI 14.9-17.7)	Grades 3&4 (%) / P + B / B Thrombocyto-penia / 70(24.0) / 13(4.4) Neutropenia / 83(28.4) / 136(45.6) Anemia / 46(15.8) / 5(1.7) Fatigue / 35(12.0 / 8(2.7)

Zinner 2013 [29] ASCO abstract LBA8003	pemetrexed 500 mg/m^2 bevacizumab 15 mg/kg	23.6% 27.4%	HR 1.06 (95%CI 0.84-1.35) p=0.610	HR 1.07 (95%CI 0.83-1.36) p=0.616	)

Grades 3&4 %	P+B	B
Anemia	18.7	5.4
Neutropenia	48.8	24.6

Abbreviations: BSC, best supportive care; CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; HR, hazard ratio; NR, not reported; NS, not significant; PR, partial response; TKI, tyrosine kinase inhibitor ; TTP, time to progression; vs, versus; WBC, white blood cell

Table 3. Quality of life and subgroup analyses.

Reference	Quality of Life	Subgroup analyses with significant interactions (p<0.05) PFS	Subgroup analyses with significant interactions (p<0.05) OS
EGFR TKIs			
Cappuzzo 2010 and Brugger 2011 [10,28] Coudert 2012 [35] SATURN phase 3	FACT–L - no difference for time to deterioration (HR 0.96; 95% CI 0.79–1.16) post-hoc analysis - time to pain (HR 0.61; 95% CI 0.42–0.88; p=0.008) and time to analgesic use (HR 0.66; 95% CI 0.46–0.94; p=0.02) improved with Erlotinib	Ethnic origin and PFS (interaction p=0.01): White HR 0.75 (95% CI 0.64-0.88) Asian HR 0.58 (95% CI 0.38-0.87) Gender and PFS (interaction p=0.04): Male HR 0.78 (95% CI 0.66-0.92) Female HR 0.56 (95% CI 0.42-0.76)	Ethnic origin and OS (interaction p=0.03) White HR 0.86 (95% CI 0.73-1.01) Asian HR 0.66 (95% CI 0.42-1.05)
Johnson 2013 [11] ATLAS Phase 3	NR	No interactions	No interactions
Perol 2012 [8] IFCT-GFPC 0502 Phase 3	NR	No interactions	No interactions
Zhang 2012 [9] INFORM: C-TONG 0804 Phase 3 East Asian population	FACT-L - improvement in lung cancer symptoms with gefitinib (OR 3.41; 95% CI 1.65-7.06, p=0.0009) Median time to worsening in lung cancer symptoms 4.3 months (95% CI 2.8-7.1) with Gefitinib and 2.3 months (95% CI 1.5-2.8) with placebo	Histology and PFS (interaction p=0.027): Adenocarcinoma (HR 0.33; 95% CI 0.24-0.46) Non-adenocarcinoma (HR 0.72; 95% CI 0.46-1.14) EFGR mutation status and PFS (interaction p=0.0063) EGFR positive (HR 0.17; 95% CI 0.07-0.42) EGFR wild-type (HR 0.86; 95% CI 0.48-0.1.51) EGFR unknown (HR 0.40; 95% CI 0.29-0.54)	NR
Pemetrexed			
Barlesi 2013 [5] Rittmeyer 2013 [7] AVAPERL Phase3	Mean scores for global health and most functional scales similar between arms Patient-reported role functional status, fatigue symptoms and appetite loss higher in Bev + Pem arm Pain in arm or shoulder higher in Bev arm	No interactions	NR
Ciuleanu 2009 [3] Belani 2012 [36] Obasaju 2013 [33] Phase 3	Significant delays in symptom worsening in favour of pemetrexed for pain 4.6 months (HR 0.76; 95% CI 0.59-0.99; p=0.041) and haemoptysis (HR 0.58; 95% CI 0.34-0.97; p=0.038)	Histology and PFS (interaction p=0.036): Non-squamous (HR 0.44; 95% CI 0.36-0.55; p<0.0001) Adenocarcinoma (HR 0.51; 95% CI 0.38-0.68; p<0.0001) Squamous	Histology and OS (interaction p=0.033): Non-squamous (HR 0.70; 95% CI 0.56-0.88; p=0.002) Adenocarcinoma (HR 0.73; 95% CI 0.56-0.96; p=0.026)

		(HR 0.69 ;95% CI 0.49-0.98; p=0.039)	Squamous (HR 1.07; 95% CI 0.77-1.50; p=0.678)
Paz-Ares 2012/13 [4,6] Reck 2014 [34] PARAMOUNT Phase 3	No significant treatment-by-time interaction and no overall treatment differences No significant interaction of response by treatment	No interactions	No interactions
Gemcitabine			
Belani 2010 [12] Phase 3 Abstr 7506	NR	NR	NR
Brodowicz 2006 [13] Phase 3	LCSS - trend towards better control on the Gem arm for cough, hemoptysis and pain	NR	NR
Nagy 2014 [32] Abstr 115P	NR	NR	NR
Docetaxel			
Fidias 2009 [14] Phase 3	No difference between groups p=0.76	NR	NR
Zhang 2013, Lu 2013 [15,30] TFINE study, C-TONG 0904 Abstr Phase 4 NCT01038661 Asian population	NR	NR	NR
Other			
Patel 2013 [31] Pointbreak Phase 3	NR	NR	NR
Zinner 2013 [29] ASCO abstr LBA8003	NR	NR	NR

Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; FACT-L, Functional Assessment of Cancer Therapy - Lung; HR, hazard ratio; LCSS, Lung Cancer Symptom Scale; NR, not reported; OR, odds ratio; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; pts, patients

Table 4. Study quality assessment

Study	Treatment	Primary outcome	Required sample size	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Losses to follow-up (% of pts)	Funding (issues)
EGFR TKIs										
Cappuzzo 2010 and Brugger 2011 [10,28]	Switch to erlotinib versus placebo	PFS	427 per group	438 versus 451	Central, stratified by EGFR status, disease stage, ECOG performance status, first-line therapy, smoking history, region	yes	Personnel, outcome assessors	Yes	NR	Industry (no)
Johnson 2013 [11]	Continuous with bevacizumab + switch to erlotinib versus continuous with bevacizumab + placebo	PFS	800 patients	743 patients, 370 versus 373	Central, stratified by sex, smoking history, ECOG performance status, first-line therapy	Yes	Participants, personnel	Yes	NR	Industry (unclear)
Perol 2012 [8]	Continuous with gemcitabine versus switch to erlotinib versus observation	PFS	435 patients, 278 progression events	454 patients, 154 versus 155 versus 155, 381 progression events	Central, stratified by centre, gender, histology, smoking status, response to first-line therapy	Yes	Outcome assessors	Yes	≤6/154 ≤8/155 0/155	Public funding and industry (No)
Zhang 2012 [9]	Switch to gefitinib versus Placebo	PFS	265 progression events	148 versus 148, 268 progression events	Central, stratified by histology, smoking history	Yes	Participants, personnel, outcome assessors	Yes	1/148 (0.7) 1/148 (0.7)	Industry (No)
Pemetrexed										
Barlesi 2013 [5,7]	Continuous with bevacizumab versus continuous	PFS	228 patients	253 patients, 125 versus 128	NR, stratified by sex, smoking status, tumour response	NR	Open label	Yes	0/125 1/128 (0.8)	Industry (unclear)

Study	Treatment	Primary outcome	Required sample size	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Losses to follow-up (% of pts)	Funding (issues)
	with bevacizumab + pemetrexed									
Ciuleanu 2009 [3]	Switch to pemetrexed versus placebo	PFS	660 patients	663 patients, 441 versus 222	Central, stratified by disease stage, ECOG performance status, sex, response to first-line therapy, type of first-line therapy, history of brain metastases	yes	Participants, personnel	Yes	≤39/441 ≤8/222	Industry (no)
Paz-Ares 2012/2013 [4,6]	Continuous with pemetrexed versus placebo	PFS	390 deaths	359 versus 180, 397 deaths	Central, stratified by ECOG performance status, response to first-line therapy, disease stage	Yes	Participants, personnel, partial outcome assessors	Yes	≤4/359 0/180	Industry (no)
Gemcitabine										
Belani 2010 [12] abstract	Continuous gemcitabine versus best supportive care	OS	NR	128 versus 127	NR	NR	NR	NR	NR	NR
Brodowicz 2006 [13]	Continuous with gemcitabine versus best supportive care	TTP	200 patients	206 patients, 138 versus 68	Unclear, stratified by disease stage, KPS	Unclear	NR	No	NR	Industry (unclear)
Nagy 2014 [32] abstract	Continuous gemcitabine versus best supportive care	NR	NR	120	NR	NR	NR	NR	NR	NR
Docataxel										
Fidias 2009 [14]	Switch to immediate docetaxel	OS	238 deaths	153 versus 156, 256 deaths	Central	Yes	NR	Yes	0/153 1/156 (0.6)	Industry (unclear)

Study	Treatment	Primary outcome	Required sample size	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Losses to follow-up (% of pts)	Funding (issues)
	versus switch to delayed docetaxel									
Zhang 2013, Lu 2013 [15,30] abstracts	Continuous docetaxel versus best supportive care	PFS	NR	123 versus 61	NR	NR	NR	NR	NR	NR
Other										
Patel 2013 [31]	First-line + continuous pemetrexed + bevacizumab versus first-line + continuous bevacizumab	OS	900 patients	939 patients, 472 versus 467	NR, stratified by disease stage, ECOG performance status, sex, measurable versus non-measurable disease	NR	Open label	Yes	NR	Industry (unclear)
Zinner 2013 [29] abstract	First-line + switch to pemetrexed versus first-line + continuous bevacizumab	PFS	NR but calculated	182 versus 179	NR	NR	Open label	yes	NR	NR

Red = high risk-of-bias; yellow = unclear risk-of-bias; clear (excluding abstracts) = low risk-of-bias
Abbreviations: ECOG, Eastern Cooperative, Oncology Group; ITT, intention-to-treat; KPS, Karnofsky performance status; NR, not reported; OS, overall survival; PFS, progression-free survival; pts, patients; TTP, time-to-progression

Outcomes

1. In patients with advanced non-small cell lung cancer who have received initial first-line platinum-based chemotherapy for a minimum of four cycles, does maintenance systemic therapy improve overall survival, progression free survival, or quality of life in comparison to either placebo or second-line therapy at the time of progression?

The quality of the aggregate evidence for the outcomes the working group believed to be critical and important can be found in Table 5. The quality of the evidence was moderate to high and was marked down due to the indirectness of the control groups with various second-line treatment strategies.

Moderate aggregate quality evidence from nine studies provided enough information for OS to be included in a meta-analysis [3,5,6,8-12,14]. Patients who received maintenance therapy had longer overall survival compared with those who did not receive maintenance therapy (HR, 0.83; 95% CI, 0.77 to 0.89, p<0.00001) (Figure 1).

The OS at 12 months was estimated by visual inspection from each of the Kaplan-Meier curves and the median was 49%; therefore the baseline risk of mortality was estimated to be 51%. The median PFS at six months estimated from each study's Kaplan-Meier curves was 18%; therefore, the baseline risk of a PFS event was estimated to be 82%. These baseline risks were used for all comparisons. At a 51% baseline risk of mortality, there would be 6% (63 per 1000) fewer deaths at 12 months (95% CI from 40 fewer to 87 fewer) for patients in the maintenance arm.

High overall quality evidence from seven studies reported data for PFS that could be included in a meta-analysis [3,5,6,8-11]. The results for PFS were statistically significant (HR, 0.57; 95% CI, 0.49 to 0.66, p<0.00001) (Figure 2). However, the I^2 was high at 72%, which showed considerable statistical heterogeneity. The Working Group believed the cause of the statistical heterogeneity was due to the variety of maintenance treatment strategies used across studies. They did not believe the statistical heterogeneity should lower the overall quality of the meta-analysis because all point estimates and their confidence intervals favoured maintenance therapy. At an 82% baseline risk of a PFS event at six months, there would be 20% (196 per 1000) fewer PFS events (95% CI from 142 fewer to 252 fewer) for patients in the maintenance arm.

There were seven moderate aggregate quality RCTs that reported on quality of life [3,6,7,9,10,13,14]. Five of the trials showed no significant difference in quality of life between the arms, although Cappuzzo 2010 showed that time to pain or time to analgesic use were significantly improved with maintenance therapy in post hoc analysis [6,10,13,14]. Also, Brodowicz 2006 found less cough, hemoptysis and pain with maintenance therapy, but the difference was not significant [13]. Zhang 2012 and Ciuleanu 2009 found significant symptom improvement and delays in symptom worsening in favour of patients who received maintenance treatment [3,9]. Rittmeyer 2013 also found less pain in the arm and shoulder symptoms in the maintenance group but patient-reported role functional status, fatigue and appetite loss were worse in patients receiving maintenance therapy [7].

Ten moderate overall quality studies reported on adverse effects [3,5,6,9-14,32]. Depending on the type of maintenance therapy used, there was an increase in the percentage of patients who experienced neutropenia, anemia, rash, fatigue, or diarrhea among those patients who received maintenance treatment.

Table 5: Quality of evidence for maintenance therapy versus no maintenance therapy for systemic treatment in NSCLC

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	maintenance	no maintenance	Relative (95% CI)	Absolute		
Overall survival (OS)												
9	RCT	not serious[1]	not serious	serious[2]	not serious	none	2319	1937 baseline risk 51%[4]	HR 0.83 (0.77 to 0.89)	63 fewer per 1000 (from 40 fewer to 87 fewer) [4]	⊕⊕⊕◯ MODERATE	critical
Progression-free survival (PFS)												
7	RCT	not serious[1]	not serious[3]	not serious	not serious	none	2038	1654 baseline risk 82%[5]	HR 0.57 (0.49 to 0.66)	196 fewer per 1000 (from 142 fewer to 252 fewer) [5]	⊕⊕⊕⊕ HIGH	important
Quality of life												
7	RCT	not serious[1]	not serious	serious[2]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	critical
Adverse effects												
10	RCT	not serious[1]	not serious	serious[2]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	important

Abbreviations: no, number; RCT, randomized controlled trial
GRADE Working Group grades of evidence
High quality = We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Although the randomization method was not reported in some studies, masking is difficult to achieve. Allocation concealment would have been addressed in most cases because most studies used centralized randomization.
2. The Working Group wanted to compare maintenance therapy to usual clinical care. Many of the studies used various second-line therapies that were left to the physicians' discretion, which is different from using a standard intervention. Also, there were different treatment strategies in the control arms. The Working Group would have preferred trials that compared immediate versus delayed treatment, which was only performed by Fidias 2009 [14].
3. Although there was statistical heterogeneity, the Working Group believed this was not a serious threat to the overall quality because every point estimate as well as their confidence intervals favoured maintenance therapy. They attributed the heterogeneity to the different treatment strategies that were used.
4. At 12 months
5. At 6 months

Figure 1: Overall survival for maintenance therapy versus no maintenance therapy for systemic treatment in non-small cell lung cancer

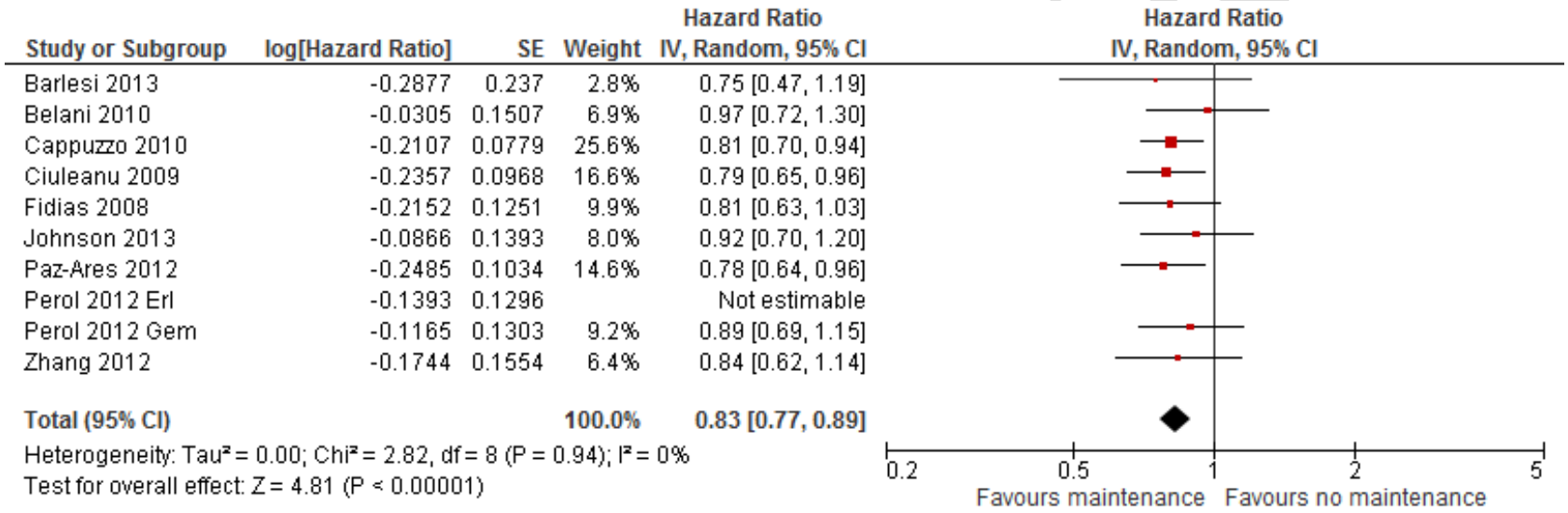
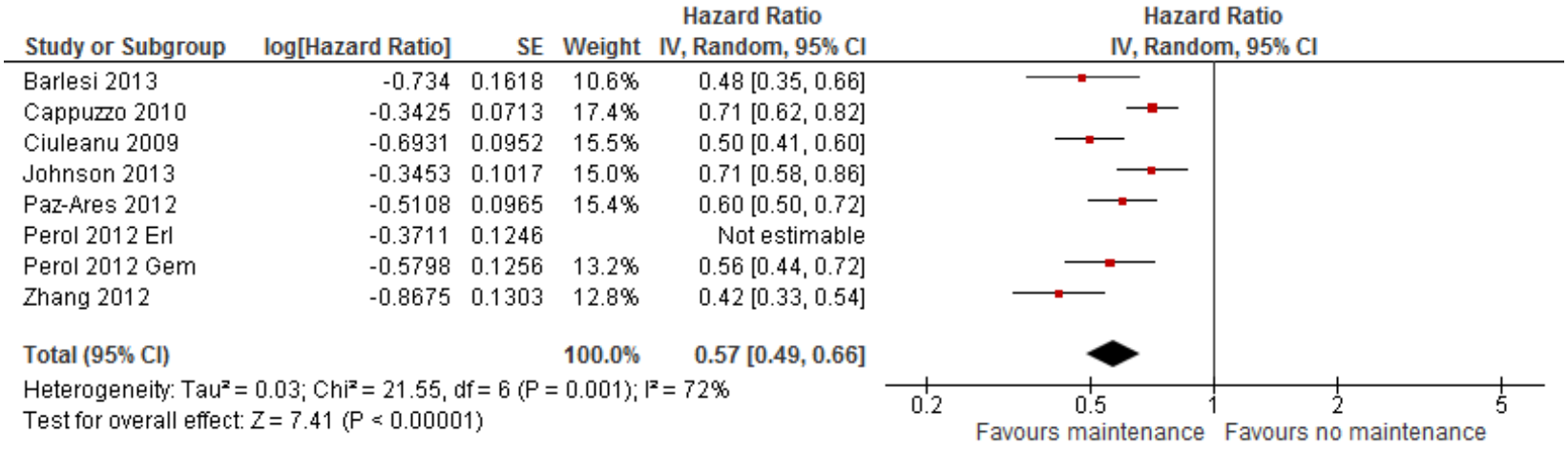


Figure 2: Progression-free survival for maintenance therapy versus no maintenance therapy for systemic treatment in non-small cell lung cancer



2. In patients with advanced NSCLC who have received initial first-line platinum-based chemotherapy for a minimum of four cycles, does any systemic therapy agent improve OS, PFS or quality of life in comparison with other systemic therapies?

None of the trials compared one systemic maintenance therapy with other systemic maintenance therapies. The only available evidence was comparisons of one systemic maintenance therapy against no systemic maintenance therapy. These are described below.

Pemetrexed versus no pemetrexed

The quality of the aggregate evidence for the critical and important outcomes can be found in Table 6. The quality of the evidence was high for PFS and was rated down to moderate for other outcomes due to the indirectness of the comparison groups.

Data for OS from three studies of moderate aggregate quality were included in a meta-analysis [3-5]. Patients who received pemetrexed as maintenance therapy had longer OS compared with those who did not receive pemetrexed as maintenance therapy (HR, 0.78; 95% CI, 0.69 to 0.89; p=0.0003) (Figure 3). At a baseline risk of 51% at 12 months, there would be 8% (83 per 1000) fewer deaths at 12 months (95% CI from 40 fewer to 121 fewer) for patients who received pemetrexed maintenance therapy. The HRs for OS were similar for those trials using continuous maintenance therapy (HR, 0.78; 95% CI, 0.64 to 0.96) [4,5] compared with the trial using a switch strategy (HR, 0.79; 95% CI, 0.65 to 0.96) [3].

High overall quality evidence from three studies reported data for PFS that could be included in a meta-analysis [3,5,6]. The results for PFS were statistically significant (HR, 0.54; 95% CI, 0.47 to 0.61, p<0.00001) (Figure 4). At a baseline risk of 82% at six months, there would be 22% (216 per 1000) fewer PFS events (95% CI from 171 fewer to 267 fewer) for patients in the pemetrexed maintenance arm.

There were three moderate aggregate quality RCTs that reported on quality of life [3,6,7]. Paz-Ares 2012 found no significant difference in quality of life between the arms, but Ciuleanu 2009 found significant delays in symptom worsening in favour of patients who received pemetrexed maintenance treatment [3,6]. Rittmeyer 2013 found no difference in global health status and the majority of functional scale scores [7]. They found that patient-reported role functional status, fatigue, and appetite loss were worse in patients receiving pemetrexed maintenance therapy, but less arm and shoulder pain than patients not receiving pemetrexed.

Three moderate overall quality studies reported on adverse effects [3,5,6]. The proportion of patients who experienced neutropenia, anemia, or fatigue was higher in the pemetrexed maintenance treatment group.

Table 6: Quality of evidence for pemetrexed versus no pemetrexed for systemic maintenance in non-small cell lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pem	no Pem	Relative (95% CI)	Absolute		
Overall survival (OS)												
3	RCT	not serious	not serious	serious[1]	not serious	none	928	527 baseline risk 51%[2]	HR 0.78 (0.69 to 0.89)	83 fewer per 1000 (from 40 fewer to 121 fewer) [2]	⊕⊕⊕◯ MODERATE	critical
Progression-free survival (PFS)												
3	RCT	not serious	not serious	not serious	not serious	none	928	527 baseline risk 82%[3]	HR 0.54 (0.47 to 0.61)	216 fewer per 1000 (from 171 fewer to 267 fewer) [3]	⊕⊕⊕⊕ HIGH	important
Quality of life												
3	RCT	not serious	not serious	serious[1]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	critical
Adverse effects												
3	RCT	not serious	not serious	serious[1]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	important

Abbreviations: CI; confidence interval; HR, hazard ratio; no, number; pem, pemetrexed; RCT, randomized controlled trial

1. The Working Group would have preferred trials that compared immediate versus delayed treatment

2. At 12 months
3. At 6 months

Figure 3: Overall survival for pemetrexed versus no pemetrexed for systemic maintenance in non-small cell lung cancer

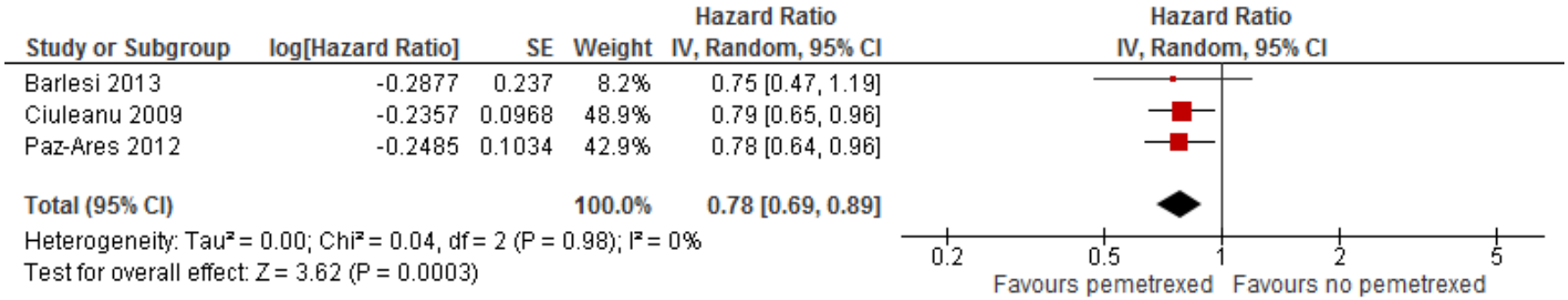
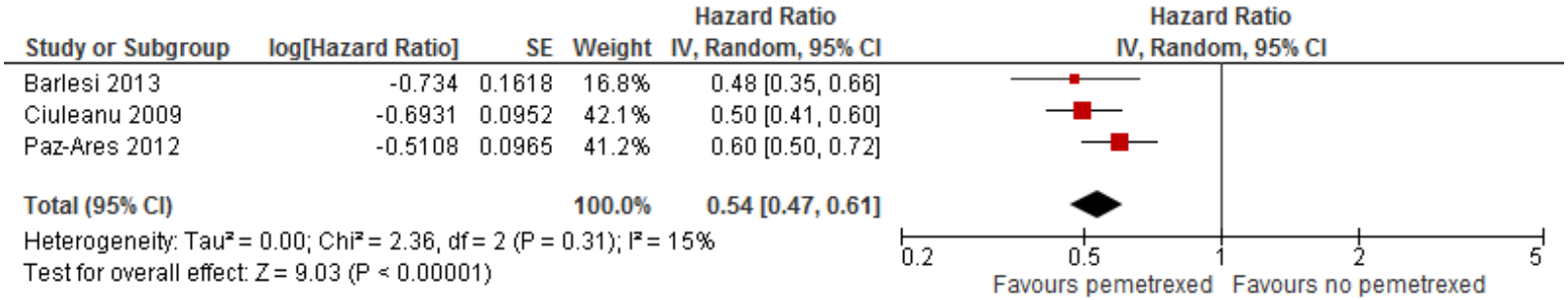


Figure 4: Progression-free survival for pemetrexed versus no pemetrexed for systemic maintenance in non-small cell lung cancer



EGFR TKI versus no EGFR TKI

The quality of the aggregate evidence for the outcomes the working group believed to be critical and important can be found in Table 7. The quality of the evidence was mainly moderate. Three trials compared erlotinib maintenance treatment with a control group [8,10,11] and one trial examined the use of gefinitib maintenance therapy [9]. There were no trials that compared these agents with each other.

Four studies with moderate aggregate quality provided enough information for OS to be included in a meta-analysis [8-11]. OS was better in patients who received EGFR TKIs as maintenance therapy compared with those who did not receive EGFR TKIs as maintenance therapy (HR, 0.84; 95% CI, 0.75 to 0.94; p=0.002) (Figure 5). At a baseline risk of 51% at 12 months, there would be 6% (59 fewer per 1000) fewer deaths at 12 months (95% CI from 21 fewer to 96 fewer per 1000) for patients who received EGFR TKI maintenance therapy.

High overall quality evidence from four studies reported data for PFS that could be included in a meta-analysis [8-11]. The results favoured PFS for patients randomized to maintenance therapy with EGFR TKIs (HR, 0.63; 95% CI, 0.50-0.78; p<0.0001) (Figure 6). However, the I^2 was high at 78%, which showed evidence of statistical heterogeneity but this was attributed to the different treatment strategies of gefitinib and erlotinib and was reduced to zero when the Zhang 2012 trial was removed [9]. At a baseline risk of 82% at six months, there would be 16% (159 fewer per 1000) fewer PFS events at six months (95% CI from 82 fewer to 244 fewer) for patients in the EGFR TKI maintenance arm.

Quality of life was discussed in two RCTs with moderate aggregate quality [9,10]. Cappuzzo 2010 found no difference in quality of life but did show that time to pain or time to analgesic use were significantly improved with erlotinib in post hoc analysis [10]. Zhang 2012 also found significant symptom improvement in favour of patients who received gefitinib as maintenance treatment [9].

Four moderate overall quality studies reported on adverse effects [8-11]. The most significant toxicities from EGFR TKIs were diarrhea and rash.

Table 7: Quality of evidence for EGFR versus no EGFR for systemic maintenance in non-small cell lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGFR	no EGFR	Relative (95% CI)	Absolute		
Overall survival (OS)												
4	RCT	not serious	not serious	serious[1]	not serious	none	1111	1127 baseline risk 51%[2]	HR 0.84 (0.75 to 0.94)	59 fewer per 1000 (from 21 fewer to 96 fewer) [2]	⊕⊕⊕◯ MODERATE	critical
Progression-free survival (PFS)												
4	RCT	not serious	not serious[3]	not serious	not serious	none	1111	1127 baseline risk 82%[4]	HR 0.63 (0.5 to 0.78)	159 fewer per 1000 (from 82 fewer to 244 fewer) [4]	⊕⊕⊕⊕ HIGH	important
Quality of life												
2	RCT	not serious	not serious	serious[1]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	critical
Adverse effects												
4	RCT	not serious	not serious	serious[1]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	important

Abbreviations: CI, confidence interval; EGRF, epidermal growth factor receptor; HR, hazard ratio; no, number; RCT, randomized controlled trial

1. The Working Group would have preferred trials that compared immediate versus delayed treatment
2. at 12 months
3. The overall statistical heterogeneity was attributed to different treatment strategies between gefitinib and erlotinib.
4. at 6 months

Figure 5: Overall survival for epidermal growth factor receptor (EGFR) versus no EGFR for systemic maintenance in non-small cell lung cancer

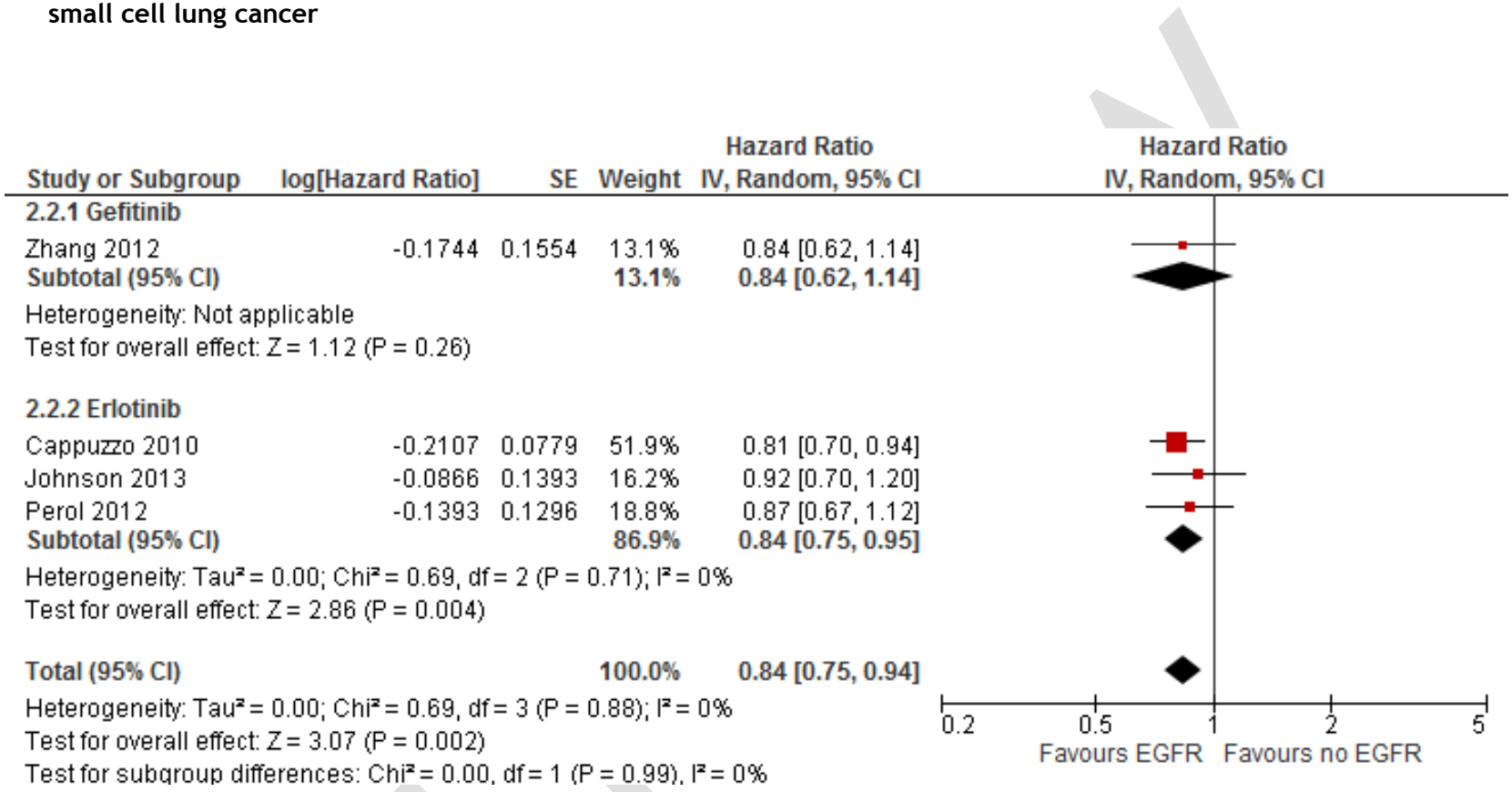
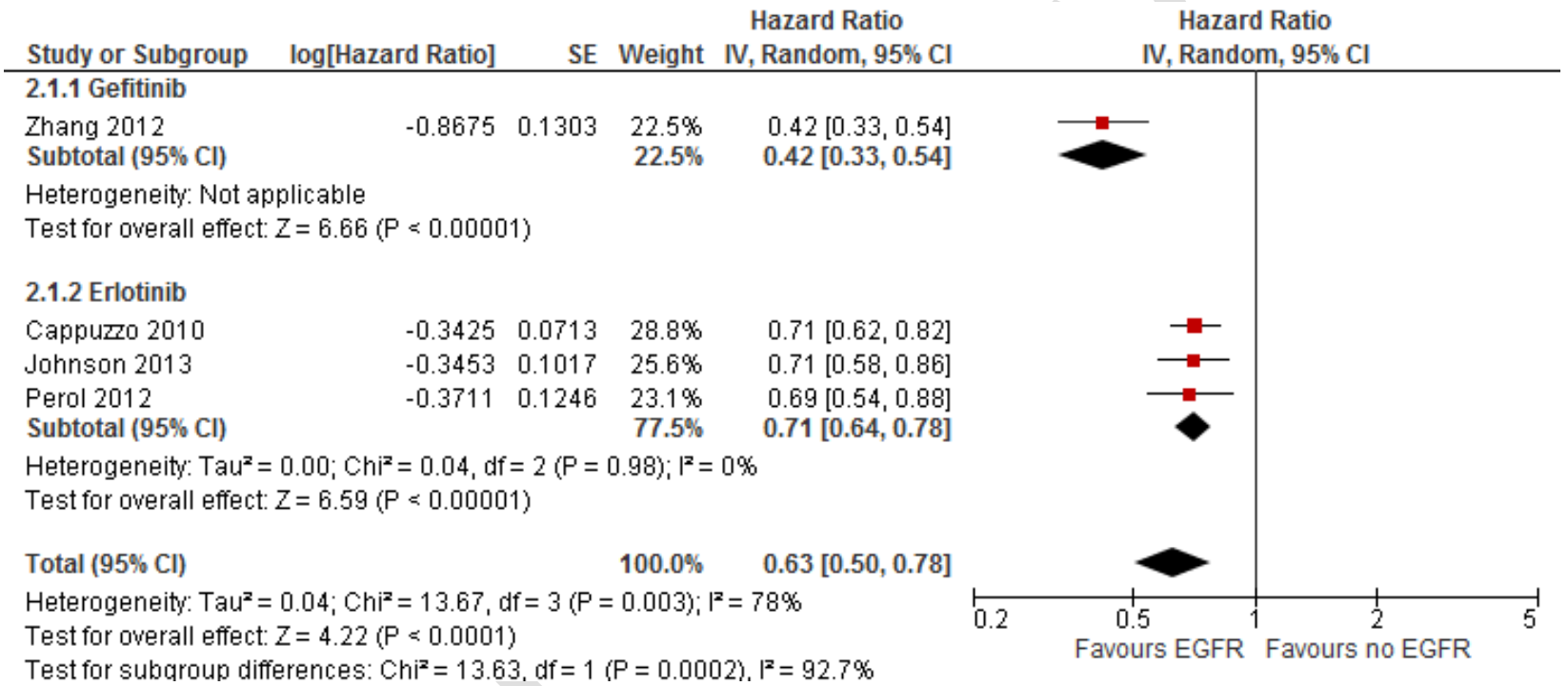


Figure 6: Progression-free survival for epidermal growth factor receptor (EGFR) versus no EGFR for systemic maintenance in non-small cell lung cancer



Gemcitabine versus no gemcitabine

The quality of the aggregate evidence for critical outcomes can be found in Table 8. The quality of the evidence was moderate to low owing to the indirectness of the comparison group, the inclusion of an abstract and the small number of studies included.

Data from two studies with low quality could be included in a meta-analysis for OS [8,12]. There was no difference in OS between patients who received gemcitabine as maintenance therapy compared with those who did not receive gemcitabine as maintenance therapy (Figure 7). Furthermore, two other studies whose data could not be pooled also found no difference in OS between arms (Nagy 2014 p=0.994, Brodowicz 2006 p=0.172) [13,32].

Moderate quality evidence from one study showed a significant effect of PFS (HR, 0.56; 95% CI, 0.44 to 0.72; p<0.001) [8]. At a baseline PFS risk of 82%, there would be 20% (203 per 1000) fewer PFS events (95% CI from 111 fewer to 290 fewer) for patients in the gemcitabine maintenance arm.

There was one low-quality RCT that reported on quality of life [13]. Brodowicz 2006 found a better control for cough, hemoptysis and pain with maintenance, but this was not statistically significant [13].

Four moderate overall quality studies reported on adverse effects [8,12,13,32]. There were more patients who experienced neutropenia, anemia, or fatigue in the gemcitabine maintenance treatment group.

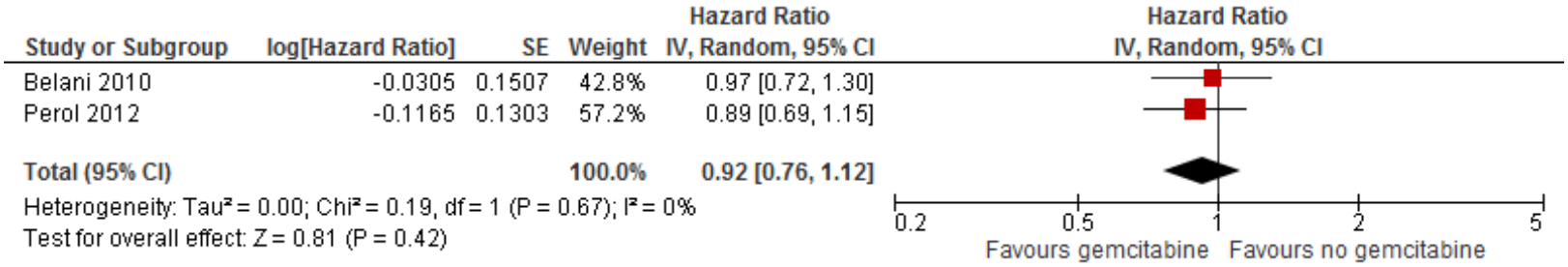
Table 8: Quality of evidence for gemcitabine versus no gemcitabine for systemic maintenance in non-small cell lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gem	no Gem	Relative (95% CI)	Absolute		
Overall survival (OS)												
2	RCT	serious[1]	not serious	serious[2]	not serious	none	282	282 baseline risk 51%[3]	HR 0.92 (0.76 to 1.12)	29 fewer per 1000 (from 40 more to 91 fewer) [3]	⊕⊕◯◯ LOW	critical
Progression-free survival (PFS)												
1	RCT	not serious	not serious	not serious	serious[3]	none	154	155 baseline risk 82%[5]	HR 0.56 (0.44 to 0.72)	203 fewer per 1000 (from 111 fewer to 290 fewer) [5]	⊕⊕⊕◯ MODERATE	important
Quality of life												
1	RCT	not serious	not serious	serious[2]	serious[4]	none			not estimable		⊕⊕◯◯ LOW	critical
Adverse effects												
4	RCT	not serious	not serious	serious[2]	not serious	none			not pooled		⊕⊕⊕◯ MODERATE	important

Abbreviations: CI, confidence interval; gem, gemcitabine; HR, hazard ratio; no, number; RCT, randomized controlled trial

1. Belani 2010 is an abstract
2. The Working Group would have preferred trials that compared immediate versus delayed treatment
3. At 12 months
4. Only one study
5. At 6 months

Figure 7: Overall survival for gemcitabine versus no gemcitabine for systemic maintenance in non-small cell lung cancer



Docetaxel versus no docetaxel

The quality of the aggregate evidence for critical outcomes can be found in Table 9. The quality of the evidence was judged to be moderate due to the included abstracts and very few studies found.

Moderate quality evidence from two studies each found no difference in OS between patients who received docetaxel as maintenance therapy compared with those who did not receive docetaxel as maintenance therapy (Fidias 2009 p=0.853, Lu 2013 p=0.77; data could not be pooled) [14,15].

Moderate overall quality evidence from two studies reported PFS [14,30]. Although there were insufficient data to be pooled, both studies showed a significant effect of PFS (Fidias 2009 p=0.0001, Zhang 2013 p=0.002) [14,30].

There was one moderate quality RCT that reported on quality of life [14]. Fidias 2009 found no significant difference in quality of life between the arms [14].

One moderate quality study reported on adverse effects [14]. Neutropenia and fatigue occurred more frequently in patients who received docetaxel maintenance treatment.

Table 9: Quality of evidence for docetaxel versus no docetaxel for systemic maintenance in non-small cell lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Docetaxel	no Docetaxel	Relative (95% CI)	Absolute		
Overall survival												
2	RCT	serious[1]	not serious	not serious	not serious	none	271	217	not pooled		⊕⊕⊕◯ MODERATE	critical
Progression-free survival												
2	RCT	serious[1]	not serious	not serious	not serious	none	276	217	not pooled		⊕⊕⊕◯ MODERATE	important
Quality of life												
1	RCT	not serious	not serious	not serious	serious[2]	none			not estimable		⊕⊕⊕◯ MODERATE	critical
Adverse effects												
1	RCT	not serious	not serious	not serious	serious[2]	none			not estimable		⊕⊕⊕◯ MODERATE	important

Abbreviations: CI, confidence interval; HR, hazard ratio; no, number; RCT, randomized controlled trial

1. Zhang 2013 is an abstract
2. Only one study

3. In patients with advanced NSCLC, are there any clinical or molecular characteristics that identify subgroups of patients who derive greater benefit from maintenance systemic therapy?

Pemetrexed

Ciuleanu 2009 found a significant interaction favouring non-squamous compared with squamous histology for OS and PFS (Table 10). Based on the results of this study as well as evidence from first-line and second-line pemetrexed treatment that showed patients with non-squamous cell carcinoma had a statistically better OS compared with patients with squamous cell carcinoma [37,38], the other two RCTs [5,6] selected patients with non-squamous histology. Meta-analyses for OS and PFS, including only those patients with non-squamous cell carcinoma from the Ciuleanu 2009, are shown in Figures 8 and 9. Patients with non-squamous cell carcinoma who received pemetrexed as maintenance therapy had longer OS (HR, 0.74; 95% CI, 0.64 to 0.86; $p<0.0001$) and progression-free survival (HR, 0.51; 95% CI, 0.41 to 0.63; $p<0.00001$) compared with those who did not receive pemetrexed as maintenance therapy.

Table 10. Criteria for judging the credibility of subgroup analyses (interactions) for pemetrexed (based on Guyatt 2011 [25])

Criterion	OS/PFS and squamous
Is the subgroup variable a characteristic specified at baseline (in contrast with after randomization)?	Yes
Is the subgroup difference suggested by comparisons within rather than between studies?	Yes
Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?	OS: Ciuleanu 2009 p=0.033 PFS: Ciuleanu 2009 p=0.036
Did the hypothesis precede rather than follow the analysis, and include a hypothesized direction that was subsequently confirmed?	Yes
Was the subgroup hypothesis one of a small number tested?	Yes
Is the subgroup difference consistent across studies and across important outcomes?	No (only 1 study)
Does external evidence (biological or sociological rationale) support the hypothesized subgroup difference?	Yes

Abbreviation: NS, not significant; OS, overall survival; PFS, progression-free survival

Figure 8: Overall survival and non-squamous carcinoma

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Barlesi 2013	-0.2877	0.237	9.5%	0.75 [0.47, 1.19]
Ciuleanu 2009	-0.3567	0.1153	40.3%	0.70 [0.56, 0.88]
Paz-Ares 2012	-0.2485	0.1034	50.1%	0.78 [0.64, 0.96]
Total (95% CI)			**100.0%**	**0.74 [0.64, 0.86]**

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 4.04 (P < 0.0001)

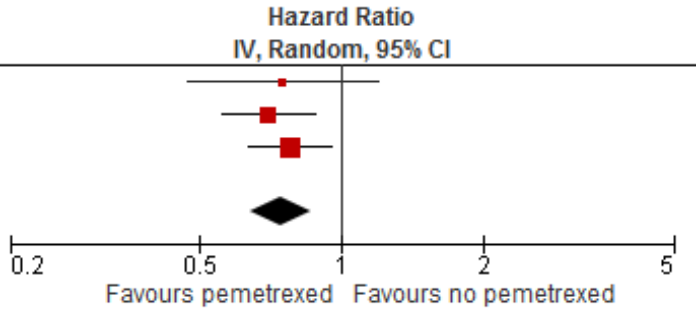
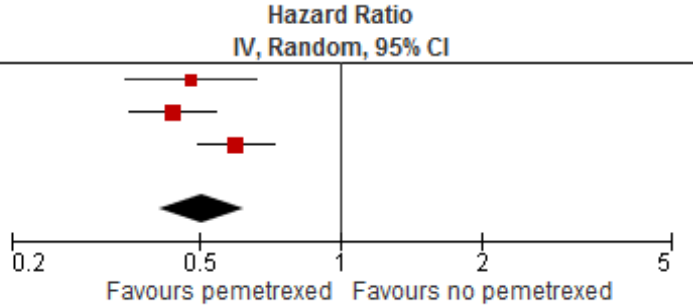


Figure 9: Progression-free survival and non-squamous carcinoma

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Barlesi 2013	-0.734	0.1618	24.7%	0.48 [0.35, 0.66]
Ciuleanu 2009	-0.821	0.1081	36.2%	0.44 [0.36, 0.54]
Paz-Ares 2012	-0.5108	0.0965	39.1%	0.60 [0.50, 0.72]
Total (95% CI)			**100.0%**	**0.51 [0.41, 0.63]**

Heterogeneity: Tau² = 0.02; Chi² = 4.82, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 6.37 (P < 0.00001)



EGFR TKI

There were four factors that had significant interactions in at least one study. The criteria for judging the credibility of these subgroup interactions can be found in Table 11 [25]. While most of the answers to these questions were yes, the overall interaction was not always statistically significant. Because the RCTs were not powered to detect these subgroup differences, any overall significant interactions were judged to be likely credible. However, in the absence of an overall statistically significant interaction, no conclusions can be drawn.

Two studies reported significant interactions between EGFR mutation status and PFS [9,28] with improved PFS in patients with EGFR mutations. Combining the hazard ratios from the studies based on EGFR mutation status yielded a significant interaction between treatment and EGFR mutation status for PFS ($p=0.0007$, $I^2=91.2\%$) but not for OS (Figures 10 and 11).

Cappuzzo 2010 found a significant interaction between gender and PFS, whereas two other studies did not find a significant interaction [8-10]. Combining the hazard ratios by gender for each study found no overall interaction between gender and OS or PFS (Figures 12 and 13).

Zhang 2012 found a significant interaction with the presence or absence of adenocarcinoma and PFS, whereas Perol 2012 did not find a significant interaction [8,9]. When the hazard ratios between adenocarcinoma and no adenocarcinoma were combined a non-significant interaction for PFS was found (Figure 14).

Cappuzzo 2010 found a significant interaction between race and PFS or OS [10]. When these hazard ratios were combined with Johnson 2013 the interaction for PFS did not reach statistical significance (Figure 15) [11].

Table 11. Criteria for judging the credibility of subgroup analyses (interactions) for EGFR TKIs

Criterion	OS/PFS and EGFR mutation status	OS/PFS and gender	PFS and adenocarcinoma	PFS/OS and (white/Asian)
Is the subgroup variable a characteristic specified at baseline (in contrast with after randomization)?	Yes	Yes	Yes	Yes
Is the subgroup difference suggested by comparisons within rather than between studies?	Yes	Yes	Yes	Yes
Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?	OS: p=0.22 PFS: p=0.0007	OS: p=0.19 PFS: p=0.10	PFS: p=0.16	PFS: p=0.21 OS: Capuzzo 2010 p=0.03 Perol 2012 NR Zhang 2012 NR
Did the hypothesis precede rather than follow the analysis, and include a hypothesized direction that was subsequently confirmed?	Yes	Yes	Yes	Yes
Was the subgroup hypothesis one of a small number tested?	Yes	Yes	Yes	Yes
Is the subgroup difference consistent across studies and across important outcomes?	No	No	No	No
Does external evidence (biological	Yes	Yes	Yes	Yes

or sociological rationale) support the hypothesized subgroup difference?				

Abbreviations: EGFR, epidermal growth factor receptor; NR, not reported; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase receptor

Figure 10: Overall survival and epidermal growth factor receptor mutation status

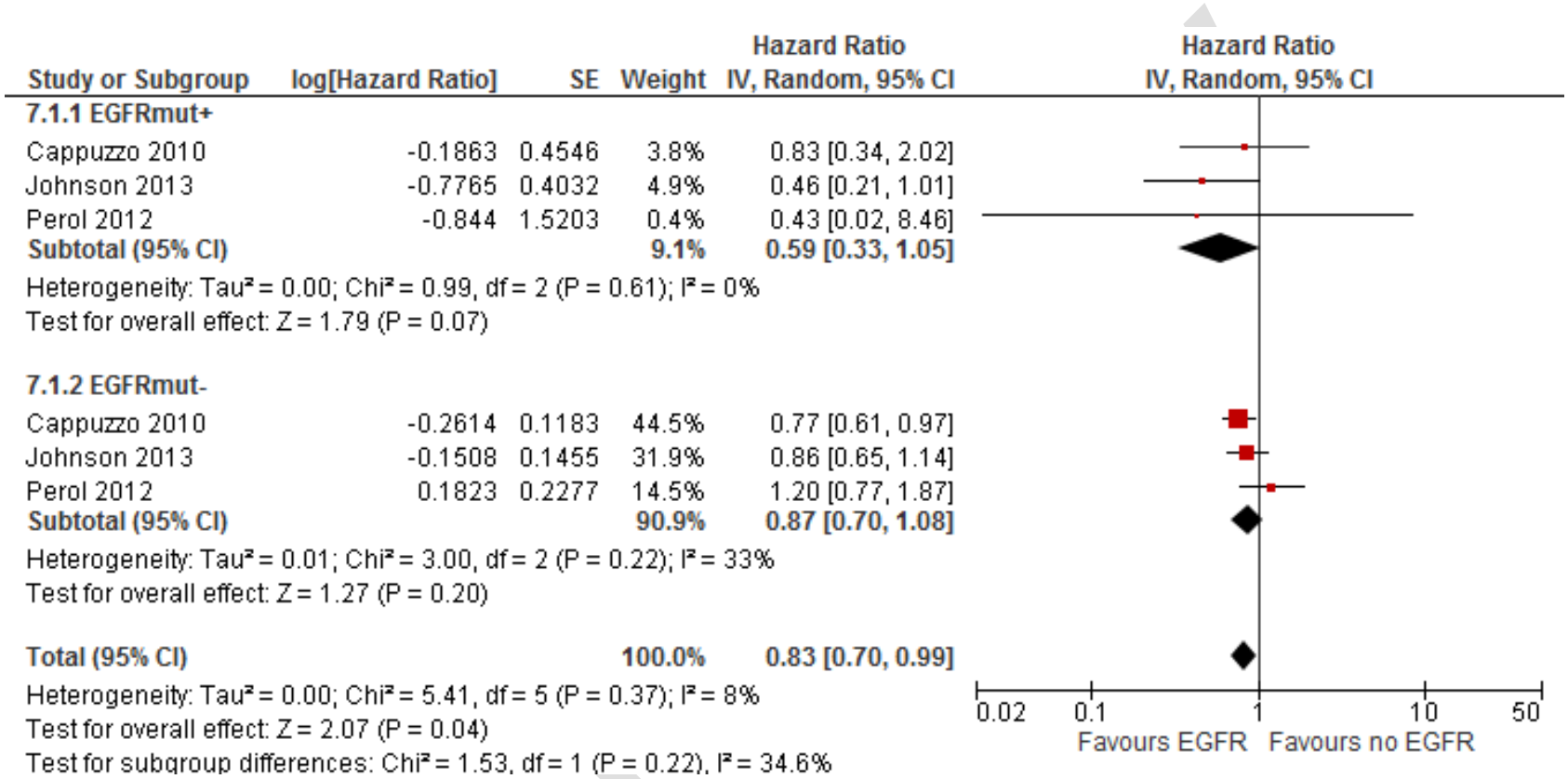


Figure 11: Progression-free survival and epidermal growth factor receptor mutation status

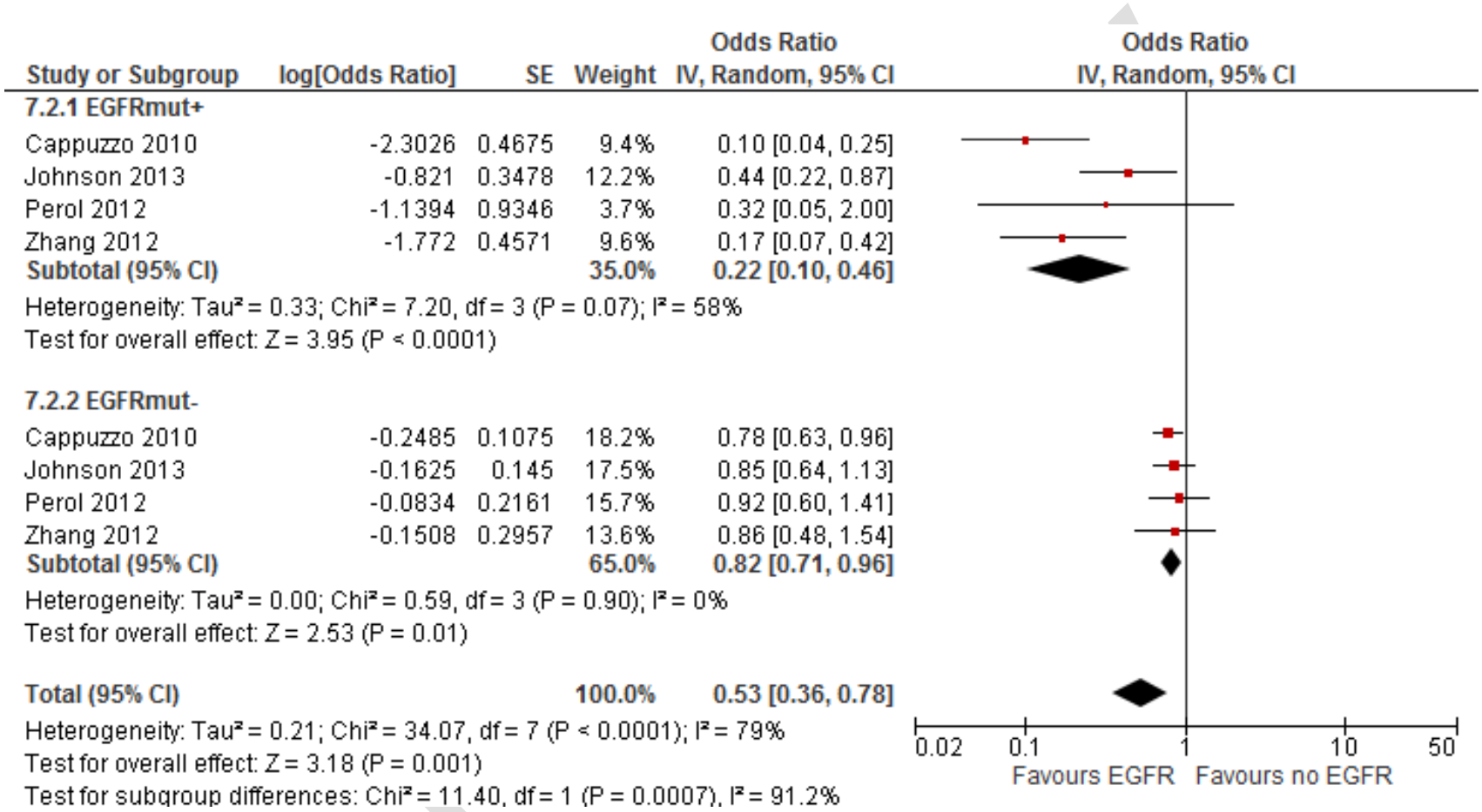


Figure 12: Overall survival and gender

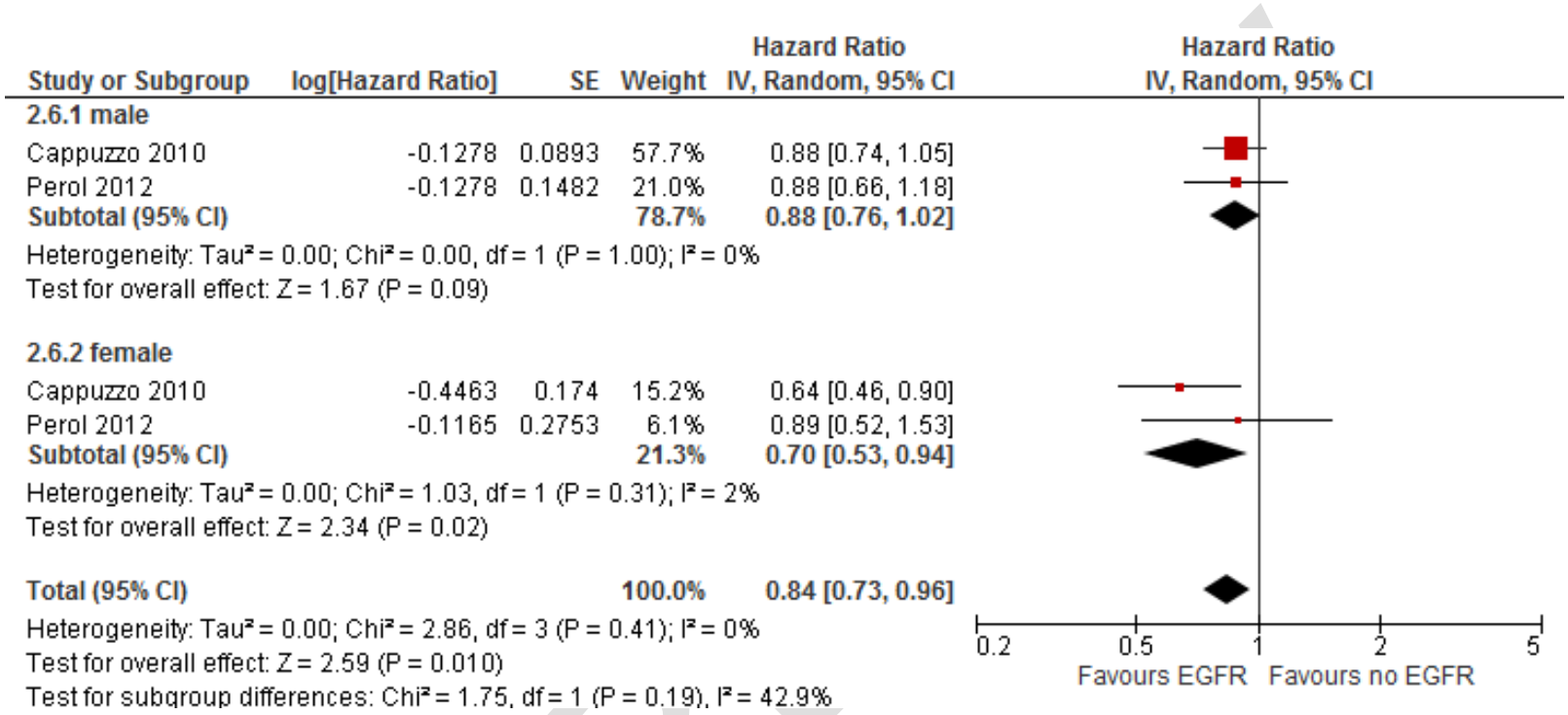


Figure 13: Progression-free survival and gender

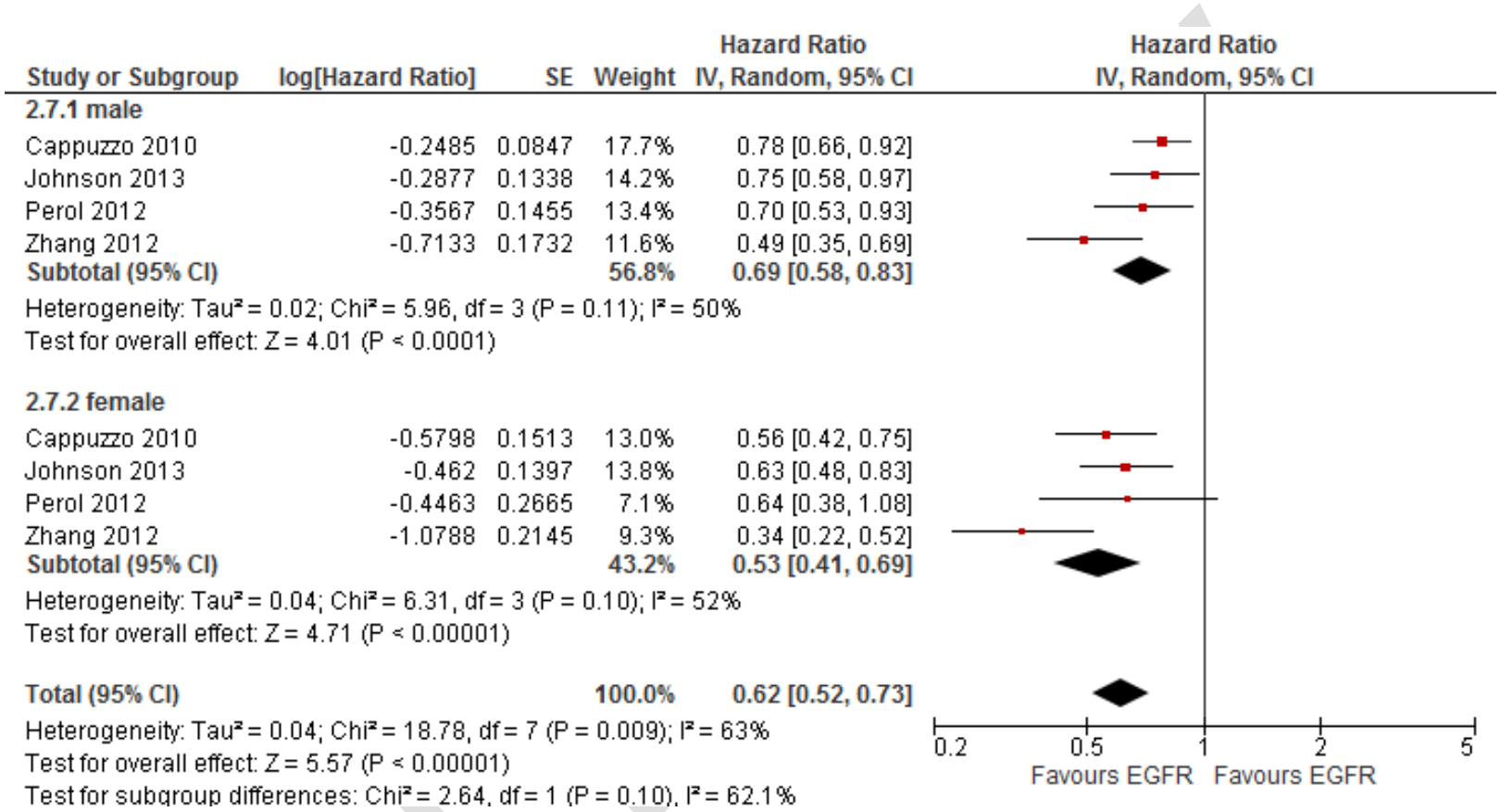


Figure 14: Progression-free survival and adenocarcinoma

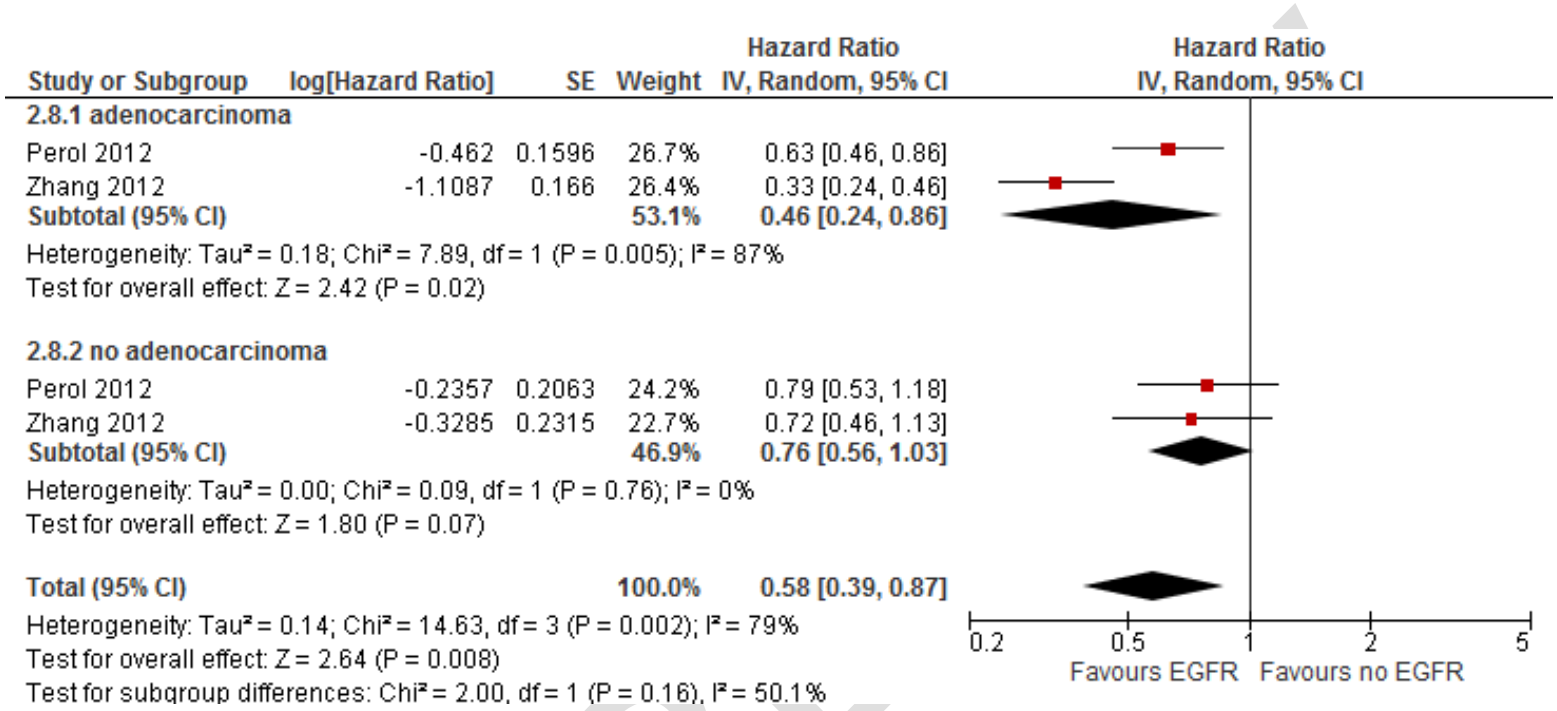
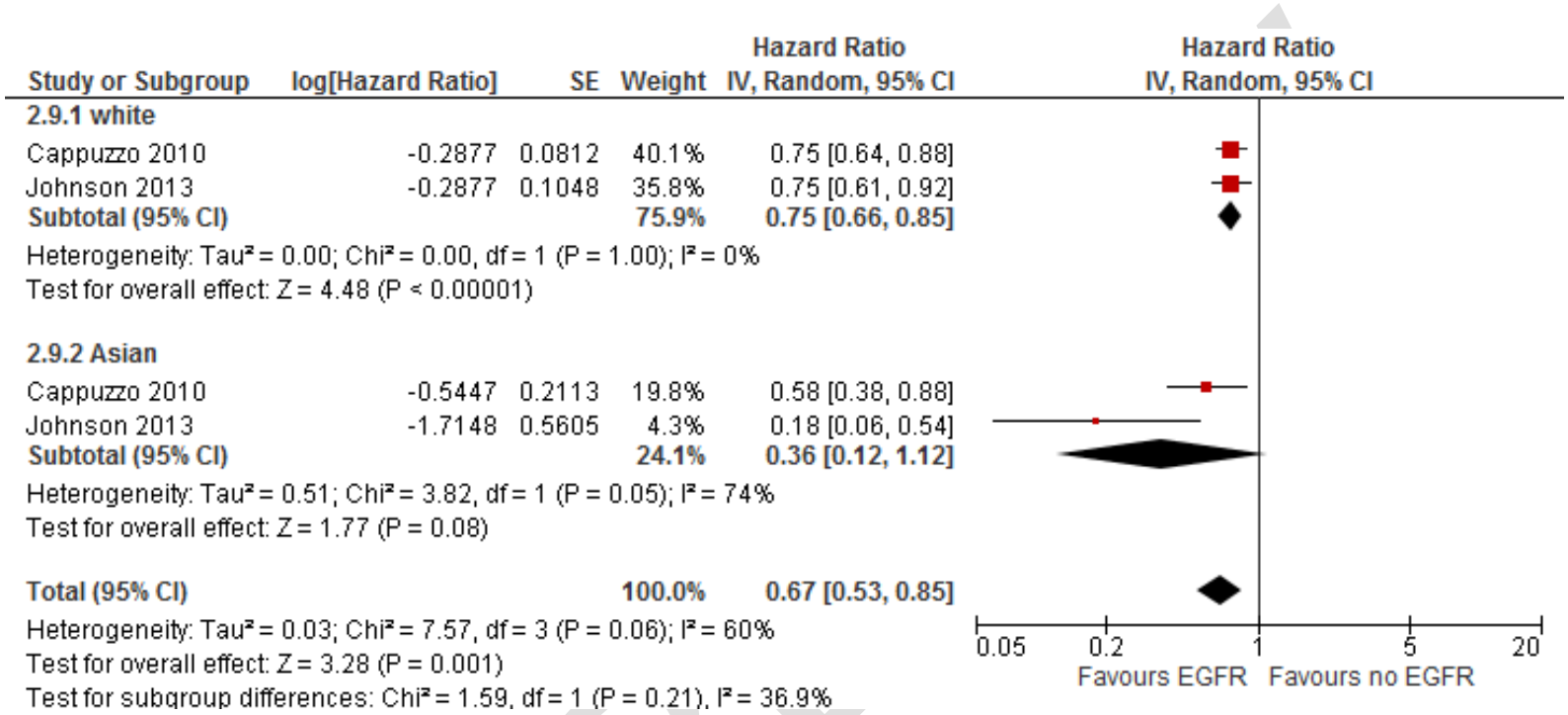


Figure 15: Progression-free survival and race/ethnicity



Gemcitabine and docetaxel

No significant interactions were found for either of these treatments.

Ongoing, Unpublished, or Incomplete Studies

See Appendix D.

DISCUSSION

Maintenance therapy appeared to show modest improvements in OS and PFS, favourable quality of life outcomes, and few adverse effects in patients with advanced, stage IIIB/IV NSCLC who have not progressed (i.e., complete response, partial response, or stable disease) after at least four cycles of platinum-based chemotherapy.

Of the studies identified on this topic, none directly compared one systemic therapy to another; however, it appeared that the strongest evidence was from studies of pemetrexed and EGFR TKIs for OS and PFS. Of the maintenance therapies, pemetrexed had the largest effects, especially in patients with non-squamous cell carcinoma. Two of three RCTs selected for patients with this histology and an RCT with a subgroup of such patients found a significant interaction in favour of nonsquamous-cell carcinoma [3,5,6]. Therefore, a recommendation for maintenance therapy with pemetrexed should be directed specifically toward this subgroup of patients. For patients with squamous cell histology, either the RCTs excluded these patients or were not powered to detect effects in this subgroup of patients. However, the product information for pemetrexed in many jurisdictions limits its use to patients with non-squamous histology and an interaction between treatment and histology in first- and second-line therapy has been demonstrated [16,17]. Trials evaluating pemetrexed in combination with a platinum agent in first-line treatment or compared with docetaxel in second-line therapy demonstrated a significant interaction between histology and treatment.

An updated review of EGFR TKI maintenance treatment since the previous PEBC guideline on this topic resulted in similar conclusions [1]. EGFR TKI maintenance therapy had a significant effect on OS and PFS but the magnitude of effect was smaller than with pemetrexed. There was an interaction between EGFR mutation status and PFS, but not for OS. Therefore, a specific recommendation for patients with EGFR mutations could not be supported. Furthermore, there were no trials that compared different EGFR TKIs against each other; however, the strongest data would support the use of erlotinib in this setting, although the OS advantage is modest for both agents.

There were no other subgroups, such as stable disease versus good responders, performance status, age or gender that showed an interaction between maintenance therapy and OS.

Fewer studies examined gemcitabine and docetaxel as maintenance treatments. Although administration of either drug as maintenance therapy resulted in better PFS, neither therapy had an impact on OS. The quality-of-life scores were not different between groups and more adverse effects were associated with patients in the maintenance arm. Therefore, there is insufficient evidence to support gemcitabine and docetaxel for maintenance therapy.

There are several limitations to this systematic review. First, there were no direct comparisons between different agents as well as no comparisons between immediate versus delayed treatment, except for Fidias 2009, which compared immediate versus delayed treatment with docetaxel maintenance therapy [14]. Second, the control group was not uniform across comparisons: control groups included best supportive care, a combination of drugs, or removal of one drug. Third, the second-line therapies differed across trials. Finally, switch and continuous maintenance therapies were combined in the meta-analyses, but because the effect sizes for OS with pemetrexed were similar with either the switch or continuous maintenance approaches, it was believed this would not adversely affect the

integrity of the meta-analysis. In another systematic review, separate meta-analyses for switch and continuous maintenance therapies were conducted but combined different drugs thus making drug-specific recommendations difficult [39].

CONCLUSIONS

In patients with advanced, stage IIIB/IV NSCLC who have not progressed (i.e., complete response, partial response, or stable disease) after at least four cycles of platinum-based chemotherapy, there is evidence for a beneficial effect of OS with few adverse events to support the use of pemetrexed and EGFR TKI maintenance therapy. For pemetrexed, the evidence is strongest for patients with non-squamous NSCLC**.** There is insufficient evidence to recommend either gemcitabine or docetaxel for maintenance therapy.

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer: Internal and External Review

INTERNAL REVIEW

Program in Evidence-Based Care (PEBC) guidelines were reviewed by a panel of content experts—the Expert Panel and a methodology panel—the Report Approval Panel (RAP). Both panels were required to approve the document. The Working Group was responsible for incorporating the feedback and required changes of both of these panels. The details of these reviews and actions taken are described below. Appendix A provides a list of members of the Working Group, RAP and Expert Panel and summarizes conflict of interest declarations for all members. The PEBC conflict of interest policy is available at: https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=103568.

Expert Panel Review and Approval

The Lung Cancer Disease Site Group acted as the Expert Panel for this document. For approval of the guideline document, 75% of the Lung Cancer Disease Site Group membership was required to cast a vote or abstain, and of those that voted, 75% were required to approve the document. At the time of the voting, Lung Cancer Disease Site Group members could suggest changes to the document, and make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Of the 26 members of the Lung Cancer Disease Site Group, 20 members cast votes and zero abstained, for a total of 77% response. Of those that cast votes, 20 approved the document (100%). The main comments from the Expert Panel and the Working Group's modifications/actions/responses taken in response are summarized in Table 1.

Table 1. Modifications/actions/responses regarding main comments from the Expert Panel.

Main comments	Modifications, actions, or responses
1. In the target population, include "Completed first line chemotherapy (usually 4-6 cycles) and have a performance status of less than 2.	This has been added.
2. In the initial discussion, perhaps mention that the issue of maintenance for stable disease vs. good responders was considered (even in so far as, it was determined that this was not useful for determining benefit of maintenance), or mention that the guideline does not address who the optimal people are for a maintenance strategy.	This sentence has been added to the discussion. "There were no other subgroups, such as stable disease versus good responders, performance status, age or gender that showed an interaction between maintenance therapy and overall survival."
3. There is no mention of bevacizumab maintenance in the recommendations, despite the fact that carbo-taxol-avastin is a reasonable strategy in first-line patients (albeit not currently funded in Ontario). Something along the lines of "Maintenance chemotherapy with pemetrexed is not	A qualifying statement has been added.

recommended if the patient is also receiving bevacizumab maintenance".	
4. I think the language of the recommendation ***"should be considered an option"*** should reflect the evidence – that, albeit imperfect, there is a meaningful survival advantage for maintenance pemetrexed in patients with non-squamous histology, and should read "***The recommendation is that in suitable patients with non-squamous histology, maintenance pemetrexed therapy is a recommended strategy after first line pemetrexed or non-pemetrexed doublet chemotherapy***". This would still allow the discretion of the treating physician regarding suitable and unsuitable, but seems like a stronger recommendation for a life prolonging intervention than it currently reads.	'Should' for pemetrexed implies a stronger recommendation than 'may' for EGFR TKIs; therefore the working group decided to keep the original wording so that a preference for pemetrexed over EGFR TKIs is reflected in the recommendations.

Report Approval Panel Review and Approval

Three RAP members reviewed this document in March 2015. The RAP approved the document March 3, 2015. The summary of main comments from the RAP and the Working Group's modifications/actions/responses taken in response are showed in Table 2.

Table 2. Modifications/actions/responses regarding main comments from the Expert Panel.

Main comments	Modifications, actions, or responses
1. Add absolute values under key evidence for the recommendations	These have been added.
2. There are multiple meta-analyses in the subgroup analysis section – does p level need modification?	Only one of the five factors that were examined had a significant subgroup effect for overall survival. It was believed that five factors is a small enough number to not require a p level modification. Also, the credibility of the one significant factor was high and is supported in research with first- and second-line therapies.
3. Given that EGFR TKIs has a quality-of-life benefit over the pemetrexed and they are about equal for overall survival, I'm not sure why pemetrexed is preferred.	Because there have been no direct comparisons between EGFR TKIs and pemetrexed, the preference for pemetrexed is based on consensus of the Lung Cancer Disease Site Group.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Eleven targeted peer reviewers who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Four agreed to be the reviewers and three responses were received (Appendix A). Results of the feedback survey are summarized in Table 3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 4.

Table 3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)

Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**	0	0	0	0	3
2. **Rate the guideline presentation.**	0	0	0	1	2
3. **Rate the guideline recommendations.**	0	0	0	1	2
4. Rate the completeness of reporting.	0	0	0	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	1	2
6. Rate the overall quality of the guideline report.	0	0	0	0	3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	1	2
8. I would recommend this guideline for use in practice.	0	0	0	1	2
9. What are the barriers or enablers to the implementation of this guideline report?	The primary barrier is funding in Canada.				

Table 4. Responses regarding main written comments from targeted peer reviewers.

Comments	Responses
1. I would question the recommendation for after four to six cycles of chemotherapy, particularly for pemetrexed. The trials showing benefit as well as the great majority of trials reviewed used four cycles of platinum doublet. There is no evidence that more than four cycles is needed.	The Working Group agreed that most trials were designed with four cycles of platinum doublet therapy; however, because the effectiveness of additional cycles was not investigated in this review, the Working Group believed the target population should not change.
2. I have some concern about the TKI maintenance recommendations. In the Interpretation of the evidence section it is stated that the Working Group believed that the desirable effects of TKI maintenance were clinically meaningful. The review suggests that the desirable effects do not meet the ASCO recommendation for clinically meaningful (HR<0.8 and /or mOS benefit 2.5-6 mos). What criteria were used to determine clinically meaningful? This recommendation to use maintenance TKI regardless of EGFR mutation status would also be contrary to the Choosing Wisely recommendation that molecularly targeted therapies should only be used if the tumour cells possess the target.	The Working Group believed the desirable effects of EGFR TKI maintenance therapy to be clinically meaningful because its confidence interval overlapped with those of pemetrexed. They did, however, favour the use of pemetrexed over EGFR TKI. In regard to the comment about Choosing Wisely, the data support the use of an EGFR TKI in patients who are EGFR WT, so the Working Group based the recommendations on the data.
3. The one issue I have here relates to the median follow-up particularly for the maintenance TKI trials (SATURN in particular). The median follow-up at the time of publication is short and less than or similar to the mOS reported. Doesn't such a short follow-up impact	Although the median follow-up was shorter or less than the median overall survival in some of the trials, the losses to follow-up were not substantial and the Working Group believed this would not change any of the recommendations.

the stability of the mOS? If so, should this not be commented on in the document?	

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists in the PEBC database who have lung cancer as a subject of interest were contacted by email to inform them of the survey. Twenty-nine medical oncologists were contacted, of which three were from outside Ontario. Six (21%) responses were received. The results of the feedback survey from six people are summarized in Table 5. There were no issues to address from their comments.

Table 5. Responses to four items on the professional consultation survey.

	Number = 6				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	1	5
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	0	1	5
3. I would recommend this guideline for use in practice.	0	0	0	1	5
4. What are the barriers or enablers to the implementation of this guideline report?	Again, the primary barrier is funding.				

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the Working Group and approved by the Expert Panel and the PEBC RAP.

Appendix A. Members of the Maintenance Systemic Treatment in Non-small cell Lung Cancer Working Group, Expert Panel, Report Approval Panel and Target Peer Reviewers and their Conflict of Interest Declaration

Name and Affiliation	Declarations of interest
Working Group	
Swati Kulkarni Medical Oncologist Lung Cancer Disease Site Group	Received $5,000 from Roche in 2011 to attend a world lung conference
Emily Vella Health Research Methodologist Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON	None declared
Nadia Coakley Health Research Methodologist Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON	None declared
Susanna Cheng Medical Oncologist Lung Cancer Disease Site Group	None declared
Richard Gregg Medical Oncologist Lung Cancer Disease Site Group	None declared
Yee Ung Radiation Oncologist Lung Cancer Disease Site Group	None declared
Peter Ellis Medical Oncologist Lung Cancer Disease Site Group	• Received $5,000 or more in a single year from an honoraria from Eli Lilly for speaking tours in South Korea and Taiwan in 2009 and Australia in 2011 • Received research grant from Eli Lilly and Roche for $25,000 each
Lung Cancer Disease Site Group Expert Panel	
Jaro Kotalik Bioethics Lung Cancer Disease Site Group	None declared
Adrien Chan Medical Oncologist Lung Cancer Disease Site Group	None declared
Ronald Feld Medical Oncologist Lung Cancer Disease Site Group	• Received >$100,000 as principal investigator of a mesothelioma protocol from an Eli Lilly Canada study involving pemetrexed • Was principal investigator of a cross-Canada and Italy study involving erlotinib and received >$200,000 for the study from Roche Canada
John Goffin Medical Oncologist Lung Cancer Disease Site Group	None declared
Glen Goss	None declared

Medical Oncologist Lung Cancer Disease Site Group	
Sara Kuruvilla Medical Oncologist Lung Cancer Disease Site Group	None declared
Scott Laurie Medical Oncologist Lung Cancer Disease Site Group	None declared
Natasha Leighl Medical Oncologist Lung Cancer Disease Site Group	None declared
Andrew Robinson Medical Oncologist Lung Cancer Disease Site Group	None declared
Mark Vincent Medical Oncologist Lung Cancer Disease Site Group	• Received $5,000 or more in a single year in a consulting capacity from Eli Lilly • Received financial or material support of $5,000 or more in a single year from Astra Zeneca and Boehringer-Ingelheim • Received grants or research support, either as principal investigator or co-investigator, from Roche
Penny Bradbury Medical Oncologist Lung Cancer Disease Site Group	Was senior investigator at the NCIC Clinical Trials Group (a cooperative oncology group which carries out clinical trials in cancer therapy, supportive care and prevention across Canada and internationally). The NCIC CTG receives research funding from pharmaceutical companies to undertake specific clinical trials. She did not receive personal research funding from any business entities.
Medhat El-Mallah Radiation Oncologist Lung Cancer Disease Site Group	None declared
Conrad Falkson Radiation Oncologist Lung Cancer Disease Site Group	None declared
Robert MacRae Radiation Oncologist Lung Cancer Disease Site Group	None declared
Andrew Pearce Radiation Oncologist Lung Cancer Disease Site Group	None declared
Kevin Ramchandar Radiation Oncologist Lung Cancer Disease Site Group	None declared
Anand Swaminath Radiation Oncologist Lung Cancer Disease Site Group	None declared
Mojgan Taremi	None declared

Radiation Oncologist Lung Cancer Disease Site Group	
Edward Yu Radiation Oncologist Lung Cancer Disease Site Group	None declared
Alex Sun Radiation Oncologist Lung Cancer Disease Site Group	None declared
Abdollah Behzadi Surgeon Lung Cancer Disease Site Group	None declared
Donald Jones Surgeon Lung Cancer Disease Site Group	None declared
Richard Malthaner Surgeon Lung Cancer Disease Site Group	None declared
Donna Maziak Surgeon Lung Cancer Disease Site Group	None declared
Kazuhiro Yasufuku Surgeon Lung Cancer Disease Site Group	None declared
Robert Zeldin Surgeon Lung Cancer Disease Site Group	None declared
Report Approval Panel	
Melissa Brouwers Director Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON	None declared
Craig Earle Medical Oncologist Sunnybrook's Odette Cancer Centre	None declared
Shailendra Verma Medical Oncologist Ottawa Hospital Cancer Centre	None declared
Target Peer Reviewers	
Charles Butts Medical Oncologist Cross Cancer Institute, Edmonton, AB	• Received greater than $5,000 in a single year for participation in Advisory Boards for MSD and Pfizer • As President of CAMO organization, received greater than $5,000 for meeting and fellowship programs from a number of pharmaceutical companies
Desiree Hao Medical Oncologist Southern Alberta Cancer Research Institute, Calgary, AB	None declared

Morzycki Wojciech Medical Oncologist Dalhousie University, Halifax, NS	Received $5,000 or more in a single year as a consultant on advisory boards and in education grants from several pharmaceutical companies

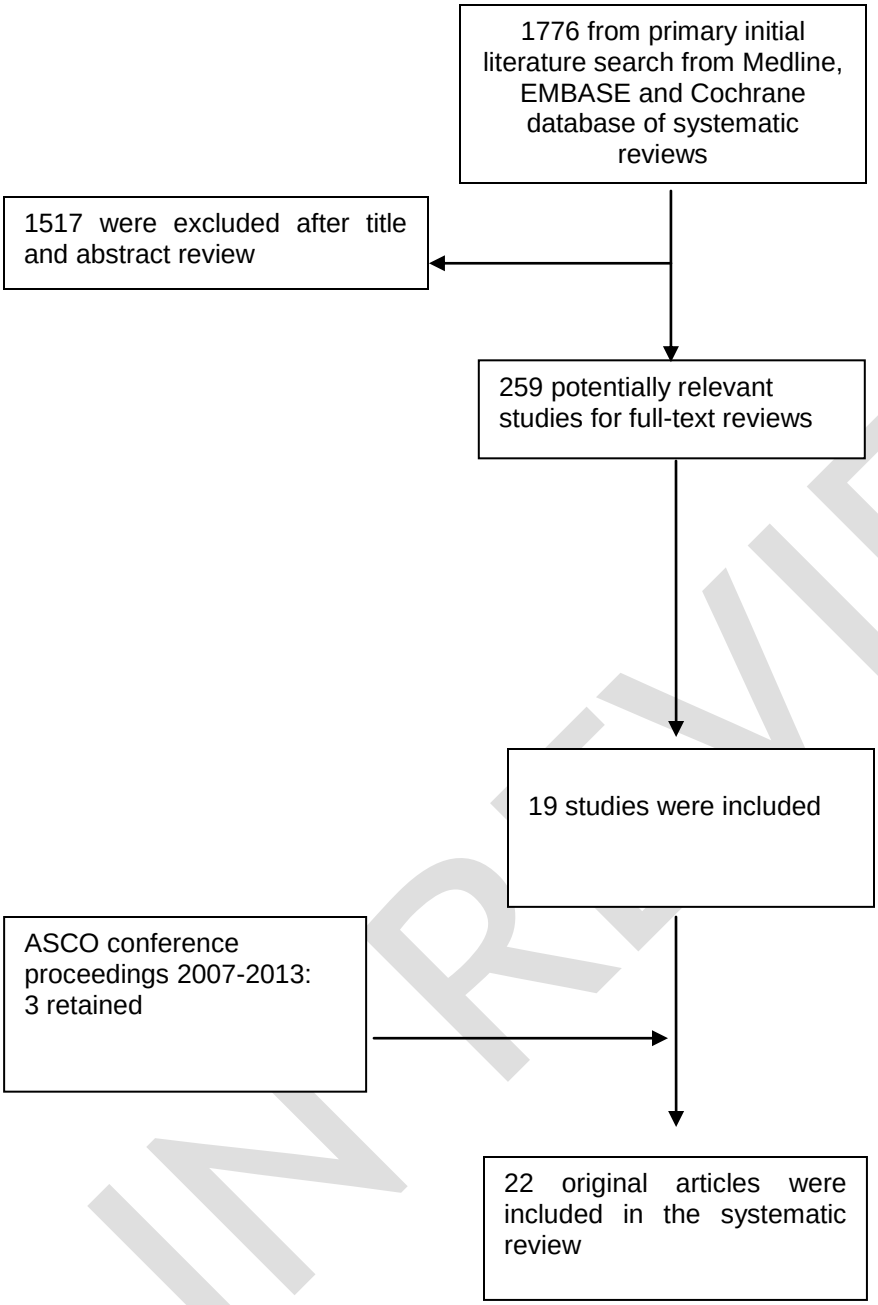
Appendix B: Search strategies
Medline/Cochrane:

1. practice guidelines/
2. practice guideline.pt.
3. practice guideline?.tw.
4. practice guideline?.mp.
5. systematic review?.mp.
6. systematic overview?.mp.
7. Meta-analysis/
8. meta analysis.pt.
9. metaanalys$.mp.
10. meta analys$.mp.
11. metaanal$.mp.
12. random$.mp.
13. randomized controlled trials/
14. randomized controlled trial.pt.
15. randomised controlled trial.mp.
16. controlled clinical trials/
17. controlled clinical trial.pt.
18. random allocation/
19. clinical trials/
20. (random$ and (trial$ or stud$)).mp.
21. quantitative overview?.mp.
22. quantitative review?.mp.
23. or/1-22
24. exp lung neoplasm/ or carcinoma, non-small-cell lung/
25. NSCLC.mp.
26. (lung and (cancer$ or neoplsm$ or carcinoma$ malignan$ or tomo?r$)).mp.
27. non small cell lung.mp.
28. (lung adj3 (cancer? or carcinoma?)).mp.
29. or/24-28
30. 23 and 29
31. maintenance.mp.
32. 30 and 31
33. limit 32 to yr="1985 -Current"

Embase:
1. exp Meta Analysis/ or exp "Systematic Review"/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp "Review"/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.

8. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
9. exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp randomized controlled trial/ or methodology/ or exp cohort analysis/ or exp double blind procedure/ or exp single blind procedure/ or exp meta analysis/ or exp practice guideline/
10. (random: adj3 (trial or study)).tw.
11. (systematic adj3 (review or overview)).tw.
12. (quantitative adj3 (review or overview or synthesis or syntheses)).tw.
13. meta-anal:.tw.
14. metaanal:.tw.
15. metanal:.tw.
16. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
17. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
18. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
19. randomization/ or single blind procedure/ or double blind procedure/
20. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
21. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
22. random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebo/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/1-27
29. exp lung carcinogenesis/ or exp lung adenocarcinoma/ or exp lung alveolus cell carcinoma/ or exp lung non small cell cancer/ or exp lung squamous cell carcinoma/
30. non small cell lung.tw.
31. (lung adj3 (cancer? or carcinoma?)).tw.
32. or/29-31
33. 28 and 32
34. maintenance.mp.
35. 33 and 34
36. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
37. 35 not 26
38. limit 37 to yr="1985 -Current"

Appendix C: Literature Search Flow Diagram



Abbreviation: ASCO, American Society of Clinical Oncology

Appendix D: Ongoing trials (on Oct 1 – NSCLC and maintenance)

Protocol ID	Study details
EGFR TKI	
Icotinib as First-line and Maintenance Treatment in EGFR Mutated Patients With Lung Adenocarcinoma NCT01665417	This study is designed to compare the efficacy and safety of first-line icotinib treatment and first-line chemotherapy followed by maintenance treatment with icotinib.
Intercalating and Maintenance Use of Iressa Versus Chemotherapy in Selected Advanced Non Small Cell Lung Cancer NCT01404260	In this study, the investigators compared the efficacy, safety, and adverse-event profile of chemotherapy plus gefitinib with those of chemotherapy alone, when these drugs were used as first-line treatment in nonsmokers or former light smokers in China, who had lung adenocarcinoma with EGFR gene mutation unknown.
Icotinib Versus First-line Chemotherapy Plus Maintenance Treatment in EGFR Positive Lung Adenocarcinoma Patients NCT01719536	The purpose of this study is to compare icotinib with induction and maintenance chemotherapy in the first-line treatment of advanced NSCLC patients with EGFR mutation.
Pemetrexed	
Strategies for Maintenance Therapies in Advanced Non-Small Cell Lung Cancer NCT01631136	The aim of this study is to compare two maintenance strategies • A continuous maintenance by pemetrexed • A switch maintenance or a continuous maintenance according to the response of induction chemotherapy.
MODEL (Maintenance Versus Observation After inDuction Chemotherapy in Non-progressing Elderly Patients With Advanced Non-small Cell Lung Cancer) NCT01850303	The objective of this trial is to evaluate the switch maintenance in elderly patient with a controlled disease after four cycles of chemotherapy carboplatin-paclitaxel.
Pemetrexed in Advanced Non-Small Cell Lung Cancer: at Progression vs Maintenance Therapy After Induction Chemotherapy NCT02004184	The overall aim of this study is to investigate whether immediate maintenance pemetrexed therapy prolongs survival compared to observation and pemetrexed therapy at progression in patients with advanced NSCLC. Furthermore, it will be explored whether patients with 'performance status' 2 and elderly ≥ 70 years tolerate and benefit from maintenance therapy; and what characteristics and blood biomarkers are associated with sensitivity and tolerability of such therapy.
Bevacizumab or Pemetrexed Disodium Alone or In Combination After Induction Therapy in Treating Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer NCT01107626	Bevacizumab or Pemetrexed Disodium Alone or In Combination After Induction To compare the overall survival of patients with advanced NSCLC treated with maintenance therapy with bevacizumab vs pemetrexed disodium vs bevacizumab and pemetrexed disodium following induction therapy.
Pemetrexed With or Without Carboplatin for Elderly Non-squamous Non-small Cell Lung Cancer NCT01593293	This study compares the doublet therapy of pemetrexed (500 mg/m^2) and carboplatin (AUC 5 mg/mL*min) administered intravenously every 21 days for four cycles followed by pemetrexed (500 mg/m^2) every 21 days for maintenance therapy (Arm A) to single therapy of pemetrexed (500 mg/m^2) every 21 days till progression or unacceptable toxicity (Arm B).
Gemcitabine	
Maintenance Gemcitabine in the Chinese Advanced Lung Cancer NCT01336192	We investigate the efficacy and safety of continuation of gemcitabine maintenance therapy for patients with metastatic NSCLC with ECOG performance status of 0-1 and without PD after four cycles of first-line chemotherapy with gemcitabine and cisplatin in China.
Other	

Protocol ID	Study details
Safety and Efficacy Study of Abraxane as Maintenance Treatment After Abraxane Plus Carboplatin in 1st Line Stage IIIB / IV Squamous Cell Non-small Cell Lung Cancer (aboundsqm) NCT02027428	A phase III, randomized, open-label, cross-over, multicenter study of nab-paclitaxel plus best palliative care or best palliative care alone as maintenance treatment after response or stable disease with nab-paclitaxel plus carboplatin as induction in subjects with squamous cell NSCLC.
Maintenance Therapy With Autologous Cytokine-induced Killer Cells for Nonsquamous Non-small Cell Lung Cancer NCT01481259	A randomized controlled study was conducted to compare CIK cells with pemetrexed as maintenance therapy for stage IIIb-IV nonsquamous NSCLC.
A Study of Avastin (Bevacizumab) in Combination With Standard of Care Treatment in Patients With Lung Cancer NCT01351415	Patients will be randomly assigned to one of two treatment arms to receive either Avastin plus standard of care treatment or standard of care treatment alone.
Nintedanib Plus Docetaxel in Advanced Non-small Cell Lung Cancer NCT02231164	The present trial will investigate the efficacy and safety of nintedanib in combination with docetaxel as compared to placebo in combination with docetaxel in patients with stage IIIB/IV or recurrent NSCLC of adenocarcinoma histology after failure of first-line platinum-based chemotherapy.

Abbreviations: AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD, disease progression; vs, versus

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