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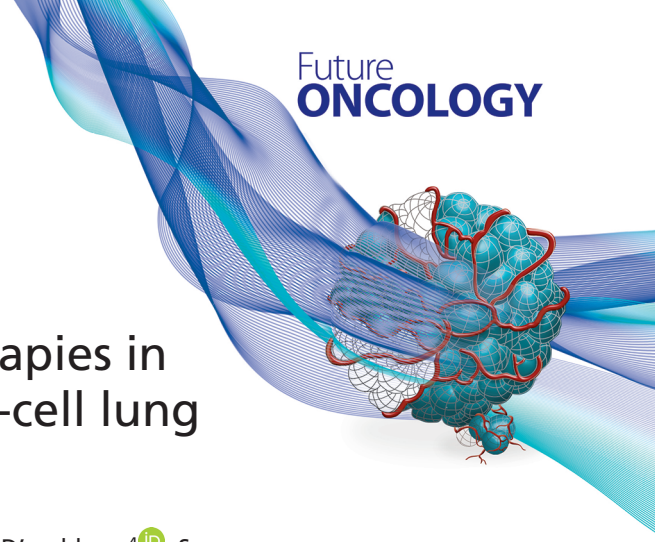

Efficacy and safety of first-line therapies in *EGFR*-mutated advanced non-small-cell lung cancer: a network meta-analysis

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Aim: To evaluate the comparative efficacy and safety of identified first-line therapies for patients with *EGFR* mutation-positive (*EGFR*m+) advanced non-small-cell lung cancer (NSCLC), with a focus on ramucirumab + erlotinib. **Methods:** In the absence of head-to-head studies, a Bayesian network meta-analysis was conducted using randomized clinical trial data to evaluate first-line systemic therapies with erlotinib/gefitinib as the reference treatment. **Results:** For progression-free survival, ramucirumab + erlotinib was comparable to osimertinib and dacomitinib in the primary analysis. **Conclusion:** The analysis showed ramucirumab + erlotinib efficacy to be comparable to best-in-class treatment options for previously untreated patients with *EGFR*m$^+$ advanced NSCLC.

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Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related mortality across the world [1]. Non-small-cell lung cancer (NSCLC) accounts for 85–90% of all lung cancer cases, with more than 50% of patients diagnosed with advanced disease [2]. The three major types of NSCLC are adenocarcinoma, squamous cell carcinoma and large-cell carcinoma [3]. Within adenocarcinoma, the *EGFR* activating mutation is one of the most common genetic alterations, estimated to occur in 21% of patients with NSCLC depending on smoking status, histology, ethnicity and gender [4]. The most common *EGFR* mutations are *exon 19del* and *exon 21 L858R*, and these are associated with a more favorable prognosis than general advanced disease and sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs). TKIs such as first (erlotinib and gefitinib), second (dacomitinib and afatinib) and third (osimertinib) generation, are therefore standard-of-care treatment for advanced *EGFR* mutation-positive (*EGFR*m$^+$) disease [5,6].

Ramucirumab is a human receptor-targeted antibody that specifically binds to *VEGF* receptor 2 and blocks the binding of *VEGF* ligands A, C and D [7]. The RELAY (NCT02411448) trial investigates ramucirumab in combination with erlotinib in previously untreated patients with *EGFR*m$^+$ metastatic (stage IV) NSCLC [8,9]. At the time of primary analysis, the median progression-free survival (PFS) was significantly longer in the ramucirumab + erlotinib group (19.4 months, 95% CI: 15.4–21.6) than in the placebo + erlotinib group (12.4 months, 95% CI: 11.0–

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13.5), with a hazard ratio (HR) of 0.59 (95% CI: 0.46–0.76; p < 0.0001). Interim overall survival (OS) data were immature and the median OS was not reached. The corresponding interim OS HR was 0.83 (95% CI: 0.53–1.30, p = 0.4209) in favor of ramucirumab + erlotinib over placebo + erlotinib. Grade 3–4 treatment-emergent adverse events (TEAEs) were reported more frequently in the ramucirumab + erlotinib group (159/221 patients, 72%) than in the placebo + erlotinib group (121/225 patients, 54%). Based on these results, ramucirumab + erlotinib is approved and included as a first-line (1L) treatment option in clinical practice guidelines [10,11].

As new treatments are approved and incorporated into guidelines for *EGFR*m+ NSCLC, getting an understanding of how they compare to each other is an important part of decision making. In the absence of head-to-head comparisons, network meta-analysis (NMA) serves as the mechanism to generate comparative data among treatment options. This publication reports the methodology and results of an NMA conducted to assess the efficacy and safety of ramucirumab in combination with erlotinib, relative to systematically-identified 1L treatment options for patients with advanced *EGFR*m$^+$ NSCLC.

Materials & methods

A systematic literature review (SLR) was conducted to evaluate all relevant individual studies in the field of advanced NSCLC. Since no head-to-head studies of ramucirumab + erlotinib and second- or third-generation TKIs were identified, an NMA was conducted to indirectly compare the interventions of interest via the reference treatment erlotinib/gefitinib. The SLR followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12,13], and the search was conducted on 9 May 2020. The NMA was performed following the NICE Decision Support Unit (DSU) guidelines [14].

Search strategy

The search was run through the Ovid SP® platform in the following electronic databases: MEDLINE and MEDLINE in-process and E-pubs ahead of print; EMBASE; Cochrane Central Register of Controlled Trials (CCRCT); and Cochrane Database of Systematic Reviews (CDSR). The search strategies used in each database can be found in Supplementary Tables 1–3. To complement the search for published trials, abstracts published between January 2017 and May 2020 from the following key international conferences were searched: American Society of Clinical Oncology (ASCO); European Society for Medical Oncology (ESMO); and International Association for the Study of Lung Cancer (IASLC). A manual search was also conducted in the following clinical trial registries to ensure that ongoing studies and completed third-party studies were exhaustively identified: Clinicaltrials.gov by the US National Library of Medicine; EU Clinical Trials Register; and WHO International Clinical Trials Registry Platform Search Portal.

Selection criteria

The population of interest consisted of adult patients (≥18 years) with *EGFR*m$^+$ locally advanced (stage IIIB/IIIC) or metastatic (stage IV) NSCLC previously untreated with systemic therapies for advanced disease. Interventions of interest included all 1L pharmacological treatments (both monotherapies and combination therapies) including licensed and investigational chemotherapy, *EGFR* TKIs, antiangiogenics, monoclonal antibodies and immunotherapies. The comparators included the interventions of interest and the best supportive care/placebo. Studies reporting efficacy outcomes including OS and PFS, safety and/or quality of life or health status outcomes were included. The quality of life outcomes, however, could not be analyzed in the NMA due to insufficient data. In the NMA, randomized clinical trials (RCTs) of 1L treatment were exclusively considered. Additionally, prospective phase II, III and IV RCTs of 1L treatment, long-term follow-up studies and pooled analyses of included trials containing new data of interest were included. Single-arm clinical trials were excluded and there were no geographical or language restrictions. Two reviewers independently screened all identified items at two levels (titles/abstracts and full-text articles). Any disagreements were resolved by a third independent reviewer. SLRs found in abstract screening were hand searched for relevant trials.

Data extraction & quality assessment

All data (trial details, patient characteristics, treatments and outcomes) were extracted by one reviewer and then validated by a second independent reviewer. Trial details included treatment arms, the number of patients randomized (intention-to-treat [ITT] population) and study duration. Patient characteristics included age, geographic region, gender, histology, *EGFR* mutation subtype (*exon 19del* or *exon 21 L858R*), stage of disease, ethnicity,

smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), brain/CNS metastases and other characteristics not listed here. Treatment characteristics included dose, administration frequency, cycle length, number of cycles, route of administration and treatment discontinuation criteria. Efficacy outcomes included OS, PFS, objective response rate (ORR) and disease control rate (DCR), among others. Safety outcomes identified in the SLR included overall mortality, treatment discontinuations, discontinuations due to adverse events (AEs), any grade treatment-related AEs (TRAEs) or treatment-emergent AEs (TEAEs) and grade ≥3 TREAEs. However, evidence synthesis could exclusively be conducted on one safety outcome (grade ≥3 TREAEs) due to the fact that the most frequently occurring AEs were usually not reported among the included trials. Depending on the intervention, the reported AEs differed considerably. In contrast, TREAEs were reported in the majority of studies. Each included study was critically appraised using the Cochrane Risk of Bias Tool, and the following factors were assessed: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias [15].

Evidence synthesis

The NMA included RCTs identified from the SLR that reported data for any end point assessed and directly or indirectly connected to a treatment in the RELAY trial through TKI monotherapy or combination therapies. The primary focus was on efficacy outcomes and limited saftey outcomes: PFS (time-to-event data); OS (time-to-event data); ORR; DCR; and occurrence of grade ≥3 TREAEs due to differences in reporting of specific AEs across the studies. AEs not clearly defined as treatment-emergent were only considered if no data on TEAEs were reported. Two sensitivity analyses were conducted to reflect differences in data availability. In the first sensitivity analysis, TRAEs were considered if TEAEs were not reported. In the second sensitivity analysis, AE input data were not considered if it was not clearly defined whether these were treatment-emergent or treatment-related events. The studies identified in the SLR did not report the same individual AEs. For example, hypertension and dermatitis acneiform were the most common grade ≥3 TEAEs in the ramucirumab + erlotinib arm [9]; whereas second- or third-generation TKIs generally showed different AE profiles. Therefore, the comparison of safety end points was limited to grade ≥3 TREAEs and specific AEs could not be pooled.

The primary analysis assumed equivalent efficacy between erlotinib and gefitinib since this has been shown in previous NICE technology appraisals for osimertinib and dacomitinib, respectively [16,17], as well as in a recent review of NMAs [18]; and to allow linking osimertinib to the network of evidence via the FLAURA trial [19]. The recent FLAURA trial was designed under this same assumption of equivalent efficacy and the effect of osimertinib was not estimated separately relative to erlotinib or gefitinib [19]. To explore the impact of this assumption, a sensitivity analysis was conducted in which erlotinib and gefitinib were not considered equally effective and the two were included as separate nodes in the networks of evidence. The corresponding networks of evidence for PFS and OS are shown in Supplementary Figures 9 & 10. Each treatment regimen linked to the network is termed a node.

Statistical methodology

A global network of evidence was generated to identify the studies that were eligible for the NMA among the studies identified in the SLR. These were identified as part of a thorough similarity assessment. For each end point, a separate network diagram was generated to allow anchored comparisons of the identified treatments. Evidence networks were linked for each end point, allowing comparisons to be made between treatments included in the SLR (where there was a connected network). Heterogeneity and inconsistency (for both direct and indirect comparisons) within each of these networks were assessed. To evaluate whether the similarity assumption held, patient characteristics across studies and study characteristics were compared graphically through box plots and bar charts. In a Bayesian analysis, heterogeneity assessment is commonly conducted graphically, by running both fixed- and random-effects (FE and RE) models. Absolute model fit to the data is assessed by comparing the total residual deviance to the number of data points. Additionally, relative model fit is assessed through the deviance information criterion (DIC). Both FE and RE models were conducted to pool treatment effects across trial data. Relative-effect models automatically account for heterogeneity. A lower DIC indicates a better relative model fit. If the DIC of the RE model was at least five points lower than the DIC of the FE model, this was an indicator of heterogeneity in the network of evidence. A consistency assessment was conducted through unrelated means models whenever there was a closed loop in the network of evidence [20]. A closed loop implies that both direct (obtained through head-to-head studies) and indirect (obtained through indirect comparisons via common comparator) evidence were available to inform a relative treatment effect.

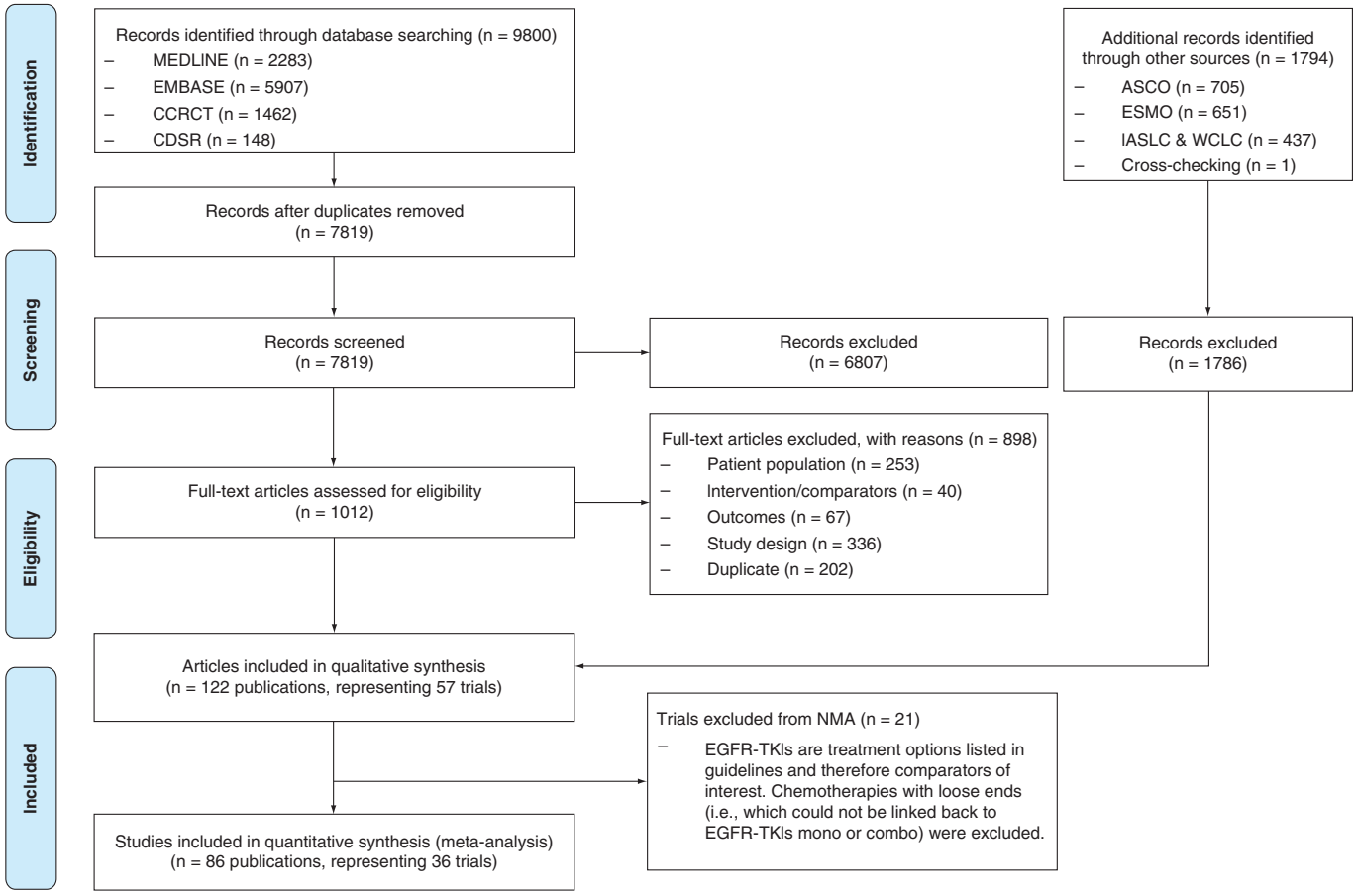

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for systematic literature review and network meta-analysis.
ASCO: American Society of Clinical Oncology; CCRCT: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; *EGFR*-TKI: *EGFR*-tyrosine kinase inhibitor; ESMO: European Society for Medical Oncology; IASLC: International Association for the Study of Lung Cancer; NMA: Network meta-analysis; SLR: Systematic literature review; WCLC: World Conference on Lung Cancer.

The methodological approaches differed according to the type of end point being modeled. For time-to-event outcomes (PFS and OS), the NMA was conducted under the proportional hazards (PHs) assumption following Woods *et al.* [21]. Standard errors on log HRs were imputed from CIs. A binomial model was considered for binary outcomes, including ORR, DCR and grade 3–5 TRAEs. The relative-effect measure was the odds ratio (OR). Imputation was conducted when the number of events was not reported. If the proportion of events was reported, the number of events was imputed through the product of the proportion of events and sample size. There were differences in the duration of follow-up across trials and treatments. To account for these differences, further sensitivity analysis based on a Poisson model was conducted for grade ≥3 TREAEs using both event rates and follow-up duration. The relative-effect measure was the rate ratio (RaR). Imputation was conducted on the number of person-days at risk, imputed through the average of the sample size for the ITT populations and the study completers, multiplied by treatment exposure duration in days. Analyses were conducted using OpenBUGS version 3.2.3 and R version 3.4.4. The package "R2OpenBUGS" allowed the use of OpenBUGS from within R. Analyses were run with 30,000 iterations after 12,000 burn-in iterations were discarded, and a thinning parameter was tested with two chains to identify the combinations of the linear predictors with the best fit. Convergence and autocorrelation were assessed through the Gelman-Rubin statistic and in terms of effective sample size.

Subgroup and sensitivity analyses were conducted to assess the robustness of the NMA results. This included a sensitivity analysis with erlotinib and gefitinib as separate nodes in the network of evidence as previously described. Another sensitivity analysis investigated the difference in using an independent review committee to assess end

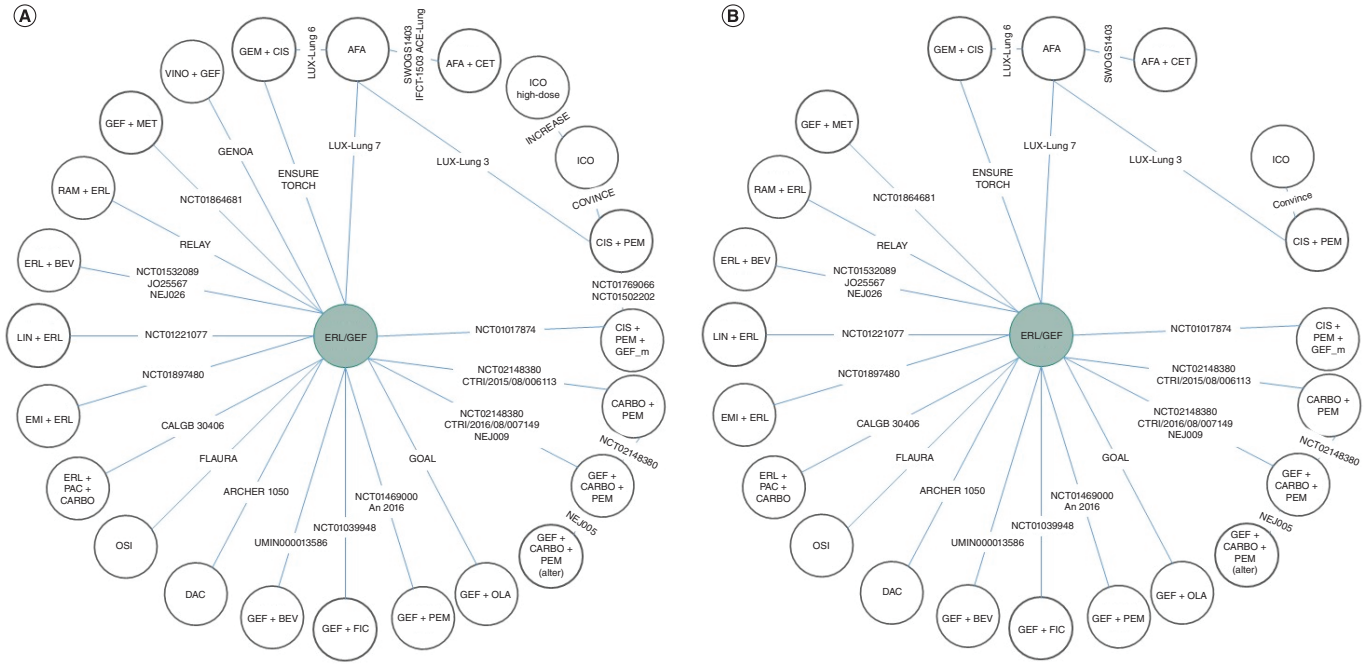

Figure 2. Network of evidence for (A) progression-free survival and (B) overall survival.
AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CET: Cetuximab; CIS: Cisplatin; DAC: Dacomitinib; EMI: Emibutazumab; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEM: Gemcitabine; GEF_m: Gefitinib maintenance; ICO: Icotinib; LIN: Linsitinib; MET: Metformin; OLA: Olaparib; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; RAM: Ramucirumab; VIN: Vinorelbine.

point data (primary analysis used investigator-assessed data). A third sensitivity analysis was conducted for patients without brain metastases. Subgroup analyses were performed for patients with *EGFR exon 19del* and *exon 21 L858R* mutations and for patients of east Asian and non-east Asian geographical regions. In contrast to *exon 19del* and *exon 21 L858R* mutations, rare mutations could not be accounted for due to a lack of subgroup data. The presence of uncommon mutations could, however, act as an effect modifier. NMA results were summarized by the median of the posterior distribution of relative treatment effects, such as HR or OR and the corresponding 95% credible interval (CrI). If the estimated CrI excluded the value of equity, that is the value of one in the case of HR and OR, the interpretation was that the treatment was favorable or unfavorable over the comparator treatment. If the CrI included one, the interventions were called comparable. This interpretation does not necessarily imply that treatment effects are similar since in a small network, especially for subgroup and sensitivity analyses, the findings are rather inconclusive with wide CrIs that indicate a large amount of uncertainty in the estimate.

Results

Search results

A total of 9800 references were identified in the specified databases (Figure 1). After excluding 1981 duplicate citations, 7819 citations underwent abstract screening. From the abstract screening, 1012 citations were considered relevant for full-text screening. Of the 1012 articles screened, a total of 122 publications (including 39 conference abstracts/posters) were included that represented 57 unique clinical trials (a list of all included publications can be found in Supplementary Table 4).

Network construction

Networks of evidence were constructed based on the selected studies identified through the SLR. For inclusion in the network, studies must have included a first-, second- or third-generation *EGFR*-TKI that connected to ramucirumab + erlotinib via a common comparator and they must have reported data on one or several outcomes of interest. A total of 36 studies and 24 interventions met the inclusion criteria for the NMA. Further details on study selection are shown in the study flow chart in Figure 1. Of the 34 studies included in the primary analysis, 33 studies formed the network of evidence for PFS (Figure 2A). The majority of the nodes were connected to

Table 1. Characteristics of trials included in the network meta-analysis.

Study	Study design	Centers/countries (n)	*EGFR* testing method	Ref.
RELAY	RCT, DB, phase Ib (part A) and phase III (part B), MC	100/13 countries globally	Therascreen® (Qiagen, Hilden, Germany), Cobas® (Roche, Basel, Switzerland) and other PCR and sequencing-based methods	[25]
An 2016	RCT, DB	NR	NR	[26]
ARCHER 1050	RCT, OL, phase III, MC	71/MC (China, Hong Kong, Japan, South Korea, Poland, Italy, Spain)	Qiagen Therascreen *EGFR* RGQ PCR kit (version 1 and 2)	[27–29]
CALGB 30406 Trial	RCT, OL, phase II	USA	Sensitive heteroduplex method coupled with enzymatic digestion	[30]
CONVINCE	RCT, OL, phase III, MC	18/China	Central laboratory using the amplification refractory mutation system (ARMS; Therascreen *EGFR* mutation test kit)	[31]
CTONG0901	RCT, phase III	NR/China	Direct DNA sequencing	[32]
CTRI/2015/08/006113	RCT, OL, phase III, SC	SC study/India	Nested real-time PCR	[23]
CTRI/2016/08/007149	RCT, phase III	NR/NR	NR	[33]
ENSURE	RCT, OL, phase III, MC	30/Malaysia, Philippines, China	Real-time PCR	[34–36]
FLAURA	RCT, DB, phase III, MC	132/29 countries (including China, Korea, Vietnam, Malaysia, Taiwan, Thailand, Philippines, Japan)	Real-time PCR	[37–43]
GENOA/NCT02319577	RCT, OL, phase II, MC	MC/NR	NR	[44]
GOAL	RCT, OL, phase II, MC	NR/Spain	Mutations could be first assessed by a local or national certified laboratory. Tumor material had to be submitted to the reference laboratory for central *EGFR* confirmatory testing. *EGFR* mutations were centrally confirmed based on laser microdissection and TaqMan assay in the presence of PNA designed to inhibit the amplification of the wild-type allele	[45]
IFCT-1503 ACE-Lung	RCT, OL, phase II, MC	France	NR	[46]
INCREASE	RCT, OL, phase II	NR/China	NR	[47]
JO25567 (JapicCTI-111390)	RCT, OL, phase II, MC	30/Japan	Real-time PCR	[48–51]
LUX-Lung 3	RCT, OL, phase III, MC	133/25 countries (16/Japan)	Real-time PCR kit	[52–62]
LUX-Lung 6	RCT, OL, phase III, MC	36/MC in China, Thailand, South Korea	Standardized allele-specific quantitative real-time PCR kit	[53,57–65]
LUX-Lung 7	RCT, OL, phase IIb, MC	64/MC in 13 countries	NR	[59–62,66–70]
NCT00294762	RCT, phase II, MC	37/USA and 5/UK	PCR	[71]
NCT01017874	RCT, OL, phase III, MC	12/Hong Kong, Republic of Korea, Singapore, Taiwan, Thailand	A standardized Scorpions ARMS *EGFR* mutation assay using an *EGFR* PCR test kit	[72,73]
NCT01039948	RCT, OL, phase II, MC	Hong Kong, Malaysia, the Philippines, Singapore, Republic of Korea, China, Thailand	Clarient *EGFR* kit, in a real-time PCR assay based on DxS Scorpions technology.	[74]
NCT01221077	RCT, DB, phase II, MC (Unblinded early: 15 Feb 2013)	29/MC	NR	[75]
NCT01469000	RCT, OL, phase II, MC	35/China, Japan, Republic of Korea, Taiwan	NR	[76,77]
NCT01502202	RCT, phase II	Korea	NR	[78]
NCT01532089	RCT, phase II, MC	USA	NR	[79]
NCT01769066	RCT, OL, phase II, SC	1/China	Using direct sequencing of exons 18–21	[80]
NCT01864681	RCT, DB, phase II, MC	MC/China	Amplification refractory mutation system-PCR	[81,82]
NCT01897480	RCT, OL, phase II	Global	NR	[83]
NCT02148380	RCT, OL, phase II, SC	1/China	ARMS according to the protocol of the DxS *EGFR* mutation test kit (DxS)	[84]
NEJ005/TCOG0902	RCT, phase II	NR/Japan	NR	[85,86]
NEJ009	RCT, OL, phase III	47/Japan	NR	[87]
NEJ026	RCT, OL, phase III, MC	69/Japan	NR	[88]

ARMS: Amplification Refractory Mutation System; DB: Double-blind; MC: Multi-center; NMA: Network meta-analysis; NR: Not reported; OL: Open-label; RCT: Randomized controlled trial; SC: Single-center.

Table 1. Characteristics of trials included in the network meta-analysis (cont.).

Study	Study design	Centers/countries (n)	*EGFR* testing method	Ref.
SWOG S1403	RCT, OL, phase II and III, MC	USA	NR	[89]
TORCH	RCT, OL, phase III, MC	Italy: NR Canada: NR	*EGFR* exon 19 deletion was analyzed using the PCR fragment analysis method; positive cases were confirmed by capillary sequencing of independent PCR products. Capillary sequencing was also used to identify mutations on *EGFR* exon 21	[24,90]
UMIN000013586	RCT, OL, phase II, MC	10/Japan	NR	[91]
Xie 2015	RCT, SC	1/China	NR	[92]

ARMS: Amplification Refractory Mutation System; DB: Double-blind; MC: Multi-center; NMA: Network meta-analysis; NR: Not reported; OL: Open-label; RCT: Randomized controlled trial; SC: Single-center.

erlotinib/gefitinib by one trial. However, the following treatments were not directly connected to erlotinib/gefitinib: afatinib + cetuximab, icotinib (high-dose or normal-dose) and gefitinib + carboplatin + pemetrexed (alternating). The network of evidence for OS was formed by 28 trials (Figure 2B). Icotinib (high-dose) and vinorelbine + gefitinib were excluded from this network due to a lack of evidence.

As erlotinib/gefitinib was in the center of the network of evidence and thus connected to many interventions, erlotinib/gefitinib was selected as the reference treatment. Additional networks were created for the sensitivity analyses (erlotinib and gefitinib as separate nodes with erlotinib defined as the reference treatment). Networks for subgroup analyses of PFS included *exon 19del* (18 trials), *exon 21 L858R* (19 trials), patients without brain metastasis (16 trials), east Asian population (23 trials) and other regions (15 trials).

Trial & patient characteristics

A list of identified 1L studies included in the NMA is provided in Table 1. Trial design, geographic location and follow-up time varied across the studies. The majority of trials (n = 24) were open-label in design, five RCTs were double-blinded and eight did not report the blinding of trial participants and assessors. A majority of these event-driven trials had a follow-up of 1–3 years. The longest median follow-up for OS was reported in the ARCHER 1050 trial with 47.9 months [22] and CTRI/2015/08/006113 had the shortest median follow-up of 14.2 months [23]. The distribution of patients' baseline characteristics also varied across the included studies. Eight trials reported the mean age ranging from 53 to 67 years, while 23 trials reported the median age ranging from 56 to 74 years. The percentage of females was highly variable, ranging from 33 to 88%. Among studies that reported ethnicity, the majority included patients of mostly east Asian race; including 19 studies that were exclusively conducted among east Asian patients (thus the impact of ethnicity was included in a subgroup analysis). The distribution of NSCLC histology types did not vary substantially across the interventions and studies with the exception of the TORCH trial [24] that included 55% of patients with adenocarcinoma and 45% with squamous, large-cell or mixed carcinoma for the overall patient population. The percentage of current/former smokers ranged from 5 to 80%, and the percentage of patients with ECOG PS 0–1 ranged from 61 to 100% across all included studies. Brain metastases were reported in only 18 trials of which 10 trials excluded patients with CNS or brain metastases. Therefore, the corresponding subgroup analysis was based on a limited network of evidence. Patient characteristics can be found in Table 2.

Overall, the similarity assumption was deemed to hold except for patients with CNS or brain metastases. In the RELAY trial and nine other trials, patients with brain metastases were excluded. However, nine trials in the network of evidence included patients with brain metastases. To assess the robustness of the NMA results concerning these differences in baseline characteristics, a sensitivity analysis was carried out focusing on patients without brain metastasis if these were reported separately (as in FLAURA [19]).

NMA results

NMA is based on the assumptions of similarity, consistency and transitivity. To ensure that the similarity assumption holds, an assessment of the comparability of trial and patient characteristics was conducted as previously described. The assumption of consistency was tested through unrelated means models as described in the methods section. No evidence of inconsistency between direct and indirect evidence was identified. The transitivity assumption implies, for example, that if ramucirumab + erlotinib was more effective than erlotinib/gefitinib, and erlotinib/gefitinib was more effective than erlotinib + paclitaxel, then ramucirumab + erlotinib would have to be more effective

Table 2. Patient characteristics for trials included in the network meta-analysis.

Study (first author, year)	Intervention	Patients (n), (ITT)	Age, years, mean (median [range])	Male (%)	NSCLC Stage IV (%)	Brain metastases (%)	ECOG PS (%)		Never smoked (%)	*EGFR* mutations (%)		NSCLC histology(%)				Ref.
							0–1	2		exon 19 deletion	*exon 21 L858R*	Adenocarcinoma	Large cell	Squamous cell	Undifferentiated NSCLC	
RELAY (Nakagawa, 2019)	RAM + ERL	224	NR (65 [27–86])	37	100	0	100	NR	60	55	44	96	NR	NR	4	[9]
	ERL + PBO	225	NR (64 [23–89])	37	100	0	100	NR	62	53	47	97	NR	NR	3	
An 2016	GEF + PBO	45	67	56	87	51	NR	NR	42	38	62	100	NR	NR	NR	[26]
	GEF + PEM	45	66	56	91	53	NR	NR	44	36	64	100	NR	NR	NR	
ARCHER 1050 (Wu, 2017)	DAC	227	NR (62 [53–68])	36	81	0	100	0	65	59	41	NR	NR	NR	NR	[27]
	GEF	225	NR (61 [54–68])	44	81	0	100	0	64	59	41	NR	NR	NR	NR	
CALGB 30406 (NCT00126581; Janne, 2012)	ERL	81	NR (58 [32–78])	40	NR	NR	100	0	79	70	30	88	NR	NR	NR	[30]
	ERL + CARBO + PAC	100	NR (60 [34–81])	42	NR	NR	100	0	79	48	52	84	NR	NR	NR	
CONVINCE (Shi, 2017)	ICO	148	NR (56 [35–74])	29	91	28	95	5	NR	54	46	100	0	0	0	[31]
	CIS + PEM	148	NR (56 [31–77])	31	89	29	95	5	NR	54	46	100	0	0	0	
CTONG0901 (Yang, 2017)	GEF	84	NR (59 [30–85])†	46†	98†	NR	97†	3†	NR	50†	50†	96†	NR	NR	NR	[32]
	ERL	81	NR (59 [30–85])†	47†	97†	NR	98†	2†	NR	50†	50†	96†	NR	NR	NR	
CTRI/2015/08/006113 (Patil, 2017)	GEF	145	54 (NR)	46	99	16	93	7	78	52	45	NR	NR	NR	NR	[23]
	PEM + CARBO	145	53 (NR)	67	98	16	95	5	81	63	35	NR	NR	NR	NR	
CTRI/2016/08/007149 (Noronha, 2019b)	GEF	176	NR (56 [27–78])	53	97	19	78	21	85	62	34	97	NR	1	NR	[93]
	GEF + CARBO + PEM	174	NR (64 [27–75])	51	98	17	80	22	83	62	35	98	NR	1	NR	
ENSURE (Wu, 2015)	ERL	110	NR (58 [33–79])	38	91	0	94	6	72	52	48	95	0	2	0	[36]
	GEM + CIS	107	NR (56 [30–78])	39	94	0	94	6	69	57	43	94	0	2	0	
FLAURA (Soria, 2018)	OSI	279	NR (64 [26–85])	36	NR	19	100	0	65	63	37	99	<1	<1	0	[19]
	GEF or ERL	277	NR (64 [35–93])	38	NR	23	100	0	63	63	37	98	<1	<1	0	
GENOA/NCT02319577 (Genova, 2019)	VIN + GEF / GEF	44	NR	NR	NR	NR	NR	NR	NR	36	48	NR	NR	NR	NR	[44]
	VIN + GEF	23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
	GEF	21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
GOAL (Campelo, 2018)	GEF + OLA	91	NR (65 [39–85])	27	100	NR	91	9	60	63	27	NR	NR	NR	NR	[45]
	GEF	91	NR (68 [36–85])	37	100	NR	92	8	66	57	38	NR	NR	NR	NR	

† Percentages taken from a mixed (*EGFR* wild-type and mutation-positive) population. This is necessary for studies that include *EGFR* wild-type and mutation-positive patients but do not report patient characteristics separately for the mutated population;

‡ Percentages include squamous, large-cell, mixed and undefined histology type.

AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CIS: Cisplatin; DAC: Dacomitinib; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEF_m: Gefitinib maintenance; GEM: Gemcitabine; ICO: Icotinib; ITT: Intention to treat; LIN: Linsitinib; MET: Metformin; NMA: Network meta-analysis; NSCLC: Non-small-cell lung cancer; NR: Not reported; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; RAM: Ramucirumab; VIN: Vinorelbine.

Table 2. Patient characteristics for trials included in the network meta-analysis (cont.).

Study (first author, year)	Intervention	Patients (n), (ITT)	Age, years, mean (median [range])	Male (%)	NSCLC Stage IV (%)	Brain metastases (%)	ECOG PS (%)		Never smoked (%)	*EGFR* mutations (%)		NSCLC histology(%)				Ref.
							0–1	2		exon 19 deletion	*exon 21 L858R*	Adenocarcinoma	Large cell	Squamous cell	Undifferentiated NSCLC	
IFCT-1503 ACE-Lung (Cortot, 2019)	AFA	59	NR	NR	NR	NR	NR	NR	NR	56	39	NR	NR	NR	NR	[94]
	AFA + CET	59	NR	NR	NR	NR	NR	NR	NR	51	41	NR	NR	NR	NR	
INCREASE (Li, 2018)	Routine-dose ICO	86	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	[47]
	High-dose ICO	90	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
	ICO	77	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
JO25567 (JapicCTI-111390; Seto, 2014)	ERL + BEV	75	NR (67 [59–73])	40	80	0	100	0	56	53	47	99	0	1	0	[48]
	ERL	77	NR (67 [60–73])	34	81	0	100	0	58	52	48	99	1	0	0	
LUX-Lung 3 (Sequist, 2013)	AFA	230	NR (62 [28–86])	36	91	0	100	0	67	49	40	100	0	0	0	[52]
	CIS + PEM	115	NR (61 [31–83])	33	85	0	99	1	70	50	41	100	0	0	0	
LUX-Lung 6 (Wu, 2014a)	AFA	242	NR (58 [49–65])	36	93	NR	100	0	75	51	38	100	0	0	0	[63]
	GEM + CIS	122	NR (58 [49–62])	32	95	NR	100	0	81	51	38	100	0	0	0	
LUX-Lung 7 (Park, 2016)	AFA	160	NR (63 [30–86])	43	95	16	100	0	66	58	42	100	0	0	0	[66]
	GEF	159	NR (63 [32–89])	33	98	15	100	0	67	58	42	100	0	0	0	
NCT00294762 (Hirsch, 2011)	ERL	72	NR	39	NR	0	90	10	26	11	1	NR	NR	NR	NR	[71]
	CARBO + PAC + ERL	71	NR	56	NR	0	96	3	30	4	6	NR	NR	NR	NR	
NCT01017874 (Yang, 2014)	PEM + CIS + GEF (as maintenance)	118	59 (NR [24–81])	25	95	NR	100	0	92	54	38	97	NR	NR	NR	[72]
	GEF	118	59 (NR [31–79])	25	93	NR	100	0	92	46	54	97	NR	NR	NR	
NCT01039948 (Mok, 2016a)	GEF + FIC	94	NR	20	98	NR	97	3	94	48	45	100	NR	NR	NR	[74]
	GEF	94	NR	20	91	NR	97	3	95	53	45	100	NR	NR	NR	
NCT01221077 (Leighl, 2017)	LIN + ERL	44	NR (62 [44–82])	32	98	NR	100	0	75	59	41	93	0	2	5	[75]
	PBO + ERL	44	NR (58 [36–85])	27	100	NR	100	0	73	57	43	96	0	0	5	
NCT01469000 (Cheng, 2016)	PEM + GEF	126	62 (62 [33–84])	35	83	NR	100	0	64	52	41	NR	NR	NR	NR	[76]
	GEF	65	61 (62 [41–80])	37	88	NR	100	0	72	62	35	NR	NR	NR	NR	

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AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CIS: Cisplatin; DAC: Dacomitinib; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEF_m: Gefitinib maintenance; GEM: Gemcitabine; ICO: Icotinib; ITT: Intention to treat; LIN: Linsitinib; MET: Metformin; NMA: Network meta-analysis; NSCLC: Non-small-cell lung cancer; NR: Not reported; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; RAM: Ramucirumab; VIN: Vinorelbine.

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							0–1	2		exon 19 deletion	*exon 21 L858R*	Adenocarcinoma	Large cell	Squamous cell	Undifferentiated NSCLC	
NCT01502202 (Lee, 2016)	GEF + PEM + CIS	39	NR (58 [32–75])†	12	95	NR	NR	NR	NR	NR	NR	100	NR	NR	NR	[78]
	PBO + PEM + CIS	37	NR (58 [32–75])†	12	95	NR	NR	NR	NR	NR	NR	100	NR	NR	NR	
NCT01532089 (Stinchcomb, 2019)	ERL	45	NR (63 [47–84])	31	100	31	100	NR	51	67	33	NR	NR	NR	NR	[95]
	ERL + BEV	43	NR (65 [31–84])	28	100	26	100	NR	60	67	33	NR	NR	NR	NR	
NCT01769066 (Yu, 2014)	GEF + PEM+ (CIS/CARBO)	58	55 (NR [36–72])	57	91	0	100	0	50	24	NR	100	0	0	0	[80]
	PEM+ (CIS/CARBO)	59	55 (NR [33–70])	42	92	0	100	0	66	31	NR	100	0	0	0	
NCT01864681 (Li, 2019)	GEF + MET	112	60 (60 [35–78])	41	93	0	NR	13	75	48	47	93	NR	1	6	[81]
	GEF + Plb	111	58 (59 [32–76])	43	91	0	NR	9	77	54	38	97	NR	1	2	
NCT01897480 (Scagliotti, 2020)	EMI + ERL	71	NR	39	100	28	NR	4	56	51	3	NR	NR	NR	NR	[96]
	ERL	70	NR	41	100	20	NR	6	50	57	29	NR	NR	NR	NR	
NCT02148380 (Han, 2017)	PEM + CARBO + GEF	40	NR	38	80	NR	100	0	68	53	48	100	0	0	0	[84]
	PEM + CARBO	40	NR	43	83	NR	100	0	73	50	50	100	0	0	0	
	GEF	41	NR	44	88	NR	100	0	66	51	48	100	0	0	0	
NEJ005/TCOG0902 (Sugawara, 2015)	Concurrent GEF + CARBO + PEM	41	NR (62 [41–75])	37	90	0	95	2	54	59	42	100	NR	NR	NR	[86]
	Sequential alternating GEF + CARBO + PEM	39	NR (61 [39–75])	33	92	0	100	0	56	44	51	100	NR	NR	NR	
NEJ009 (Hosomi, 2019)	GEF	172	64 (NR [37–75])	37	80	NR	100	0	56	55	39	99	NR	NR	NR	[97]
	GEF + CARBO + PEM (GCP)	170	65 (NR [34–75])	33	82	NR	100	0	57	55	41	99	NR	NR	NR	
NEJ026 (Saito, 2019)	ERL + BEV	112	NR (67 [61–73])	37	73	32	100	0	58	50	50	98	1	0	NR	[98]
	ERL	112	NR (68 [62–73])	35	75	32	99	2	57	49	51	100	0	0	NR	
SWOG S1403 (Goldberg, 2018)	AFA + CET	86	NR (66 [NR])†	34†	NR	NR	NR	NR	NR	64†	36†	NR	NR	NR	NR	[89]
	AFA	84	NR (66 [NR])†	34†	NR	NR	NR	NR	NR	64†	36†	NR	NR	NR	NR	
TORCH (Gridelli, 2012)	CIS + GEM	380	NR (62 [34–81])	66	90	NR	100	0	21	NR	NR	56†	44†,‡	44†,‡	44†,‡	[24]
	ERL	380	NR (63 [27–79])	66	88	NR	100	0	21	NR	NR	55†	45†,‡	45†,‡	45†,‡	
UMIN000013586 (Kitagawa, 2019)	GEF	10	NR (73 [66–82])	30	90	0	100	0	80	60	30	90	NR	NR	NR	[91]
	GEF + BEV	6	NR (74 [68–79])	17	100	0	100	0	67	67	33	100	NR	NR	NR	
Xie 2015	GEF	27	63† (NR)	37	67	NR	70	30	NR	56	44	NR	NR	NR	NR	[92]
	ERL	23	63† (NR)	43	70	NR	61	39	NR	52	48	NR	NR	NR	NR	

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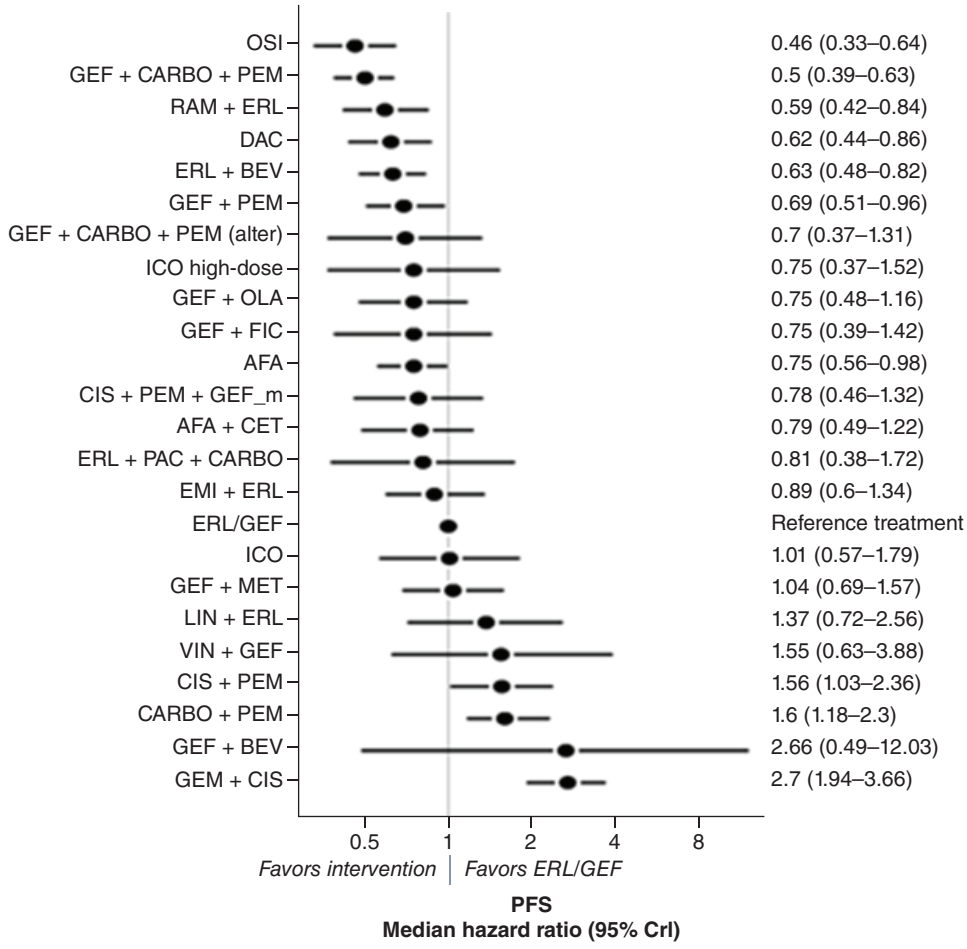

Figure 3. Summary of progression-free survival for treatments versus erlotinib/gefitinib (base case random-effects model).

AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CET: Cetuximab; CIS: Cisplatin; CrI: Credible interval; DAC: Dacomitinib; EMI: Emibutazumab; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEM: Gemcitabine; GEF_m: Gefitinib maintenance; IA: Investigator-assessed; ICO: Icotinib; LIN: Linsitinib; MET: Metformin; OLA: Olaparib; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; PFS: Progression-free survival; RAM: Ramucirumab; VIN: Vinorelbine.

than erlotinib + paclitaxel [99]. It also relates to the assumption of similar distributions for known effect modifiers between the studies. The transitivity assumption is closely related to the similarity and consistency assumptions and was assumed to be valid since these were not violated.

In the primary analysis, PFS based on investigator-assessed progression status was compared. However, the vast majority of studies did not specify if progression was assessed by the investigator or independent review; in these cases, investigator-assessed was assumed. Ten studies reported investigator assessment for PFS data (RELAY [9], FLAURA [19], ARCHER 1050 [27], CTRI/2016/08/007149 [93], CONVINCE [31], ENSURE [34], LUX-Lung 3 [52], LUX-Lung 6 [63], LUX-Lung 7 [66] and NCT01532089 [95]), whereas four studies (INCREASE [47,48], JO25567 [48], NEJ026 [98] and NCT01864681 [81]) reported independent review committee assessment (for PFS data, see Supplementary Table 5).

All results are presented in terms of median and 95% CrIs of the posterior distributions. Figure 3 shows the forest plot for the primary PFS analysis with median HR and corresponding 95% CrIs. The following interventions were deemed favorable over erlotinib/gefitinib: osimertinib, gefitinib + carboplatin + pemetrexed, ramucirumab + erlotinib, dacomitinib, erlotinib + bevacizumab, gefitinib + pemetrexed and afatinib. Three interventions, cisplatin + pemetrexed, carboplatin + pemetrexed and gemcitabine + cisplatin, were deemed unfavorable over erlotinib/gefitinib. The remaining interventions were deemed comparable to erlotinib/gefitinib.

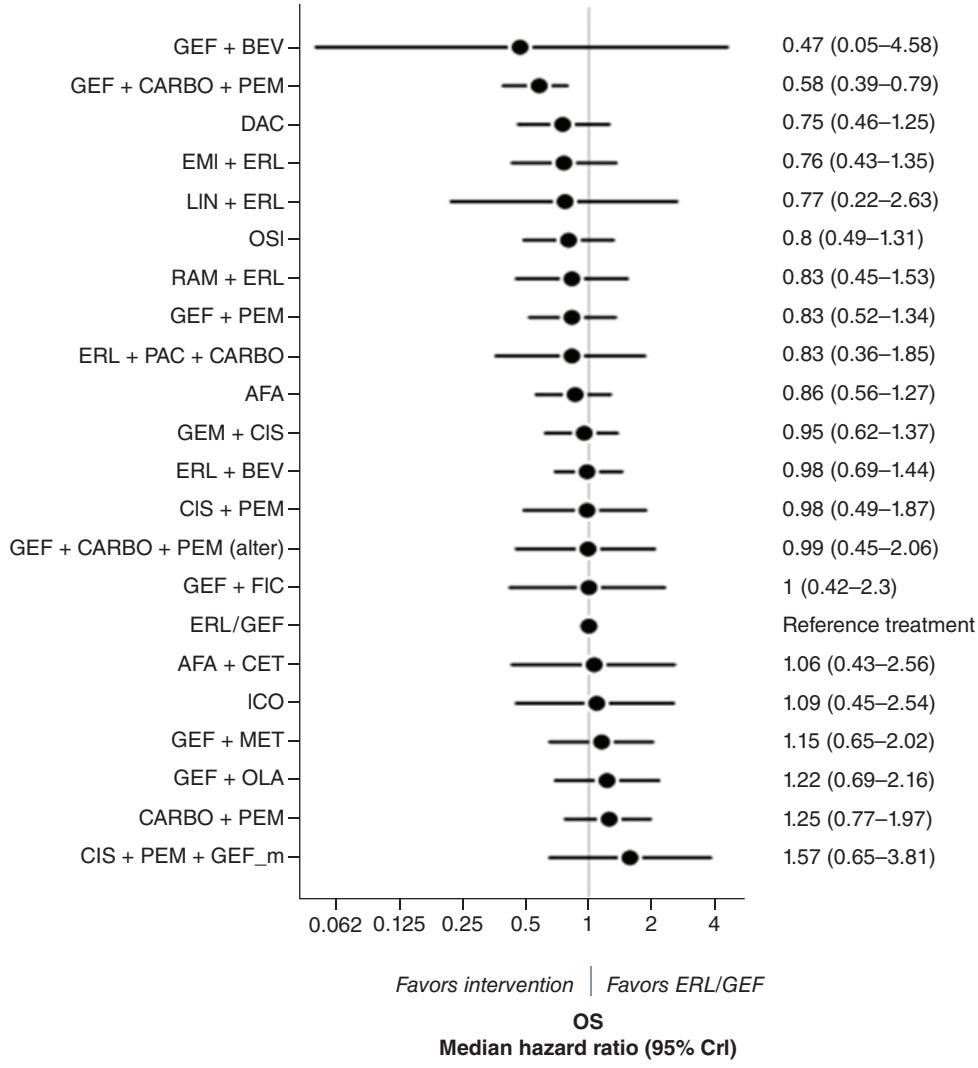

Figure 4. Summary of overall survival of treatments versus erlotinib/gefitinib (base case random-effects model).
AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CET: Cetuximab; CIS: Cisplatin; CrI: Credible interval; DAC: Dacomitinib; EMI: Emibutazumab; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEF_m: Gefitinib maintenance; GEM: Gemcitabine; ICO: Icotinib; LIN: Linsitinib; MET: Metformin; OLA: Olaparib; OS: Overall survival; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; RAM: Ramucirumab.

Supplementary Table 7 shows the pairwise comparisons of all interventions and comparators for base case PFS. Ramucirumab + erlotinib was comparable to osimertinib and dacomitinib (HR: 1.29, 95% CrI: 0.80–2.09; HR: 0.95, 95% CrI: 0.59–1.55) in the primary analysis, respectively. The conclusion drawn from the PFS primary analysis that ramucirumab + erlotinib was favorable over erlotinib/gefitinib did not hold in some of the conducted sensitivity and subgroup analyses. In the sensitivity analysis splitting the erlotinib and gefitinib node, ramucirumab + erlotinib was favorable over erlotinib (HR: 0.59, 95% CrI: 0.43–0.81) and gefitinib (HR: 0.60, 95% CrI: 0.41–0.88; for forest plots, see Supplementary Figures 1–6). In the east Asian subpopulation, ramucirumab + erlotinib was favorable over erlotinib/gefitinib (HR: 0.64, 95% CrI: 0.41–0.98). In the non-east Asian subgroup, the *exon 19del* subgroup, the *exon 21 L858R* subgroup and the subgroup analysis that excluded patients with brain metastasis, ramucirumab + erlotinib was found comparable to erlotinib/gefitinib. While the RELAY trial excluded patients with brain metastasis, other trials included such patients, reflecting the variance in inclusion criteria between different studies.

Figure 4 shows the forest plots for the OS analysis (see Supplementary Table 6 for OS data). Interim OS for ramucirumab + erlotinib was found comparable to erlotinib/gefitinib (HR: 0.83, 95% CrI: 0.45–1.53). The

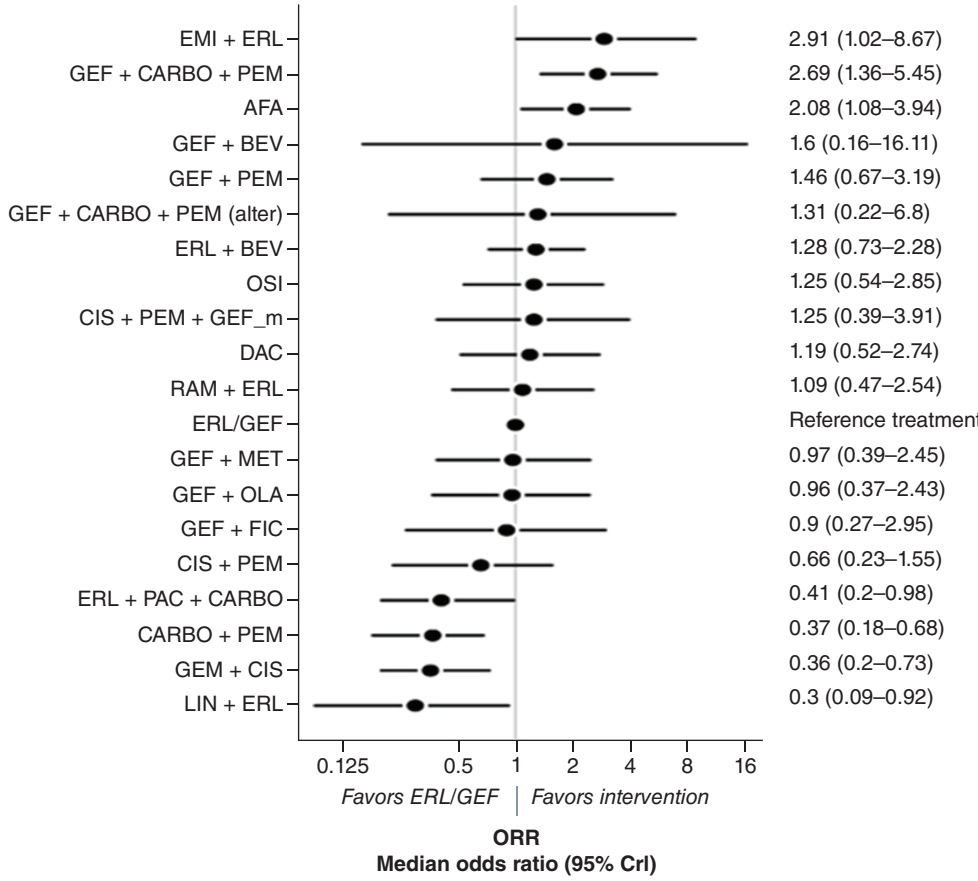

Figure 5. Summary of objective response rate of treatments versus erlotinib/gefitinib (random-effects model, odds ratio on log scale).
AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CIS: Cisplatin; CrI: Credible interval; DAC: Dacomitinib; EMI: Emibetuzumab; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEF_m: Gefitinib maintenance; GEM: Gemcitabine; LIN: Linsitinib; MET: Metformin; OLA: Olaparib; ORR: Objective response rate; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; RAM: Ramucirumab.

majority of other treatments were also found to be comparable to erlotinib/gefitinib. The conclusions drawn in the primary analysis were mainly in line with the conclusions drawn in the sensitivity and subgroup analyses (for forest plots, see Supplementary Figures 7 & 8).

Figure 5 shows the forest plot for the ORR analysis. Ramucirumab + erlotinib was found comparable to erlotinib/gefitinib (HR: 1.09, 95% CrI: 0.47–2.54). The majority of other treatments were also found to be comparable to erlotinib/gefitinib. However, for seven interventions, erlotinib/gefitinib was either deemed unfavorable or favorable over the intervention. Overall, objective response did not differ widely over the treatments.

Figure 6 shows the forest plot for the DCR analysis. Ramucirumab + erlotinib was found comparable to erlotinib/gefitinib (HR: 0.89, 95% CrI: 0.05–14.84). All treatments except erlotinib + paclitaxel + carboplatin were also found to be comparable to erlotinib/gefitinib.

The forest plot of the safety outcome ≥grade 3 TEAEs or AEs is shown in Figure 7. Ramucirumab + erlotinib was found comparable to erlotinib/gefitinib (HR: 1.22, 95% CrI: 0.03–53.36). All other treatments in the safety analysis were found comparable to erlotinib/gefitinib.

Discussion

The results of this NMA indicated that of the 24 included interventions for the 1L treatment of *EGFR*m$^+$ NSCLC, seven were estimated to prolong PFS compared with erlotinib/gefitinib: second- and third-generation *EGFR*-TKIs and some guideline-recommended combinations including ramucirumab + erlotinib. Ramucirumab + erlotinib showed a lower hazard of disease progression compared with erlotinib/gefitinib (HR: 0.59, 95% CrI:

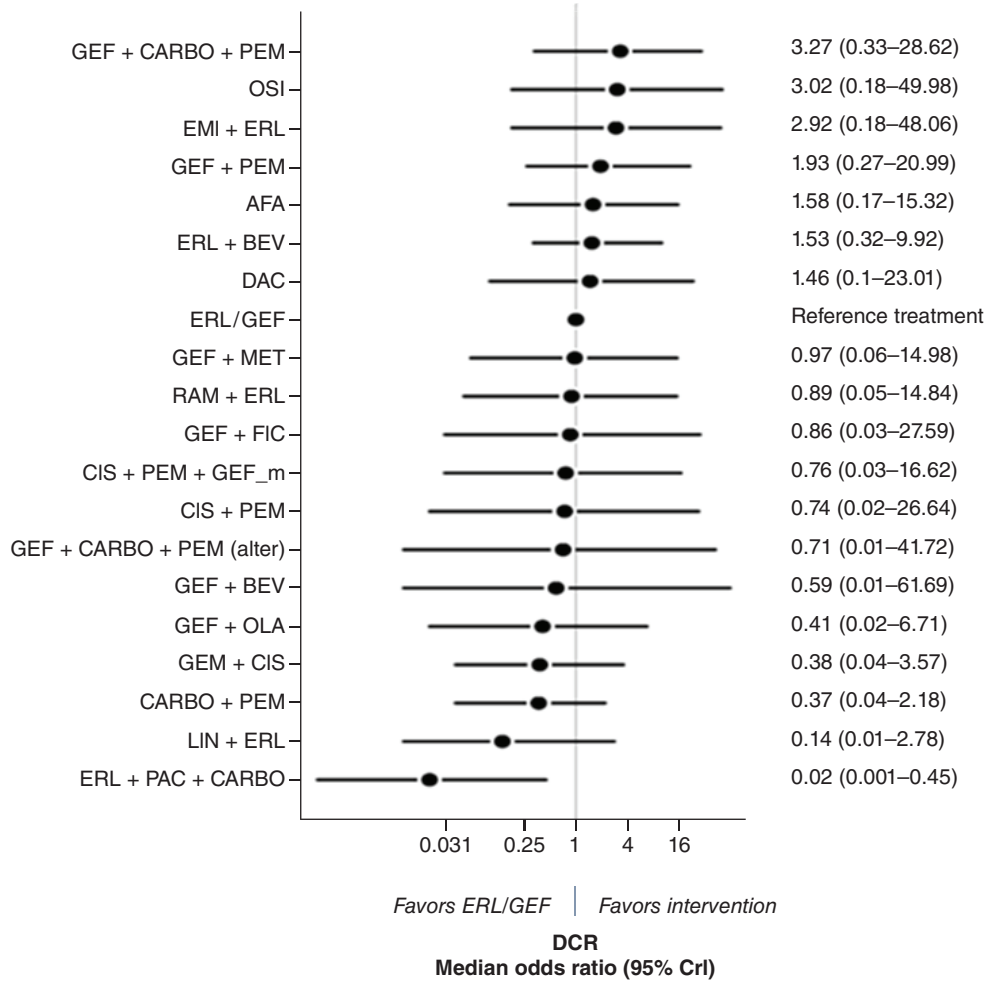

Figure 6. Summary of disease control rate of treatments versus erlotinib/gefitinib (random-effects model, odds ratio on log scale).
AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CIS: Cisplatin; CrI: Credible interval; DAC: Dacomitinib; DCR: Disease control rate; ERL: Erlotinib; FIC: Ficlatuzumab; GEF: Gefitinib; GEF_m: Gefitinib maintenance; GEM: Gemcitabine; LIN: Linsitinib; MET: Metformin; OLA: Olaparib; OSI: Osimertinib; PAC: Paclitaxel; PEM: Pemetrexed; RAM: Ramucirumab.

0.42–0.84), carboplatin + pemetrexed (HR: 0.37, 95% CrI: 0.22–0.58), cisplatin + pemetrexed (HR: 0.38, 95% CrI: 0.22–0.65), gefitinib + metformin (HR: 0.57, 95% CrI: 0.33–0.97etwork), gemcitabine + cisplatin (HR: 0.22, 95% CrI: 0.14–0.36) and linsitinib + erlotinib (HR: 0.43, 95% CrI: 0.21–0.89) as shown in Supplementary Table 7. The observed trend for PFS was reflective of what has been observed in clinical practice and in RCTs. Platinum-doublet chemotherapies were unfavorable compared with erlotinib/gefitinib and *EGFR*-TKI combinations not recommended by ESMO/NCCN and ICO were inconclusive in comparison with erlotinib/gefitinib. Ramucirumab + erlotinib PFS results for the east Asian subpopulation were consistent with the treatment effects demonstrated for the ramucirumab + erlotinib overall population evaluated in the primary analysis. In the *exon 19del* subgroup and the *exon 21 L858R* subgroup, ramucirumab + erlotinib was deemed comparable to erlotinib/gefitinib in contrast to the primary analysis.

Multiple systematic reviews and meta-analyses comparing second- and third-generation TKIs to established interventions have been published but predated ramucirumab + erlotinib as an approved regimen. Nakagawa *et al.* [100] conducted a Bayesian NMA to assess *EGFR*-TKI comparisons in Japanese patients. Their network of evidence was considerably smaller compared with the network reported here. The conclusions drawn by Nakagawa *et al.* were in line with those of the subgroup analysis on the east Asian region. Zhao *et al.* [101] conducted a systematic review and a Bayesian NMA to assess the efficacy and safety of 1L treatments for patients with advanced *EGFR*m$^+$

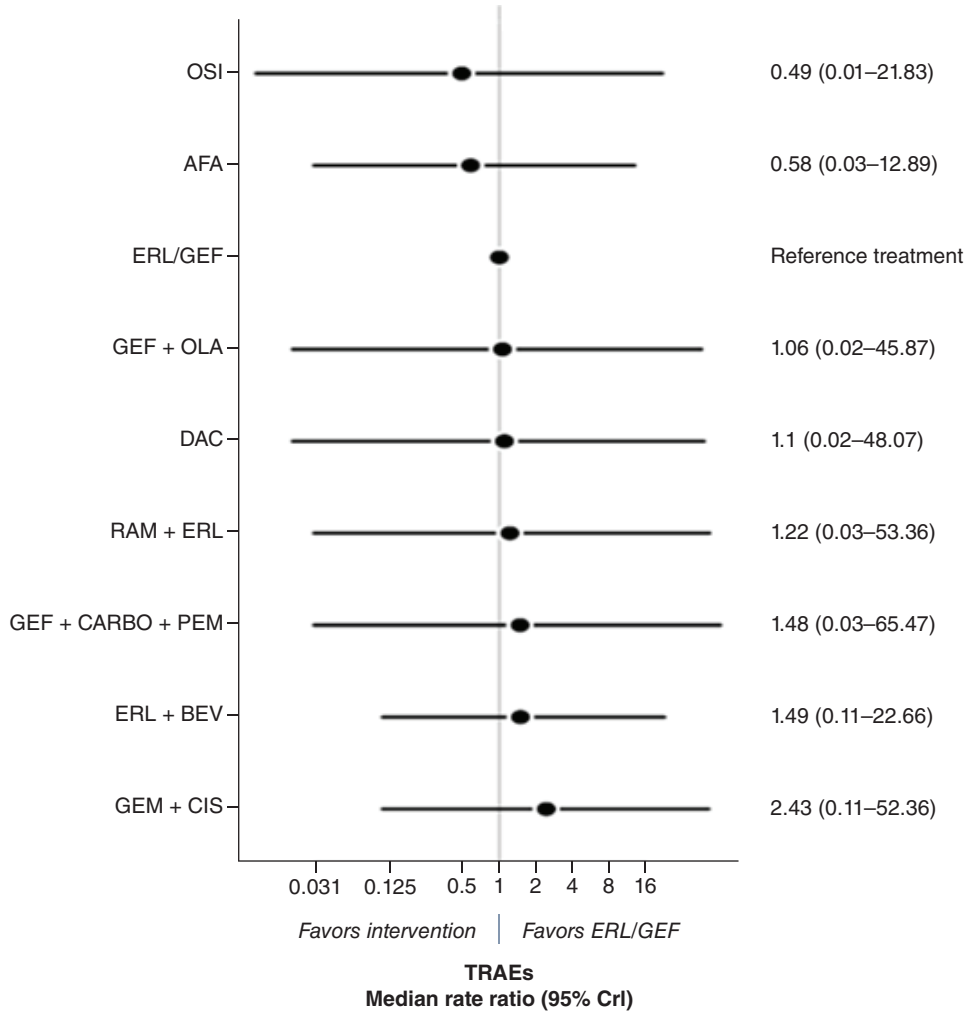

Figure 7. Summary of ≥grade 3 treatment-emergent adverse events or adverse events of treatments versus erlotinib/gefitinib (random-effects model, rate ratio on log scale).
AE: Adverse event; AFA: Afatinib; BEV: Bevacizumab; CARBO: Carboplatin; CIS: Cisplatin; CrI: Credible interval; DAC: Dacomitinib; ERL: Erlotinib; GEF: Gefitinib; GEM: Gemcitabine; OLA: Olaparib; OSI: Osimertinib; PEM: Pemetrexed; RAM: Ramucirumab; TEAE: Treatment-emergent adverse event.

NSCLC. For PFS primary analysis, osimertinib, dacomitinib and erlotinib + bevacizumab were favorable over erlotinib and gefitinib, which is consistent with this NMA; however, Zhao *et al.* did not pool the erlotinib and gefitinib node. For the PFS subgroup *exon 19del* and *exon 21 L858R* mutations, Zhao *et al.* reported that osimertinib and dacomitinib were favorable in comparison to erlotinib and gefitinib. In the corresponding subgroup analysis of the NMA reported here, however, all results were deemed comparable. A notable difference between the two studies is the pooling of erlotinib and gefitinib in the analysis. Zhang *et al.* [102] conducted a frequentist pairwise meta-analysis and a Bayesian NMA on 1L treatments in *EGFR*m$^+$ advanced NSCLC. For PFS, second-generation TKIs were deemed favorable over classical chemotherapy and first-generation TKIs. Osimertinib was deemed comparable to second-generation TKIs. These findings were in line with this NMA.

Limitations

As with every statistical method, NMA also has a variety of limitations. Since exclusively RCTs were included in the NMA, there was no risk of bias due to imbalanced effect modifiers within the trials. However, randomization does not control for known treatment effect modifiers across studies; in addition, unknown treatment effect modifiers could still bias the results. Known treatment effect modifiers were accounted for through sensitivity and subgroup analysis.

The assumption of consistency was tested through unrelated means models, comparing total residual deviance and DIC of the NMA models to the independent means models. No evidence of inconsistency was found. However, even if total residual deviance and DIC of the NMA and independent means models are in line, it is still possible for inconsistency to be present since inconsistency tests are generally underpowered [103]. If the similarity and consistency assumptions hold, one can be certain that the transitivity assumption also holds [99].

Another methodological limitation surrounds the assumption of PHs. The Woods NMA is based on the PH assumption which did not hold in each trial included in the networks of evidence. The global test to assess the PH assumption based on the Schoenfeld residuals was conducted. The results suggested a potential violation of the PH assumption in eight out of 29 studies for PFS and two out of 26 studies for OS [23,45,71,72,74,75,83,104]. Further sensitivity analysis relaxing the PH assumption is therefore of high interest as part of future work.

In addition to methodological limitations, there were limitations in the available data, such as small sample sizes in subgroup analyses and immature OS data. Data immaturity can result in an inability to estimate some summary data; for example, the median survival has not been reached in at least one arm at the time of data cutoff. This was the case for the RELAY [9], LUX-Lung 3 [53], LUX-Lung 6 [53], NCT01469000 [105] and GENOA / NCT02319577 [44] studies. As a consequence, the results of the NMA for OS were uncertain for the corresponding interventions, resulting in wide CrIs.

In addition to data maturity, another limitation was introduced by the way outcomes were assessed. The vast majority of studies did not specify if disease progression was assessed by the investigator (IA) or independent review (IRC); in these cases, investigator assessment was assumed. Where data were available, the response reported by the investigator was preferred over IRC assessed. The rationale for this decision was that the primary end point of the RELAY trial was IA PFS, and therefore the data used for the analysis were aligned more closely with the RELAY trial. A sensitivity analysis on PFS was performed considering IRC assessment data from these trials. In cases where definitions of response (PFS IRC or IA) were not similar, additional sensitivity analyses were conducted excluding the studies with unclear definitions from the network of evidence. If a response was reported at more than one data cutoff point in different publications of the same study, data reported for the longer follow-up time was used in the analysis. In comparison to the base case analysis, the CrIs became wider, resulting in inconclusive results for the vast majority of comparisons.

As for the comparability of baseline characteristics, overall, the similarity assumption was deemed to hold. Reporting of potential treatment effect modifiers such as age was not consistent throughout the studies. Eleven trials reported the mean age ranging from 53 to 78 years, while 36 trials reported the median age ranging from 54 to 77 years. Of the baseline characteristics assessed, sex could act as a potential treatment effect modifier. In contrast to Buonerba *et al.* [106], the RELAY study did not find a statistically significant treatment-by-subgroup interaction for sex that was assessed through an unstratified Cox model (p of Wald test 0.1678). The results in terms of HR by subgroup showed that ramucirumab + erlotinib was significantly more effective than placebo + erlotinib in males as well as in females; the HR in females was numerically higher, yet the conclusions did not change (HR in males 0.505, 95% CI: 0.342–0.747; HR in females 0.731, 95% CI: 0.541–0.988) [9]. The differences in the inclusion of patients with brain metastases over the studies were accounted for through sensitivity analysis.

Conclusion

Overall, the network meta-analysis included 36 RCTs on 24 interventions in patients with previously untreated *EGFR*m$^+$ advanced NSCLC and compared key efficacy and safety end points. The analysis showed ramucirumab + erlotinib to be comparable to best-in-class treatment options. More mature data from the included studies, should it become available, may help to further support these findings, especially with respect to OS.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0885

Author contributions

All the authors participated in the interpretation of data and in critical revision and approval of the final version of the manuscript. K Haeussler, X Wang, KB Winfree, S Traore, T Puri and K Taipale were involved in the study conception. K Haeussler, X Wang, KB Winfree, S Traore and H Thom were involved in the study design. K Haeussler, X Wang, C Papagiannopoulos and M Nassim were

involved in data acquisition. K Haeussler, X Wang, H Thom, C Papagiannopoulos and M Nassim were involved in data analysis. K Haeussler and X Wang drafted the manuscript.

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Summary points

- Ramucirumab (LY3009806) is a fully human receptor-targeted antibody that specifically binds *VEGF* receptor 2 and blocks binding of *VEGF* ligands A, C and D.
- The ongoing, multicenter, randomized, double-blind RELAY (NCT02411448) trial investigates ramucirumab in combination with erlotinib in previously untreated patients with *EGFR* mutation-positive (*EGFR*m$^+$) metastatic (stage IV) NSCLC.
- Here, we report the methodology and results of a network meta-analysis (NMA) of RELAY-comparable populations to assess the efficacy and safety of ramucirumab in combination with erlotinib relative to other treatment options for patients with advanced *EGFR*m$^+$ NSCLC in the first-line (1L) setting.
- A systematic literature review was completed based on published guidelines. Three electronic databases were searched in addition to manual searches of the relevant conference for the last two years. Searches were limited to randomized controlled trials measuring clinical efficacy and safety of 1L therapies.
- Clinical efficacy outcomes included overall survival and progression-free survival.
- The methodological approaches of the NMAs differed according to the type of end point being modeled.
- A variety of subgroup and sensitivity analyses were conducted to assess the robustness of the NMA results.
- A total of 36 randomized controlled trials were eligible for the NMA, of which 34 were included in the base-case analysis.
- As the erlotinib/gefitinib treatment was in the center of the network of evidence and thus connected to a large number of interventions, erlotinib/gefitinib was selected as the reference treatment.
- In the base-case analysis, the following interventions were deemed favorable over erlotinib/gefitinib: osimertinib, gefitinib + carboplatin + pemetrexed, ramucirumab + erlotinib, dacomitinib, erlotinib + bevacizumab, gefitinib + pemetrexed and afatinib.

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