Therapeutic options for advanced epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer: a Bayesian network secondary analysis

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ABSTRACT

The most favorable treatments for advanced EGFR-mutant NSCLC are less indicated. Forty-one studies were eligible for this Bayesian network secondary analysis. For PFS, erlotinib (Erlo)+bevacizumab (Bev) (HR 0.26, 95% CrI: 0.08-0.75 vs placebo), osimertinib (Osi) (HR 0.29, 0.11-0.70 vs placebo), and afatinib (Afa) were top-ranking individual treatments, while immunotherapy (IT)+anti-VEGFR (aVEGFR)+platinum-based therapy (Plat) (HR 0.42, 0.06-2.63 vs placebo), EGFR-TKI (ET)+aVEGFR (HR 0.35, 0.14-0.85 vs placebo), and ET+aVEGFR+Plat were top-ranking medication classes. For OS, Osi (HR 0.52, 0.10-2.00 vs placebo), cetuximab (Cet)+Bev+Plat (HR 0.51, 0.06-3.38 vs placebo), and cilengitide (Cil)+Cet+Plat were top-ranking individual treatments, while ET+aVEGFR+Plat, ET+Plat, and third-generation EGFR-TKI (3rd ET) were top-ranking medication classes. For PFS regarding the EGFR genomic aberration status, Erlo+Bev, Osi, and Afa were superior for exon 19 deletion status, whereas ET+Bev, Osi, and gefitinib (Gef)+pemetrexed (Peme) were excellent for exon 21 L858Arg mutation status. The results were consistent in terms of the ORR and DoR and remained robust across sensitivity analyses. However, Erlo + Bev had the most grade 3 or higher adverse events. Osi, Erlo+Bev, and Erlo+Bev+Plat are reasonably recommended to balance PFS and OS, but adverse events should be considered. IT+aVEGFR+Plat shows potential superiority, but more clinical evidence is needed.

INTRODUCTION

Non-small cell lung cancer (NSCLC) represents approximately 85% to 90% of lung cancer cases and is the leading cause of cancer-related death worldwide, with a lower than 15% 5-year survival [1, 2]. Since treat-

ment selections have become increasingly related to the biological subtypes of NSCLC, attention has been drawn to tumors harboring epidermal growth factor receptor (EGFR) mutations, which are estimated to exist in 10%-15% of patients with nonsquamous NSCLC [3]. The identification of EGFR mutations has led to the

development of targeted therapies, including small molecule tyrosine kinase inhibitors (TKIs) directed at the signal transduction pathway as well as immuno-therapies incorporating checkpoint monoclonal antibodies that bind to and inactivate the receptors on cell membranes [4].

As a monotherapy, gefitinib, erlotinib and, more recently, afatinib have been licensed and recommended as first-line treatment regimens for EGFR-mutant NSCLC patients by the European Society for Medical Oncology (ESMO) guidelines. In August 2015, the American Society of Clinical Oncology (ASCO) clinical guidelines recommended two cytotoxic drugs, docetaxel and pemetrexed, and two EGFR-TKIs, erlotinib and gefitinib, to patients who experienced treatment failure with conventional first-line chemotherapy [4]. Nevertheless, several new regimens have been approved by the US FDA, such as the combination of docetaxel and ramucirumab, nivolumab, pembrolizumab, and atezolizumab. At the same time, more than 40 therapeutic options are being assessed in randomized controlled trials (RCTs) [5]. With more clinical trials emerging [4–46], the FLAURA trial [42] has shown that osimertinib has superior efficacy compared with standard EGFR-TKIs in treating advanced EGFR-mutant NSCLC with less serious adverse effects (18.9 months vs 10.2 months for progression-free survival (PFS), P<0.001). The newest National Comprehensive Cancer Network (NCCN) guidelines also regarded osimertinib as category 1 for advanced EGFR-mutant NSCLC.

There is an urgent need to identify complete information on the most effective and latest treatment for advanced EGFR-mutant NSCLC. Conventional meta-analyses have only partially captured the available evidence for treating the intended populations; their outcomes are not comprehensive. This work is a generalized version of a pairwise meta-analysis integrating direct and indirect evidence [4–46] to aid in clinical decision making. Thus, the aim of this article is to comprehensively evaluate the effectiveness and safety of various therapeutics for advanced EGFR-mutant NSCLC.

RESULTS

Study selection and characteristics of the included studies

We identified a total of 1749 records from a database search and 34 records from other available literature; of these, 1721 were excluded based on the selection criteria. Subsequently, 62 potential articles went through full-text review, and 41 studies were

ultimately eligible for inclusion (Appendix Figure 1 in the Supplementary Data).

Forty-one RCTs [6–46] consisting of 8430 total participants were included in the analysis. The characteristics and results of the studies are detailed in Appendix Table 2 in the Supplementary Data. The included RCTs encompassed 22 unique treatments and 15 medication classes; there were 39 direct comparisons for PFS (38 trials [6–24, 26–28, 30–40, 42–46]; n= 7670) and 23 direct comparisons for OS (22 trials [6, 7, 9, 11–13, 15, 19–22, 25, 27, 29, 35, 36, 38–42, 45]; n= 3842). Data were extracted from survival plots in 5 studies [9, 11, 18, 22, 35]. Most treatments in eligible trials were first-line setting, the abbreviations for the medication classes and their constituent individual treatments are listed in Table 1. The mean age of the participants ranged from 56.0 to 74.0 years, with a median age of 61.9 years. The follow-up period ranged from 10 to 70 months with a median duration of 27.5 months. Ten studies [14, 26, 31, 34, 35, 38, 39, 42, 43, 46] reported data on metastases, 9 [14, 26, 34, 35, 38, 39, 42, 43, 46] reported data on central nervous system (CNS) metastases, and 5 [14, 26, 31, 34, 42] reported data on visceral, bone or other metastases. Of the 41 total studies, 40 were two-arm trials, 1 [45] was a three-arm trial, 34 studies were phase III clinical trials, and 7 [6, 7, 18, 22, 27, 30, 31] were phase II trials. Of note, 16 studies [10, 14, 22, 23, 28–32, 34, 35, 38, 39, 41, 42, 46] provided EGFR genomic aberration data (19 del and/or 21 L858R), 14 [10, 14, 22, 23, 28, 30–32, 34, 35, 38, 39, 42, 46] for PFS and 2 [29, 41] for OS. There were 12 trials involving Asian patients and 29 trials involving 6408 non-Asian patients (multiple nations or no Asian region).

Risk of bias and quality assessment

In the quality assessment, we found that a vast majority of the included studies had a low risk of bias (Appendix Table 3 in the Supplementary Data). Two [24, 46] studies had "other bias" according to the Cochrane risk of bias tool, and 16 [10, 13, 15, 19, 20, 22, 26–29, 31, 35, 38, 39, 41, 44] had an unclear "other bias". Most of the risk stemmed from the blinding of participants and personnel and blinding of outcome assessment categories due to the open-label method.

Bayesian NMA at the individual-treatment level

A total of 37 RCTs with 37 arms and 21 unique treatment levels were included in the treatment level analysis for PFS; a study by Reck et al. [45] was omitted for not contributing to a complete loop (Figure 1A). Twenty-one unique nodes were presented in this analysis, with every node representing a unique

Table 1. List of medication classes and individual treatments.

Medication class level	Treatment level
	Gef: gefitinib
	Erlo: erlotinib
	Ico: icotinib
	Afa: afatinib
	Dac: dacomitinib
	Osi: osimertinib
	Naq: naquotinib
	Erlo+Bev: erlotinib+bevacizumab
	Sun+Erlo: sunitinib+erlotinib
	Ona+Erlo: onartuzumab+erlotinib
	Erlo+Tiv: erlotinib+tivantinib
ET+CT: EGFR-TKI+cytotoxic therapy	**Gef+Peme**: gefitinib+pemetrexed
	Cil+Cet+Plat: cilengitide+cetuximab+platinum-based therapy
	Cet+Bev+Plat: cetuximab+bevacizumab+platinum-based therapy
	Cet+Plat: cetuximab+platinum-based therapy
	Erlo+Plat: erlotinib+platinum-based therapy
aVEGFR+Plat: anti-VEGFR+platinum-based therapy	**Mot+Plat**: motesanib+platinum-based therapy
Plat*	**Plat**: platinum-based therapy
	Doc: docetaxel
	Vin: vinorelbine
WBRT	**WBRT**: whole-brain radiotherapy
Placebo	Placebo

*In this study, platinum-based therapy contains: pemetrexed + cisplatin/carboplatin, gemcitabine + cisplatin/carboplatin, vinorelbine + cisplatin/carboplatin, paclitaxel + cisplatin/carboplatin, docetaxel + cisplatin/carboplatin, docetaxel + gemcitabine + cisplatin/carboplatin, pemetrexed + gemcitabine+cisplatin/carboplatin.

intervention. The nodes with the most direct interactions were between Plat and Erlo, Plat and Gef, and Osi and Plat (Figure 1B). Erlo+Bev (HR 0.26, 95% CrI: 0.08-0.75), Osi (HR 0.29, 95% CrI: 0.11-0.70), Afa (HR 0.37, 95% CrI: 0.17-0.78), and Erlo (HR 0.46, 95% CrI: 0.21-0.93) showed significant superiority over placebo in terms of PFS. Moreover, the probability for Erlo+Bev ranked first, followed by Osi, Afa, and Erlo; the ranking probabilities were 0.164, 0.164, 0.120, and 0.128, respectively (Figure 1C, 1D). The results of the comparisons among those treatments and all treatments are shown in Figure 1C and Appendix Table 4 in the Supplementary Data. The model fit was good, and there was no significant heterogeneity or loop inconsistency (Table 2).

A total of 21 RCTs with 21 arms and 18 unique treatment levels were considered in the OS analysis; a study by Reck et al. [45] was excluded from the network (Figure 2A). Eighteen nodes were included in the treatment-level analysis for OS. The most direct interactions were in nodes between Erlo and Plat (Figure 2B). Osi (HR 0.52, 95% CrI: 0.10-2.00), Cet+Bev+Plat (HR 0.51, 95% CrI: 0.06-3.38), Cil+Cet+Plat (HR 0.59, 95% CrI: 0.06-4.30), and Cet+Plat (HR 0.63, 95% CrI: 0.10-3.03) appeared to benefit OS over placebo even though the favorable efficacy was nonsignificant. Osi (ranking probability: 0.183) ranked first, followed by Cet+Bev+Plat (0.157), Cil+Cet+Plat (0.117), and Cet+Plat (0.147) (Figure 2C, 2D). The results of the comparisons among those treatments and all treatments are shown in Figure 2C and Appendix Table 4 in the Supplementary Data. The statistical model was good, and no evidence of heterogeneity or loop inconsistency was observed (Table 2). A total of 13 trials with 10 unique treatment levels were analyzed for ORR after excluding Reck et al. [45] and Yang et al. (2) [38] (Appendix Figure 2 in

Supplementary Data). The primary data are shown in Appendix Table 5 in the Supplementary Data. Afa ranked first and had the best ORR (OR 7.67, 95% CrI: 2.93-20.68 vs Plat), followed by Dac (OR 6.10, 95% CrI: 1.34-29.20), Gef (OR 5.14, 95% CrI: 1.96-14.10), and Gef + Peme (OR 6.02, 95% CrI: 1.42-23.13) (Appendix Table 6 in the Supplementary Data). No evidence of heterogeneity was found. A total of 17 trials with 13 unique treatment levels focused on grade 3 or higher AEs (Appendix Figure 3 in the Supplementary Data). The primary data are shown in Appendix Table 7 in the Supplementary Data. Erlo + Bev had the most grade 3 or higher AEs (OR 24.22, 95% CrI: 0.64-NA vs Ico), followed by Gef +Peme (OR 15.28, 95% CrI: 0.43-NA), Plat (OR 12.61, 95% CrI: 0.86-NA) and Dac (OR 11.09, 95% CrI: 0.33-NA) (Appendix Table 8 in the Supplementary Data). No significant heterogeneity was noted (Table 2). The outcome of DoR was not analyzed for insufficient comparisons.

Bayesian NMA at the medication-class level

There were 35 RCTs with 36 arms and 15 unique class levels included in the class-level analysis for PFS; the studies of Yang et al. [39], Urata et al. [32], and Shi et al. [17] were excluded for having two of the same class

interventions. A total of 15 nodes were presented, in which the most direct interventions were between 1st-gen ET and Plat, 1st-gen ET and 2nd-gen ET, and 1st-gen ET and Placebo (Figure 3A and Figure 3B). ET+aVEGFR (HR 0.35, 95% CrI: 0.14-0.85) and 3rd-gen ET (HR 0.39, 95% CrI: 0.16-0.91) were better than placebo, while ET+aVEGFR+Plat (HR 0.40, 95% CrI: 0.11-1.37) and IT+aVEGFR+Plat (HR 0.42, 95% CrI: 0.06-2.63) seemed to be superior than placebo, but the data were not statistically significant (Figure 3C). Our work demonstrated that statistically, ET+aVEGFR ranked first, followed by 3rd-gen ET, ET+aVEGFR+Plat, and IT+aVEGFR+Plat (Figure 3D). The results of the comparisons among those treatments and all treatments are shown in Figure 3C and Appendix Table 9 in the Supplementary Data. The model was good, and no heterogeneity or inconsistency was observed.

In total, 21 RCTs with 11 arms and 11 unique class levels were selected for the class-level analysis of OS; studies by Yang et al. [39] and Reck et al. [45] were excluded for comparing the same class interventions (Figure 4A). The 11 nodes with the most direct interactions were between 1st-gen ET and Plat (Figure 4B). When compared with placebo, the HR for
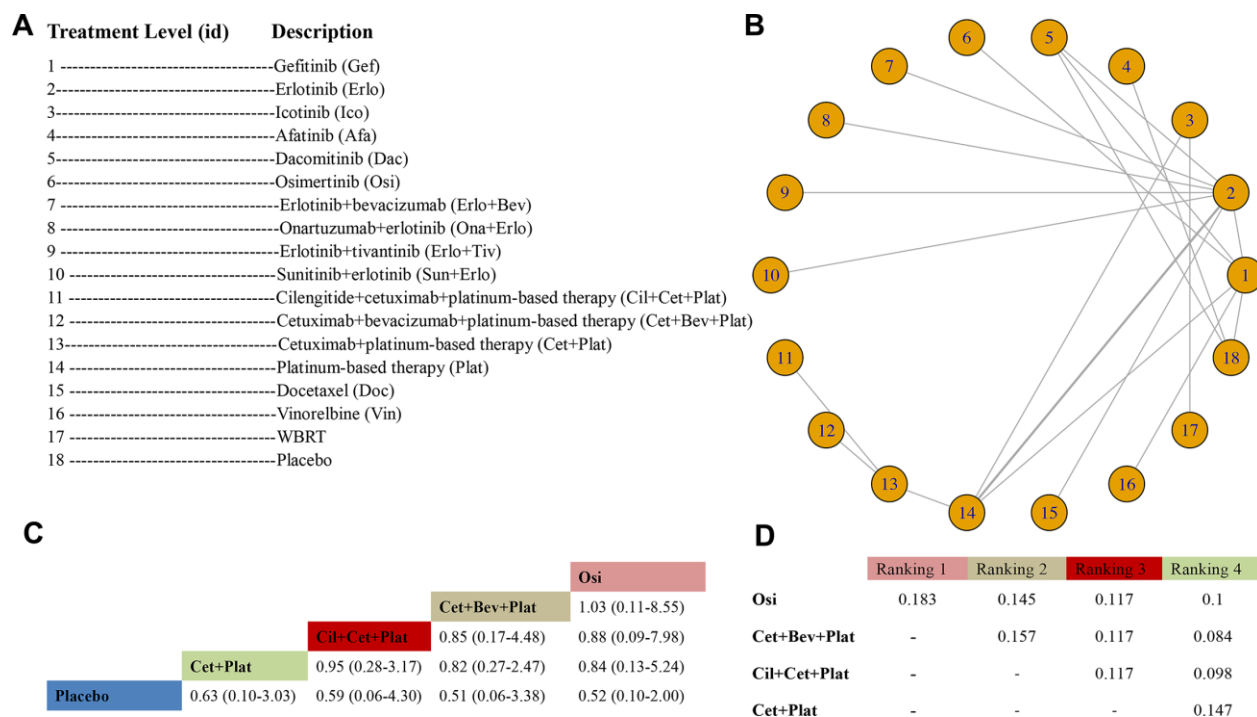

Figure 1. Meta-analysis of efficacy for PFS at the individual-treatment level. (**A**) Descriptions of the individual treatments included in this analysis. (**B**) Network plots showing comparisons between nodes (yellow circles), each representing a unique individual treatment. Each line corresponds to direct comparisons between treatments with the width corresponding to the number of direct within-trial comparisons. (**C**) Comparison results of the most efficacious treatments and placebo (HR (95% CrI)). Each result is a comparison between the column-defining drug and the row-defining treatment. (**D**) Schematic detailing the most efficacious treatments according to the rankograms.

Table 2. Edge-splitting method for direct and indirect evidence relating to PFS, OS, ORR and grade 3 or higher AEs in treatment-level.

Multiple-treatment	Direct comparison outcome	Indirect comparison outcome	Combined outcome	I^2
PFS (HR and 95% CrI)				
Erlo vs Gef	0.94 (0.42-2.10)	0.84 (0.41-1.70)	0.88 (0.53-1.50)	< 50%
Afa vs Gef	0.73 (0.23-2.30)	0.71 (0.28-1.80)	0.72 (0.36-1.50)	< 50%
Dac vs Gef	0.62 (0.20-1.90)	0.97 (0.38-2.60)	0.79 (0.40-1.60)	< 50%
Osi vs Gef	0.46 (0.15-1.40)	0.65 (0.23-1.80)	0.55 (0.27-1.10)	< 50%
Plat vs Gef	1.90 (0.94-3.80)	2.10 (1.10-4.20)	2.0 (1.30-3.20)	< 50%
Placebo vs Gef	2.40 (1.20-5.30)	1.40 (0.48-3.80)	1.90 (1.10-3.60)	< 50%
Ico vs Erlo	0.78 (0.24-2.50)	1.60 (0.47-5.30)	1.10 (0.47-2.50)	< 50%
Dac vs Erlo	1.00 (0.30-3.60)	0.83 (0.30-2.40)	0.90 (0.43-2.00)	< 50%
Plat vs Erlo	2.50 (1.40-4.50)	2.00 (0.88-4.30)	2.30 (1.40-3.60)	< 50%
Plat vs Ico	1.50 (0.51-4.70)	3.10 (0.86-11.00)	2.10 (0.91-4.80)	< 50%
Plat vs Afa	3.90 (1.20-12.00)	2.20 (0.79-5.90)	2.80 (1.30-5.80)	< 50%
Plat vs Osi	3.20 (1.40-7.70)	4.60 (1.30-16.00)	3.70 (1.80-7.20)	< 50%
Placebo vs Afa	2.00 (0.58-6.70)	3.50 (1.30-11.00)	2.70 (1.30-6.00)	< 50%
Placebo vs Dac	2.1 (0.65-6.70)	2.80 (0.96-8.80)	2.40 (1.10-5.30)	< 50%
OS (HR and 95% CrI)				
Plat vs Gef	1.30 (0.25-7.00)	0.93 (0.32-2.60)	1.00 (0.44-2.60)	< 50%
Vin vs Gef	0.35 (0.06-2.10)	NA	0.35 (0.09-1.40)	NA
Placebo vs Gef	2.30 (0.36-14.00)	0.91 (0.26-3.20)	1.20 (0.51-4.00)	< 50%
Erlo vs Gef	0.84 (0.17-4.60)	1.10 (0.43-2.70)	1.00 (0.48-2.40)	< 50%
Dac vs Gef	0.77 (0.15-4.10)	0.99 (0.37-2.60)	0.92 (0.44-2.40)	< 50%
Osi vs Gef	0.63 (0.12-3.30)	NA	0.63 (0.20-2.00)	NA
Erlo vs Sun + Erlo	0.72 (0.13-4.00)	NA	0.72 (0.21-2.50)	NA
Cet + Plat vs Cil + Cet +Plat	1.00 (0.19-5.70)	NA	1.10 (0.32-3.50)	NA
Cet + Plat vs Cet + Bev +Plat	1.20 (0.24-6.30)	NA	1.20 (0.39-3.80)	NA
Plat vs Cet + Plat	1.40 (0.26-7.40)	NA	1.40 (0.44-4.30)	NA
Erlo vs Plat	1.20 (0.33-4.10)	0.88 (0.32-2.50)	0.99 (0.46-2.20)	< 50%
Ico vs Plat	1.00 (0.20-5.30)	NA	1.00 (0.32-3.30)	NA
Erlo vs Doc	0.38 (0.05-2.70)	NA	0.38 (0.08-1.90)	NA
Ico vs WBRT	0.93 (0.17-4.90)	NA	0.94 (0.29-3.10)	NA
Afa vs Placebo	1.60 (0.30-9.20)	NA	1.60 (0.47-5.80)	NA
Dac vs Placebo	0.98 (0.19-5.20)	0.68 (0.20-2.30)	0.77 (0.27-1.90)	< 50%
Dac vs Erlo	0.94 (0.16-5.80)	0.90 (0.30-2.70)	0.91 (0.37-2.40)	< 50%
Erlo + Bev vs Erlo	1.20 (0.19-7.20)	NA	1.2 (0.28-4.80)	NA
Ona +Erlo vs Erlo	4.60 (0.54-41.00)	NA	4.70 (0.71-30.00)	NA
Erlo + Tiv vs Erlo	0.72 (0.35-1.50)	NA	0.72 (0.20-2.60)	NA
ORR (OR and 95% CrI)				
Plat vs Gef	0.16 (0.03-0.72)	0.22 (0.06-0.78)	0.19 (0.07-0.49)	< 50%
Afa vs Gef	1.78 (0.39-8.07)	1.33 (0.39-4.54)	1.49 (0.56-3.78)	< 50%
Dac vs Gef	1.17 (0.26-5.23)	NA	1.19 (0.37-3.70)	NA

Gef + Peme vs Gef	1.16 (0.33-3.51)	NA	1.16 (0.42-3.00)	NA
Afa vs Plat	6.38 (1.43-29.91)	8.84 (2.60-30.11)	7.78 (3.02-20.37)	< 50%
Osi vs Plat	2.81 (0.89-7.70)	NA	2.96 (1.16-6.36)	NA
Cet + Plat vs Plat	2.08 (0.45-9.29)	NA	2.03 (0.65-6.60)	NA
Osi vs Erlo	1.26 (0.27-5.57)	NA	1.26 (0.41-3.98)	NA
Naq vs Erlo	0.53 (0.12-2.39)	NA	0,53 (0.17-1.67)	NA
Erlo + Bev vs Erlo	1.30 (0.44-3.90)	NA	1.32 (0.55-3.11)	NA
Grade 3 or higher AEs (OR and 95% CrI)				
Plat vs Gef	0.16 (0.03-0.72)	0.22 (0.06-0.78)	0.19 (0.07-0.49)	< 50%
Afa vs Gef	1.78 (0.39-8.07)	1.33 (0.39-4.54)	1.49 (0.56-3.78)	< 50%
Dac vs Gef	1.17 (0.26-5.23)	NA	1.19 (0.37-3.70)	NA
Gef + Peme vs Gef	1.16 (0.33-3.51)	NA	1.16 (0.42-3.00)	NA
Afa vs Plat	6.38 (1.43-29.91)	8.84 (2.60-30.11)	7.78 (3.02-20.37)	< 50%
Osi vs Plat	2.81 (0.89-7.70)	NA	2.96 (1.16-6.36)	NA
Cet + Plat vs Plat	2.08 (0.45-9.29)	NA	2.03 (0.64-6.60)	NA
Osi vs Erlo	1.26 (0.27-5.57)	NA	1.26 (0.41-3.98)	NA
Naq vs Erlo	0.53 (0.12-2.39)	NA	0.53 (0.17-1.67)	NA
Erlo + Bev vs Erlo	1.30 (0.44-3.90)	NA	1.32 (0.55-3.11)	NA

Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; AEs, adverse events; NA, not available.

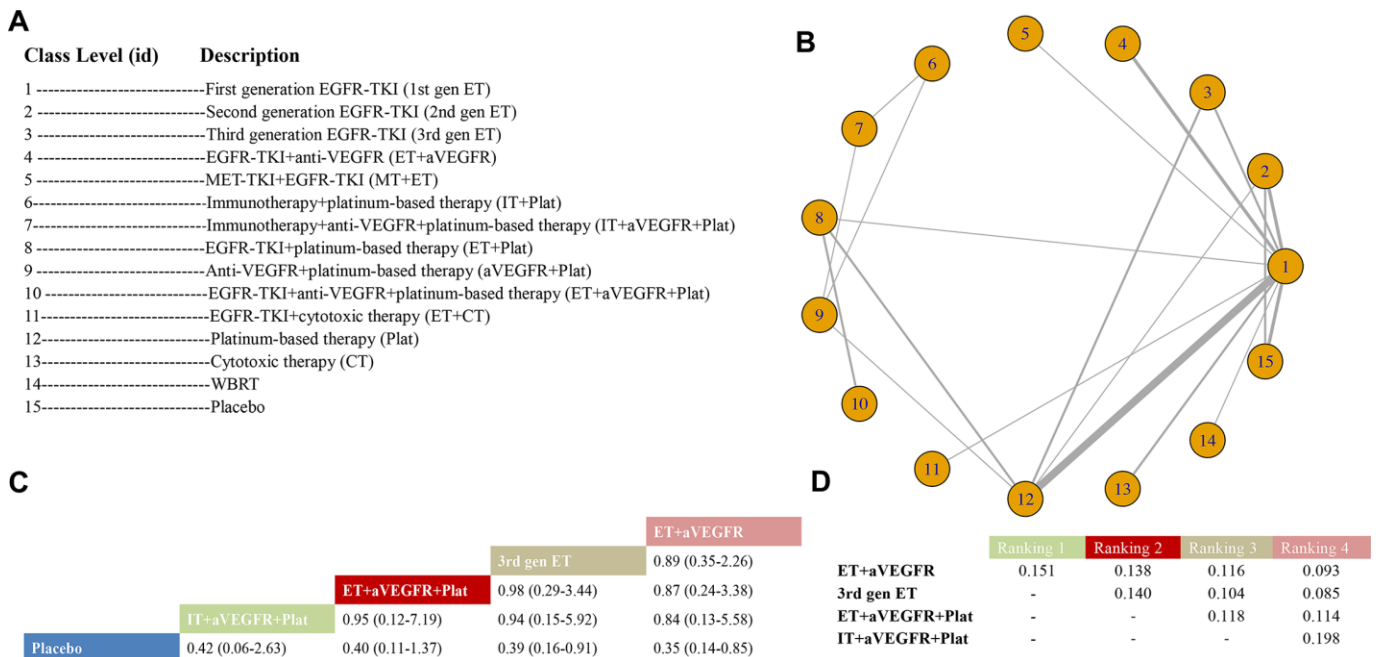Abbreviations of available treatments could be found in the main body of manuscript.

Figure 2. Meta-analysis of efficacy for OS at the individual-treatment level. (**A**) Descriptions of the individual treatments included in this analysis. (**B**) Network plots showing comparisons between nodes (yellow circles), each representing a unique individual treatment. Each line corresponds to direct comparisons between treatments, with the width corresponding to the number of direct within-trial comparisons. (**C**) Comparison results of the most efficacious treatments and placebo (HR (95% CrI)). Each result is a comparison between the column-defining drug and the row-defining treatment. (**D**) Schematic detailing the most efficacious treatments according to the rankograms.

ET+aVEGFR+Plat was 0.65 (95% CrI: 0.13-2.71), the HR for ET+Plat was 0.76 (95% CrI: 0.17-2.65), and the HR for 3rd-gen ET was 0.66 (95% CrI: 0.16-2.04) (Figure 4C). Bayesian analysis revealed that ET+aVEGFR+Plat was significantly ranked first, followed by ET+Plat, and then 3rd-gen ET (Figure 4D). Additional data on the interactions can be found in Figure 4C and Appendix Table 9 in the Supplementary Data. The fitness for this model was good, and no significant heterogeneity or inconsistencies were observed.

In medication-class level analysis for ORR (Appendix Figure 4 in the Supplementary Data, Appendix Table 5 in the Supplementary Data), 2nd-gen ET was the best (OR 12.52, 95% CrI: 3.38-49.41 vs WBRT), followed by ET + aVEGFR (OR 11.64, 95% CrI: 2.87-49.19) and 1st-gen ET (OR 8.82, 95% CrI: 2.79-29.56) (Appendix Table 10 in the Supplementary Data). Analysis for DoR (Appendix Figure 5 in the Supplementary Data, Appendix Table 11 in the Supplementary Data) revealed that 2nd-gen ET had the longest DoR (MD 5.08, 95% CrI: -11.44 to 21.63 vs ET + aVEGFR), followed by 3rd-gen ET (MD 3.04, 95% CrI: -11.29 to 17.31) and ET + CT (MD 3.87, 95% CrI: -12.47 to 20.38) (Appendix Table 12 in the Supplementary Data). Analysis for grade 3 or higher AEs (Appendix Figure 6

in the Supplementary Data, Appendix Table 7 in the Supplementary Data) revealed that ET + aVEGFR had the most grade 3 or higher AEs (OR 9.01, 95% CrI: 0.99-92.27 vs Placebo), followed by Plat (OR 5.25, 95% CrI: 0.98-29.83) and ET + CT (OR 3.82, 95% CrI: 0.39-37.26) (Appendix Table 13 in the Supplementary Data). There was low to moderate heterogeneity among medication-level comparisons on ORR, DoR and grade 3 or higher AEs.

EGFR genomic status

Multiple treatment-level comparisons (10 treatments) were specifically performed for 19 del and 21 L858R mutations regarding PFS. We found that Erlo+Bev, Osi, Afa, and Erlo were top-ranking alternatives for patients harboring 19 del mutations to prolong PFS; additionally, Erlo+Bev, Osi, Gef+Pem, and Dac were optimal treatments among the available treatments for patients with 21 L858R mutations (Table 3). Overall, Erlo+Bev, Osi, and 2nd-gen ET (including Afa and Dac) were the most viable treatment options, and no significant differences were found in terms of the best strategies for 19 del and 21 L858R mutations. The evidence was insufficient to assess these mutations in terms of OS as well as uncommon mutations.
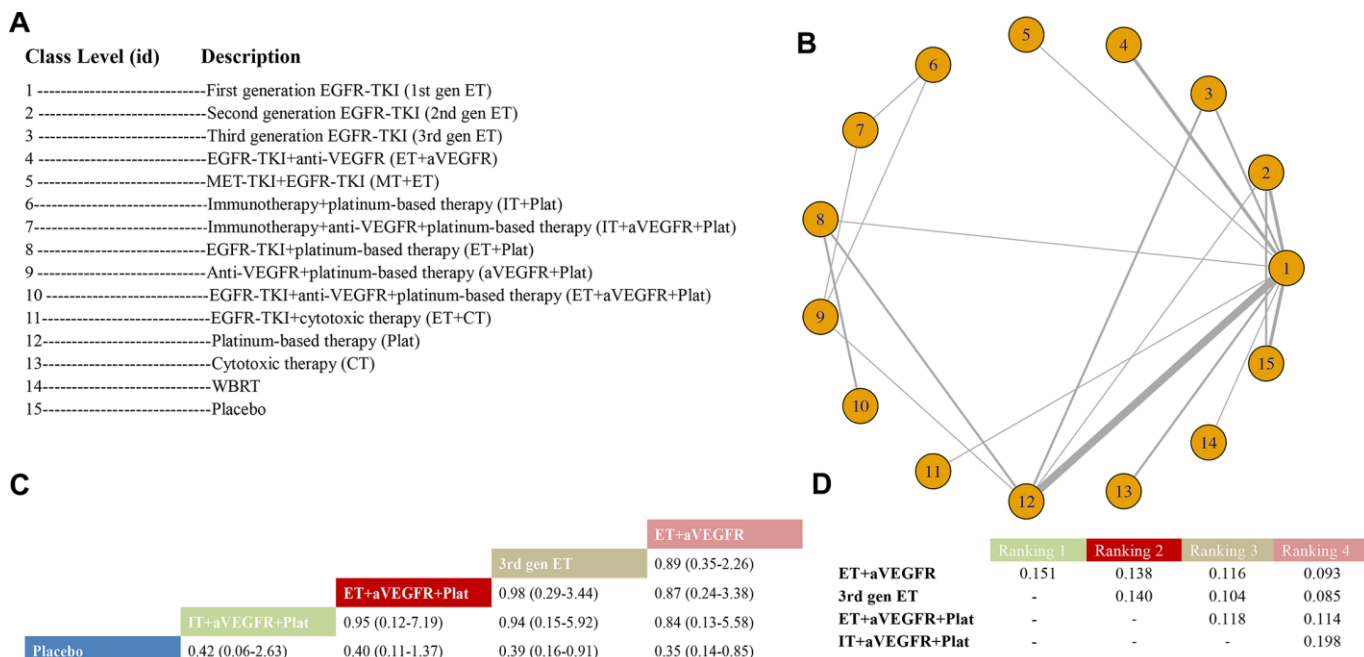

Figure 3. Meta-analysis of efficacy for PFS at the medication-class level. (**A**) Descriptions of the medication classes included in this analysis. (**B**) Network plots showing comparisons between nodes (yellow circles), each representing a unique medication class. Each line corresponds to direct comparisons between treatments, with the width corresponding to the number of direct within-trial comparisons. (**C**) Comparison results of the most efficacious class and placebo (HR (95% CrI)). Each result is a comparison between the column-defining drug and the row-defining class. (**D**) Schematic detailing the most efficacious medication classes according to the rankograms.

Sensitivity analysis

Sensitivity analyses helped to confirm the robustness of these findings, which put more weight on main outcomes. The results restricted to phase III trials (trial number = 34 and patient number = 7448) did not show significant deviations compared with the original network Bayesian analyses; however, they showed a more robust status of Osi that had better OS and PFS. Superiority of Erlo + Bev on PFS was also stressed. The results of the primary meta-analysis remained stable across sensitivity analyses by removing Reck et al. [45], (IMpower150) and Soria et al. [42], (FLAURA), respectively. The superiority of Osi was confirmed to be robust. When restricted to Asia (trial number = 12 and patient number = 1977), the superiority of Osi on PFS slightly declined, but Osi was still among the top-ranking treatments. Erlo + Bev and EGFR-TKI + aVEGFR + Plat showed favorable PFS across Asian and non-Asian populations (trial number = 29 and patient number = 6408).

DISCUSSION

With increasing molecular research focused on biomarkers for NSCLC, attention has been drawn to targeted therapies and immunotherapy. The available guidelines have helped improve the level of clinical treatment, but they still need to be updated as more evidence and clinical trials emerge. In the present study, we gathered evidence from 41 RCTs assessing the role of 22 treatment-level options and 22 class-level options for the intended populations. Herein, we found that Erlo+Bev, Osi, Afa, and Erlo are optimal treatment-level options in terms of PFS and that Osi, Cet+Bev+Plat, Cil+Cet+Plat, and Cet+Plat are successively optimal options in terms of OS. For medications at the class level, ET+aVEGFR, 3rd-gen ET, ET+aVEGFR+Plat,
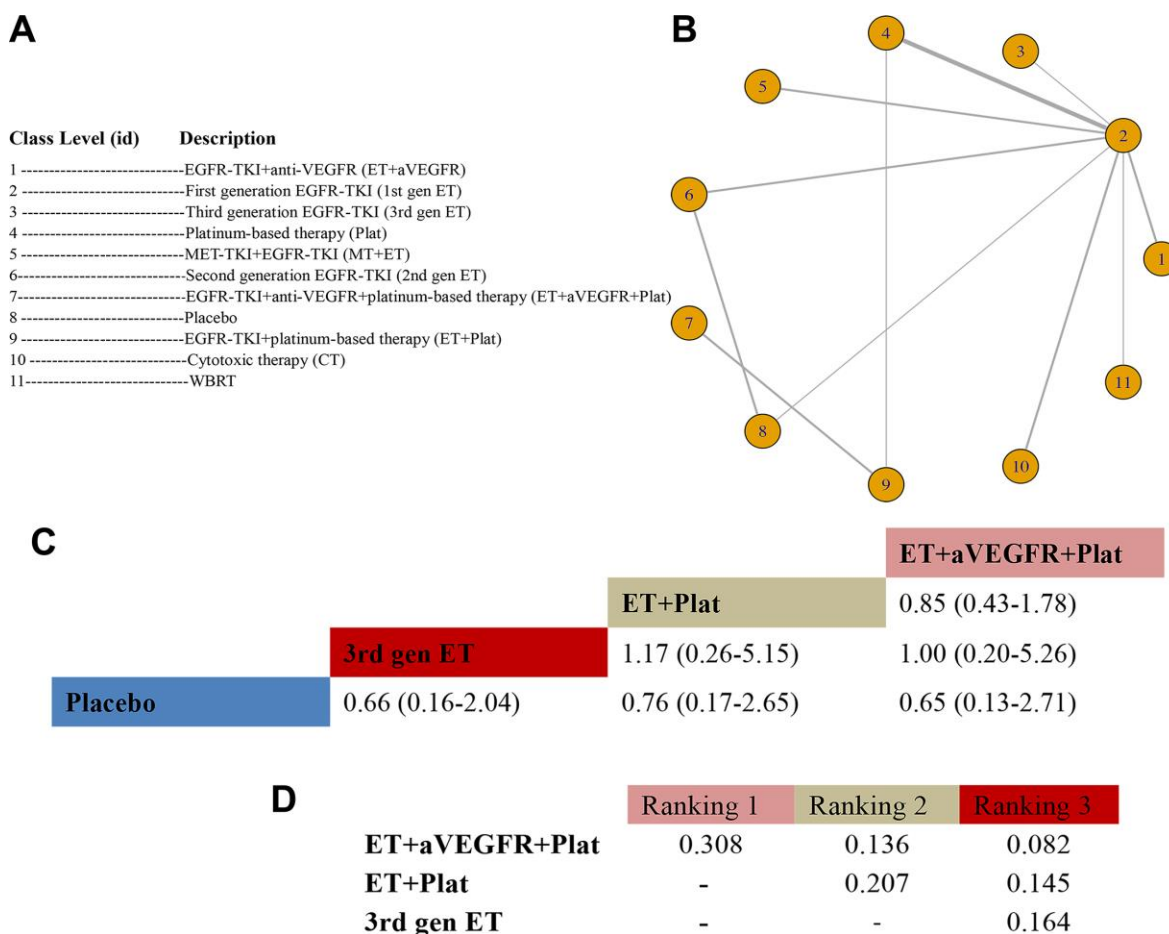

Figure 4. Meta-analysis of efficacy for OS at the medication-class level. (**A**) Descriptions of the medication classes included in this analysis. (**B**) Network plots showing comparisons between nodes (yellow circles), each representing a unique medication class. Each line corresponds to direct comparisons between treatments, with the width corresponding to the number of direct within-trial comparisons. (**C**) Comparison results of the most efficacious class and placebo (HR (95% CrI)). Each result is a comparison between the column-defining drug and the row-defining class. (**D**) Schematic detailing the most efficacious medication classes according to the rankograms.

Table 3. Comparisons of PFS for exon 19 deletion and exon 21 Leu-858Arg mutation according to treatment-level Bayesian analysis.

Gef	0.76 (0.26-2.20)	1.63 (0.27-10.40)	0.56 (0.13-2.23)	0.70 (0.22-2.23)	0.68 (0.22-2.15)	0.41 (0.09-1.80)	0.67 (0.16-2.95)	**3.19 (1.10-9.82)**	4.18 (0.41-44.40)
1.31 (0.45-3.89)	Erlo	2.15 (0.44-11.80)	0.73 (0.13-4.30)	0.92 (0.26-3.40)	0.90 (0.26-3.40)	0.54 (0.19-1.54)	0.88 (0.15-5.69)	**4.21 (1.99-9.59)**	5.49 (0.61-53.60)
0.61 (0.10-3.67)	0.47 (0.08-2.26)	Ico	0.34 (0.03-3.25)	0.43 (0.07-2.63)	0.42 (0.06-2.59)	0.25 (0.03-1.66)	0.41 (0.04-4.07)	1.96 (0.46-8.03)	2.57 (0.56-11.70)
1.80 (0.45-7.48)	1.37 (0.23-7.84)	2.95 (0.31-30.60)	Dac	1.27 (0.21-7.83)	1.23 (0.21-7.75)	0.74 (0.09-5.51)	1.21 (0.16-9.75)	**5.76 (1.91-34.90)**	7.53 (0.51-125.00)
1.43 (0.45-4.46)	1.09 (0.29-3.86)	2.34 (0.38-15.40)	0.79 (0.13-4.88)	Afa	0.97 (0.23-4.14)	0.58 (0.11-2.97)	0.95 (0.15-6.19)	**4.57 (1.46-15.10)**	5.99 (0.57-64.80)
1.47 (0.47-4.50)	1.12 (0.31-3.86)	2.41 (0.39-15.90)	0.81 (0.13-4.85)	1.03 (0.24-4.31)	Osi	0.60 (0.11-3.05)	0.99 (0.15-6.34)	**4.69 (1.50-14.70)**	6.15 (0.57-67.30)
2.47 (0.56-11.30)	1.87 (0.65-5.33)	4.06 (0.60-28.70)	1.36 (0.18-10.90)	1.73 (0.34-9.23)	1.68 (0.33-9.23)	Erlo+Bev	1.65 (0.21-14.20)	**7.90 (2.24-30.00)**	10.30 (0.92-121.00)
1.50 (0.34-6.39)	1.13 (0.18-6.72)	2.45 (0.25-25.50)	0.83 (0.10-6.24)	1.05 (0.16-6.84)	1.01 (0.16-6.54)	0.61 (0.07-4.83)	Gef+Peme	4.79 (0.76-31.20)	6.24 (0.41-100.00)
0.31 (0.10-0.91)	**0.24 (0.10-0.50)**	0.51 (0.13-2.19)	**0.17 (0.03-0.99)**	0.22 (0.07-0.69)	**0.21 (0.07-0.67)**	**0.13 (0.03-0.45)**	0.21 (0.03-1.31)	Plat	1.30 (0.16-10.70)
0.24 (0.02-2.47)	0.18 (0.02-1.63)	0.39 (0.09-1.79)	0.13 (0.01-1.95)	0.17 (0.02-1.76)	0.16 (0.01-1.76)	0.10 (0.01-1.09)	0.16 (0.01-2.44)	0.77 (0.09-6.16)	WBRT

Results for exon 19 deletion are shown in blue-colour cells, results for exon 21 Leu 858Arg mutation are in gray-color cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. For 19 del and 21 L858R mutations, HRs (and 95% CrI) less than 1 favour the column-defining treatment. To obtain HRs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored. Abbreviations: Gef, gefitinib; Erlo, erlotinib; Ico, icotinib; Dac, dacomitinib; Afa, afatinib; Osi, osimertinib; Erlo+Bev, erlotinib+bevacizumab; Gef+Peme, gefitinib+pemetrexed; Plat, platinum-based therapy.

and IT+aVEGFR+Plat outperform other treatments in terms of PFS, while ET+aVEGFR+Plat, followed by ET+Plat and 3rd-gen ET, are better alternatives in terms of OS. Additionally, Erlo+Bev and Osi were superior to other treatments for 19 del and 21 L858R mutations in terms of PFS. Although these were modest differences, most ORR and DoR results were consistent with the PFS and OS results. Erlo +Bev elicited the most severe AEs, which should be properly managed during clinical use. Regarding the efficacy, top-ranking treatments for advanced EGFR-mutant NSCLC also include first-line settings such as osimertinib, while their AEs should be considered in clinical medication. These findings provide crucial implications for clinical reference.

ET monotherapy has been established as the standard treatment for patients with EGFR-positive NSCLC, and a meta-analysis involving patients who had not previously received treatment showed a median PFS of 11 months with ET (gefitinib/erlotinib) versus 5.6 months with chemotherapy [56]. However, most patients with lung cancer are diagnosed at an advanced stage, and the prognosis remains poor despite novel therapeutics. To improve PFS, combination treatments with 1st-gen ET and 2nd-gen ET have been evaluated in several clinical trials [57]. Bev inhibits angiogenesis by restricting oxygen and nutrient supplies to suppress tumor growth, and combination chemotherapy with Bev has been shown to be effective against CNS metastasis and pleural effusion [58, 59], but the conclusion is controversial. Several clinical trials (JO25567, NEJ026) [22, 46] included in this study also compared the efficacy of Erlo+Bev with that of Erlo, and the results showed that PFS was significantly prolonged in the Erlo+Bev group. A meta-analysis [60] investigating Erlo+Bev compared with monotherapy for NSCLC

found no substantial benefits for the OS or PFS of all patients, but the combination treatment significantly enhanced OS for EGFR-mutant patients. The mechanism by which Erlo+Bev improves PFS is still unclear, but there are some hypotheses. Bev might normalize blood flow, thus improving drug delivery to tumor blood vessels [61, 62]. Autocrine or paracrine signaling by the VEGF receptor might catalyze cancer cell proliferation and produce anti-apoptotic effects, which could be inhibited by Bev to restore apoptosis [63]. Resistance by Erlo+Bev to the VEGF-mediated pathway has been confirmed in basic research [64]. Previous evidence has demonstrated that the response induced by the 21 L858R mutation was inferior to that induced by the 19 del mutation, which could be improved by Erlo+Bev. However, in this study, Erlo+Bev was found to be the preferred treatment for both 21 L858R and 19 del mutations. Although the OS endpoint was or met and was not significantly different, further clinical validation is still needed. When combined with ET, Bev+Plat has shown promising efficacy among patients with liver metastasis harboring EGFR mutations, which was consistent with our findings. Accordingly, Erlo+ET+Plat also offers potential benefits for patients with advanced EGFR-mutant NSCLC.

Osi is an oral 3rd-gen ET that selectively inhibits ET sensitivity and EGFR T790M resistance (present in almost 60% of patients) and has been approved for the treatment of patients with metastatic T790M-positive NSCLC. Preclinical and clinical data (AURA3) [34, 65] support the ability of Osi to cross the blood-brain barrier and penetrate the CNS; the PFS of advanced EGFR-mutant NSCLC in the FLAURA trial [42] was significantly enhanced in the Osi group. Moreover, the OS of the Osi group was also significantly enhanced (38.6 months vs 31.8 months of standard ET; HR 0.48, 95% CI, 0.26-0.86), as reported by an abstract presented at the 2019 ESMO conference. Patients with T790M resistance mutations who receive Osi may still eventually exhibit progression, and thus, they require better treatment options. Reck et al. [45] noted improved survival with immunotherapy+Bev+Plat compared with Bev+Plat, which suggested the potential priority of immunotherapy in the intended populations. The randomized phase III trial CheckMate 227 [66] demonstrated that nivolumab+ipilimumab resulted in a longer OS duration than chemotherapy, regardless of the programmed cell death-ligand 1 (PD-L1) expression level. Before the further application of immunotherapy in real clinical practice, we should understand the role of tumor mutational burden (TMB) as a biomarker and note safety concerns.

This study has several clinical implications and strengths that should be mentioned. To the best of our knowledge, this study is the most comprehensive work comparing treatment effectiveness for advanced EGFR-mutant NSCLC to date. Current national and international guidelines are mostly based on the results of single RCTs, as well as standard meta-analyses dedicated to the pairwise comparisons of two or three treatments. Moreover, with the large number of treatment options, meta-analyses of direct comparisons are inevitably limited by the relatively small number of studies assessing a particular pair of treatments. Meta-analyses on multiple treatments reduce this issue by creating indirect comparisons and allowing data synthesis that helps to identify the best treatment. This study is the first to address the efficacy of therapeutics for advanced EGFR-mutant NSCLC with state-of-the art Bayesian methods. The conclusions are also strengthened by the highest level of evidence. Finally, this study is based on multivariable, time-varying HRs that assumed proportional hazards, examined the relative treatment efficacy based on parameters of survival plots (shape and scale), and considered the influence of time [67]. Network studies regarding relative risks or odds ratios do not have these strengths.

There are also several limitations that should be acknowledged. First, one or two studies were omitted from the treatment-level and medication-level analyses for not contributing to a complete network loop. Although the credibility of our conclusion might not be maximized, the omitted studies had little impact on our final results. Second, the results on ORR and DoR might not be as well reported because of the limited study number. Additionally, potential AEs could influence our judgment on the preferred treatment. Third, the OS outcome was not as comprehensively reported by the primary studies as PFS, and the results based on statistical data still need clinical validation.

CONCLUSIONS

This is the first Bayesian NMA to show promising, significant efficacy and safety for Erlo+Bev, Erlo+Bev+Plat and Osi over other available treatments for advanced EGFR-mutant NSCLC, considering the balance between PFS and OS. Erlo+Bev and Osi are the top-ranked regimens for patients with either 19 del or 21 L858R mutations. Accordingly, the three strategies can be reasonably recommended to these intended patients based on their effectiveness. However, their AEs should also be determined in real clinical practice. IT+aVEGFR+Plat is a potential superior regimen but still needs to be confirmed by more clinical trials. The current study not only provides evidence for the use of Erlo+Bev but also addresses the landscape of the use of Osi in advanced EGFR-mutant NSCLC. In the future, more evidence is needed to develop novel therapies and

to identify the best treatment options for patients according to their NSCLC subtype and for those with site-specific metastases.

MATERIALS AND METHODS

This article was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analyses of health care interventions (Appendix Table 1 in the Supplementary Data). The protocol was registered with PROSPERO (CRD42019137033).

Search strategy

Related published trials were identified after a rigorous literature search in PubMed, EMBASE, Cochrane Library and Clinical Trials.gov from their inception to September 2019. The key terms used were "EGFR mutant", "non-small cell lung cancer", "NSCLC", and "randomized controlled trials" (Appendix Material and Methods in the Supplementary Data). No language restrictions were applied. Reference lists were searched manually for additional records.

Selection criteria

All published RCTs involving adult patients (≥18 years) whose Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 and comparing any systematic interventions (pharmaceutical, surgical, radiological, combinations, etc.) for histologically or cytologically confirmed advanced (stage III/IV/ recurrent/distant metastasis (brain, liver, bone, etc.)) EGFR-mutant NSCLC was identified. There were no mandatory restrictions on first-line treatment settings or other-line settings. The included patients within the selected trials must have positive and clear advanced EGFR-mutant cancer diagnoses. The duration period of the eligible trials was no less than 6 months. No further restrictions were applied on other individual-level (i.e., age, sex) or program-level characteristics (i.e., start year, follow-up period). If a multi-arm trial compared one treatment to two or more different treatments, we extracted every arm/comparison. The most recent and informative publication was selected to avoid duplications. We excluded trials comparing different administration schemes with the same drug or combinations. Dose-expansion trials, reviews, and fundamental experiments were also excluded.

Definitions of outcomes and treatment arms

In this study, the primary outcomes were PFS and OS according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The secondary outcomes were objective response rate (ORR), duration of response (DoR, month) and grade 3 or higher adverse events (AEs) (severe AEs). Eligible studies should report at least one of both clinical outcomes. EGFR mutations included exon 19 deletion (19 del), exon 21 Leu858Arg mutation (21 L858R) and other uncommon mutations (19 del and 21 L858R were the main focus) [47].

To organize the current treatment options in clinical trials into clinically meaningful arms, we used general prespecified criteria, as shown in Table 1. Cilengitide (Cil) and cetuximab (Cet) are seldom used in NSCLC, and for statistical convenience and network simplification, Cil is categorized in the aVEGFR class, and Cet is categorized in the ET class [48].

Data extraction and quality assessment

Relevant data were independently extracted by two investigators following our prespecified protocol. Any discrepancies were resolved by discussion with a third investigator. The extracted information included characteristics of the eligible trials (publication year, first author, trial name, follow-up period, number of arms, etc.), characteristics of the populations (mean age, number of enrolled patients, etc.), and characteristics of the program (types of systematic interventions, outcomes of intended endpoints, registration information, etc.). Outcome estimates were extracted using fully adjusted models. Additionally, we contacted the authors if there were any missing data. If we received no response, the analysis was performed without these data. Intent-to-treat data were used when available.

The risk of bias of the included RCTs was assessed using the modified Cochrane Collaboration's risk of bias tool [49]. The two coauthors performed a quality assessment on all the included RCTs. In the case of disagreements, the two authors rechecked the original articles, and a consensus was achieved after a discussion.

Statistical analysis

For PFS and OS, the hazard ratios (HRs) and confidence intervals (CIs) were directly extracted from the original studies or were calculated by methods provided by Tierney et al. [50]. We also tried to contact the authors if the study provided only figures without exact data. If the authors did not respond, the program Engauge Digitizer 4.1 (http://digitizer.sourceforge.net) was run to extract the exact data from the figures. Odd ratios (ORs) for ORR and grade 3 or higher AEs were manually calculated based on extracted information.

A Bayesian network meta-analysis (NMA) was performed with a random effects model to estimate the HR and 95% credible interval (95% CrI) for direct and indirect evidence on advanced EGFR-mutant NSCLC by combining multiple systematic arms across studies with all the information regarding PFS and OS. In the case of multi-arm trials (trials with three or more interventions), adjustments were made to preserve randomization and correlation within the multi-arm trials by converting log-HRs to log-hazards. ORs and 95% CrI in the random effects model were prepared for ORR and grade 3 or higher AEs for direct and indirect evidence; the mean difference (MD) and 95% CrI in random effects was conducted for DoR because DoR was regarded as a continuous variable. Following the Cochrane Handbook [49], the standard deviation (SD) was roughly computed by the (Xmax-Xmin)/range difference for further analysis.

The Markov chain Monte Carlo (MCMC) method was used to estimate the posterior distribution of each parameter, and the fit of the random effects model was assessed by the deviance information criteria (DIC) [51, 52]. A hierarchical Bayesian model synthesizes comparisons between the treatment pairs and simultaneously summarizes all outcomes of interest by assuming a common heterogeneity parameter (a derived I^2 statistic > 50% or a P value for Cochran Q chi-square test <0.1 was regarded as indicating significant heterogeneity) [53, 54]; the inconsistency of this model was evaluated by the edge-splitting method based on all direct and indirect evidence [54]. To confirm the robustness of our findings, sensitivity analyses were performed with studies restricted to phase III trials, studies excluding Reck et al. [45] and Soria et al. [42], respectively and Asian and non-Asian studies. The relative treatment rankings were graphically displayed with rankograms [55].

In the Bayesian context, the statistical significance of HRs and ORs was established when the 95% CrI did not contain 1, and that of MDs was established when it did not contain 0. Calculations were performed in R version 3.5.3 (https://www.r-project.org) using the gemtc and rjags packages, which are publicly available. The detailed statistical methods are provided in the Appendix Material and Methods in the Supplementary Data.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Abbreviations

EGFR: epidermal growth factor receptor; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC: non-small cell lung cancer; RCT: randomized controlled trials; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; DoR: duration of response; NMAs: network meta-analyses; HR: hazard ratio; OR: odd ratio; MD: mean difference; CrI: credible interval; SD: standard deviation; Gef: gefitinib; Erlo: erlotinib; Ico: icotinib; Afa: afatinib; Dac: dacomitinib; Osi: osimertinib; Naq: naquotinib; Bev: bevacizumab; Ona: onartuzumab; Tiv: tivantinib; Sun: sunitinib; Peme: pemetrexed; Cil: cilengitide; Cet: cetuximab; Plat: platinum-based therapy; Mot: motesanib; Doc: docetaxel; Vin: vinorelbine; WBRT: whole-brain radiotherapy; ET: EGFR-TKI; VEGF: vascular endothelial growth factor ; VEGFR: vascular endothelial growth factor receptor; MT: MET-TKI; CT: cytotoxic therapy; 19 del: exon 19 deletion; 21 L858R: 21 L858Arg mutation; ESMO: the European Society for Medical Oncology; ASCO: the American Society of Clinical Oncology; FDA: food and drug administration; NCCN: National Comprehensive Cancer Network; DIC: deviance information criteria; MCMC: The Markov Chain Monte Carlo; CNS: central nervous system; PD-L1: the programmed cell death-ligand 1; TMB: tumor mutational burden; AEs: adverse events.

AUTHOR CONTRIBUTIONS

All authors designed and conducted this review. Xinmin Zeng, and Binghao Zhao wrote the paper. Xinmin Zeng and Qinghua Zeng helped the study design. Wenxiong Zhang revised the statistical methodology. Qinghua Zeng and Binghao Zhao had primary responsibility for the final content. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIALS

Supplementary Materials and Methods

This article was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analysis for health care. The protocol was registered with PROSPERO (CRD42019137033).

Search strategy

Relating published trials were identified after a rigorous literature search on PubMed, EMBASE, Cochrane Library and Clinical Trials.gov from inception to Sep 2019. The key items used were "EGFR mutant", "EGFR mutation", "non-small cell lung cancer", "NSCLC", "randomized controlled trials". No restrictions were applied on language. Reference lists were searched manually for additional records [1, 2].

\# Comprehensive searches were conducted in four electronic databases:

(1) PubMed/Medline (NLM)
(2) EMBASE (Elsevier)
(3) Cochrane Library (CENTRAL/Wiley)
(4) Clinical Trials.gov (NIH)

The literature search strategy was developed first in PubMed and then translated to the other databases. A combination of relevant keywords and controlled vocabulary (MeSH - Medical Subject Headings in PubMed and Emtree in EMBASE) were used in the PubMed and EMBASE searches. Comparable keyword search strategies were used in Cochrane Central Register of Controlled Trials (CENTRAL) and Clinical Trials.gov [3].

No date or language restrictions were applied. Results were limited to Human clinical trials. MEDLINE records were excluded from EMBASE results sets.

\# Four component concepts made up the search strategy:

(1) NSCLC
(2) EGFR-mutant
(3) Advanced cancer
(4) RCTs

Before total search, we used the Cochrane Childhood Cancer Group search strategy for *Cancer* in PubMed: (and adapted it to the other databases) for more restrictions and precision.(cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant).

For search set #4, we used Cochrane Handbook recommended search filters for finding RCTs.

Search filters were used for finding RCTs in PubMed and EMBASE. Available database limiters were used in Cochrane CENTRAL (Trials)

http://work.cochrane.org/pubmed
sensitivity- and precision-maximizing version (2008 revision); PubMed format

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])

http://work.cochrane.org/embase
Embase search strategy for finding RCTs in Embase

('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti)

Each of the four components of the search strategy was first searched upon individually, combining synonyms describing that concept with the Boolean operator OR. The four individual component search sets were then combined together using the Boolean operator AND.

Resulting citations were managed and duplicates removed using the Endnote citation management software program X8 (Thomson Reuters).

PubMed/MEDLINE Search Strategy	
1 non-small cell lung cancer (NSCLC)	("Carcinoma, non-small cell lung"[Mesh] OR "carcinomas, non-small cell lung" OR "lung carcinoma, non-small cell" OR " lung carcinomas, non-small cell " OR "non-small cell lung carcinomas" OR "nonsmall cell lung cancer" OR "non-small-cell lung carcinoma" OR "non small cell lung carcinoma" OR "carcinoma, non-small cell lung " OR "non-small cell lung cancer")
2 EGFR mutant	("EGFR" OR "EGFR-mutant" OR "EGFR mutations" OR "egfr" OR "aerobic capacity" OR " epidermal growth factor receptor" OR

	"EGFR-mutant patients" OR "patients with EGFR mutations")
3 Advanced	("Advanced" OR "terminal" OR "late" OR "late stage" OR " stage IIIA " OR " stage IIIB" OR " stage III" OR " stage IV" OR "metastasis" OR "recurrent" OR "recurrence")
4 RCT	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])
5	(animals[mh] NOT humans [mh])
6	1 AND 2 AND 3 AND 4
7	6 NOT 5

Abbreviations: Mesh = Medical Subject Heading, pt = Publication Type, tiab = Title/Abstract, ti = Title, mh = MeSH Terms.

Selection criteria

All the published RCTs of adult patients (≥18 year) whose ECOG status was 0 or 1 that compared any systematic interventions (pharmaceutical, surgical, radiological, combinations etc.) for advanced EGFR-mutant NSCLC were identified. No mandatory restrictions on first-line treatment settings or other-line settings. The included patients within selected trials must have positive and clear advanced EGFR mutant cancer diagnoses. Duration period of eligible trials should not be less than 1 year. No further restrictions were applied on other individual-level and program-level characteristics. If a multi-arm trial compared one treatment to two or more different treatments, we extracted every arm/comparison respectively. The most recent and informative publication was selected for avoiding duplication. We excluded trials comparing different administration schemes with the same drug or combinations. Dose-expansion trials, reviews, fundamental experiments were also excluded.

Definitions of outcomes and treatment arms

In this study, the primary outcomes were PFS and overall survival (OS) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The secondary outcomes were objective response rate (ORR), duration of response (DoR, month) and grade 3 or higher adverse events (AEs) (severe AEs). Eligible studies should report at least one of the both clinical outcomes. EGFR mutations include regular exon 19 deletion (19 del) and exon 21 Leu858Arg mutation (21 L858R) and other uncommon mutations (19 del and 21 L858R were mainly focused).

To organize the current treatment options took in clinical trials into clinically meaningfully arms, we used general prespecified criteria. Systematic treatments in the study were summarized as treatment level and medication class level. Treatment level included: gefitinib (Gef), erlotinib (Erlo), icotinib (Ico), afatinib (Afa), dacomitinib (Dac), osimertinib (Osi), naquotinib (Naq), erlotinib+bevacizumab (Erlo+Bev), onartuzumab+erlotinib (Ona+Erlo), erlotinib+tivantinib (Erlo+Tiv), sunitinib+erlotinib (Sun+Erlo), gefitinib+pemetrexed (Gef+Peme), cilengitide+cetuximab+platinum-based therapy (Cil+Cet+Plat), cetuximab+bevacizumab+platinum-based therapy (Cet+Bev+Plat), cetuximab+platinum-based therapy (Cet+Plat), erlotinib+platinum-based therapy (Erlo+Plat), motesanib+platinum-based therapy (Mot+Plat), platinum-based therapy (Plat), docetaxel (Doc), vinorelbine (Vin), whole-brain radiotherapy (WBRT) and placebo.

Medication class level included: first generation EGFR-TKI (1st-gen ET), second generation EGFR-TKI (2nd-gen ET), third generation EGFR-TKI (3rd-gen ET), EGFR-TKI+anti-VEGFR (ET+aVEGFR), MET-TKI+EGFR-TKI (MT+ET), immunotherapy+platinum-based therapy (IT+Plat), immunotherapy+anti-VEGFR+platinum-based therapy (IT+aVEGFR+Plat), EGFR-TKI+platinum-based therapy (ET+Plat), anti-VEGFR+platinum-based therapy (aVEGFR+Plat), EGFR-TKI+anti-VEGFR+platinum-based therapy (ET+aVEGFR+Plat), EGFR-TKI+anti-VEGFR+platinum-based therapy (ET+aVEGFR+Plat), EGFR-TKI+cytotoxic therapy (ET+CT), platinum-based therapy (Plat), cytotoxic therapy (CT), whole-brain radiotherapy (WBRT), and placebo.

Actually, cilengitide and cetuximab were rarely used in NSCLC, for the statistical convenience and the network simplification, cilengitide was regarded as aVEGFR class and cetuximab was outlined into ET class.

Data extraction and quality assessment

Relevant data were extracted by two independent investigators following our prespecified protocol. Any discrepancies would be resolved by a discussion with a third investigator. The extracted information included: characteristics of the eligible trials (publication year, the first author, trial name, follow-up period, number of arms etc.), characteristics of the populations (mean age, number of enrolled patients etc.), characteristics of the program (types of systematic interventions, outcomes of intended endpoints, registration information etc.). Outcome estimates were extracted in fully adjusted models. Additionally, we contacted the authors if there were any miss data. If we received no response, analysis was performed without these data. Intent-to-treat data were used when available.

Risk of bias of included RCTs was assessed using the modified Cochrane Collaboration's Risk-of-Bias Tool [3]. Two coauthors performed quality assessment on all the included RCTs. The Cochrane Risk of Bias Tool was adopted to assess risk of bias for each RCT. Seven items were used to evaluate heterogeneity in each trial: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The quality of each study was categorized as high, low, or unclear. In case of disagreement, the two authors would recheck the original articles and a consensus would be achieved after a discussion.

Statistical analysis

For PFS and OS, the hazard ratios (HR) and confidence intervals (CI) were directly extracted from the original studies or were calculated by methods provided by Tierney et al [4]. We also tried to contact the authors if the study provided only figures without exact data. In case the authors did not respond, the program Engauage Digitizer 4.1 (http://digitizer.sourceforge.net) was run to extract the exact data from the figures. This program can calculate clear values by digitizing data points from an image file after the manual setting of the coordinate axis. Odd ratios (ORs) for ORR and grade 3 or higher AEs were manually calculated based on extracted information.

A Bayesian network meta-analysis (NMA) was performed with a random effects model to estimate the HR and 95% credible interval (95% CrI) for direct and indirect evidence on advanced EGFR-mutant NSCLC by combining multiple systematic arms across studies with all the information regarding PFS and OS. In the case of multi-arm trials (trials with three or more interventions), adjustments were made to preserve randomization and correlation within the multi-arm trials by converting log-HRs to log-hazards. ORs and 95% CrI in random effects model were prepared for ORR and grade 3 or higher AEs for direct and indirect evidence; mean difference (MD) and 95% CrI in random effects was conducted for DoR, because DoR was a continuous variable. Following Cochrane Handbook, standard deviation (SD) was roughly computed by (Xmax-Xmin)/range difference for further analysis. The Markov Chain Monte Carlo (MCMC) method was used to estimate the posterior distribution of each parameter, the fit of the random effects model was assessed by the deviance information criteria (DIC) [5–8]. A three-chain model with non-informative priors was run with an adaptation phase of 10000 iterations followed by 100000 model iterations. The thin ratio was set to 10. Non-convergence was assessed by the Gelman-Rubin statistic. Relative treatment rankings (probability for each treatment to be the most effective (first best regime), the second best, the third best and so on) were displayed graphically with rankograms, which indicated the probable best and worst therapies [9]. A hierarchical Bayesian model synthesizes comparisons between the treatment pairs and simultaneously summarizes all outcomes of interest by assuming a common heterogeneity parameter (a derived I^2 statistic > 50% or a P value for Cochran Q chi-square test <0.1 was regarded as indicating significant heterogeneity), the inconsistency of this model was evaluated by the edge-splitting method based on all direct and indirect evidence [3, 8]. Trace, density and comsol estimations/plots were used to inspect the uncertainty of the MCMC model [5–8]. To confirm the robustness of our findings, sensitivity analyses were performed restricted on phase III trials, studies excluding Reck et al, 2019 and excluded Soria et al, 2018 respectively and Asian and non-Asian.

In the Bayesian context, statistical significance of HRs and ORs was established when the 95% CrI did not contain 1, of MDs was established when did not contain 0. Calculations were performed in R version 3.5.3 (https://www.r-project.org) using the gemtc and jag etc. public packages.

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Appendix Figures
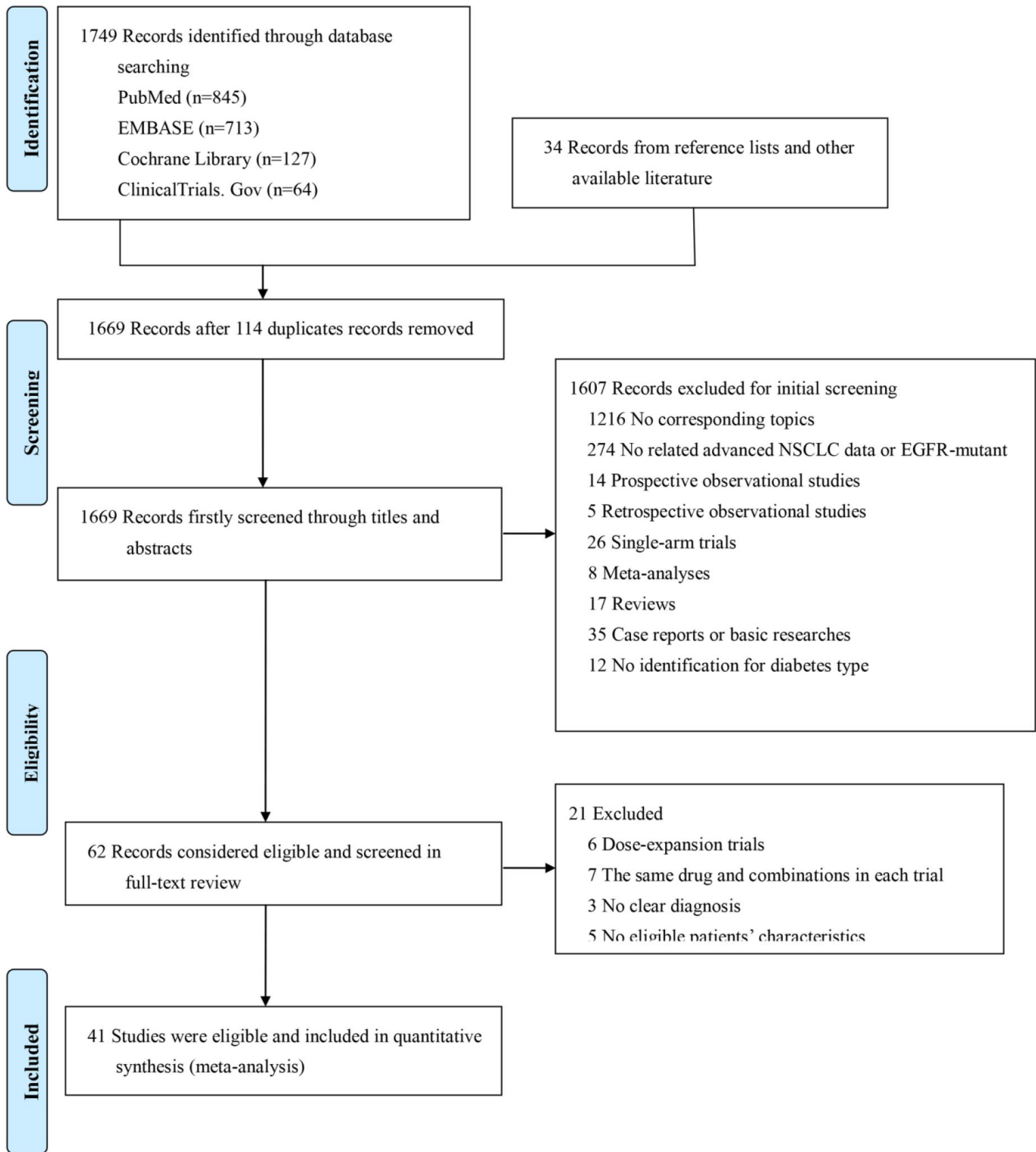
Appendix Figure 1. Study flow chart.
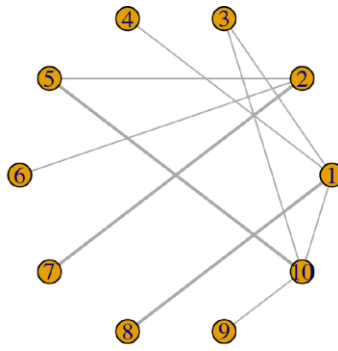
1 = Gef   2 = Erlo   3 = Afa   4 = Dac   5 = Osi   6 = Naq   7 = Erlo + Bev   8 = Gef + Peme   9 = Cet + Plat   10 = Plat

Appendix Figure 2. Network plot for ORR in treatment-level analysis.
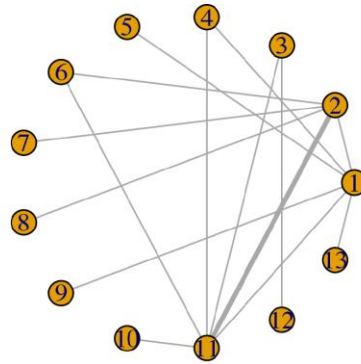
1 = Gef   2 = Erlo   3 = Ico   4 = Afa   5 = Dac   6 = Osi   7 = Naq

8 = Erlo + Bev   9 = Gef + Peme   10 = Cet + Plat   11 = Plat

12 = WBRT   13 = Placebo

Appendix Figure 3. Network plot for grade 3 or higher AEs in treatment-level analysis.
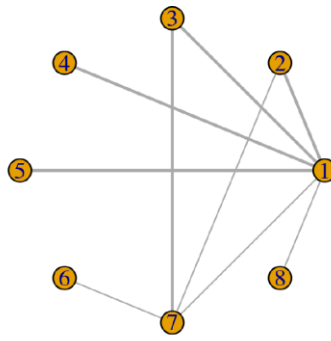
1 = 1st gen ET   2 = 2nd gen ET   3 = 3rd gen ET   4 = ET + aVEGFR

5 = ET + CT   6 = ET + Plat   7 = Plat   8 = WBRT

Appendix Figure 4. Network plot for ORR in class-level analysis.
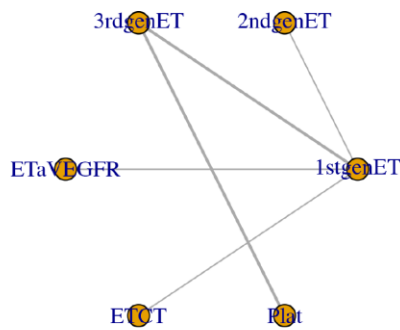
Treatments include: **1st gen ET**, **2nd gen ET**, **3rd gen ET**, **ET + aVEGFR**,

ET + CT, **Plat**

Appendix Figure 5. Network plot for DoR in class-level analysis.
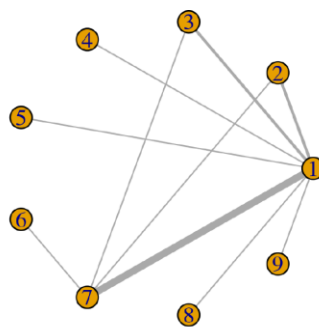
1 = 1st gen ET   2 = 2nd gen ET   3 = 3rd gen ET   4 = ET + aVEGFR

5 = ET + CT   6 = ET + Plat   7 = Plat   8 = WBRT   9 = Placebo

Appendix Figure 6. Network plot for grade 3 or higher AEs in class-level analysis.

Appendix Tables

Please browse Full Text version to see the data of Supplementary Tables 1, 2, 4, 5.

Appendix Table 1. PRISMA statements.

Appendix Table 2. Baseline characteristics of included studies in this Bayesian study.

Appendix Table 3. Cochrane Risk of Bias for the Included Studies.

	Randomization sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Crino, 2008[6]	+	+	?	?	+	+	+
Goss, 2009[7]	+	+	?	?	+	+	+
Mok , 2009[8]	+	+	-	-	+	+	+
Maemondo, 2010[9]	+	+	+	+	+	+	+
Zhou, 2011[10]	+	+	-	-	+	+	?
Gridelli, 2012[11]	+	+	-	-	+	+	+
Miller, 2012[12]	+	+	+	+	+	?	+
Pirker, 2012[13]	+	+	-	-	+	+	?
Rosell, 2012[14]	+	+	-	-	+	+	+
Scagliotti, 2012[15]	+	+	+	+	+	+	?
Zhang, 2012[16]	+	+	+	+	+	+	+
Shi, 2013[17]	+	+	+	+	?	+	+
Wu, 2013[18]	+	+	+	+	+	+	+
Ellis, 2014[19]	+	+	+	+	+	+	?
Kawaguchi, 2014[20]	+	+	-	-	+	+	?
Ramalingam, 2014[21]	+	+	+	+	+	+	+

Seto, 2014[22]	+	+	-	-	+	?	?
Wu, 2014[23]	+	+	-	-	+	+	+
Yang, 2014[24]	+	+	-	-	+	?	-
Scagliotti, 2015[25]	+	+	+	+	+	+	+
Soria, 2015[26]	+	+	?	?	+	+	?
Vansteenkiste , 2015[27]	+	+	-	-	+	+	?
Wu, 2015[28]	+	+	-	-	+	?	?
Zhou, 2015[29]	+	+	-	-	+	+	?
Cheng, 2016[30]	+	+	-	-	+	+	+
Park, 2016[31]	+	+	-	-	+	+	?
Urata, 2016[32]	+	+	-	-	+	+	+
Kubota, 2017[33]	+	+	+	+	+	+	+
Mok, 2017[34]	+	+	-	-	+	+	+
Shi, 2017[35]	+	+	-	-	+	?	?
Spigel, 2017[36]	+	+	+	+	+	+	+
Wu, 2017[37]	+	+	-	-	+	+	+
Yang (2), 2017[38]	+	+	-	-	+	+	?
Yang, 2017[39]	+	+	?	?	+	+	?
Herbst, 2018[40]	+	+	-	-	+	+	+
Mok, 2018[41]	+	+	-	-	+	+	?
Soria, 2018[42]	+	+	+	+	+	+	+
Wu, 2018[43]	+	+	-	-	+	+	+
Kelly, 2019[44]	+	+	-	-	+	+	?
Reck, 2019[45]	+	+	-	-	+	+	+
Saito, 2019[46]	+	+	-	-	?	+	-

'+', yes; '-', no; '?', unclear.

Appendix Table 4. Efficacy of all available interventions according to treatment-level Bayesian network analysis.

Appendix Table 5. Efficacy of all available interventions according to class-level Bayesian network analysis.

Appendix Table 6. ORR of all available interventions according to treatment-level Bayesian network analysis.

Gef								
2.22 (0.44-14.61)	Erlo							
0.67 (0.25-1.80)	0.30 (0.05-1.56)	Afa						
0.84 (0.26-2.71)	0.38 (0.04-2.79)	1.26 (0.28-5.73)	Dac					
1.76 (0.53-7.49)	0.79 (0.24-2.53)	2.62 (0.79-10.86)	2.07 (0.40-13.87)	Osi				
4.14 (0.57-39.21)	1.87 (0.59-6.08)	6.22 (0.86-57.60)	4.90 (0.50-64.65)	2.37 (0.46-12.50)	Naq			
1.68 (0.27-13.68)	0.76 (0.31-1.82)	2.50 (0.40-20.46)	1.99 (0.23-22.56)	0.95 (0.23-4.17)	0.40 (0.09-1.77)	Erlo + Bev		
0.86 (0.34-2.44)	0.39 (0.05-2.74)	1.29 (0.34-5.32)	1.01 (0.23-5.02)	0.49 (0.09-2.37)	0.21 (0.02-1.98)	0.51 (0.05-4.30)	Gef + Peme	
2.52 (0.56-11.83)	1.13 (0.16-6.68)	3.77 (0.81-17.54)	3.01 (0.44-21.60)	1.44 (0.30-5.72)	0.61 (0.06-4.92)	1.51 (0.17-10.61)	2.94 (0.45-17.49)	Cet + Plat
<u>5.14 (1.96-14.10)</u>	2.32 (0.48-8.90)	7.67 (2.93-20.68)	6.10 (1.34-29.20)	2.93 (1.10-6.37)	1.25 (0.17-7.18)	3.06 (0.50-14.90)	6.02 (1.42-23.13)	2.04 (0.62-6.58)	Plat

Note: Results for objective response rate (ORR) are shown in blue-colour cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. ORs (and 95% CrI) more than 1 favour the column-defining treatment (the column-defining treatment has superior ORR). To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.
Abbreviations: Gef: gefitinib; Erlo: erlotinib; Dac: dacomitinib; Afa: afatinib; Osi: osimertinib; Naq: naquotinib; Erlo+Bev: erlotinib+bevacizumab; Gef+Peme: gefitinib+pemetrexed; Cet+Plat: cetuximab+platinum-based therapy; Plat: platinum-based therapy.

Appendix Table 7. Results of eligible studies on grade 3 or higher AEs.

Study	Intervention	Control	AEs in intervention arm	AEs in control arm	OR value
Saito et al, 2019[46] (Japan)	erlotinib + bevacizumab (112)	erlotinib (112)	88% (98/112)	46% (53/114)	8.06 (4.12-15.75)
Kelly et al, 2019[44] (America)	naquotinib (267)	gefitinib/erlotinib (263)	46% (122/267)	25.6% (67/262)	2.45 (1.70-3.54)
Soria et al, 2018[42] (multiple nations)	osimertinib (279)	gefitinib/erlotinib (277)	32% (89/279)	41% (114/271)	0.65 (0.46-0.91)
Yang et al, 2017[39] (China)	erlotinib (128)	gefitinib (128)	0% (0/128)	4.6% (6/128)	0.16 (0.02-1.35)
Yang et al (2), 2017[38] (China)	icotinib (85)	WBRT (73)	8% (7/85)	38% (28/73)	0.14 (0.06-0.36)
Wu et al, 2017[37] (multiple nations)	dacomitinib (227)	gefitinib (225)	63% (143/227)	41% (92/224)	2.44 (1.67-3.57)
Shi et al, 2017[35] (China)	icotinib (148)	cisplatin+pemetrexed (137)	0.7 % (1/148)	5.8% (8/137)	0.11 (0.01-1.89)
Mok et al, 2017[34] (multiple nations)	osimertinib (279)	pemetrexed+carboplatin/ cisplatin (140)	9% (34/279)	53.7% (73/136)	0.12 (0.07-0.20)
Park et al, 2016[31] (multiple nations)	afatinib (160)	gefitinib (159)	31% (50/160)	18% (29/159)	2.04 (1.21-3.44)
Cheng et al, 2016[30] (multiple nations)	gefitinib+pemetrexed (126)	gefitinib (65)	42% (53/126)	19% (12/65)	3.21 (1.56-6.58)
Wu et al, 2015[28] (China)	erlotinib (110)	gemcitabine/cisplatin (107)	40% (44/110)	56.7% (59/104)	0.51 (0.30-0.88)
Soria et al, 2015[26] (multiple nations)	gefitinib (133)	placebo (132)	45% (59/132)	47% (55/132)	1.13 (0.70-1.84)
Wu et al, 2014[23] (multiple nations)	afatinib (242)	cisplatin+gemcitabine (122)	36% (86/239)	60.2% (68/113)	0.37 (0.23-0.59)
Rosell et al, 2012[14] (multiple nations)	erlotinib (86)	cisplatin+docetaxel/ gemcitabine (87)	45% (38/84)	67% (55/82)	0.41 (0.22-0.76)
Pirker et al, 2012[13] (multiple nations)	cetuximab+cisplatin+ vinorelbine (178)	cisplatin+vinorelbine (167)	87% (153/175)	90% (151/168)	0.78 (0.40-1.53)
Zhou et al, 2011[10] (China)	erlotinib (82)	gemcitabine+carboplatin (72)	17% (14/83)	65% (47/72)	0.11 (0.05-0.23)
Maemondo et al, 2010[9] (Japan)	gefitinib (114)	carboplatin+paclitaxel (114)	41.2% (47/114)	71.7% (81/113)	0.28 (0.16-0.48)

Abbreviation: AE: adverse events.

Appendix Table 8. Grade 3 or higher AEs of all available interventions according to treatment-level Bayesian network analysis.

Gef												
1.52 (0.41-9.54)	**Erlo**											
4.52 (0.24-NA)	2.83 (0.15-107.80)	**Ico**										
0.67 (0.15-3.61)	0.45 (0.06-2.28)	0.15 (0.003-3.16)	**Afa**									
0.41 (0.06-2.99)	0.27 (0.02-2.57)	0.09 (0.001-3.00)	0.61 (0.04-6.93)	**Dac**								
2.58 (0.45-23.67)	1.71 (0.37-7.30)	0.59 (0.01-13.45)	3.81 (0.53-36.59)	6.32 (0.50-130.80)	**Osi**							
0.72 (0.07-12.15)	0.48 (0.07-3.43)	0.16 (0.003-5.75)	1.06 (0.09-19.10)	1.75 (0.09-56.96)	0.28 (0.02-3.42)	**Naq**						
0.18 (0.02-3.13)	**_0.12 (0.02-0.94)_**	0.04 (0.001-1.56)	0.27 (0.02-4.92)	0.45 (0.02-14.84)	**_0.07 (0.005-0.92)_**	0.25 (0.01-4.46)	**Erlo + Bev**					
0.30 (0.04-2.33)	0.20 (0.01-2.03)	0.07 (0.001-2.35)	0.44 (0.03-5.54)	0.74 (0.04-12.85)	0.12 (0.005-1.60)	0.42 (0.01-8.40)	1.64 (0.05-34.07)	**Gef + Peme**				
0.44 (0.04-6.42)	0.29 (0.03-2.66)	0.10 (0.002-2.93)	0.66 (0.06-9.74)	1.08 (0.05-31.43)	0.17 (0.01-2.06)	0.62 (0.03-11.77)	2.44 (0.10-46.58)	1.47 (0.07-46.40)	**Cet + Plat**			
0.34 (0.10-1.68)	**_0.23 (0.07-0.58)_**	0.08 (0.002-1.16)	0.51 (0.12-2.63)	0.84 (0.09-11.47)	**_0.13 (0.03-0.56)_**	0.48 (0.05-4.03)	1.88 (0.17-17.01)	1.15 (0.11-16.61)	0.77 (0.10-5.88)	**Plat**		
0.64 (0.02-51.08)	0.40 (0.01-25.27)	0.14 (0.02-1.12)	0.93 (0.02-76.56)	1.57 (0.02-192.40)	0.24 (0.005-17.54)	0.86 (0.01-78.54)	3.41 (0.05-NA)	2.12 (0.03-NA)	1.40 (0.03-132.70)	1.81 (0.05-106.70)	**WBRT**	
1.13 (0.15-8.31)	0.75 (0.04-7.33)	0.25 (0.01-8.52)	1.68 (0.12-19.88)	2.78 (0.17-47.19)	0.44 (0.02-5.78)	1.58 (0.05-30.47)	6.21 (0.18-128.00)	3.76 (0.22-68.63)	2.57 (0.09-52.73)	3.31 (0.24-32.34)	1.77 (0.01-107.60)	**Placebo**

Note: Results for grade 3 or higher adverse events (AEs) in individual-treatment level are shown in blue-colour cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. ORs (and 95% CrI) less than 1 favour the column-defining treatment, which shows the column-defining treatment has less grade 3 or higher AEs. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.

Abbreviations: Gef: gefitinib; Erlo: erlotinib; Ico: icotinib; Dac: dacomitinib; Afa: afatinib; Osi: osimertinib; Naq: naquotinib; Erlo+Bev: erlotinib+bevacizumab; Gef+Peme: gefitinib+pemetrexed; Cet+Plat: cetuximab+platinum-based therapy; Plat: platinum-based therapy; WBRT: whole-brain radiotherapy; NA: not available.

Appendix Table 9. PFS and OS of all available interventions according to class-level Bayesian network analysis.

1st-gen ET	0.96 (0.54-2.14)	0.63 (0.24-1.68)	1.30 (0.56-2.98)	1.14 (0.47-3.43)	NA	NA	0.74 (0.24-2.20)	NA	0.63 (0.18-2.38)	NA	1.01 (0.58-1.72)	0.77 (0.30-2.09)	1.07 (0.39-2.97)	0.97 (0.48-2.50)
1.25 (0.73-2.07)	**2nd-gen ET**	0.66 (0.18-1.92)	1.34 (0.41-3.58)	1.17 (0.38-3.90)	NA	NA	0.77 (0.19-2.47)	NA	0.66 (0.14-2.59)	NA	1.05 (0.39-2.24)	0.78 (0.24-2.48)	1.12 (0.29-3.40)	1.01 (0.52-2.00)
1.27 (0.69-2.32)	1.02 (0.47-2.26)	**3rd-gen ET**	2.06 (0.56-7.47)	1.79 (0.52-8.36)	NA	NA	1.17 (0.26-5.15)	NA	1.00 (0.20-5.26)	NA	1.59 (0.52-4.90)	1.20 (0.33-5.08)	1.71 (0.42-7.03)	1.52 (0.49-6.31)
1.42 (0.71-2.83)	1.14 (0.49-2.75)	1.12 (0.44-2.82)	**ET+aVEGFR**	0.88 (0.26-3.56)	NA	NA	0.56 (0.15-2.26)	NA	0.48 (0.11-2.31)	NA	0.77 (0.29-2.10)	0.59 (0.18-2.23)	0.83 (0.22-3.08)	0.75 (0.26-2.75)
0.87 (0.21-3.51)	0.70 (0.16-3.09)	0.68 (0.15-3.18)	0.62 (0.13-2.88)	**MT+ET**	NA	NA	0.66 (0.13-2.40)	NA	0.56 (0.10-2.46)	NA	0.89 (0.26-2.41)	0.67 (0.17-2.46)	0.95 (0.20-3.42)	0.86 (0.24-2.98)
0.63 (0.11-3.65)	0.51 (0.08-3.09)	0.50 (0.08-3.13)	0.45 (0.07-2.95)	0.73 (0.08-7.14)	**IT+Plat**	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.19 (0.20-6.93)	0.95 (0.15-5.94)	0.94 (0.15-5.92)	0.84 (0.13-5.58)	1.36 (0.15-13.40)	1.87 (0.53-6.70)	**IT+aVEGFR+Plat**	NA	NA	NA	NA	NA	NA	NA	NA
0.92 (0.44-1.97)	0.74 (0.31-1.88)	0.73 (0.30-1.88)	0.65 (0.24-1.85)	1.07 (0.22-5.26)	1.45 (0.24-9.65)	0.77 (0.12-5.08)	**ET+Plat**	NA	0.85 (0.43-1.78)	NA	1.37 (0.53-3.58)	1.03 (0.26-4.72)	1.46 (0.33-6.42)	1.31 (0.38-5.88)
0.73 (0.20-2.64)	0.58 (0.15-2.31)	0.57 (0.15-2.28)	0.51 (0.12-2.21)	0.84 (0.13-5.74)	1.14 (0.35-3.77)	0.61 (0.18-2.04)	0.79 (0.19-3.16)	**aVEGFR+Plat**	NA	NA	NA	NA	NA	NA
1.24 (0.42-3.85)	1.00 (0.30-3.44)	0.87 (0.24-3.38)	1.44 (0.24-8.64)	1.96 (0.27-15.20)	1.05 (0.14-8.14)	1.35 (0.59-3.07)	1.71 (0.34-9.10)	0.84 (0.17-4.34)	**ET+aVEGFR+Plat**	NA	1.60 (0.48-5.10)	1.20 (0.26-6.20)	1.70 (0.32-8.68)	1.54 (0.37-7.99)
1.46 (0.47-4.73)	1.17 (0.34-4.28)	1.16 (0.32-4.41)	1.04 (0.28-4.09)	1.69 (0.28-10.60)	2.32 (0.28-19.00)	1.24 (0.15-10.40)	1.60 (0.40-6.39)	2.02 (0.36-11.40)	1.19 (0.23-5.84)	**ET+CT**	NA	NA	NA	NA
0.41 (0.28-0.61)	**0.33 (0.19-0.62)**	**0.33 (0.18-0.61)**	**0.29 (0.13-0.65)**	0.48 (0.11-2.06)	0.65 (0.12-3.63)	0.35 (0.06-1.98)	**0.45 (0.22-0.90)**	0.57 (0.17-1.94)	**0.33 (0.11-0.97)**	**0.28 (0.08-0.94)**	**Plat**	0.76 (0.27-2.43)	1.07 (0.34-3.40)	0.97 (0.41-2.89)
1.53 (0.61-3.87)	1.23 (0.43-3.57)	1.21 (0.41-3.67)	1.08 (0.34-3.48)	1.77 (0.33-9.37)	2.42 (0.34-17.60)	1.29 (0.18-9.49)	1.66 (0.50-5.38)	2.11 (0.43-10.30)	1.23 (0.29-5.19)	1.04 (0.23-4.53)	3.69 (1.34-10.01)	**CT**	1.41 (0.33-5.34)	1.29 (0.38-4.70)
0.56 (0.17-1.85)	0.45 (0.13-1.68)	0.44 (0.12-1.67)	0.40 (0.10-1.59)	0.65 (0.11-4.08)	0.88 (0.11-7.50)	0.47 (0.06-4.04)	0.61 (0.15-2.47)	0.77 (0.14-4.51)	0.45 (0.09-2.24)	0.38 (0.07-2.00)	1.35 (0.40-4.75)	1.13 (0.31-4.46)	**WBRT**	0.90 (0.27-3.77)
0.50 (0.27-0.89)	**0.40 (0.21-0.73)**	**0.39 (0.16-0.91)**	**0.35 (0.14-0.85)**	0.57 (0.12-2.59)	0.79 (0.12-4.90)	0.42 (0.06-2.63)	0.54 (0.20-1.36)	0.69 (0.16-2.72)	0.40 (0.11-1.37)	0.34 (0.09-1.19)	1.20 (0.58-1.19)	**0.32 (0.10-0.95)**	0.88 (0.22-3.27)	**Placebo**

Note: Results for PFS are shown in blue-colour cells, results for OS are in gray-color cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. For PFS and OS, HRs (and 95% CI) less than 1 favour the column-defining treatment. To obtain HRs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.

Abbreviations: 1st-gen ET: first generation EGFR-TKI; 2nd-gen ET, second generation EGFR-TKI; 3rd-gen ET: third generation EGFR-TKI; ET+aVEGFR: EGFR-TKI+anti-VEGFR; MT+ET: MET-TKI+EGFR-TKI; IT+Plat: immunotherapy+platinum-based therapy;

IT+aVEGFR+Plat: immunotherapy+anti-VEGFR+platinum-based therapy; ET+Plat: EGFR-TKI+platinum-based therapy; aVEGFR+Plat: anti-VEGFR+platinum-based therapy; ET+aVEGFR+Plat: EGFR-TKI+anti-VEGFR+platinum-based therapy; ET+CT: EGFR-TKI+cytotoxic therapy; Plat: platinum-based therapy; CT: cytotoxic therapy: WBRT: whole-brain radiotherapy; PFS: progression-free survival; OS: overall survival; HR: hazard-ratio; CI: confidence interval.

Appendix Table 10. ORR of all available interventions according to class-level Bayesian network analysis.

1st-gen ET							
0.71 (0.37-1.33)	2nd-gen ET						
1.38 (0.78-2.59)	1.96 (0.92-4.57)	3rd-gen ET					
0.76 (0.35-1.66)	1.08 (0.40-2.99)	0.55 (0.20-2.99)	ET + aVEGFR				
0.86 (0.35-2.21)	1.22 (0.42-3.90)	0.62 (0.21-1.87)	1.13 (0.34-3.91)	ET + CT			
2.27 (0.66-7.47)	3.22 (0.89-11.32)	1.64 (0.47-5.21)	2.99 (0.69-12.45)	2.66 (0.54-11.41)	ET + Plat		
4.65 (2.42-8.79)	**6.60 (3.14-13.78)**	**3.35 (1.70-6.09)**	**6.14 (2.19-16.81)**	**5.44 (1.67-15.96)**	2.06 (0.73-5.81)	Plat	
8.82 (2.79-29.56)	**12.52 (3.38-49.41)**	**6.33 (1.69-24.30)**	**11.64 (2.87-49.19)**	**10.28 (2.28-45.82)**	3.89 (0.74-21.81)	1.90 (0.52-7.58)	WBRT

Note: Results for objective response rate (ORR) are shown in blue-colour cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. ORs (and 95% CrI) more than 1 favour the column-defining treatment (the column-defining treatment has superior ORR). To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.
Abbreviations: 1st-gen ET: first generation EGFR-TKI; 2nd-gen ET: second generation EGFR-TKI; 3rd-gen ET: third generation EGFR-TKI; ET+aVEGFR: EGFR-TKI+anti-VEGFR; ET+CT: EGFR-TKI+cytotoxic therapy; ET+Plat: EGFR-TKI+platinum-based therapy; Plat: platinum-based therapy; WBRT: whole brain radiotherapy.

Appendix Table 11. Results of eligible studies on DoR.

Study	Intervention	Control	DoR of intervention arm (Mons)	DoR of control arm (Mons)
Saito et al, 2019[46] (Japan)	erlotinib + bevacizumab (112)	erlotinib (112)	13.5 (0.2–26.9)	12.1 (1.43–24.5)
		atezolizumab+carboplatin and paclitaxel (45)		5·6 (2·6–15·2)
		bevacizumab+carboplatin and paclitaxel (45)		4·7 (2·6–13·5)
Kelly et al, 2019[44] (America)	naquotinib (267)	gefitinib/erlotinib (263)	9.17 (5.45-NA)	9.03 (7.39-NA)
Wu et al, 2018[43] (multiple nations)	osimertinib (75)	platinum-pemetrexed (41)	8.9 (4.3-NA)	5.7 (4.4-5.7)
Soria et al, 2018[42] (multiple nations)	osimertinib (279)	gefitinib/erlotinib (277)	17.2 (13.8–22.0)	8.5 (7.3–9.8)
Wu et al, 2017[37] (multiple nations)	dacomitinib (227)	gefitinib (225)	14·8 (12·0–17·4)	8·3 (7·4–9·2)
Mok et al, 2017[34] (multiple nations)	osimertinib (279)	pemetrexed+carboplatin/cis platin (140)	9.7 (8.3-11.6)	4.1 (3.0-5.6)
Cheng et al, 2016[30] (multiple nations)	gefitinib+pemetrexed (126)	gefitinib (65)	16.2 (12.6-18.7)	10.9 (9.7-12.8)

Abbreviations: DoR: duration of response; NA: not available.

Appendix Table 12. DoR of all available interventions according to class-level Bayesian network analysis.

1st-gen ET					
-6.48 (-18.19 to 5.16)	2nd-gen ET				
-4.43 (-12.62 to 3.80)	2.09 (-12.16 to 16.42)	3rd-gen ET			
-1.36 (-13.18 to 10.23)	5.08 (-11.44 to 21.63)	3.04 (-11.29 to 17.31)	ET + aVEGFR		
-0.04 (-11.68 to 11.60)	6.46 (-9.97 to 22.94)	4.40 (-3.79 to 12.65)	1.36 (-15.13 to 17.78)	Plat	
-5.28 (-16.81 to 6.27)	1.22 (-15.28 to 17.66)	-0.84 (-15.06 to 13.50)	-3.87 (-20.38 to 12.47)	-5.25 (-21.64 to 11.28)	ET + CT

Note: Results for Duration of response (DoR) are shown in blue-colour cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. MDs (Mean Difference, MD and 95% CrI) more than 0 favour the column-defining treatment (the column-defining treatment has superior DoR). To obtain MDs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.

Abbreviations: 1st-gen ET: first generation EGFR-TKI; 2nd-gen ET: second generation EGFR-TKI; 3rd-gen ET: third generation EGFR-TKI; ET+aVEGFR: EGFR-TKI+anti-VEGFR; ET+CT: EGFR-TKI+cytotoxic therapy; Plat: platinum-based therapy.

Appendix Table 13. Grade 3 or higher AEs of all available interventions according to class-level Bayesian network analysis.

1st-gen ET								
0.49 (0.19-1.23)	2nd-gen ET							
1.09 (0.43-2.75)	2.24 (0.63-8.12)	3rd-gen ET						
0.12 (0.02-0.61)	0.25 (0.04-1.61)	**0.11 (0.02-0.72)**	ET + aVEGFR					
0.30 (0.06-1.57)	0.61 (0.09-4.15)	0.27 (0.04-1.84)	2.48 (0.25-26.12)	ET + CT				
0.28 (0.05-1.60)	0.57 (0.08-3.85)	0.25 (0.04-1.73)	2.33 (0.21-25.33)	0.94 (0.08-10.14)	ET + Plat			
0.22 (0.11-0.41)	0.45 (0.16-1.20)	**0.20 (0.07-0.53)**	1.81 (0.31-10.43)	0.73 (0.12-4.15)	0.78 (0.15-4.00)	Plat		
0.14 (0.02-0.77)	0.28 (0.04-2.04)	**0.13 (0.02-0.89)**	1.14 (0.10-12.42)	0.46 (0.04-4.87)	0.49 (0.04-5.91)	0.63 (0.10-4.16)	WBRT	
1.14 (0.24-5.60)	2.34 (0.38-14.82)	1.05 (0.17-6.52)	9.51 (1.00-92.27)	3.82 (0.39-37.26)	4.07 (0.39-45.12)	5.25 (0.98-29.83)	8.36 (0.81-87.95)	Placebo

Note: Results for grade 3 or higher adverse events (AEs) are shown in blue-colour cells. Comparisons should be read from left to right and the estimate is in the cell in common between the column-defining drugs and the row-defining treatment. ORs (and 95% CrI) less than 1 favour the column-defining treatment (the column-defining treatment has less grade 3 or higher AEs. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored.

Abbreviations: 1st-gen ET: first generation EGFR-TKI; 2nd-gen ET: second generation EGFR-TKI; 3rd-gen ET: third generation EGFR-TKI; ET+aVEGFR: EGFR-TKI+anti-VEGFR; ET+CT: EGFR-TKI+cytotoxic therapy; ET+Plat: EGFR-TKI+platinum-based therapy; Plat: platinum-based therapy; WBRT: whole brain radiotherapy.