Efficacy and safety of immune checkpoint inhibitors for individuals with advanced *EGFR*-mutated non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitors: a systematic review, meta-analysis, and network meta-analysis

Yi Zhao, Ying He*, Wei Wang*, Qi Cai*, Fan Ge*, Zisheng Chen*, Jianqi Zheng, Yuan Zhang, Hongsheng Deng, Ying Chen, Shen Lao, Hengrui Liang, Wenhua Liang†, Jianxing He†*

Summary

Background The clinical benefits of immune checkpoint inhibitor (ICI)-based treatments in treating individuals with advanced *EGFR*-mutated non-small-cell lung cancer (NSCLC) who have progressed on EGFR tyrosine-kinase inhibitors (TKIs) remain controversial. We aimed to review the literature to comprehensively investigate the individual and comparative clinical outcomes of various ICI-based treatment strategies in this population.

Methods In this systematic review and meta-analysis, we used single-arm, pairwise, and network meta-analytical approaches. We searched PubMed, Embase, Cochrane Library, Web of Science, ClinicalTrials.gov, and relevant international conference proceedings from database inception to Jan 31, 2024, without language restrictions, to identify eligible clinical trials that assessed ICI-based treatments for individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs. Studies considered eligible were published and unpublished phase 1, 2, or 3 clinical trials enrolling participants with histologically or cytologically confirmed advanced *EGFR*-mutated NSCLC who had progressed after at least one EGFR-TKI treatment, and that evaluated ICI-based treatment strategies on at least one of the clinical outcomes of interest. The primary outcome analysed was progression-free survival. The protocol is registered with PROSPERO, CRD42021292626.

Findings 17 single-arm trials and 15 randomised controlled trials, involving 2886 participants and seven ICI-based treatment strategies (ICI monotherapy, ICI plus chemotherapy [ICI-chemo], ICI plus antiangiogenesis [ICI-antiangio], ICI plus antiangiogenesis plus chemotherapy [ICI-antiangio-chemo], dual ICIs [ICI-ICI], dual ICIs plus chemotherapy [ICI-ICI-chemo], and ICI plus EGFR-TKI [ICI-TKI]), were included. Three of these strategies—ICI monotherapy, ICI-antiangio-chemo, and ICI-chemo—had sufficient data across the included studies to perform a pairwise meta-analysis. The pairwise meta-analysis showed that, compared with chemotherapy, ICI monotherapy led to shorter progression-free survival (hazard ratio [HR] 1·73 [95% CI 1·30–2·29], I^2=0%), whereas ICI-antiangio-chemo (HR 0·54 [0·44–0·67], I^2=0%) and ICI-chemo (HR 0·77 [0·67–0·88], I^2=0%) prolonged progression-free survival. The network meta-analysis showed that ICI-antiangio-chemo yielded the best progression-free survival results, with substantial benefits over ICI-chemo (HR 0·71 [95% credible interval 0·59–0·85]), ICI monotherapy (HR 0·30 [0·22–0·41]), and non-ICI treatment strategies including antiangio-chemo (HR 0·76 [0·58–1·00]) and chemotherapy alone (HR 0·54 [0·45–0·64]). ICI-antiangio-chemo was associated with higher risks of both any-grade and grade 3 or worse adverse events over ICI-chemo and chemotherapy in the network meta-analysis.

Interpretation For individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs, ICI-antiangio-chemo was identified as the optimal treatment option. The toxicity of this treatment was acceptable but needs careful attention. ICI-chemo showed appreciably greater efficacy than the standard-of-care chemotherapy. These findings clarified the roles of ICI-based treatment strategies in this difficult-to-treat refractory population, potentially complementing recent guidelines.

Funding None.

Lancet Oncol 2024; 25: 1347–56

Published **Online** August 16, 2024 https://doi.org/10.1016/S1470-2045(24)00379-6

*Co-first authors, contributed equally

†Co-leading authors, contributed equally

Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, National Clinical Research Centre for Respiratory Disease, Guangzhou, China (Y Zhao MD, Y He MD, W Wang MD, Q Cai MD, J Zheng MD, Y Zhang MD, H Deng MD, Y Chen BSN, S Lao MD, H Liang MD, Prof W Liang MD, Prof J He MD); **Department of Dermatology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China** (Y He); **Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China** (F Ge MD); **Department of Respiratory and Critical Care Medicine, The Affiliated Qingyuan Hospital (Qingyuan People's Hospital), Guangzhou Medical University, Qingyuan, China** (Z Chen MD)

Introduction

Approximately 40–50% of East Asian and 10–20% of White people with non-small-cell lung cancer (NSCLC) carry the *EGFR* mutation.[1,2] For these individuals, various EGFR tyrosine-kinase inhibitors (TKIs), including erlotinib and gefitinib (first-generation), afatinib and

Correspondence to:
Prof Jianxing He, Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, National Clinical Research Centre for Respiratory Disease, Guangzhou 510120, China
drjianxing.he@gmail.com

Research in context

Evidence before this study

In individuals with advanced *EGFR*-mutated non-small-cell lung cancer (NSCLC), durable benefits of EGFR tyrosine-kinase inhibitors (TKIs) remain a challenge owing to the inevitable development of acquired resistance. Previous evidence has revealed the insufficient efficacy of immune checkpoint inhibitors (ICIs) as salvage therapies in individuals with resistance to tyrosine-kinase inhibitors. However, it remains unclear whether these individuals could benefit from the combination of ICIs with other treatments, including chemotherapies, antiangiogenic therapies, and EGFR-TKIs. We conducted a comprehensive meta-analysis using single-arm, pairwise, and network approaches to evaluate the individual and comparative clinical outcomes of various ICI-based treatment strategies in individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs. We searched PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov, and relevant international conference proceedings for clinical trials from database inception to Jan 31, 2024, using terms including "EGFR", "NSCLC", "immunotherapy", "immune checkpoint inhibitor", "PD-1", "PD-L1", and "CTLA-4" (full names and abbreviations), without language restrictions.

Added value of this study

This study, to our knowledge, is the first to summarise the efficacy and safety of all ICI-based treatment strategies, including ICI monotherapy and its combinations with other treatments, in individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs. Our findings indicate that, for this population, ICI combined with chemotherapy resulted in improved outcomes compared with standard-of-care chemotherapy alone. Addition of antiangiogenic therapy to the ICI-chemotherapy combination further prolonged progression-free survival. However, the increased toxicity of this treatment approach should be carefully considered as it caused more adverse events than chemotherapy or ICI combined with chemotherapy. Subgroup analyses underscore the importance of using a personalised approach to these ICI-based treatment strategies according to PD-L1 expression level, *EGFR* mutation type, and Thr790Met mutation status.

Implications of all the available evidence

Our study clarified the roles of ICI-based treatment strategies in individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs. Our findings will potentially aid the decision-making process and complement recent treatment guidelines for this difficult-to-treat population.

dacomitinib (second-generation), and osimertinib (third-generation), have been established as the upfront standard-of-care treatments.[3] However, acquired resistance inevitably occurs in almost all responding individuals, with a median progression-free survival of 10–14 months for first-generation and second-generation and 18·9 months for third-generation EGFR-TKIs in a first-line setting.[4–8] Although third-generation EGFR-TKIs can be an effective salvage therapy for individuals with a Thr790Met mutation—emerging in 50% or more patients progressing on earlier-generation EGFR-TKIs—their efficacy remains low due to other resistance factors, such as *MET* amplification.[9,10]

The advancement of immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1, or CTLA-4 checkpoint proteins has led to increased investigations into their role in patients who progressed on third-generation EGFR-TKIs or on earlier-generation EGFR-TKIs without the Thr790Met mutation. However, ICI monotherapies have shown inadequate efficacy in this setting,[11–14] and ICI-based combination treatments have shown inconsistent results.[15,16] For example, ICI plus chemotherapy (ICI-chemo) showed significant improvement in progression-free survival compared with chemotherapy in the ORIENT-31 study (hazard ratio [HR] 0·72 [95% CI 0·55–0·95], p=0·016)[17] and KEYNOTE-789 study (HR 0·80 [0·65–0·97], p=0·012),[18] but not in the CheckMate 722 study (HR 0·75 [0·56–1·00], p=0·053).[19] ICI plus antiangiogenesis and chemotherapy (ICI-antiangio-chemo) consistently showed encouraging outcomes over non-ICI-based therapies in the ORIENT-31 and IMpower150 studies.[17,20] However, the antitumour activity of ICI-antiangio-chemo therapy has not been conclusively established due to the absence of direct comparisons with other ICI-based combination treatments in randomised controlled trials.

In this difficult-to-treat population, another key issue is the absence of reliable efficacy biomarkers for guiding the use of ICI-based treatments, as individuals with distinct clinical and pathological characteristics might have different treatment responses. For instance, the ORIENT-31 study showed that individuals who were Thr790Met negative experienced greater progression-free survival benefits from sintilimab plus chemotherapy compared with those who were Thr790Met positive, and that those with a Leu858Arg mutation experienced greater benefits than those with exon 19 deletions.[21] Therefore, developing accurate biomarkers is essential for guiding appropriate selection of individuals who could benefit from ICI-based treatments after progressing on EGFR-TKIs.

We conducted this single-arm, pairwise, and network meta-analysis to investigate the individual and comparative efficacy and safety of ICI-combination treatment strategies as well as their efficacy biomarkers, which are crucial for clinicians in making the optimal treatment decision for this population of individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs.

Methods

Search strategy and selection criteria

We did a systematic review, meta-analysis, and network meta-analysis of clinical trials on ICI-based treatment strategies for individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs, following PRISMA guidelines (appendix pp 2–5).[22] The review protocol was prospectively registered in PROSPERO, CRD42021292626.[23]

We searched the PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov databases for clinical trials from database inception to Jan 31, 2024, with combined search terms "NSCLC", "EGFR", "immunotherapy", "immune checkpoint inhibitor", "PD-1", "PD-L1", and "CTLA-4" (appendix pp 6–7). We also reviewed abstracts and presentations from major international conferences (American Association for Cancer Research Annual Meeting, American Society of Clinical Oncology Annual Meeting, European Society for Medical Oncology Congress, World Conference on Lung Cancer, and European Lung Cancer Congress) from 2019 to 2024, and checked reference lists of recent relevant reviews and meta-analyses to ensure complete literature retrieval.

Studies were deemed eligible if they were: published and unpublished phase 1, 2, or 3 clinical trials; trials enrolling participants with histologically or cytologically confirmed advanced (stage III, IV, or recurrent) *EGFR*-mutated NSCLC who have progressed after at least one EGFR-TKI treatment; and trials evaluating ICI-based treatment strategies on at least one of the clinical outcomes of interest, including progression-free survival, overall survival, objective response rate, disease control rate, and adverse events of any grade or severe grade (grade ≥3). Studies not adhering to the inclusion criteria were excluded. Other exclusion criteria were: trials that grouped the participants with *EGFR* mutations together with those with other gene aberrations (eg, anaplastic lymphoma kinase) or with no confirmed gene aberrations, yet without providing separate outcome data for participants with each specific gene aberration; and trials enrolling participants who had received a previous ICI treatment.

We extracted data including the study characteristics (study identification number, phase status, publication year, and sample size), demographic information (sex, age in years, ethnicity, and smoking status), treatments, and outcomes (HRs and their corresponding 95% CIs for progression-free survival and overall survival, and the number of participants with objective response, disease control, and any-grade or severe-grade adverse events). We prioritised data assessed by the blinded independent review committee based on the intention-to-treat principle, and the most recent data from multiple reports of a single trial with different follow-up durations. In case of missing data in a study, supplementary materials were checked and, if necessary, the corresponding author was contacted. We independently did the literature search (YiZ, YH, and ZC) and data extraction (WW and FG). Any discordance was resolved by discussion with a senior investigator (WL).

Data analysis

The data analysis was conducted using R software (version 4.3.2), within which we used the meta package for both the single-arm (*metaprop* function) and pairwise (*metagen* and *metabin* functions) meta-analyses, and the gemtc package for the network meta-analysis. The primary outcome analysed was progression-free survival, and secondary outcomes analysed were overall survival, objective response rate, disease control rate, and any-grade and severe-grade adverse events (appendix p 1). Risk of bias of the included studies was assessed using two tools: the Methodological Index for Nonrandomized Studies tool for single-arm clinical trials without randomisation,[24] and the Cochrane risk of bias tool for randomised controlled trials[25] (appendix pp 8–9).

See Online for appendix

The single-arm meta-analysis was conducted to calculate the overall rates of objective response and disease control, and risks of any-grade and severe-grade adverse events of each treatment strategy from all eligible trials reporting these outcomes. The pairwise meta-analysis was conducted for head-to-head comparisons involving two or more randomised controlled trials. Hazard ratios (HRs) for survival outcomes (progression-free survival and overall survival) and odds ratios (ORs) for binary outcomes (objective response rate, disease control rate, and any-grade and severe-grade adverse events) were calculated, along with their 95% CIs. For both the single-arm and pairwise meta-analyses, heterogeneity was assessed through the I^2 statistic and Q-test (appendix p 1).[26,27] When statistical heterogeneity was substantial (I^2>50% or Q-test p<0·10), the random-effects model was employed; otherwise, the fixed-effect model was adopted.

Network meta-analysis was conducted using a Markov chain Monte Carlo simulation technique, allowing for comparisons between any two ICI-based treatment strategies by synthesising direct and indirect evidence simultaneously.[28] Frequentist and Bayesian approaches are two typical frameworks fitting network meta-analysis. We adopted the Bayesian framework for its capacity to incorporate existing knowledge and manage uncertainty and sparse data, addressing challenges associated with frequentist approaches such as estimation bias and overconfident conclusions in such scenarios.[29,30] The fixed-effect consistency model was used, as most direct evidence was from a single trial.[29] Four different chains were run with 100 000 iterations, discarding 50 000 initial burn-in iterations per chain. We assessed convergence based on the shape of the posterior distributions and Gelman–Rubin diagnostics.[31] Summary estimate statistics were reported as HRs or ORs for the corresponding outcomes, along with their 95% credible intervals (CrIs).

Treatment rankings were determined by probabilities of superiority and summarised using the surface under the cumulative rank (SUCRA) value, ranging from 0 (certainly the least efficacious or toxic treatment) to 1 (contrary indication compared with the 0 value).[30] Transitivity and consistency are key assumptions underlying the network meta-analysis. The transitivity of indirect comparisons was assessed by Bayesian metaregression analyses on the potential effects of modifiers like sample size, sex, age, ethnicity, and smoking status. Local inconsistency of direct and indirect results was assessed by the comparison of estimates from the pairwise meta-analyses (in both frequentist and Bayesian frameworks) and network meta-analyses.[32,33] Global inconsistency was assessed by the comparison between consistency and inconsistency models regarding the goodness of model fit.[33–35]

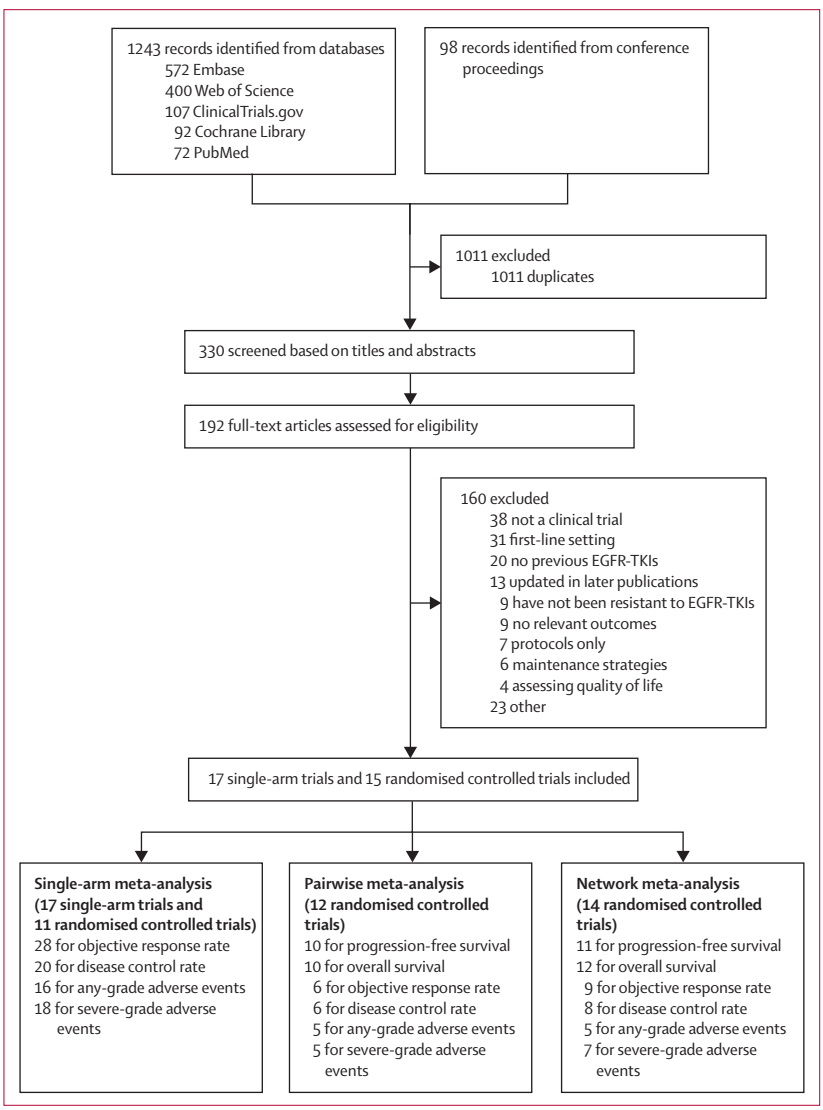

Figure 1: **Flowchart of study selection**
TKI=tyrosine-kinase inhibitor.

We conducted subgroup analyses to investigate the effect of key clinical modifiers and potential predictive markers of treatment efficacy. This included a single-arm meta-analysis of the objective response rate by PD-L1 expression level, and pairwise and network analyses of progression-free survival by PD-L1 expression level, EGFR mutation type (exon 19 deletion and exon 21 Leu858Arg mutation), Thr790Met mutation status, and smoking status.

Role of the funding source

There was no funding source for this study.

Results

1243 records through database searches and an additional 98 studies from conference proceedings were identified (figure 1). 17 single-arm trials[36–52] and 15 randomised controlled trials[17–20,53–63] met the inclusion criteria, comprising a total of 2886 enrolled participants with *EGFR* mutations. These trials evaluated seven ICI-based treatment strategies: ICI monotherapy,[36–39,53–57,59,62] ICI-chemo,[17,19,20,40–43,58,59] ICI-antiangio-chemo,[17,20,44–46,61] ICI plus antiangiogenesis (ICI-antiangio),[47] dual ICIs (ICI-ICI),[48,62] dual ICIs plus chemotherapy (ICI-ICI-chemo),[50] and ICI-TKI.[49,51,52,63] Of all the included trials, 18 reported characteristics for participants with *EGFR* mutations, with higher proportions of women (1152 [59·0%] of 1952) and never smokers (1265 [65·6%] of 1929). More detailed baseline characteristics are presented in the appendix (pp 10–14). All single-arm trials were considered high quality with low risk for bias, providing clear research aims, inclusion and exclusion criteria, an appropriate follow-up period, and evaluation of results (appendix p 25). 11 randomised controlled trials were at high risk of bias, predominantly due to inadequate blinding control arising from their open-label study designs (appendix p 26).

In the single-arm meta-analysis, 28 studies (2482 participants)[18–21,36–52,56–59,61–63] for objective response rate, 20 studies (2205 participants)[18–21,36,40,41,43–47,50–52,57,58,61–63] for disease control rate, 16 studies (1970 participants)[17–19,40,41,43,44,47,49,51,52,61–65] for any-grade adverse events, and 18 studies (2167 participants)[18,19,40,41,44,46,47,49–52,57,61–65] for severe-grade adverse events were included. Across all ICI-based treatment strategies, the pooled objective response rate was 29·0% (95% CI 21·3–36·7, I^2=94%) and the disease control rate was 77·7% (69·9–85·4, I^2=93%; appendix pp 17–18). Similarly, the pooled objective response rate of chemotherapy was 29·7% (26·3–33·0, I^2=25%) and the disease control rate was 78·2% (72·9–83·5, I^2=59%; appendix p 21). ICI-antiangio-chemo had the most favourable pooled objective response rate of 60·6% (51·0–70·2, I^2=76%) and disease control rate of 94·6% (89·4–99·7, I^2=78%), followed by ICI-chemo with an objective response rate of 35·8% (28·1–43·4, I^2=69%) and disease control rate of 82·8% (80·1–85·5, I^2=16%; appendix pp 17–18). Similar efficacy

was observed between ICI-TKI and chemotherapy, as well as between ICI-ICI and ICI monotherapy (appendix pp 17–18, 21). The pooled incidence of any-grade adverse events across all ICI-based treatment strategies was 91·6% (86·0–97·2, I^2=89%) and that of severe-grade adverse events was 37·0% (27·7–46·3, I^2=95%; appendix pp 19–20). The pooled incidence of any-grade adverse events of chemotherapy was 87·2% (79·0–95·3, I^2=91%) and that of severe-grade adverse events was 29·3% (15·5–43·0, I^2=93%; appendix p 21). Combination treatments caused more any-grade and severe-grade adverse events than ICI monotherapy, with ICI-antiangio-chemo (47·0% [35·0–59·0], I^2=82%) and ICI-chemo (47·2% [41·3–53·2], I^2=54%) showing the highest risk of severe-grade adverse events (appendix p 20).

The pairwise meta-analysis was available in several comparisons: ICI-antiangio-chemo versus ICI-chemo for objective response rate, disease control rate, any-grade adverse events, and severe-grade adverse events; ICI-antiangio-chemo or ICI-chemo versus chemotherapy for all assessed outcomes; ICI-antiangio-chemo versus antiangio-chemo for progression-free survival; and ICI versus chemotherapy for progression-free survival and overall survival (figure 2; appendix pp 22–24). ICI-antiangio-chemo showed an improved objective response rate compared with both ICI-chemo (OR 2·48 [95% CI 1·03-5·98], I^2=65%) and chemotherapy (OR 2·56 [1·78-3·67], I^2=0%). ICI monotherapy was associated with shorter progression-free survival than chemotherapy (HR 1·73 [95% CI 1·30–2·29], I^2=0%), whereas ICI-antiangio-chemo (HR 0·54 [0·44–0·67], I^2=0%) and ICI-chemo (HR 0·77 [0·67–0·88], I^2=0%) had prolonged progression-free survival compared with chemotherapy. Additionally, ICI-chemo had superior overall survival to chemotherapy (HR 0·86 [0·75–0·99], I^2=0%). The safety analysis indicated that ICI-antiangio-chemo had a higher incidence of any-grade adverse events compared with chemotherapy (OR 6·37 [95% CI 2·65–15·29], I^2=43%) and of severe-grade adverse events compared with ICI-chemo (OR 1·75 [1·17–2·62], I^2=0%). No increased toxicity was detected for ICI-chemo, compared with chemotherapy, with respect to both any-grade adverse events (OR 1·14 [0·77–1·71], I^2=0%) and severe-grade adverse events (OR 1·19 [0·69–2·04], I^2=77%).

In the network meta-analysis, a total of 14 randomised controlled trials (2768 participants)[17–20,53–62] were included. ICI-TKI could not be assessed due to insufficient data. Among the remaining six ICI-based treatment strategies, all were assessable for objective response rate, disease control rate, and severe-grade adverse events, five for progression-free survival and overall survival, and three for any-grade adverse events for their comparative estimates (figure 3). The transitivity assumption was accepted based on the absence of significant variabilities (appendix p 15). Consistency was ensured locally by the consistent results of pairwise meta-analyses (either frequentist or Bayesian) and network meta-analyses (appendix pp 27–28), and globally by similar fit of consistency and inconsistency models (appendix p 16).

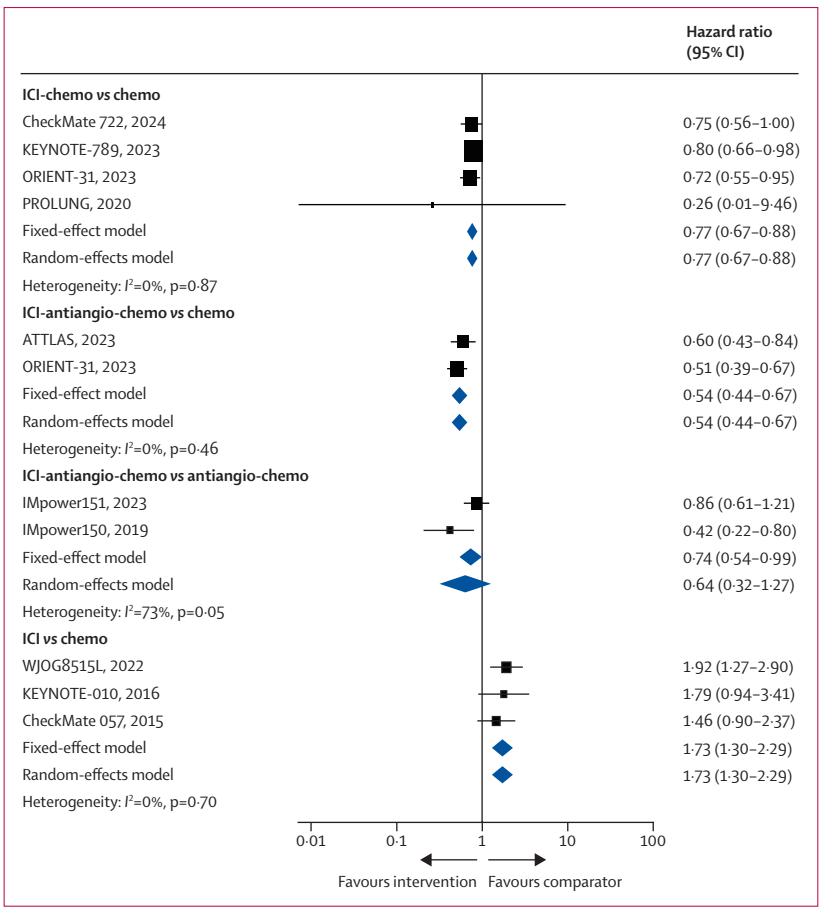

Figure 2: **Pooled progression-free survival of each head-to-head comparison in pairwise meta-analysis**
Pooled HRs for progression-free survival and their corresponding 95% CIs. Antiangio-chemo=antiangiogenesis plus chemotherapy. Chemo=chemotherapy. HR=hazard ratio. ICI=immune checkpoint inhibitor. ICI-antiangio-chemo=ICI plus antiangiogenesis plus chemotherapy. ICI-chemo=ICI plus chemotherapy.

In the network meta-analysis, ICI-antiangio-chemo yielded the best progression-free survival, with significant benefits over ICI-chemo (HR 0·71 [95% CrI 0·59–0·85]), ICI monotherapy (HR 0·30 [0·22–0·41]), antiangio-chemo (HR 0·76 [0·58–1·00]), and chemotherapy (HR 0·54 [0·45–0·64]). ICI-chemo had better progression-free survival than ICI monotherapy (HR 0·42 [0·31–0·57]) and chemotherapy (HR 0·76 [0·67–0·86]). ICI monotherapy did not provide progression-free survival benefits over the non-ICI-based strategies, including chemotherapy (HR 1·80 [1·38–2·37]) and antiangio-chemo (HR 2·57 [1·72–3·84]). No significant differences were found among all the comparable treatment strategies in overall survival, except the benefit of ICI-chemo over chemotherapy alone (HR 1·15 [1·00–1·33]; figure 4A).

In terms of response rates, addition of chemotherapy to ICIs improved objective response rate compared with ICI monotherapy, and the addition of anti-angiogenic

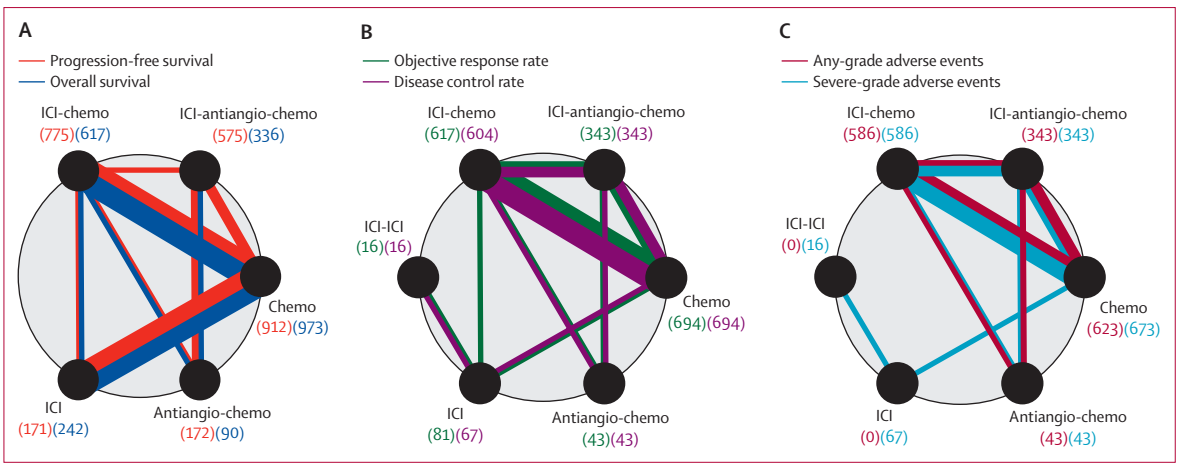

Figure 3: **Eligible comparisons for each outcome in the network meta-analysis**
Network plots illustrating the direct and indirect comparisons for (A) progression-free survival and overall survival (B) objective response rate and disease control rate, and (C) any-grade and severe-grade adverse events. Circular nodes represent treatment strategies with the total number of involved participants in brackets. Lines represent the direct comparisons, with thicknesses proportional to the number of involved studies. Indirect comparisons in the network plots are derived from the combination of direct comparisons within the network. Antiangio-chemo=antiangiogenesis plus chemotherapy. Chemo=chemotherapy. ICI=immune checkpoint inhibitor. ICI-antiangio-chemo=ICI plus antiangiogenesis plus chemotherapy. ICI-chemo=ICI plus chemotherapy. ICI-ICI=dual ICIs.

therapy to this combination further improved objective response rate (figure 4B). ICI-antiangio-chemo and ICI-chemo showed no significant difference in disease control rate, and they both controlled the disease better than ICI monotherapy and dual therapy, and chemotherapy (figure 4B). ICI monotherapy showed inferior objective response rate and disease control rate compared with the non-ICI-based strategies. In terms of safety, ICI-antiangio-chemo was associated with higher risks of both any-grade and severe-grade adverse events over ICI-chemo and chemotherapy (figure 4C).

The Bayesian ranking profiles, based on the SUCRA values of the comparable treatment strategies for each outcome, were consistent with the results based on HR and OR estimates (appendix p 29). Of note, ICI-antiangio-chemo ranked first for the efficacy outcomes—progression-free survival (SUCRA=0·99), objective response rate (SUCRA=0·97), and disease control rate (SUCRA=0·89). However, it also ranked first in causing adverse events of any-grade (SUCRA=0·94) and severe-grade (SUCRA=0·85).

In subgroup single-arm meta-analysis, the pooled objective response rate of ICI-based treatment strategies was improved for PD-L1 expression of 1% or greater compared with less than 1% (appendix p 30). When examining each individual treatment strategy, a significantly improved objective response rate in participants with PD-L1 expression of 1% or greater compared with less than 1% could be observed for ICI-chemo but not for ICI-antiangio-chemo (appendix p 31). In subgroup pairwise meta-analysis (appendix pp 32–34), relative progression-free survival efficacy could be explored for the comparison of ICI-antiangio-chemo versus chemotherapy involving two trials.[21,61] Compared with chemotherapy alone, ICI-antiangio-chemo showed a favourable HR for progression-free survival across most subgroups, except for participants with Thr790Met mutations; progression-free survival was greater for participants with Leu858Arg mutation than for those with exon 19 deletion, and did not change with the smoking status of the participants (appendix p 34). In subgroup network meta-analysis (appendix pp 35–38), ICI-antiangio-chemo yielded progression-free survival benefits over ICI monotherapy and chemotherapy across most subgroups, except in participants with Thr790Met mutations when compared with chemotherapy. ICI-antiangio-chemo yielded progression-free survival benefits over ICI-chemo for participants with PD-L1 expression of 50% or greater, negative Thr790Met mutations, and smoking history, but not in those with PD-L1 expression below 1% or those with EGFR exon 19 deletion, EGFR exon 21 Leu858Arg mutation, or Thr790Met mutations.

Discussion

In this meta-analysis, we comprehensively summarised the efficacy and safety of currently available ICI-based treatment strategies, including ICI monotherapy and its combination with chemotherapy, antiangiogenic agents, another ICI, and EGFR-TKIs for individuals with advanced *EGFR*-mutated NSCLC who progressed on EGFR-TKIs. The pooled results from single-arm, pairwise, and network meta-analyses were highly consistent, indicating that the efficacy of ICI monotherapy can be improved by combination with non-ICI-based treatments. Specifically, ICI-chemo showed encouraging antitumour activity with significant improvements in progression-free survival and disease control rate over ICI monotherapy and chemotherapy alone. Furthermore, the addition of an antiangiogenic therapy to

the ICI-chemo combination (ICI-antiangio-chemo) appeared to be the most effective treatment strategy, offering the best benefits in terms of progression-free survival, objective response rate, and disease control rate amongst all comparable treatment options.

The benefits observed with these combination therapies over their individual components suggest a synergetic effect of ICI-based and non-ICI based therapies in enhancing the anticancer activity in the *EGFR*-mutated tumour microenvironment, which is known to be immunosuppressive.[66] Although the precise mechanisms underlying these synergistic effects remain to be fully understood, studies suggest that chemotherapy-induced neoantigen release and antiangiogenesis-induced immune reprogramming play important roles in activating the tumour microenvironment from an immunosuppressive state.[67–70] In addition, multiple preclinical studies[71,72] have shown that EGFR-TKI resistance is associated with increased tumour VEGF levels, and targeted anti-angiogenic therapy could enhance antitumour activity in this resistant tumour. The subgroup analyses showed that the level of PD-L1 expression could be a beneficial biomarker of ICI-based treatment strategies. However, this predictive value varied across different individual treatment strategies. Specifically, PD-L1 expression levels showed a predictive value for ICI-chemo with a cutoff point of 1%, whereas this was not the case for ICI-antiangio-chemo, possibly due to the immune effect of the interaction between VEGF level signalling and its inhibition.[73,74] Our study also elucidated that the *EGFR* Leu858Arg mutation serves as a positive and Thr790Met mutations as negative prognostic indicators for ICI-antiangio-chemo. Partial explanations for this finding might be the higher tumour mutation burden in tumours with Leu858Arg mutation than those with exon 19 deletion,[75] and a lower PD-L1 expression level in Thr790Met-mutated tumours than in Thr790Met-negative tumours;[76] moreover, CD8+PD-1+ T cells infiltrate more in tumours with Leu858Arg mutation than in those with exon 19 deletion, and less in Thr790Met-mutated tumours than in Thr790Met-negative tumours.[77] Subgroup network meta-analysis supported the use of ICI-antiangio-chemo and ICI-chemo according to the participant characteristics. These findings underscore the complex interplay between genetic mutations, the tumour microenvironment, and immune response, and thus highlight the value of a biomarker-directed approach in selecting tailored ICI-based treatment strategies for individuals with advanced *EGFR*-mutated NSCLC who have progressed on EGFR-TKIs. However, these subgroup findings should be interpreted with caution due to limitations such as small sample sizes, imbalanced baseline characteristics, and low statistical power. Consequently, there is a need for further clinical research to validate these potential efficacy predictors.

A

Overall survival

Progression-free survival

ICI-antiangio-chemo	0·92 (0·70–1·20)	1·14 (0·81–1·60)	0·97 (0·61–1·55)	1·06 (0·84–1·34)
0·71 (0·59–0·85)	**ICI-chemo**	1·24 (0·94–1·65)	1·05 (0·67–1·68)	**1·15 (1·00–1·33)**
0·30 (0·22–0·41)	**0·42 (0·31–0·57)**	**ICI**	0·85 (0·50–1·44)	0·93 (0·72–1·20)
0·76 (0·58–1·00)	1·08 (0·80–1·46)	**2·57 (1·72–3·84)**	**Antiangio-chemo**	1·09 (0·69–1·75)
0·54 (0·45–0·64)	**0·76 (0·67–0·86)**	**1·80 (1·38–2·37)**	**0·70 (0·52–0·95)**	**Chemo**

B

Disease control rate

Objective response rate

ICI-antiangio-chemo	0·67 (0·41–1·06)	**0·11 (0·02–0·60)**	**0·09 (0·03–0·23)**	0·98 (0·33–3·11)	**0·46 (0·29–0·73)**
2·21 (1·58–3·11)	**ICI-chemo**	**0·16 (0·03–0·87)**	**0·13 (0·05–0·32)**	1·46 (0·51–4·61)	**0·69 (0·52–0·92)**
6·05 (0·15–11·86)	2·76 (0·07–48·89)	**ICI-ICI**	0·84 (0·19–3·74)	**9·35 (1·22–76·07)**	4·37 (0·82–25·26)
14·59 (5·34–45·27)	**6·59 (2·48–19·97)**	2·42 (0·17–84·18)	**ICI**	**11·16 (2·81–47·02)**	**5·21 (2·25–12·82)**
2·25 (1·03–4·98)	1·02 (0·47–2·23)	0·37 (0·02–15·88)	**0·15 (0·04–0·54)**	**Antiangio-chemo**	0·47 (0·15–1·39)
2·66 (1·93–3·68)	1·20 (0·94–1·54)	0·44 (0·02–17·33)	**0·18 (0·06–0·48)**	1·18 (0·53–2·61)	**Chemo**

C

Any-grade adverse events

Severe-grade adverse events

ICI-antiangio-chemo	**0·14 (0·05–0·34)**	NA	NA	0·36 (0·06–3·36)	**0·12 (0·05–0·28)**
1·59 (1·13–2·23)	**ICI-chemo**	NA	NA	2·59 (0·49–20·73)	0·87 (0·59–1·30)
1·03 (0·02–21·34)	0·65 (0·01–13·23)	**ICI-ICI**	NA	NA	NA
2·52 (0·68–9·84)	1·58 (0·43–6·12)	2·42 (0·16–84·90)	**ICI**	NA	NA
1·48 (0·66–3·28)	0·93 (0·43–2·01)	1·44 (0·06–67·53)	0·59 (0·13–2·64)	**Antiangio-chemo**	0·34 (0·04–1·83)
1·94 (1·40–2·70)	1·22 (0·96–1·54)	1·87 (0·09–80·53)	0·77 (0·21–2·75)	1·31 (0·60–2·92)	**Chemo**

Figure 4: **Pooled efficacy and safety estimates of multiple comparisons in network meta-analysis**
(A) Progression-free survival and overall survival. (B) Objective response rate and disease control rate. (C) Any-grade and severe-grade adverse events. Data are pooled HR (95% credible interval) for A and OR (95% credible interval) for B and C. Bold data indicate a significant difference. Antiangio-chemo=antiangiogenesis plus chemotherapy. Chemo=chemotherapy. ICI=immune checkpoint inhibitor. ICI-chemo=ICI plus chemotherapy. ICI-antiangio-chemo=ICI plus antiangiogenesis plus chemotherapy. NA=not applicable.

Previous studies have consistently supported the idea that the toxicity profile of ICI-antiangio-chemo is generally well tolerated, with grade 3 or worse adverse events predominant in haematological parameters (neutropenia, anaemia, thrombocytopenia, decreased blood cell count, and myelosuppression) and non-haematological parameters (peripheral neuropathy, myalgia, alopecia, and fatigue).[20,21,45,46,61] Moreover, in the ORIENT-31 study,[17] participants receiving ICI-antiangio-chemo had a favourable Eastern Cooperative Oncology Group performance status without a loss in quality of life compared with those receiving chemotherapy. Our pairwise and network meta-analyses found no additional toxicity

signals for ICI-chemo compared with chemotherapy. However, the risk of severe-grade adverse events was higher with ICI-antiangio-chemo than with ICI-chemo or chemotherapy, reflecting the expected increase in toxicity associated with increased treatment. Furthermore, the single-arm meta-analysis, including a larger sample size, revealed that ICI-antiangio-chemo and ICI-chemo consistently ranked first in severe-grade adverse events. Therefore, clinicians should bear in mind the possibility of increased toxicity when prescribing these combination treatment strategies, aiming to maintain an optimal balance between efficacy and adverse effects for patient care.

To our knowledge, this study is the first comprehensive investigation of the efficacy and safety of multiple ICI-based treatment strategies for individuals with advanced *EGFR*-mutated NSCLC who have progressed on EGFR-TKIs. The findings challenge the widely accepted theory in current clinical practice that ICIs do not offer substantial benefits to this population and propose that this theory only applies to ICI monotherapy and not to specific ICI-based combination treatments such as ICI-antiangio-chemo and ICI-chemo.

Previous meta-analyses on ICI treatments for advanced *EGFR*-mutated NSCLC have often overlooked individuals resistant to EGFR-TKIs and ICI-based combination treatments.[11,13] Two more recent meta-analyses[78,79] have highlighted the antitumour benefits of ICI-based combinations for individuals who are TKI resistant, but had notable confounding factors. Qian and colleagues[78] focused on a subset of ICI-based combination treatments and used a non-uniform control group with chemotherapy and antiangio-chemo mixed together. Wang and colleagues[79] might not offer robust comparisons across various treatment strategies due to the inclusion of numerous non-randomised controlled trials and scarce randomised controlled trials for each treatment strategy. In comparison, the main strengths of this study include: an up-to-date time window covering new and updated data, allowing the inclusion of the largest number of studies and all available ICI-based treatment strategies; enhanced robustness and reliability by employing diverse meta-analytical techniques on data from not only multi-arm trials but also an extensive collection of single-arm trials; and assessments in multiple key subpopulations stratified by PD-L1 expression level, *EGFR* mutation type, Thr790Met mutation status, and smoking status, substantially expanding the clinical applicability of the findings.

However, several limitations of our work should be considered. First, our study used reported trial data rather than individual data. Despite the inclusion of only prospectively registered clinical trials, differences in trial design and heterogeneity among participants inherently persisted as possible unmeasured confounders impairing estimates. For instance, previous EGFR-TKIs to which participants were resistant to varied across trials, and some trials only provided investigator-assessed outcome data. Second, the robustness and reliability of results might have been undermined by data sparseness. There were a relatively low number of trials and participants involving some ICI-based treatment strategies like ICI-antiangio (only one trial[47]) and ICI-ICI (only one trial[62]). Nonetheless, we employed three meta-analytical methods (single-arm, pairwise, and network) for multifaceted evaluations, yielding mostly consistent results. Third, molecular mechanisms of EGFR-TKI resistance, such as *MET* amplification,[80] are increasingly recognised but were not addressed in our study due to insufficient accessible information. Lastly, there was little evidence of the translation of progression-free survival benefits to overall survival improvement, except for ICI-chemo over chemotherapy. The overall survival findings should be carefully interpreted considering the often immature reports, high rate of subsequent treatments, and common treatment switching in included randomised controlled trials. Hence, we have chosen progression-free survival as the primary outcome measure, given its substantially mature follow-up and low influence from post-progression treatments. It will be particularly interesting to investigate overall survival outcomes with ICI-antiangio-chemo and ICI-chemo in future studies for patients with *EGFR*-mutated NSCLC resistant to EGFR-TKIs, compared with other treatment strategies.

Contributors

YiZ, YH, WL, and JH conceived the study and contributed to study design and data interpretation. YiZ, YH, WW, QC, FG, ZC, JZ, YuZ, HD, SL, and HL did the literature search, data extraction, and data analysis. WL and JH accessed and verified the data. YiZ, YH, QC, FG, and HD wrote the manuscript. WW, ZC, JZ, YuZ, YC, SL, and HL provided material support. All authors read and approved the final version of the manuscript, had full access to the study data, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data and any code used for the analysis will be shared with individuals upon reasonable request to the corresponding author from the time of publication.

References

1 Yang CY, Yang JC, Yang PC. Precision management of advanced non-small cell lung cancer. *Annu Rev Med* 2020; **71:** 117–36.

2 Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res* 2015; **5:** 2892–911.

3 NCCN clinical practice guidelines in oncology for non-small cell lung cancer. Version 2. 2023. https://www.nccn.org/guidelines (accessed March 15, 2023).

4 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361:** 947–57.

5 Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13:** 239–46.

6 Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31:** 3327–34.

7 Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017; **18:** 1454–66.

8 Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 113–25.

9 Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol* 2018; **29** (suppl 1)**:** i10–19.

10 Piper-Vallillo AJ, Sequist LV, Piotrowska Z. Emerging treatment paradigms for EGFR-mutant lung cancers progressing on osimertinib: a review. *J Clin Oncol* 2020; **38:** 2926–36.

11 Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer—a meta-analysis. *J Thorac Oncol* 2017; **12:** 403–07.

12 Garassino MC, Gelibter AJ, Grossi F, et al. Italian nivolumab expanded access program in nonsquamous non-small cell lung cancer patients: results in never-smokers and EGFR-mutant patients. *J Thorac Oncol* 2018; **13:** 1146–55.

13 Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *JAMA Oncol* 2018; **4:** 210–16.

14 Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 2019; **30:** 1321–28.

15 Otano I, Ucero AC, Zugazagoitia J, Paz-Ares L. At the crossroads of immunotherapy for oncogene-addicted subsets of NSCLC. *Nat Rev Clin Oncol* 2023; **20:** 143–59.

16 Qiao M, Jiang T, Liu X, et al. Immune checkpoint inhibitors in EGFR-mutated NSCLC: dusk or dawn? *J Thorac Oncol* 2021; **16:** 1267–88.

17 Lu S, Wu L, Jian H, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2022; **23:** 1167–79.

18 Yang JC-H, Lee DH, Lee J-S, et al. Pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor (TKI)-resistant, EGFR-mutant, metastatic nonsquamous NSCLC: phase 3 KEYNOTE-789 study. *J Clin Oncol* 2023; **41** (suppl 17)**:** LBA9000.

19 Mok T, Nakagawa K, Park K, et al. Nivolumab plus chemotherapy in epidermal growth factor receptor-mutated metastatic non-small-cell lung cancer after disease progression on epidermal growth factor receptor tyrosine kinase inhibitors: final results of CheckMate 722. *J Clin Oncol* 2024; **42:** 1252–64.

20 Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med* 2019; **7:** 387–401.

21 Lu S, Wu L, Jian H, et al. Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2023; **11:** 624–36.

22 Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162:** 777–84.

23 Zhao Y, Liang W, He J. Immune checkpoint inhibitors for patients with EGFR-mutated non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitors: a systematic review and meta-analysis. 2022. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021292626 (accessed April 26, 2023).

24 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003; **73:** 712–16.

25 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.

26 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–58.

27 Cochrane. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). 2023. https://www.training.cochrane.org/handbook (accessed Jan 20, 2024).

28 Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; **159:** 130–37.

29 Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013; **33:** 607–17.

30 Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64:** 163–71.

31 Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Stat Sci* 1992; **7:** 457–72.

32 Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013; **13:** 35.

33 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; **29:** 932–44.

34 Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013; **33:** 641–56.

35 Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Series B Stat Methodol* 2002; **64:** 583–639.

36 Garassino MC, Cho BC, Kim JH, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. *Lancet Oncol* 2018; **19:** 521–36.

37 Peters S, Gettinger S, Johnson ML, et al. Phase II trial of atezolizumab as first-line or subsequent therapy for patients with programmed death-ligand 1-selected advanced non-small-cell lung cancer (BIRCH). *J Clin Oncol* 2017; **35:** 2781–89.

38 Lu S, Cheng Y, Zhou J, et al. An open label, safety study of Asian patients with advanced non-small-cell lung cancer receiving second-line nivolumab monotherapy (CheckMate 870). *Ther Adv Med Oncol* 2022; **14:** 17588359221138380.

39 Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 2018–28.

40 Jiang T, Wang P, Zhang J, et al. Toripalimab plus chemotherapy as second-line treatment in previously EGFR-TKI treated patients with EGFR-mutant-advanced NSCLC: a multicenter phase-II trial. *Signal Transduct Target Ther* 2021; **6:** 355.

41 Zhong H, Zhang X, Tian P, et al. Tislelizumab plus chemotherapy for patients with EGFR-mutated non-squamous non-small cell lung cancer who progressed on EGFR tyrosine kinase inhibitor therapy. *J Immunother Cancer* 2023; **11:** e006887.

42 Gadgeel S, Dziubek K, Nagasaka M, et al. OA09.03 pembrolizumab in combination with platinum-based chemotherapy in recurrent EGFR/ALK-positive non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2021; **16** (suppl)**:** S863.

43 Cho BC, Ahn MJ, Baik C, et al. 13P durvalumab + chemotherapy in patients (pts) with advanced EGFR mutation-positive (EGFRm) NSCLC whose disease progressed on first-line (1L) osimertinib: an ORCHARD study interim analysis. *Ann Oncol* 2022; **33** (suppl 2)**:** S34–35.

44 Lam TC, Tsang K, Choi H, et al. 380MO a phase II trial of atezolizumab, bevacizumab, pemetrexed and carboplatin combination for metastatic EGFR-mutated NSCLC after TKI failure. *Ann Oncol* 2020; **31** (suppl 6)**:** S1389.

45 Zhao Y, Chen G, Chen J, et al. AK112, a novel PD-1/VEGF bispecific antibody, in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): an open-label, multicenter, phase II trial. *EClinicalMedicine* 2023; **62:** 102106.

46 Wu SG, Ho CC, Yang JC, et al. 12P a phase II study of atezolizumab in combination with bevacizumab, carboplatin or cisplatin, and pemetrexed for EGFR-mutant metastatic NSCLC patients after failure of EGFR TKIs. *Ann Oncol* 2022; **33** (suppl 2)**:** S33–34.

47 Fang WF, Fang J, Tian P, et al. 1032P ML41256: phase II study of atezolizumab (atezo) in combination with bevacizumab (beva) in advanced non-squamous non-small cell lung cancer (nsqNSCLC) patients (pts) pretreated with epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs). *Ann Oncol* 2022; **33** (suppl 7)**:** S1027.

48 Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016; **17:** 1497–508.

49 Oxnard GR, Yang JC, Yu H, et al. TATTON: a multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer. *Ann Oncol* 2020; **31:** 507–16.

50 Lee C, Liao BC, Subramaniam S, et al. OA09.04 ILLUMINATE: efficacy and safety of durvalumab-tremelimumab and chemotherapy in EGFR mutant NSCLC following progression on EGFR inhibitors. *J Thorac Oncol* 2023; **18** (suppl)**:** S63.

51 Gettinger S, Hellmann MD, Chow LQM, et al. Nivolumab plus erlotinib in patients with EGFR-mutant advanced NSCLC. *J Thorac Oncol* 2018; **13:** 1363–72.

52 Riudavets M, Naigeon M, Texier M, et al. Gefitinib plus tremelimumab combination in refractory non-small cell lung cancer patients harbouring EGFR mutations: the GEFTREM phase I trial. *Lung Cancer* 2022; **166:** 255–64.

53 Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387:** 1540–50.

54 Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; **387:** 1837–46.

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

56 Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373:** 1627–39.

57 Hayashi H, Sugawara S, Fukuda Y, et al. A randomized phase II study comparing nivolumab with carboplatin-pemetrexed for EGFR-mutated NSCLC with resistance to EGFR tyrosine kinase inhibitors (WJOG8515L). *Clin Cancer Res* 2022; **28:** 893–902.

58 Arrieta O, Barrón F, Ramírez-Tirado LA, et al. Efficacy and safety of pembrolizumab plus docetaxel vs docetaxel alone in patients with previously treated advanced non-small cell lung cancer: the PROLUNG phase 2 randomized clinical trial. *JAMA Oncol* 2020; **6:** 856–64.

59 Taniguchi Y, Shimokawa T, Takiguchi Y, et al. A randomized comparison of nivolumab versus nivolumab + docetaxel for previously treated advanced or recurrent ICI-naïve non-small cell lung cancer: TORG1630. *Clin Cancer Res* 2022; **28:** 4402–09.

60 Zhou C, Dong X, Chen G, et al. OA09.06 IMpower151: phase III study of atezolizumab + bevacizumab + chemotherapy in 1L metastatic nonsquamous NSCLC. *J Thorac Oncol* 2023; **18** (suppl)**:** S64–65.

61 Park S, Kim TM, Han JY, et al. Phase III, randomized study of atezolizumab plus bevacizumab and chemotherapy in patients with EGFR- or ALK-mutated non-small-cell lung cancer (ATTLAS, KCSG-LU19-04). *J Clin Oncol* 2024; **42:** 1241–51.

62 Lai G, Alvarez J, Yeo JC, et al. OA01.06 Randomised phase 2 study of nivolumab (N) versus nivolumab and ipilimumab (NI) combination in EGFR mutant NSCLC. *J Thorac Oncol* 2021; **16** (suppl)**:** S102–03.

63 Yang JC, Shepherd FA, Kim DW, et al. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. *J Thorac Oncol* 2019; **14:** 933–39.

64 Garassino MC, Cho BC, Kim JH, et al. Final overall survival and safety update for durvalumab in third- or later-line advanced NSCLC: the phase II ATLANTIC study. *Lung Cancer* 2020; **147:** 137–42.

65 Nogami N, Barlesi F, Socinski MA, et al. IMpower150 final exploratory analyses for atezolizumab plus bevacizumab and chemotherapy in key NSCLC patient subgroups with EGFR mutations or metastases in the liver or brain. *J Thorac Oncol* 2022; **17:** 309–23.

66 Yang L, He YT, Dong S, et al. Single-cell transcriptome analysis revealed a suppressive tumor immune microenvironment in EGFR mutant lung adenocarcinoma. *J Immunother Cancer* 2022; **10:** e003534.

67 Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov* 2019; **18:** 197–218.

68 Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity* 2013; **39:** 74–88.

69 Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. *Cancer Cell* 2014; **26:** 605–22.

70 Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018; **15:** 325–40.

71 Naumov GN, Nilsson MB, Cascone T, et al. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. *Clin Cancer Res* 2009; **15:** 3484–94.

72 Nilsson MB, Robichaux J, Herynk MH, et al. Altered regulation of HIF-1alpha in naive- and drug-resistant EGFR-mutant NSCLC: implications for a vascular endothelial growth factor-dependent phenotype. *J Thorac Oncol* 2021; **16:** 439–51.

73 Kuo HY, Khan KA, Kerbel RS. Antiangiogenic-immune-checkpoint inhibitor combinations: lessons from phase III clinical trials. *Nat Rev Clin Oncol* 2024; **21:** 468–82.

74 Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer* 2019; **18:** 60.

75 Hastings K, Yu HA, Wei W, et al. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer. *Ann Oncol* 2019; **30:** 1311–20.

76 Haratani K, Hayashi H, Tanaka T, et al. Tumor immune microenvironment and nivolumab efficacy in EGFR mutation-positive non-small-cell lung cancer based on T790M status after disease progression during EGFR-TKI treatment. *Ann Oncol* 2017; **28:** 1532–39.

77 Zhou J, Yu X, Hou L, et al. Epidermal growth factor receptor tyrosine kinase inhibitor remodels tumor microenvironment by upregulating LAG-3 in advanced non-small-cell lung cancer. *Lung Cancer* 2021; **153:** 143–49.

78 Qian X, Guo X, Li T, et al. Efficacy of immune checkpoint inhibitors in EGFR-mutant NSCLC patients with EGFR-TKI resistance: a systematic review and meta-analysis. *Front Pharmacol* 2022; **13:** 926890.

79 Wang Z, Zhou F, Xu S, Wang K, Ding H. The efficacy and safety of immune checkpoint inhibitors for patients with EGFR-mutated non-small cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy: a systematic review and network meta-analysis. *Cancer Med* 2023; **12:** 18516–30.

80 Wang Q, Yang S, Wang K, Sun SY. MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer. *J Hematol Oncol* 2019; **12:** 63.