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SYSTEMATIC REVIEW

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What is the optimal first-line regimen for advanced non-small cell lung cancer patients with epidermal growth factor receptor mutation: a systematic review and network meta-analysis

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Abstract

Objectives There are currently various tyrosine kinase inhibitor (TKI)-based regimens available, and it can be challenging for clinicians to determine the most effective and safe option due to the lack of direct comparisons between these regimens. In this study, we conducted a network meta-analysis comparing the efficacy and safety of distinct regimens to determine the optimal regimen for patients with EGFR-mutated non-small cell lung cancer, thereby facilitating clinical decision-making.

Materials and methods The PubMed, Embase, Cochrane Library databases and international conference databases were comprehensively searched from their inception to 02 April 2024 for collecting data regarding efficacy and safety from eligible randomized controlled trials (RCTs). Following literature screening and data extraction, a NMA was conducted to compare the efficacy and safety among 21 regimens with a random-effects consistency model in a Bayesian framework using a Markov Chain Monte Carlo simulation technique within the GEMTC package.

Results A total of 35 RCTs were included, involving 9718 individuals and 21 regimens. Compared with other interventions, combination therapies based on third-generation TKIs, especially osimertinib plus ramucirumab, showed the most favorable PFS prolongation in overall patients. Consistently, subgroup analyses showed that third-generation TKIs-based combination regimens were superior to other regimens in most prespecified subgroups with distinct clinicopathological characteristics. In terms of overall survival, despite the combination regimens based on third-generation TKIs also showing relatively superior outcomes, erlotinib plus chemotherapy and gefitinib plus chemotherapy were ranked more favorably. In terms of safety profile, combination therapies based on third-generation TKIs did not significantly increase the incidence of grade 3 or higher adverse events compared with other regimens.

Conclusion Our study concluded that combination regimens based on third-generation TKIs (osimertinib plus ramucirumab, osimertinib plus chemotherapy, osimertinib plus bevacizumab, amivantamab plus lazertinib

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and aumolertinib plus apatinib) could be the new and clinically preferable first-line, standard of care for EGFR-mutated advanced non-small cell lung cancer.

Trial registration The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42023480596).

Keywords Epidermal growth factor receptor, Tyrosine kinase inhibitors, Osimertinib, Network meta-analysis, Non-small cell lung cancer

Introduction

Non-small cell lung cancer (NSCLC) is the major histologic type of lung cancer [1–3]. Notably, it is characterized by an evident higher frequency of driver gene mutations, specifically epidermal growth factor receptor (EGFR) mutation, compared to small-cell lung cancer [4]. It is exactly the high frequency of driver gene mutations that distinguishes advanced NSCLC into two classes given different therapeutic regimens [5]. In detail, targeted therapy is preferred as the first option for patients with driver gene mutation (e.g., EGFR) [6], otherwise immunotherapy-based regimens are preferred [7].

Over the past few years, significant advances in targeted therapies against EGFR mutation have been achieved [6]. In 2009, IPASS study first found that gefitinib (GEF), the first-generation tyrosine kinase inhibitor (1G-TKI), can significantly prolong the progression-free survival (PFS) of advanced NSCLC with EGFR-sensitive mutations (e.g., 19 deletion mutation (19DEL) and 21Leu858Arg point mutation (21L858R)), thus making GEF successfully approved for the first-line treatment of advanced NSCLC with EGFR mutation, and opening the era of precision-targeted therapy for lung cancer [8]. Subsequently, the other two 1G-TKIs (erlotinib (ERL) and icotinib (ICO)) and the second-generation TKIs (2G-TKIs) (afatinib (AFA) and dacomitinib (DAC)) were also approved [6]. However, all patients eventually experience drug resistance and disease progression, with a median PFS of approximately 10 months [8, 9]. Aiming to delay the emergence of drug resistance to TKIs, researchers have developed the third-generation TKIs (3G-TKIs) [10]. As expected, the 3G-TKIs, osimertinib (OSI), aumolertinib (AUM), furmonertinib (FUR), and befotertinib (BEF), resulted in a more pronounced extension of PFS in EGFR-mutated NSCLC [11–14]. TKIs-based combination therapy is another strategy that was being extensively explored to delay drug resistance and intensify the efficacy of TKIs. Expectedly, the phase III randomized controlled trials (RCTs), NEJ009 [15] and ARTEMIS [16], demonstrated that GEF plus pemetrexed-based chemotherapy (PB) and ERL plus bevacizumab (BEV) significantly prolonged PFS versus TKI alone, thus leading to lung cancer guidelines setting them as the first-line and standard of care for EGFR-mutated NSCLC. Beyond the combination regimen based on 1/2G-TKIs, multiple RCTs in 2023 reported outcomes from the combination regimens based on 3G-TKIs, including OSI plus ramucirumab (RAM) [17], OSI plus BEV (OSI_BEV) [18], OSI plus PB (OSI_PB) [19] and AUM plus apatinib (AUM_APA) [20]. In light of the FLAURA2 study results, the 2024 NCCN guideline included OSI_PB as the new first-line treatment option for EGFR-mutated NSCLC. Also, the other combination regimens involving 3G-TKIs are potential new first-line, standard of care for this population.

Currently, multiple regimens are available for the first-line treatment of patients with EGFR-mutated NSCLC [6, 21]. Previous meta-analyses have concluded that OSI and GEF + PB were the most two effective first-line regimens [22, 23]. Nevertheless, multiple novel trials have been conducted and reported over the years, especially novel 3G-TKI-based regimens [6]. However, to date, there is a lack of studies comparing these novel regimens with classical regimens to determine the optimal regimen.

In the study, with a well-designed and comprehensive synthesis, we conducted a network meta-analysis (NMA) that directly or indirectly compared the efficacy and safety of 21 regimens to identify the optimal regimen for EGFR-mutated NSCLC. In addition, subgroup analyses were performed to investigate the consistency and robustness of the efficacy of various regimens in patients with different clinicopathologic features.

Materials and methods

This NMA was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (Table S1) [24]. The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42023480596).

Data sources and searches

Comprehensive and systematic literature searches were performed in the databases of PubMed, Embase and, Cochrane Library to retrieve relevant RCTs with no language restrictions from inception to 02 April 2024 and the main search strategy was a combination of the search terms "NSCLC", "EGFR" and "TKI". Bedsides, the abstracts of the international conferences for the

American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC) from 2014 to 2023 were also searched. Table S2 shows the detailed search strategies in databases of PubMed, Embase, and Cochrane Library.

Study eligibility and identification

The inclusion criteria were as follows: (1) Studies were RCTs in phase II or phase III; (2) Patients from enrolled trials were histologically or cytologically confirmed stage III/IV or postoperative recurrent NSCLC harboring EGFR mutation; (3) The trials were designed as two or more kinds of interventions in the first-line setting, with at least one of the interventions involving TKIs; (4) Any of the following outcomes: PFS, overall survival (OS), objective response rate (ORR), and grade 3 or higher adverse events (≥3AEs), were available.

The exclusion criteria were as follows: (1) Trials in which the treatment was administered as adjuvant or neoadjuvant therapy; (2) EGFR mutation status of the patients was unclear or tested negative for EGFR mutation.

Data extraction and quality assessment

Data extraction and quality assessment were independently conducted by two investigators (WGZ and XYZ). Any discrepancies were resolved by discussion with a third independent reviewer. The main information extracted from the original research included study ID, study phase, number and characteristics of patients, therapy regimens, and outcomes (e.g., PFS, OS, ORR, and ≥3AEs). Survival data calculated by the independent review facility were prioritized for extraction to avoid potential assessment bias by the investigator. In this NMA, the Cochrane Risk of Bias Tool was utilized to assess the risk of bias in individual studies [25].

Sensitivity analysis

To test the robustness and reliability of the results of the NMA, sensitivity analyses were performed regarding PFS, OS, ORR, and ≥3AEs in the overall patients and PFS and OS in the EGFR mutation subgroups by excluding phase II RCTs.

Data synthesis and statistical analysis

All statistical analyses in this study were conducted by R software (version 4.1.3) and Stata software (version 16.0). The network plots for direct comparisons among distinct regimens were depicted by Stata. The hazard ratios (HRs) for survival outcomes (e.g., PFS and OS) and odds ratios (ORs) for response outcomes (e.g., ORR) along with their corresponding 95% credible intervals (CIs) from enrolled RCTs were synthesized to compare the efficacy among distinct regimens, while the ORs for ≥3AEs and corresponding 95% CIs were used to evaluate the safety profile. A Markov Chain Monte Carlo simulation technique within the GEMTC and the JAGS package in R software was used to perform the NMA [26]. In terms of PFS and OS, 150,000 sample iterations were generated with 100,000 burn-ins and a thinning interval of 1. In terms of ORR and ≥3AEs, the thinning interval was increased to 10 to minimize auto-correlation. Random-effects consistency model was used in this NMA to guarantee the model's robustness. Meanwhile, deviance information criteria (DIC) were used to compare and consider the fixed and random effect models [27]. Furthermore, the node-splitting technique was applied for network consistency assessment and a p-value of less than 0.05 indicates significant inconsistency [28]. The convergence adequacy (reaching a stable equilibrium distribution) was tested by visually inspecting the trace plots and estimating the values of the Brooks–Gelman–Rubin statistic [29]. When convergence was established, the posterior distributions for the model parameters were obtained. The probability of all treatment regimens being in each ranking was calculated. The ranking of each regimen was compared based on the surface under the cumulative ranking curve (SUCRA) [30].

Results

Systematic review and characteristics of the eligible studies

As shown in Fig. 1, there was a final total of 35 eligible RCTs enrolled [8, 9, 11–20, 31–61], involving 9718 individuals and 21 regimens. The regimens included 1G-TKIs (all 1G-TKI monotherapies were merged into F_TKI), 2G-TKIs (AFA, DAC), 3G-TKIs (OSI, AUM, FUR, BEF), TKIs combination with angiogenesis inhibitors (GEF_APA, ERL_BEV, ERL_RAM, OSI_BEV, OSI_RAM, AUM_APA), TKIs combination with chemotherapy (GEF plus pemetrexed (GEF_P), GEF_PB, ERL_PB, ERL plus pemetrexed free chemotherapy (ERL_PF), ICO_PB, OSI_PB), other combination strategies (AFA plus cetuximab (AFA_CET), Amivantamab plus lazertinib (AMI_LAZ)) and chemotherapy (PB, PF). The detailed characteristics of enrolled RCTs are reported in Table 1. Regarding the quality of the trials, the risk of bias assessment indicated that the overall quality of enrolled trials was of low bias risk (Figure S1).

Network meta-analysis in overall NSCLC

PFS and OS

The network plots for PFS and OS were depicted in Fig. 2A and B, respectively. In terms of PFS, the result of NMA showed that almost all TKI-related regimens

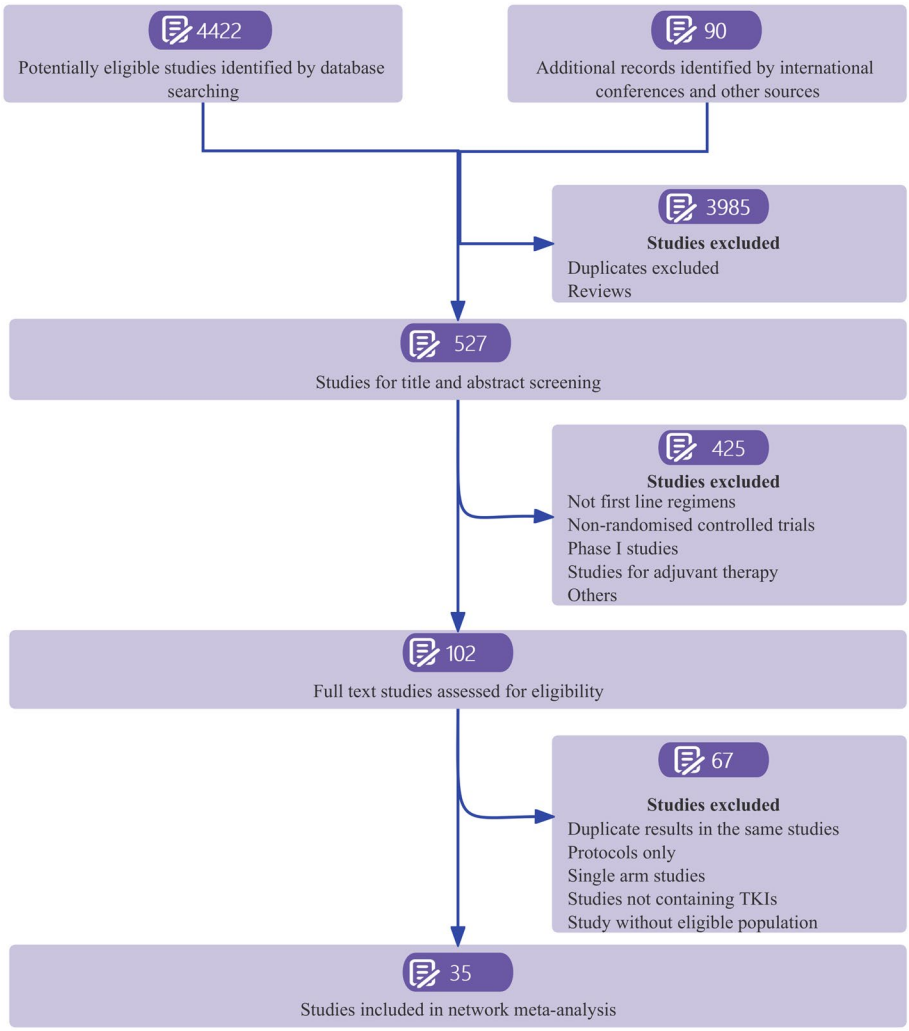


Fig. 1 Study selection

were superior over chemotherapy (all HRs < 1, and most of their 95% CIs did not cross 1) (Fig. 2C). Among TKI-related regimens, the 3G-TKI-based regimens were superior (3G-TKI-based regimens vs. the other regimens: all HRs < 1 but 95% CIs across 1.), specially OSI_RAM provided optimal PFS extension (OSI_RAM vs. the other regimens: all HRs ≤ 0.2 and most of their 95% CIs did not cross 1) (Fig. 2C). Except for OSI_RAM, there was a mild but not statistically significant tendency for the other 3G-TKI combination regimens to be superior to the 3G-TKI monotherapy (OSI_PB/AMI_LAZ/AUM_APA/OSI_BEV vs. FUR/AUM/OSI/BEF: all HRs < 1 but 95% CIs crossed 1) (Fig. 2C). Among the 3G-TKI monotherapies, PFS benefit was comparable (all HRs were nearly 1). Similar to 3G-TKIs, the combination regimens of 1G-TKIs were significantly superior to their monotherapy counterparts (GEF_PB vs. F_TKI: HR 0.5, 95% CI 0.3–0.83; ERL_BEV vs. F_TKI: HR 0.62, 95% CI 0.39–0.99) (Fig. 2C). In terms of OS, differing from PFS, there was no significant superiority of the 3G-TKI-related regimens over the other TKI regimens or chemotherapy (most HRs were nearly 1) (Fig. 2C). Notably, however, the NMA demonstrated that regimens of 1G-TKIs combined with chemotherapy significantly prolonged OS compared to chemotherapy or TKI monotherapy (GEF-PB/ERL_PF vs. AFA/F_TKI/PB/PF: all HRs < 1 and their 95% CIs did not cross 1) (Fig. 2C).

ORR

ORR was available in 35 RCTs (Fig. 3A). In line with the results of PFS, almost all TKI-related regimens showed superior efficacy over chemotherapy for NSCLC (all ORs > 1), with ERL_PF (ERL_PF vs. PF: OR 33.03, 95% CI 10.57–120.2) and GEF_PB (GEF_PB vs. PB: 8.48, 95% CI 4.8–15.03) being more evident (Fig. 3C). However, no superiority of 3G-TKIs over other TKIs was observed;

Table 1 Baseline characteristics of trials included in the network meta-analysis of patients with advanced EGFR mutated NSCLC

Trial	Year	Phase	Clinical trial number	Ethnicity	Sample size	Median age (years)	Sex Female/Male	EGFR mutation 19DEL	EGFR mutation 21L858R	Intervention arm	Control arm	Reported outcomes
The first-generation EGFR-TKIs												
IPASS	2009	III	NCT00322452	Asian	132/129	57/57	211/50	66/74	64/47	GEF(250 mg/d)	PF (pac 200 mg/m 2 + car (AUC = 5)/3w(6c))	PFS, OS, ORR
NEJ002	2010	III	UMIN000000376	Japan	114/114	64/63	145/83	58/59	49/48	GEF (250 mg/d)	PF (pac 200 mg/m 2 + car (AUC = 6)/3w)	PFS, OS, ORR, ≥3AEs
WJTOG3405	2010	III	UMIN000000539	Japan	86/86	64/64	119/53	50/37	36/49	GEF(250 mg/d)	PF (cis 80 mg/m2 + doc 60 mg/m2/3w(3-6c))	PFS, OS, ORR
OPTIMAL	2011	III	NCT00874419	China	82/72	57/59	91/63	43/39	39/33	ERL(150 mg/d))	PF (gem 1000 mg/m2 + car(AUC = 5)/3 w(4c))	PFS, OS, ORR, ≥3AEs
EURTAC	2012	III	NCT00446225	Non-Asian	86/87	65/65	126/47	57/58	29/29	ERL(150 mg/d)	PF (cis 75 mg/m2/3w + doc75 mg/m2/ or gem1250 mg/m2/3w)	PFS, OS, ORR, ≥3AEs
ENSURE	2015	III	NCT01342965	Asian	110/104	58/56	133/84	57/70	53/37	ERL(150 mg/d)	PF (gem 1250 mg/m2 + cis75 mg/m2/3w(4c))	PFS, OS, ORR,≥3AEs
CONVINCE	2017	III	NCT01719536	China	148/137	56/56	200/85	80/74	68/63	ICO(375 mg/d)	PB (cis75mg/m2 + pem 500 mg/m2/3w (4c) + pem 500 mg/m2/3w)	PFS, OS, ORR, ≥3AEs
The second-generation EGFR-TKIs												
LUX-Lung3	2013	III	NCT00949650	Global	230/115	62/61	224/121	113/57	91/47	AFA (40 mg/d)	PB (cis 75 mg/m2 + pem 500 mg/m2(6 c))	PFS, OS, ORR, ≥3AEs
Lux-Lung6	2014	III	NCT01121393	Asian	242/122	58/58	238/126	124/62	92/46	AFA (40 mg/d)	PF (gem1000 mg/m2 + cis 75 mg/m2/3w(6 c))	PFS, OS, ORR, ≥3AEs
Lux-Lung 7	2016	II	NCT01466660	Global	160/159	63/63	197/122	93/93	67/66	AFA (40 mg/d)	GEF(250 mg/d)	PFS, OS, ORR, ≥3AEs
ARCHER1050	2017	III	NCT01774721	Global	227/225	62/61	271/181	134/133	93/92	DAC (45 mg/d)	GEF(250 mg/d)	PFS, OS, ORR, ≥3AEs
The third-generation EGFR-TKIs												
FLAURA	2018	III	NCT02296125	Global	279/277	64/64	350/206	175/174	104/103	OSI (80 mg/d)	F_TKIs(GEF 250 mg/d or ERL 150 mg/d)	PFS, OS, ORR, ≥3AEs

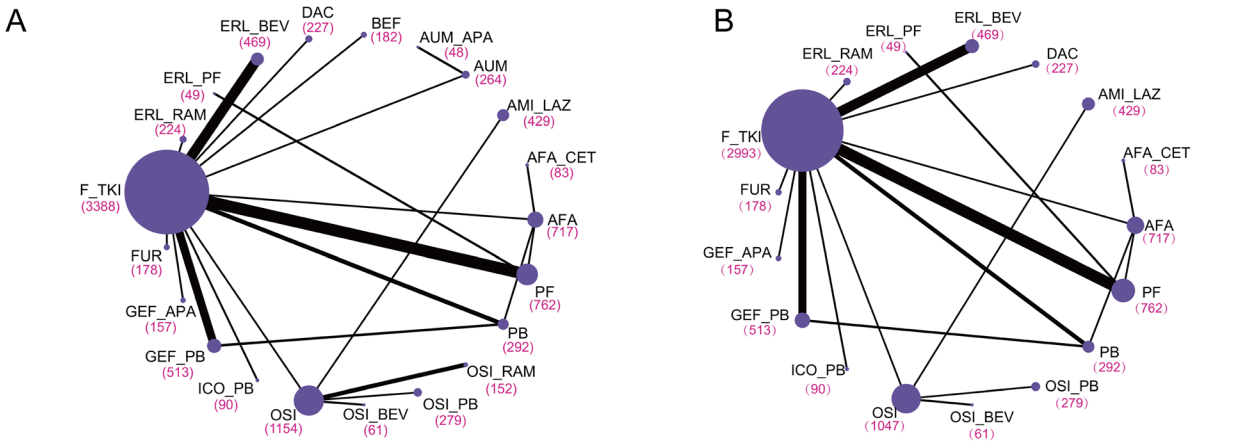
Table 1 (continued)

Trial	Year	Phase	Clinical trial number	Ethnicity	Sample size	Median age (years)	Sex Female/Male	EGFR mutation 19DEL	EGFR mutation 21L858R	Intervention arm	Control arm	Reported outcomes
The first-generation EGFR-TKIs												
AENEAS	2022	III	NCT03849768	China	214/215	59/62	269/160	140/141	74/74	AUM (110 mg/d)	GEF(250 mg/d)	PFS, OS, ORR, ≥3AEs
FURLONG	2022	III	NCT03787992	China	178/179	59/60	227/130	91/92	87/87	FUR(80 mg/d)	GEF(250 mg/d)	PFS, OS, ORR,≥3AEs
IBIO-103	2023	III	NCT04206072	China	182/180	60/58	218/144	117/117	65/63	BEF(75–100 mg/d)	ICO(375 mg /d)	PFS, ORR,≥3AEs
EGFR-TKI combination with angiogenesis inhibitor												
JO25567	2014	II	JapicCTI-111,390	Japan	75/77	67/67	96/56	40/40	35/37	ERL(150 mg/d) + BEV (15 mg/kg/3w)	ERL(150 mg/day)	PFS, OS, ORR,≥3AEs
NEJ026	2019	III	UMIN000017069	Japan	114/114	67/68	144/80	56/55	56/57	ERL (150 mg/d) + BEV (15 mg/kg/3w)	ERL(150 mg/d)	PFS, OS, ORR,≥3AEs
Stinchcombe et al.	2019	II	NCT01532089	Non-Asian	43/45	65/63	62/26	29/30	14/15	ERL(150 mg/d) + BEV (15 mg/kg/3w)	ERL(150 mg/d)	PFS, OS, ORR
RELAY	2019	III	NCT02411448	Global	224/225	65/64	283/166	123/120	99/105	ERL(150 mg/d) + RAM (10 mg/kg/2w)	ERL(150 mg/d)	PFS, OS, ORR,≥3AEs
CTONG1706	2020	III	NCT02824458	China	157/156	57/60	185/128	81/83	74/73	GEF (250 mg/d) + APA (500 mg/d)	GEF(250 mg/d)	PFS, OS, ORR,≥3AEs
ARTEMIS	2021	III	NCT02759614	China	157/154	57/59	193/118	82/79	75/75	ERL(150 mg/d) + BEV (15 mg/kg/3w)	ERL(150 mg/d)	PFS, OS, ORR,≥3AEs
WJOG9717L	2022	II	UMIN000030206	Japan	61/61	67/66	75/47	35/36	26/25	OSI(80 mg/d) + BEV(15 mg/kg/3w)	OSI(80 mg/d)	PFS, OS, ORR,≥3AEs
BEVERLY	2022	III	NCT02633189	non-Asian	80/80	68/66	102/58	44/44	32/34	ERL(150 mg/d) + BEV (15 mg/kg/3w)	ERL(150 mg/d)	PFS, OS, ORR,≥3AEs
ATTENTION	2023	III	ChiCTR2100047453	China	48/50	60/62	53/45	21/24	23/23	AUM(110 mg/d) + APA(250 mg/d)	AUM(110 mg/d)	PFS, ORR
OSIRAM-1	2023	II	jRCT2080224085 2021.11.12.	Japan	59/61	70/67	70/50	36/37	23/24	OSI(80 mg/d) + RAM(10 mg/kg/2w)	OSI(80 mg/d)	PFS, ORR
RAMOSE	2023	II	NCT03909334	non-Asian	93/46	99/40	NG	64/29	32/14	OSI(80 mg/d) + RAM(10 mg/kg/3w)	OSI(80 mg/d)	PFS, ORR,≥3AEs
EGFR-TKIs combination with chemotherapy												
FASTACT-2	2013	III	NCT00883779	Asian	49/48	NG	NG	NG	NG	ERL(150 mg/d) + PF (gem 1250 mg/m2 + car (AUC = 5) or cis 75 mg/m2/4w(6c))	PF (gem 1250 mg/m2 + car (AUC = 5) or cis 75 mg/m2/4w(6c))	PFS, OS, ORR,≥3AEs
JMIT	2016	II	NCT01469000	Asian	129/66	62/62	123/68	65/40	52/23	GEF(250 mg/d) + P (Pem 500 mg/m2/3w)		PFS, OS, ORR, ≥3AEs

Table 1 (continued)

Trial	Year	Phase	Clinical trial number	Ethnicity	Sample size	Median age (years)	Sex Female/Male	EGFR mutation 19DEL	EGFR mutation 21L858R	Intervention arm	Control arm	Reported outcomes
The first-generation EGFR-TKIs												
Han et al.	2017	II	NCT02148380	China	40	NG	25/15	21	19	GEF (250 mg/d) + PB (car(AUC = 5) + pem 500 mg/m2/4w)		PFS, OS, ORR
					41	NG	23/18	21	20	GEF(250 mg/d))		
					40	NG	23/17	20	20	PB (car(AUC = 5) + pem 500 mg/m2/4w)		
NEJ009	2019	III	UMIN000006340	Asian	170/172	65/64	222/120	93/95	69/67	GEF(250 mg/d) + PB(car (AUC = 5) + pem 500 mg/m2/3w (4-6c) + pem 500 mg/m2/3w)	GEF(250 mg/d)	PFS, OS, ORR,≥3AEs
Noronha et al.	2019	III	CTRI/2016/08/007149	India	174/176	54/56	169/181	107/109	60/60	GEF (250 mg/d) + PB (car (AUC = 5) + pem 500 mg/m2/3w(4c) + pem 500 mg/m2/3w)	GEF(250 mg/d)	PFS, OS, ORR,≥3AEs
Xu et al.	2019	II	NCT02031601	China	90/89	59/61	123/56	51/52	38/37	ICO (375 mg/d) + PB (pem 500 mg/m 2 /3w + car (AUC = 5))	ICO(375 mg /d)	PFS, OS, ORR
FLAURA2	2023	III	NCT04035486	Global	279/278	61/62	342/215	169/168	106/107	OSI(80 mg/d) + PB(pem 500 mg/m2 + cis 75 mg/m2/3w (4 c) + pem 500 mg/m2)	OSI(80 mg/d)	PFS, OS, ORR,≥3AEs
EGFR-TKIs combination with other treatment												
SWOG S1403	2020	II	NCT02438722	NG	83/85	67/66	112/56	53/54	30/31	AFA (40 mg/d) + CET (500 mg/m2/2w)	AFA (40 mg/d)	PFS, OS, ORR,≥3AEs
MARIPOSA	2023	III	NCT04487080	Global	429	64	275/154	258	172	AMI(1050 or 1400 mg/1-2w) + LAZ(240 mg/d)		PFS, OS, ORR,≥3AEs
					429	63	251/178	257	172	OSI (80 mg/d)		
					216	63	136/80	131	85	LAZ(240 mg/d)		

AEs Adverse events, *PFS* Progression-free survival, *OS* Overall survival, *ORR* Objective response rate, *NG* Not given, *AUC* Area under the concentration-time curve, PB Pemetrexed based chemotherapy, *PF* Pemetrexed free chemotherapy, *P/pem* Pemetrexed, *cis* cisplatin, *car* carboplatin, *gem* gemcitabine, *doc* docetaxel, *pac* paclitaxel, *F_TKI* First-generation TKI, *GEF* Gefitinib, *ERL* Erlotinib, *ICO* Icotinib, *AFA* Afatinib, *DAC* Dacomitinib, *OSI* Osimertinib, *AUM* Aumolertinib, *FUR* Furmonertinib, *BEF* Befotertinib, *LAZ* Lazertinib, *AMI* Amivantamab, *APA* Apatinib, *CET* Cetuximab, *RAM* Ramucirumab, *BEV* Bevacizumab, *c* cycles



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OS

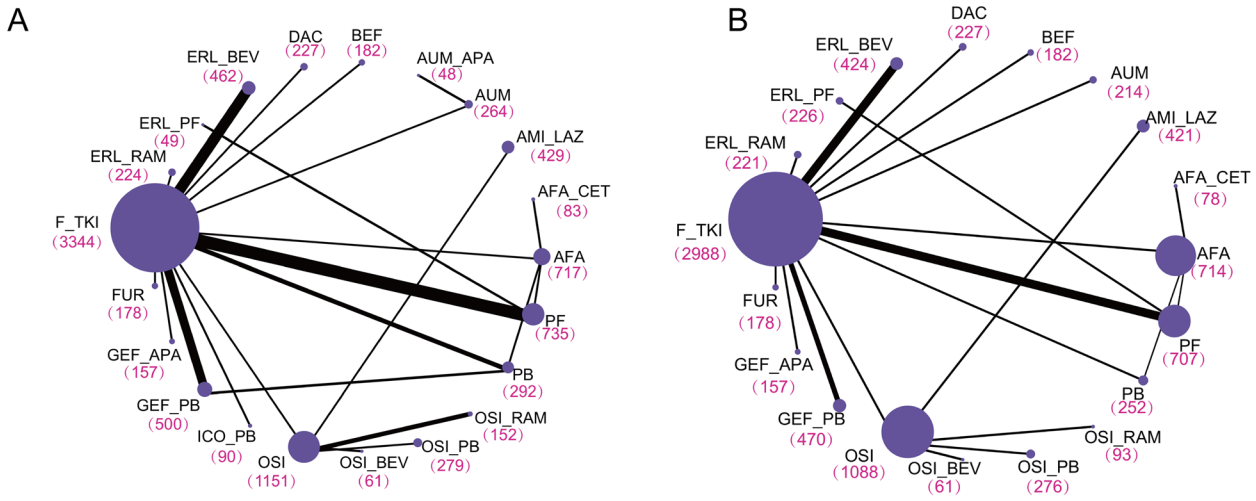
PFS	OSI_RAM	OSI_PB	AMI_LAZ	AUM_APA	OSI_BEV	FUR	AUM	OSI	BEF	AFA_CET	GEF_PB	ERL_RAM	ERL_BEV	ERL_PF	ICO_PB	GEF_APA	DAC	AFA	F_TKI	PB	PF
OSI_RAM		1.12 (0.67,1.88)		0.93 (0.43,2.05)	0.76 (0.4,1.47)		0.9 (0.61,1.32)		0.98 (0.46,2.11)	1.08 (0.64,1.88)	0.86 (0.43,1.72)	0.8 (0.47,1.35)	1.54 (0.7,3.4)	0.89 (0.45,1.75)	0.65 (0.33,1.29)	0.94 (0.52,1.73)	0.81 (0.47,1.38)	0.72 (0.44,1.17)	0.69 (0.4,1.18)	0.74 (0.45,1.24)
0.26 (0.08,0.94)	OSI_PB																				
0.23 (0.07,0.82)	0.89 (0.22,3.58)	AMI_LAZ		0.83 (0.39,1.78)	0.68 (0.36,1.27)		0.8 (0.57,1.12)		0.88 (0.42,1.84)	0.97 (0.59,1.63)	0.77 (0.4,1.5)	0.71 (0.43,1.17)	1.37 (0.64,2.97)	0.79 (0.41,1.5)	0.58 (0.3,1.13)	0.84 (0.48,1.49)	0.72 (0.43,1.19)	0.64 (0.4,1.01)	0.61 (0.36,1.02)	0.66 (0.41,1.08)
0.2 (0.03,1.53)	0.77 (0.09,6.33)	0.87 (0.11,7.17)	AUM_APA																		
0.19 (0.05,0.72)	0.72 (0.17,3.13)	0.81 (0.19,3.5)	0.93 (0.11,7.95)	OSI_BEV	0.82 (0.35,1.93)		0.96 (0.49,1.91)		1.05 (0.41,2.73)	1.16 (0.54,2.57)	0.93 (0.38,2.26)	0.85 (0.39,1.85)	1.65 (0.62,4.38)	0.95 (0.4,2.27)	0.7 (0.29,1.69)	1.01 (0.45,2.31)	0.86 (0.4,1.89)	0.77 (0.37,1.63)	0.73 (0.33,1.62)	0.8 (0.37,1.72)
0.17 (0.03,0.84)	0.63 (0.11,3.57)	0.72 (0.13,4)	0.82 (0.13,5.27)	0.88 (0.15,5.2)	FUR		1.17 (0.69,2)		1.28 (0.62,2.66)	1.42 (0.89,2.33)	1.13 (0.59,2.17)	1.04 (0.65,1.68)	2.01 (0.95,4.28)	1.16 (0.62,2.15)	0.86 (0.45,1.62)	1.24 (0.72,2.14)	1.05 (0.65,1.7)	0.94 (0.61,1.45)	0.9 (0.55,1.47)	0.97 (0.62,1.54)
0.16 (0.03,0.8)	0.61 (0.11,3.4)	0.69 (0.12,3.82)	0.78 (0.23,2.63)	0.84 (0.14,4.93)	0.95 (0.23,3.9)	AUM															
0.16 (0.08,0.36)	0.62 (0.23,1.69)	0.7 (0.26,1.88)	0.8 (0.13,5.1)	0.86 (0.29,2.53)	0.98 (0.24,4.02)	1.02 (0.25,4.18)	OSI		1.09 (0.57,2.12)	1.21 (0.84,1.79)	0.96 (0.54,1.72)	0.89 (0.61,1.27)	1.72 (0.86,3.43)	0.99 (0.57,1.71)	0.73 (0.41,1.28)	1.05 (0.67,1.67)	0.9 (0.61,1.3)	0.8 (0.59,1.09)	0.76 (0.51,1.12)	0.83 (0.59,1.17)
0.15 (0.03,0.76)	0.57 (0.1,3.24)	0.65 (0.11,3.64)	0.74 (0.11,4.77)	0.79 (0.13,4.69)	0.9 (0.22,3.74)	0.94 (0.23,3.92)	0.92 (0.22,3.8)	BEF													
0.08 (0.01,0.48)	0.32 (0.05,2)	0.36 (0.06,2.25)	0.41 (0.06,2.93)	0.44 (0.07,2.9)	0.5 (0.1,2.38)	0.52 (0.11,2.49)	0.51 (0.11,2.41)	0.55 (0.11,2.66)	AFA_CET	1.11 (0.59,2.07)	0.87 (0.41,1.87)	0.81 (0.44,1.49)	1.57 (0.66,3.62)	0.9 (0.43,1.91)	0.66 (0.31,1.41)	0.96 (0.49,1.89)	0.82 (0.48,1.41)	0.73 (0.4,1.31)	0.7 (0.38,1.27)	0.76 (0.42,1.36)
0.15 (0.04,0.58)	0.56 (0.12,2.49)	0.63 (0.14,2.8)	0.72 (0.14,3.75)	0.77 (0.16,3.64)	0.88 (0.29,2.69)	0.92 (0.3,2.83)	0.9 (0.29,2.74)	0.97 (0.31,3.03)	1.76 (0.48,6.45)	GEF_PB	0.8 (0.46,1.35)	0.73 (0.54,0.98)	1.42 (0.73,2.74)	0.82 (0.49,1.34)	0.6 (0.35,1.01)	0.87 (0.57,1.29)	0.74 (0.54,1)	0.66 (0.53,0.82)	0.63 (0.46,0.85)	0.68 (0.52,0.89)
0.12 (0.03,0.62)	0.47 (0.08,2.65)	0.54 (0.1,2.99)	0.61 (0.1,3.91)	0.66 (0.11,3.88)	0.74 (0.18,3.06)	0.78 (0.19,3.19)	0.76 (0.19,3.1)	0.83 (0.2,3.43)	1.5 (0.32,7.21)	0.85 (0.28,2.6)	ERL_RAM	0.92 (0.54,1.56)	1.79 (0.81,3.92)	1.03 (0.53,1.98)	0.76 (0.38,1.5)	1.1 (0.6,1.99)	0.93 (0.54,1.59)	0.83 (0.51,1.35)	0.79 (0.46,1.37)	0.86 (0.51,1.44)
0.12 (0.03,0.45)	0.45 (0.1,1.97)	0.51 (0.12,2.22)	0.58 (0.11,2.98)	0.63 (0.13,2.9)	0.71 (0.23,2.13)	0.74 (0.25,2.23)	0.73 (0.24,2.16)	0.79 (0.26,2.4)	1.42 (0.39,5.2)	0.81 (0.4,1.6)	0.95 (0.32,2.84)	ERL_BEV	1.94 (1.02,3.72)	1.11 (0.68,1.84)	0.82 (0.49,1.38)	1.19 (0.8,1.77)	1.01 (0.75,1.37)	0.9 (0.74,1.11)	0.86 (0.63,1.18)	0.94 (0.73,1.21)
0.1 (0.02,0.56)	0.39 (0.06,2.36)	0.44 (0.07,2.66)	0.51 (0.07,3.49)	0.54 (0.08,3.44)	0.62 (0.14,2.79)	0.65 (0.14,2.92)	0.63 (0.14,2.82)	0.69 (0.15,3.12)	1.24 (0.25,6.29)	0.71 (0.2,2.43)	0.83 (0.18,3.72)	0.87 (0.26,2.95)	ERL_PF	0.57 (0.27,1.24)	0.42 (0.2,0.92)	0.61 (0.3,1.24)	0.52 (0.28,0.99)	0.47 (0.25,0.86)	0.44 (0.23,0.86)	0.48 (0.26,0.88)
0.12 (0.02,0.64)	0.47 (0.08,2.7)	0.53 (0.09,3.03)	0.61 (0.09,3.98)	0.66 (0.11,3.95)	0.75 (0.18,3.11)	0.78 (0.19,3.26)	0.76 (0.18,3.19)	0.83 (0.2,3.49)	1.5 (0.31,7.34)	0.85 (0.27,2.67)	1 (0.24,4.16)	1.05 (0.34,3.22)	1.21 (0.26,5.6)	ICO_PB	0.74 (0.38,1.44)	1.07 (0.6,1.89)	0.91 (0.55,1.51)	0.81 (0.51,1.28)	0.77 (0.46,1.3)	0.84 (0.52,1.36)
0.1 (0.02,0.52)	0.39 (0.07,2.22)	0.44 (0.08,2.49)	0.51 (0.08,3.27)	0.55 (0.09,3.24)	0.62 (0.15,2.55)	0.65 (0.16,2.66)	0.63 (0.15,2.62)	0.69 (0.16,2.87)	1.24 (0.26,5.99)	0.71 (0.23,2.18)	0.83 (0.2,3.42)	0.87 (0.29,2.64)	1 (0.22,4.57)	0.83 (0.2,3.52)	GEF_APA	1.45 (0.81,2.58)	1.24 (0.73,2.08)	1.1 (0.68,1.76)	1.05 (0.62,1.79)	1.14 (0.69,1.87)
0.12 (0.03,0.62)	0.47 (0.08,2.64)	0.53 (0.1,2.96)	0.61 (0.1,3.9)	0.66 (0.11,3.82)	0.74 (0.18,3.02)	0.78 (0.19,3.18)	0.76 (0.19,3.08)	0.83 (0.2,3.41)	1.5 (0.32,7.15)	0.85 (0.28,2.58)	1 (0.25,4.05)	1.05 (0.35,3.13)	1.2 (0.27,5.44)	1 (0.24,4.16)	1.2 (0.29,4.9)	DAC	0.85 (0.57,1.27)	0.76 (0.54,1.07)	0.72 (0.48,1.1)	0.78 (0.54,1.15)
0.08 (0.02,0.34)	0.32 (0.07,1.48)	0.36 (0.08,1.67)	0.41 (0.08,2.23)	0.44 (0.09,2.17)	0.5 (0.15,1.64)	0.53 (0.16,1.71)	0.51 (0.16,1.66)	0.56 (0.17,1.85)	1.01 (0.36,2.81)	0.57 (0.26,1.26)	0.67 (0.21,2.19)	0.71 (0.32,1.55)	0.81 (0.23,2.85)	0.67 (0.2,2.24)	0.81 (0.25,2.66)	0.68 (0.21,2.17)	AFA	0.89 (0.72,1.11)	0.85 (0.66,1.1)	0.92 (0.73,1.17)
0.07 (0.02,0.26)	0.28 (0.07,1.14)	0.32 (0.08,1.28)	0.36 (0.08,1.73)	0.39 (0.09,1.68)	0.44 (0.16,1.2)	0.46 (0.17,1.25)	0.45 (0.17,1.21)	0.49 (0.18,1.35)	0.88 (0.27,2.96)	0.5 (0.3,0.83)	0.59 (0.22,1.6)	0.62 (0.39,0.99)	0.71 (0.23,2.23)	0.59 (0.21,1.64)	0.71 (0.26,1.94)	0.59 (0.22,1.59)	0.88 (0.47,1.66)	F_TKI	0.95 (0.75,1.21)	1.04 (0.89,1.21)
0.04 (0.01,0.15)	0.14 (0.03,0.64)	0.16 (0.03,0.73)	0.18 (0.03,0.97)	0.19 (0.04,0.94)	0.22 (0.07,0.71)	0.23 (0.07,0.74)	0.23 (0.07,0.72)	0.25 (0.07,0.8)	0.44 (0.13,1.54)	0.25 (0.12,0.52)	0.3 (0.09,0.95)	0.31 (0.14,0.67)	0.36 (0.1,1.27)	0.3 (0.09,0.97)	0.36 (0.11,1.15)	0.3 (0.09,0.94)	0.44 (0.21,0.9)	0.5 (0.27,0.92)	PB	1.08 (0.83,1.43)
0.03 (0.01,0.1)	0.1 (0.02,0.42)	0.11 (0.03,0.47)	0.13 (0.03,0.64)	0.14 (0.03,0.62)	0.15 (0.05,0.45)	0.16 (0.05,0.47)	0.16 (0.05,0.46)	0.17 (0.06,0.51)	0.31 (0.09,1.05)	0.18 (0.09,0.33)	0.21 (0.07,0.6)	0.22 (0.12,0.4)	0.25 (0.09,0.72)	0.21 (0.07,0.62)	0.25 (0.08,0.73)	0.21 (0.07,0.6)	0.31 (0.16,0.6)	0.35 (0.23,0.52)	0.7 (0.35,1.42)	PF

Fig. 2 Network meta-analysis of comparisons of progression-free survival (PFS) and overall survival (OS) in advanced EGFR mutated NSCLC. **A-B** Network diagrams of comparisons on PFS (**A**) and OS (**B**) in EGFR mutated NSCLC. Each circular node represents a type of regimen and each line represents a type of head-to-head comparison. The size of the node and the thickness of the line are weighted according to the number of trials evaluating each regimen and direct comparison, respectively. The total number of patients in each regimen was shown in brackets. **C** Pooled HR (95%CI) for OS (upper triangle) and PFS (lower triangle). Data in each cell are HR (95% CI) for the comparison of row-defining regimen versus lower column-defining regimen. HR < 1 favor row-defining regimen. Significant results were bolded and highlighted in red

rather, there was a significant superiority of 1G-TKI regimens (ERL_PF and GEF_PB) over the others (ERL_PF vs. OSI_RAM/AMI_LAZ/OSI_BEV/FUR/AUM/OSI/BEF/AFA_CET/ERL_RAM/DAC; GEF_PB vs. AUM/BEF/ERL_RAM/ERL_BEV/DAC/F_TKI: ORs > 1 and their 95% CIs did not cross 1). Among 3G-TKIs-related regimens, similar ORRs were observed (most ORs near 1 and all 95% CIs crossed 1) (Fig. 3C), meaning that combination with 3G-TKIs did not provide significant enhancement of ORR versus their monotherapy counterparts.

≥ *3AEs*

Twenty-nine RCTs were available for ≥ 3AEs (Fig. 3B). There was a clear tendency towards 1/2G-TKIs combination therapy being associated with a higher risk of adverse events compared to monotherapy (GEF_PB/AFA_CET/ERL_RAM/ERL_BEV/ERL_PF vs. F_TKI: all ORs > 1 and most their 95% CIs did not cross 1). Exceptionally, the tendency was not evident in the 3G-TKIs combination regimens, especially that ≥ 3AEs in the regimens of 3G-TKIs combined with angiogenesis



C

≥3AEs

ORR	OSI_RAM	OSI_PB	AMI_LAZ	AUM_APA	OSI_BEV	FUR	AUM	OSI	BEF	AFA_CET	GEF_PB	ERL_RAM	ERL_BEV	ERL_PF	ICO_PB	GEF_APA	DAC	AFA	F_TKI	PB	PF
OSI_RAM	0.35 (0.05,2.43)	0.41 (0.06,2.8)		1.23 (0.16,9.31)	1.81 (0.17,19.24)	1.01 (0.1,10.38)	1.66 (0.4,6.93)	0.5 (0.05,5.07)	0.17 (0.01,2.11)	0.36 (0.04,2.84)	0.47 (0.05,4.8)	0.26 (0.03,1.95)	0.32 (0.03,3.48)		0.12 (0.01,1.24)	0.42 (0.04,4.3)	0.66 (0.08,5.46)	1.04 (0.15,7.12)	0.51 (0.06,4.49)	0.27 (0.04,2.01)
0.54 (0.21,1.36)	OSI_PB	1.17 (0.19,7.24)		3.48 (0.51,23.96)	5.14 (0.52,50.91)	2.86 (0.31,27.08)	4.71 (1.29,17.24)	1.4 (0.15,13.24)	0.48 (0.04,5.63)	1.01 (0.14,7.42)	1.33 (0.14,12.57)	0.73 (0.1,5.06)	0.92 (0.09,9.15)		0.33 (0.03,3.22)	1.2 (0.13,11.3)	1.87 (0.25,14.05)	2.95 (0.48,18.47)	1.44 (0.17,11.79)	0.77 (0.11,5.23)
0.8 (0.32,1.97)	1.49 (0.63,3.49)	AMI_LAZ		2.98 (0.44,20.22)	4.39 (0.45,43.16)	2.45 (0.26,23.09)	**4.04 (1.13,14.41)**	1.2 (0.13,11.29)	0.41 (0.04,4.75)	0.86 (0.12,6.22)	1.14 (0.12,10.65)	0.62 (0.09,4.23)	0.78 (0.08,7.74)		0.28 (0.03,2.74)	1.03 (0.11,9.55)	1.6 (0.21,11.9)	2.53 (0.41,15.46)	1.23 (0.15,9.89)	0.66 (0.1,4.39)
0.66 (0.15,2.91)	1.22 (0.28,5.3)	0.82 (0.19,3.41)	AUM_APA																		
1.19 (0.33,4.51)	2.22 (0.63,8.0)	1.49 (0.43,5.39)	1.82 (0.33,10.5)	OSI_BEV	1.47 (0.14,15.78)	0.82 (0.08,8.42)	1.35 (0.32,5.65)	0.4 (0.04,4.13)	0.14 (0.01,1.73)	0.29 (0.04,2.32)	0.38 (0.04,3.91)	0.21 (0.03,1.59)	0.26 (0.02,2.83)		**0.1 (0.01,1.0)**	0.35 (0.03,3.48)	0.54 (0.06,4.4)	0.85 (0.12,5.81)	0.41 (0.04,3.64)	0.22 (0.03,1.63)
0.74 (0.23,2.43)	1.39 (0.43,4.39)	0.93 (0.3,2.9)	1.13 (0.28,4.62)	0.62 (0.14,2.7)	FUR	0.56 (0.08,3.72)	0.92 (0.14,6.1)	0.27 (0.04,1.83)	**0.09 (0.01,0.8)**	**0.2 (0.04,0.96)**	0.26 (0.04,1.72)	**0.14 (0.03,0.65)**	0.18 (0.02,1.28)		**0.06 (0.01,0.45)**	0.23 (0.04,1.56)	0.37 (0.07,1.85)	0.58 (0.15,2.28)	0.28 (0.05,1.57)	**0.15 (0.03,0.66)**
1 (0.33,3.04)	1.87 (0.64,5.49)	1.26 (0.44,3.6)	1.52 (0.58,4.15)	0.84 (0.2,3.38)	1.35 (0.5,3.61)	AUM	1.65 (0.26,10.26)	0.49 (0.08,3.11)	0.17 (0.02,1.35)	0.35 (0.08,1.61)	0.47 (0.07,2.91)	0.25 (0.06,1.09)	0.32 (0.05,2.18)		**0.12 (0.02,0.76)**	0.42 (0.07,2.62)	0.65 (0.13,3.11)	1.03 (0.28,3.77)	0.5 (0.09,2.66)	0.27 (0.06,1.1)
0.86 (0.43,1.72)	1.6 (0.86,2.98)	1.08 (0.6,1.96)	1.31 (0.35,4.93)	0.72 (0.23,2.16)	1.16 (0.44,3.07)	0.86 (0.36,2.06)	OSI	0.3 (0.05,1.86)	**0.1 (0.01,0.82)**	**0.21 (0.05,0.97)**	0.28 (0.05,1.76)	**0.15 (0.03,0.65)**	0.19 (0.03,1.3)		**0.07 (0.01,0.46)**	0.26 (0.04,1.59)	0.4 (0.08,1.87)	0.63 (0.17,2.27)	0.31 (0.06,1.6)	**0.16 (0.04,0.66)**
0.97 (0.32,2.96)	1.81 (0.62,5.34)	1.22 (0.43,3.54)	1.48 (0.4,5.64)	0.81 (0.2,3.32)	1.31 (0.49,3.54)	0.97 (0.4,2.37)	1.13 (0.47,2.74)	BEF	0.34 (0.04,2.81)	0.72 (0.15,3.31)	0.95 (0.15,6.02)	0.52 (0.12,2.24)	0.65 (0.09,4.46)		0.24 (0.04,1.56)	0.86 (0.13,5.45)	1.34 (0.27,6.43)	2.1 (0.57,7.83)	1.03 (0.19,5.45)	0.55 (0.13,2.29)
0.99 (0.27,3.64)	1.83 (0.52,6.57)	1.24 (0.36,4.37)	1.5 (0.35,6.66)	0.82 (0.17,3.93)	1.33 (0.41,4.39)	0.98 (0.33,3.01)	1.15 (0.39,3.48)	1.01 (0.34,3.09)	AFA_CET	2.1 (0.34,13.13)	2.77 (0.34,22.66)	1.51 (0.25,8.94)	1.9 (0.23,15.66)		0.69 (0.08,5.87)	2.49 (0.31,20.43)	3.89 (0.96,15.74)	**6.13 (1.19,32.02)**	2.99 (0.51,16.86)	1.6 (0.3,8.47)
0.44 (0.16,1.2)	0.82 (0.32,2.14)	0.55 (0.22,1.42)	0.67 (0.2,2.34)	0.37 (0.1,1.37)	0.59 (0.25,1.4)	**0.44 (0.21,0.92)**	0.51 (0.25,1.06)	**0.45 (0.22,0.95)**	0.45 (0.17,1.2)	GEF_PB	1.32 (0.29,6.06)	0.72 (0.25,2.03)	0.9 (0.18,4.55)		0.33 (0.07,1.58)	1.19 (0.26,5.45)	1.86 (0.57,5.98)	**2.92 (1.34,6.42)**	1.43 (0.37,5.24)	0.76 (0.29,2.01)
1 (0.33,3.01)	1.85 (0.64,5.49)	1.25 (0.43,3.6)	1.51 (0.41,5.71)	0.83 (0.2,3.36)	1.34 (0.5,3.61)	0.99 (0.41,2.41)	1.15 (0.48,2.79)	1.02 (0.42,2.49)	1.01 (0.33,3.02)	**2.26 (1.07,4.68)**	ERL_RAM	0.54 (0.12,2.35)	0.69 (0.1,4.65)		0.25 (0.04,1.64)	0.9 (0.14,5.66)	1.41 (0.29,6.68)	2.21 (0.6,8.11)	1.08 (0.2,5.71)	0.58 (0.14,2.39)
0.77 (0.29,2.07)	1.43 (0.56,3.72)	0.97 (0.39,2.46)	1.17 (0.35,4.06)	0.64 (0.17,2.39)	1.04 (0.45,2.43)	0.77 (0.37,1.6)	0.89 (0.44,1.84)	0.79 (0.38,1.65)	0.78 (0.29,2.09)	**1.75 (1.03,2.96)**	0.77 (0.37,1.61)	ERL_BEV	1.26 (0.26,6.19)		0.46 (0.1,2.13)	1.66 (0.38,7.37)	2.59 (0.85,7.96)	**4.07 (2.06,8.35)**	1.99 (0.55,7.05)	1.06 (0.43,2.66)
0.16 (0.03,0.71)	0.29 (0.06,1.28)	**0.19 (0.04,0.85)**	0.24 (0.04,1.28)	**0.13 (0.02,0.73)**	**0.21 (0.05,0.87)**	**0.15 (0.04,0.59)**	**0.18 (0.04,0.69)**	**0.16 (0.04,0.62)**	**0.16 (0.03,0.69)**	0.35 (0.09,1.23)	**0.16 (0.04,0.61)**	**0.2 (0.05,0.7)**	ERL_PF		0.36 (0.05,2.61)	1.31 (0.19,9.18)	2.05 (0.42,10.05)	3.23 (0.79,13.54)	1.58 (0.27,8.9)	0.84 (0.23,3.11)
0.55 (0.16,1.86)	1.02 (0.31,3.34)	0.69 (0.22,2.22)	0.83 (0.21,3.54)	0.46 (0.1,2.0)	0.74 (0.25,2.23)	0.55 (0.2,1.52)	0.64 (0.23,1.75)	0.56 (0.2,1.56)	0.56 (0.16,1.85)	1.25 (0.51,3.01)	0.55 (0.2,1.51)	0.71 (0.29,1.72)	3.54 (0.83,16.4)	ICO_PB						
0.91 (0.29,2.86)	1.69 (0.56,5.14)	1.14 (0.38,3.42)	1.38 (0.36,5.41)	0.76 (0.18,3.16)	1.22 (0.44,3.43)	0.91 (0.36,2.31)	1.06 (0.42,2.66)	0.94 (0.37,2.38)	0.93 (0.29,2.86)	2.06 (0.94,4.51)	0.92 (0.36,2.32)	1.18 (0.53,2.57)	**5.84 (1.5,25.81)**	1.65 (0.58,4.79)	GEF_APA	3.61 (0.55,23.64)	**5.63 (1.12,28.07)**	**8.86 (2.3,34.42)**	4.33 (0.76,23.88)	2.32 (0.53,10.08)
0.93 (0.3,2.79)	1.71 (0.59,4.99)	1.16 (0.41,3.32)	1.4 (0.38,5.32)	0.77 (0.19,3.09)	1.24 (0.46,3.32)	0.92 (0.38,2.22)	1.07 (0.45,2.55)	0.94 (0.39,2.29)	0.93 (0.31,2.79)	**2.09 (1.01,4.28)**	0.93 (0.38,2.24)	1.2 (0.58,2.44)	**5.92 (1.56,24.94)**	1.67 (0.61,4.6)	1.01 (0.4,2.55)	DAC	1.56 (0.32,7.46)	2.45 (0.67,9.05)	1.2 (0.22,6.31)	0.64 (0.15,2.65)
0.72 (0.26,1.99)	1.33 (0.51,3.56)	0.9 (0.35,2.35)	1.08 (0.32,3.83)	0.6 (0.16,2.26)	0.96 (0.41,2.33)	0.71 (0.34,1.55)	0.83 (0.4,1.77)	0.73 (0.34,1.59)	0.73 (0.32,1.62)	1.62 (0.92,2.87)	0.72 (0.34,1.54)	0.93 (0.53,1.64)	**4.6 (1.34,18.1)**	1.3 (0.53,3.27)	0.79 (0.35,1.78)	0.78 (0.37,1.66)	AFA	1.57 (0.67,3.8)	0.77 (0.27,2.15)	0.41 (0.17,1.02)
1.09 (0.44,2.73)	2.03 (0.86,4.88)	1.37 (0.59,3.23)	1.66 (0.53,5.42)	0.91 (0.25,3.19)	1.47 (0.69,3.16)	1.09 (0.59,2.05)	1.27 (0.69,2.34)	1.12 (0.6,2.11)	1.11 (0.44,2.74)	**2.48 (1.69,3.6)**	1.1 (0.59,2.05)	1.42 (0.98,2.05)	**7.01 (2.14,26.12)**	1.99 (0.9,4.49)	1.2 (0.6,2.4)	1.19 (0.64,2.2)	1.53 (0.99,2.33)	F_TKI	0.49 (0.16,1.38)	**0.26 (0.15,0.46)**
3.74 (1.36,10.54)	**6.94 (2.66,18.88)**	**4.68 (1.81,12.46)**	**5.68 (1.67,20.27)**	3.12 (0.81,11.84)	**5.03 (2.08,12.34)**	**3.72 (1.74,8.24)**	**4.33 (2.05,9.41)**	**3.83 (1.77,8.47)**	**3.79 (1.46,9.87)**	**8.48 (4.8,15.03)**	**3.76 (1.75,8.24)**	**4.84 (2.72,8.77)**	**24.05 (6.78,96.17)**	**6.78 (2.74,17.38)**	**4.1 (1.82,9.42)**	**4.05 (1.91,8.82)**	**5.22 (3.18,8.66)**	**3.41 (2.19,5.45)**	PB	0.54 (0.17,1.71)
5.16 (2,13.62)	**9.58 (3.9,24.41)**	**6.45 (2.67,16.19)**	**7.83 (2.43,26.62)**	**4.3 (1.17,15.63)**	**6.94 (3.1,15.89)**	**5.13 (2.61,10.42)**	**5.97 (3.08,11.91)**	**5.29 (2.66,10.74)**	**5.23 (2.07,13.18)**	**11.68 (7.24,18.94)**	**5.18 (2.61,10.45)**	**6.68 (4.19,10.76)**	**33.03 (10.57,120.2)**	**9.37 (4.02,22.37)**	**5.66 (2.69,12.12)**	**5.59 (2.86,11.23)**	**7.2 (4.6,11.35)**	**4.71 (3.53,6.4)**	**1.38 (0.82,2.31)**	PF

Fig. 3 Network meta-analysis of comparisons of objective response rate (ORR) and grade 3 or higher adverse events (≥ 3AEs) in advanced EGFR mutated NSCLC. **A-B** Network diagrams of comparisons on ORR (**A**) and ≥ 3AEs (**B**). Each circular node represents a type of regimen and each line represents a type of head-to-head comparison. The size of the nodes and the thickness of the lines are weighted according to the number of trials evaluating each regimen and direct comparison, respectively. The total number of patients in each regimen was shown in brackets. **C** Pooled estimates of the network meta-analysis of ORR and ≥ 3AEs. Data in each cell are OR (95% CI) for the comparison of row-defining regimen versus column-defining regimen. OR more than 1 favours row-defining treatment. Significant results were bolded and highlighted in red

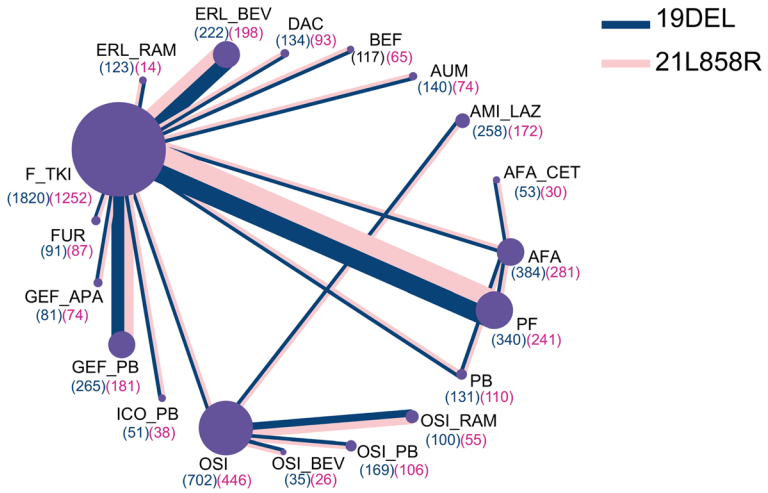
inhibitors were equivalent to that of monotherapy (ORs near 1) (Fig. 3C). In addition, varying types of ≥ 3AEs across all regimens were calculated and ranked. AFA, FUR, and ERL_BEV had the highest probability of ranking first for stomatitis, diarrhea and pruritus, respectively; AFA_CET had the highest probability of causing paronychia, dry skin and elevated ALT; The probability of ranking first for hypertension, nausea, constipation was highest in ERL_PF, and for rash, oral mucositis, cough, and elevated ALT was highest in AUM_APA (Figure S2). The incidence of each type of ≥ 3AEs in each regimen was exhibited in Figure S3.

Subgroup analysis based on various clinicopathological characteristics

EGFR mutation subtype

As shown in Figs. 4A and 30 RCTs were enrolled for both the 19DEL and 21L858R subgroup analyses for PFS. Whether 19DEL or 21L858R, TKI treatment was superior to chemotherapy in terms of PFS (Fig. 4B). In the 19DEL subgroup, the 3G-TKIs showed greater efficacy than the others, especially in combination regimens (Fig. 4B), but not statistically significant. Similar trends were observed in the 21L858R, except for OSI_BEV (Fig. 4B). Of note, compared with the 19DEL, AFA_CET provided more PFS benefit for the 21L858R (e.g., HR of AFA_CET and AFA in 19DEL vs. 21L858R: 1.23 vs. 0.7) (Fig. 4B). In terms of OS, there were 13 RCTs available both in the 19DEL and 21L858R analyses, involving 9 regimens

A



B

PFS (21L858R)

PFS (19DEL)																		
OSI_RAM	1.19 (0.56,2.63)	0.96 (0.47,1.98)	0.6 (0.23,1.59)	0.7 (0.3,1.72)	0.63 (0.26,1.55)	0.75 (0.41,1.41)	0.61 (0.23,1.59)	0.72 (0.25,2.05)	0.69 (0.31,1.57)	0.62 (0.26,1.48)	0.64 (0.29,1.41)	0.68 (0.26,1.74)	0.53 (0.22,1.3)	0.61 (0.26,1.43)	0.5 (0.22,1.14)	**0.38 (0.18,0.82)**	**0.3 (0.13,0.7)**	**0.18 (0.08,0.4)**
1.35 (0.56,3.16)	OSI_PB	0.81 (0.44,1.45)	0.5 (0.21,1.2)	0.59 (0.28,1.28)	0.53 (0.24,1.17)	**0.63 (0.4,0.98)**	0.51 (0.22,1.2)	0.6 (0.23,1.56)	0.59 (0.3,1.17)	0.52 (0.24,1.11)	0.54 (0.27,1.06)	0.57 (0.24,1.32)	**0.45 (0.2,0.98)**	0.51 (0.24,1.08)	**0.42 (0.21,0.85)**	**0.32 (0.17,0.6)**	**0.25 (0.12,0.53)**	**0.15 (0.08,0.29)**
1.25 (0.53,2.86)	0.92 (0.38,2.26)	AMI_LAZ	0.63 (0.26,1.44)	0.74 (0.36,1.53)	0.66 (0.32,1.4)	0.78 (0.53,1.14)	0.63 (0.28,1.44)	0.74 (0.29,1.88)	0.73 (0.38,1.37)	0.64 (0.31,1.32)	0.66 (0.35,1.26)	0.71 (0.32,1.58)	0.55 (0.26,1.17)	0.63 (0.31,1.29)	0.52 (0.27,1.01)	**0.4 (0.22,0.7)**	**0.31 (0.15,0.63)**	**0.19 (0.1,0.35)**
1.3 (0.45,3.67)	0.96 (0.32,2.86)	1.05 (0.36,3.06)	OSI_BEV	1.18 (0.45,3.12)	1.06 (0.4,2.84)	1.25 (0.59,2.72)	1.01 (0.36,2.83)	1.19 (0.39,3.68)	1.15 (0.47,2.87)	1.03 (0.39,2.73)	1.06 (0.43,2.65)	1.14 (0.41,3.2)	0.88 (0.33,2.38)	1.01 (0.39,2.64)	0.83 (0.33,2.12)	0.64 (0.27,1.51)	0.5 (0.19,1.31)	**0.3 (0.12,0.73)**
1 (0.33,2.94)	0.74 (0.23,2.3)	0.8 (0.26,2.46)	0.76 (0.21,2.75)	FUR	0.9 (0.47,1.73)	1.06 (0.56,1.97)	0.86 (0.4,1.8)	1.01 (0.43,2.38)	0.98 (0.57,1.67)	0.87 (0.47,1.62)	0.9 (0.53,1.53)	0.97 (0.46,2)	0.75 (0.38,1.45)	0.86 (0.46,1.6)	0.71 (0.4,1.23)	**0.54 (0.35,0.84)**	**0.43 (0.23,0.78)**	**0.25 (0.15,0.42)**
0.9 (0.3,2.56)	0.66 (0.22,2.01)	0.71 (0.24,2.15)	0.68 (0.2,2.4)	0.9 (0.35,2.32)	AUM	1.18 (0.62,2.23)	0.96 (0.45,2.03)	1.13 (0.47,2.66)	1.09 (0.63,1.91)	0.97 (0.51,1.86)	1.01 (0.57,1.74)	1.07 (0.51,2.24)	0.84 (0.42,1.64)	0.96 (0.5,1.82)	0.79 (0.44,1.4)	**0.6 (0.37,0.97)**	**0.47 (0.25,0.88)**	**0.28 (0.16,0.48)**
0.81 (0.45,1.42)	0.6 (0.31,1.14)	0.65 (0.35,1.21)	0.62 (0.26,1.51)	0.81 (0.32,2.08)	0.91 (0.37,2.25)	OSI	0.81 (0.39,1.68)	0.95 (0.41,2.23)	0.93 (0.55,1.56)	0.82 (0.45,1.52)	0.85 (0.51,1.43)	0.91 (0.44,1.85)	0.71 (0.37,1.35)	0.81 (0.44,1.49)	0.67 (0.39,1.15)	**0.51 (0.33,0.78)**	**0.4 (0.22,0.73)**	**0.24 (0.14,0.39)**
0.83 (0.28,2.42)	0.61 (0.2,1.89)	0.66 (0.22,2.03)	0.63 (0.18,2.26)	0.83 (0.32,2.2)	0.93 (0.36,2.38)	1.02 (0.41,2.58)	BEF	1.17 (0.46,3.05)	1.14 (0.59,2.23)	1.01 (0.49,2.14)	1.05 (0.54,2.01)	1.12 (0.49,2.57)	0.87 (0.4,1.89)	0.99 (0.48,2.09)	0.82 (0.41,1.64)	0.63 (0.35,1.15)	0.49 (0.24,1.03)	**0.29 (0.15,0.56)**
0.43 (0.13,1.38)	0.32 (0.09,1.08)	0.34 (0.1,1.16)	0.33 (0.08,1.28)	0.43 (0.14,1.27)	0.48 (0.17,1.38)	0.53 (0.19,1.5)	0.52 (0.18,1.51)	AFA_CET	0.97 (0.45,2.11)	0.87 (0.37,2.01)	0.9 (0.41,1.93)	0.95 (0.38,2.41)	0.75 (0.31,1.77)	0.85 (0.36,1.99)	0.7 (0.37,1.33)	0.54 (0.26,1.1)	**0.42 (0.2,0.89)**	**0.25 (0.12,0.52)**
0.67 (0.26,1.65)	0.49 (0.18,1.3)	0.53 (0.2,1.38)	0.51 (0.16,1.58)	0.67 (0.3,1.47)	0.75 (0.35,1.58)	0.82 (0.39,1.7)	0.81 (0.36,1.73)	1.56 (0.61,3.86)	GEF_PB	0.89 (0.53,1.5)	0.92 (0.61,1.38)	0.98 (0.51,1.87)	0.76 (0.43,1.34)	0.87 (0.52,1.47)	0.72 (0.46,1.12)	**0.55 (0.41,0.74)**	**0.43 (0.26,0.72)**	**0.26 (0.17,0.38)**
0.54 (0.18,1.53)	0.4 (0.13,1.2)	0.43 (0.14,1.29)	0.41 (0.12,1.44)	0.54 (0.21,1.39)	0.6 (0.24,1.51)	0.66 (0.27,1.63)	0.65 (0.25,1.65)	1.25 (0.44,3.62)	0.8 (0.38,1.73)	ERL_RAM	1.03 (0.61,1.73)	1.1 (0.54,2.26)	0.86 (0.45,1.64)	0.98 (0.53,1.81)	0.81 (0.47,1.41)	**0.62 (0.4,0.95)**	**0.49 (0.27,0.88)**	**0.29 (0.17,0.48)**
0.59 (0.23,1.48)	0.44 (0.17,1.17)	0.47 (0.18,1.25)	0.45 (0.15,1.43)	0.6 (0.27,1.31)	0.66 (0.32,1.41)	0.73 (0.35,1.53)	0.72 (0.33,1.55)	1.39 (0.56,3.47)	0.89 (0.53,1.54)	1.11 (0.52,2.34)	ERL_BEV	1.07 (0.57,2.03)	0.83 (0.47,1.47)	0.95 (0.56,1.6)	0.78 (0.5,1.23)	**0.6 (0.45,0.8)**	**0.47 (0.28,0.79)**	**0.28 (0.19,0.41)**
0.52 (0.17,1.55)	0.38 (0.12,1.21)	0.41 (0.13,1.3)	0.4 (0.11,1.45)	0.52 (0.19,1.4)	0.58 (0.22,1.52)	0.64 (0.25,1.65)	0.63 (0.24,1.67)	1.21 (0.41,3.62)	0.78 (0.35,1.77)	0.96 (0.37,2.54)	0.87 (0.39,1.94)	ICO_PB	0.78 (0.37,1.65)	0.89 (0.43,1.81)	0.73 (0.38,1.41)	**0.56 (0.32,1)**	**0.44 (0.22,0.88)**	**0.26 (0.14,0.49)**
0.52 (0.17,1.52)	0.38 (0.12,1.19)	0.42 (0.14,1.28)	0.4 (0.11,1.43)	0.52 (0.2,1.38)	0.58 (0.23,1.5)	0.64 (0.25,1.63)	0.63 (0.24,1.64)	1.21 (0.41,3.58)	0.78 (0.36,1.73)	0.97 (0.38,2.5)	0.88 (0.4,1.91)	1 (0.37,2.69)	GEF_APA	1.14 (0.6,2.19)	0.94 (0.52,1.72)	0.72 (0.45,1.17)	0.57 (0.3,1.07)	**0.34 (0.19,0.58)**
0.64 (0.22,1.81)	0.47 (0.16,1.42)	0.51 (0.17,1.52)	0.48 (0.14,1.7)	0.64 (0.25,1.64)	0.71 (0.28,1.77)	0.78 (0.32,1.93)	0.77 (0.3,1.93)	1.48 (0.52,4.25)	0.95 (0.46,2.05)	1.18 (0.47,2.95)	1.07 (0.51,2.23)	1.23 (0.47,3.17)	1.22 (0.48,3.11)	DAC	0.82 (0.47,1.44)	**0.63 (0.41,0.97)**	**0.5 (0.27,0.9)**	**0.29 (0.18,0.49)**
0.53 (0.2,1.36)	0.39 (0.14,1.07)	0.42 (0.16,1.14)	0.4 (0.13,1.3)	0.53 (0.23,1.21)	0.59 (0.27,1.3)	0.65 (0.3,1.41)	0.63 (0.28,1.43)	1.23 (0.61,2.47)	0.79 (0.44,1.45)	0.98 (0.44,2.16)	0.89 (0.49,1.58)	1.02 (0.44,2.35)	1.01 (0.44,2.3)	0.83 (0.38,1.81)	AFA	0.77 (0.54,1.07)	**0.6 (0.4,0.9)**	**0.36 (0.24,0.52)**
0.35 (0.15,0.8)	**0.26 (0.1,0.64)**	**0.28 (0.12,0.68)**	**0.27 (0.09,0.79)**	**0.35 (0.17,0.7)**	**0.39 (0.2,0.75)**	**0.43 (0.23,0.81)**	**0.42 (0.21,0.82)**	0.82 (0.35,1.88)	**0.52 (0.36,0.78)**	0.65 (0.34,1.25)	**0.59 (0.41,0.85)**	0.67 (0.33,1.37)	0.67 (0.34,1.33)	0.55 (0.29,1.04)	0.66 (0.42,1.04)	F_TKI	0.78 (0.52,1.2)	**0.47 (0.36,0.6)**
0.18 (0.07,0.5)	**0.14 (0.05,0.39)**	**0.15 (0.05,0.42)**	**0.14 (0.04,0.48)**	**0.18 (0.08,0.45)**	**0.21 (0.09,0.49)**	**0.23 (0.1,0.53)**	**0.22 (0.09,0.53)**	0.43 (0.18,1.06)	**0.28 (0.14,0.55)**	**0.34 (0.15,0.81)**	**0.31 (0.16,0.6)**	**0.36 (0.14,0.88)**	**0.35 (0.15,0.86)**	**0.29 (0.12,0.68)**	**0.35 (0.2,0.61)**	**0.53 (0.3,0.92)**	PB	**0.6 (0.37,0.96)**
0.1 (0.04,0.24)	**0.07 (0.03,0.19)**	**0.08 (0.03,0.2)**	**0.08 (0.02,0.23)**	**0.1 (0.05,0.21)**	**0.11 (0.05,0.23)**	**0.12 (0.06,0.25)**	**0.12 (0.06,0.25)**	**0.24 (0.1,0.54)**	**0.15 (0.09,0.25)**	**0.19 (0.09,0.38)**	**0.17 (0.1,0.27)**	**0.2 (0.09,0.41)**	**0.19 (0.09,0.41)**	**0.16 (0.08,0.32)**	**0.19 (0.12,0.31)**	**0.29 (0.21,0.39)**	**0.55 (0.29,0.99)**	PF

Fig. 4 Subgroup network meta-analysis of comparisons of PFS in EGFR mutated NSCLC based on EGFR mutation subtypes. **A** Network diagrams of comparisons on PFS for patients with 19DEL and 21L858R. Each circular node represents a type of regimen and each line represents a type of head-to-head comparison. The size of the node and the thickness of the line are weighted according to the number of trials evaluating each regimen and direct comparison, respectively. The total number of patients in each regimen was shown in brackets. **B** Pooled HR (95% CI) for PFS of patients with 19DEL (lower triangle) and 21L858R (upper triangle). Result in each cell is presented as HR (95% CI) for the comparison of row-defining regimen versus column-defining regimen. HR < 1 favor row-defining regimen. Significant results were bolded and highlighted in red

(Figure S4A). It was found that AFA significantly reduced the risk of death more than PB for the 19DEL instead of 21L858R (HR: 0.56, 95% CI 0.34–0.92) (Figure S4B). No significant differences were observed among the other regimens whether in the 19DEL or 21L858R subgroup (Figure S4B).

Sex

There were 29 RCTs available in the PFS analyses for the male and female (Figure S5A). Most TKIs-related regimens showed better efficacy compared with chemotherapy both in the female and male (Figure S5B). In line with the overall analysis, 3G-TKI-related regimens achieved superior PFS benefit than that of the other TKI regimens (Figure S5B). However, obvious disparities were observed between genders for OSI_RAM and ICO_PB. In the female, PFS was dramatically prolonged in patients receiving OSI_RAM than those receiving the other TKI regimens (all HRs < 1 and most of their 95% CIs did not cross 1). In contrast, the efficacy of OSI_RAM was greatly reduced in the male (most HRs > 1) (Figure S5B). A contrary tendency emerged in ICO_PB. In other words, the male benefited more from ICO_PB than the female (Figure S5B). As for OS, 13 RCTs were available in the male and female (Figure S5C). As shown in Figure S5D, no significant difference was identified among 9 regimens.

Smoking history

Twenty-six RCTs were enrolled in the PFS analysis of the smoking subgroup (Figure S6A). The NMA showed that more TKI regimens provided PFS benefits for non-smokers than smokers (Figure S6B). Similar to the gender subgroup, the efficacy of OSI_RAM and ICO_PB was significantly different between smoking subgroups, with OSI_RAM favoring non-smokers (e.g., HR of OSI_RAM and PB in non-smokers vs. smokers: 0.26 vs. 0.85) and ICO_PB favoring smokers (e.g., HR of ICO_PB and F_TKI in non-smokers vs. in smokers: 0.68 vs. 0.32) (Figure S6B). There were 13 RCTs available for OS analysis, involving 9 treatment regimens, with no statistical differences among them (Figure S6C-D).

Age

21 RCTs were available in age subgroup analysis for PFS (Figure S7A). In general, when compared with chemotherapy, TKI-related regimens were superior in both age subgroups (TKI vs. PF: all HR < 1 and most 95% CIs did not cross 1) (Figure S7B). However, ICO_PB displayed a pronounced difference between age subgroups, being significantly better in the age ≥ 65 than in the age < 65 (e.g., HR of ICO_PB and F_TKI in the age ≥ 65 vs. in the age < 65: 0.29 vs. 0.85) (Figure S7B). Regarding OS, a total of 9 RCTs were available with 9 regimens involved (Figure S7C). Regardless of being age ≥ 65 or age < 65, no significant survival differences were observed between the regimens (Figure S7D).

ECOG PS

Regarding the PFS analysis of the Eastern Cooperative Oncology Group performance status (ECOG PS) subgroup, a total of 21 RCTs were available (Figure S8A). The findings were similar to those of the overall analysis. That is, TKI regimens were superior over chemotherapy, and 3G-TKI regimens were superior over the other TKI regimens, especially combination regimens (OSI_PB, AMI_LAZ, and OSI_BEV) (Figure S8B). Regarding OS, 8 RCTs were available (Figure S8C). No significant differences were found among regimens (Figure S8D).

Brain metastasis

As for PFS analysis, 15 RCTs were enrolled (Figure S9A). In general, the 3G-TKI regimens were favorable to the others. In the brain metastasis, the PFS of OS_PB was significantly longer than the F_TKI (HR: 0.22, 95% CI 0.05–0.89) (Figure S9B). A similar result was obtained in the non-brain metastasis, but no statistical significance (OSI_PB vs. F_TKI: 0.34, 95% CI 0.11–1.07) (Figure S9B). Nevertheless, some other 3G-TKI regimens, such as AMI_LZA (0.32, 95% CI 0.1–0.97) and FUR (0.42, 95% CI 0.19–0.94), were demonstrated to significantly prolong PFS compared to F_TKI for the non-brain metastasis (Figure S9B). Only 4 RCTs were available and no difference was identified for OS analysis (Figure S9C-D).

Ethnicity

Regarding PFS, 30 RCTs and 11 RCTs were available for Asian and non-Asian subgroups, respectively (Figure S10A-B). For Asian, PFS was dramatically prolonged in patients receiving TKI regimens compared to those receiving chemotherapy alone (all HRs < 1 and all their 95% CIs did not cross 1) (Figure S10C). Among all TKI regimens, the 3G-TKI regimen was superior, with OSI_RAM being the most pronounced (OSI_RAM vs. the other regimens: all HRs < 1) (Figure S10C). With similar results to the Asian, OSI_RAM was more effective than the others for non-Asian (Figure S10C). Regarding OS, 23 RCTs and 7 RCTs were available for Asian and non-Asian subgroups, respectively (Figure S11A-B). In the Asian subgroup, findings were similar to the overall analysis, with GEF_PB and ERL_PF being the two most effective regimens for reducing the risk of death (Figure S11C). There were 7 regimens included in the non-Asian group analysis, with a mild tendency for OSI being more favorable than the others (all HRs < 1 while their 95% CIs crossed 1) (Figure S11C).

Rank probabilities

To further assess the efficacy and safety of the various regimens, the probability of all regimens being in each ranking was calculated and each regimen was ranked based on SUCRA. As shown in Fig. 5 and Figure S12-S13, regardless of the overall analysis or subgroup analysis, the results are nearly consistent with the NMAs using HRs above.

The results of the overall analysis are shown in Fig. 5A-C. It was found that the 3G-TKI combination regimens provided the optimal PFS efficacy, with OSI_RAM, OSI_PB, AMI_LAZ, AUM_APA, and OSI_BEV being ranked 1st, 2nd, 3rd, 4th, and 5th, respectively. The 3G-TKI regimens exhibited favorable efficacy in terms of OS as well (AMI_LAZ ranked 3rd, OSI_PB ranked 4th). However, the regimen that provided the optimal OS prolongation was ER_PF (ranked 1st), followed by GEF_PB (ranked 2nd). In line with OS, ER_PF (ranked 1st) and GEF_PB (ranked 2nd) were the two optimal regimens for ORR. For the 3G-TKI combination regimens, the ranking varied widely (OSI_RAM: ranked 15th; OSI_PB: 3rd; AMI_LAZ: 9th; AUM_APA: 5th; OSI_BEV: 18th) for ORR. Regarding safety and toxicity, combination regimens increased the risk of ≥3AEs, with GEF_APA, AFA_CET, ERL_BEV, and ERL_PF being ranked 1st, 2nd, 3rd, and 5th, respectively. A similar but mild tendency was found in 3G-TKI regimens. Specifically, the addition of other agents to 3G-TKI will slightly increase the odds of ≥3AEs (OSI_PB: 7th, AMI_LAZ: 8th; OSI: 19th; AUM: 15th; FUR: 18th). Besides, it is worthy of noting that the ≥3AEs of OSI_RAM is almost equivalent to that of OSI monotherapy (14th vs. 16th).

Next, PFS and OS were ranked among all regimens in various subgroups and displayed in Fig. 5B-C and Figure S12A-E. With respect to PFS, we found that the subgroup and overall analyses were generally consistent. Obviously, there were tendencies that the 3G-TKI combination regimens, including OSI_RAM, OSI_PB, AMI_LAZ, and OSI_BEV, exhibited superior and stable rankings in most subgroups, except for OSI_RAM in the male (ranked 14th) and smoking subgroups (ranked 15th) and OSI_BEV in the 21L858R subgroup (ranked 14th). Additionally, several 1/2G-TKI combination regimens offered prominent PFS benefits in specific subgroups, including AFA_CET in the 21L858R (ranked 6th), ICO_PB in the male (ranked 3rd), smoking (ranked 3rd), age≥65 (ranked 1st), and ECOG PS=1 (ranked 4th), and ERL_BEV in the smoking (ranked 5th). With respect to OS, the data of most regimens were not available, specifically the 3G-TKI regimens. OSI ranked first in the subgroups of no-Asian and without brain metastasis, while ERL_PF and ERL_BEV ranked first in the Asian and brain metastasis. ERL_BEV ranked first in smoking and ECOG PS=0 subgroups as well. AFA+CET was optimal in subgroups of 19DEL, male, non-smoker, and age≥65. Besides, GEF_PB and AFA were the best for the ECOG PS=1 and age<65 in terms of OS benefit. On the whole, OSI, GEF_PB, and ERL_BEV provided more stable and superior OS benefits in various subgroups.

Sensitivity analyses

As shown in Fig. 5B-C and Figure S14A-D, the results of the sensitivity analyses were almost in line with the original both in terms of the overall analysis and the subgroup analysis for EGFR mutation.

Consistency and inconsistency assessment

Our NMA was conducted using the random-effects consistency model. It was demonstrated that the fit of the consistency model was similar to or better than that of the inconsistency model (Table S3). In terms of inconsistency, no significant differences between direct and indirect comparisons were detected from the node-splitting analysis (Table S4). Figure S15-S41 showed the trace plot and the Brooks-Gelman-Rubin diagnostic plot, indicating the excellent stability of the model convergence.

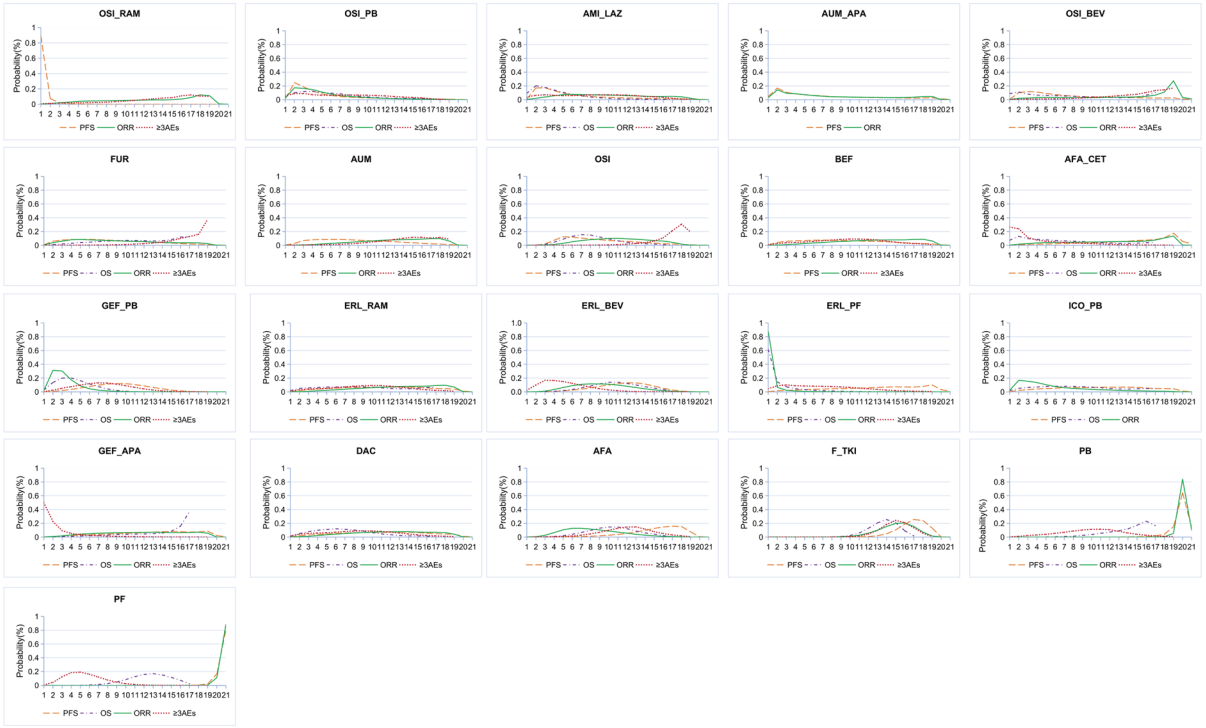
Discussion

TKI-targeted therapy is a great milestone in the history of NSCLC treatment in the last decades [3], with TKI-based therapy being the preferred first-line therapy for EGFR-mutated advanced NSCLC [6]. There is a lack of direct comparisons between TKI regimens, making it a huge challenge for clinicians to formulate the optimal treatment plan for the patient. In this NMA of 35 RCTs evaluating 9718 advanced NSCLC patients with EGFR mutation, the efficacy and safety were compared and ranked among 21 regimens, and it was first found that

(See figure on next page.)

Fig. 5 Bayesian ranking profiles of comparable regimens on efficacy and safety for advanced EGFR mutated NSCLC. **A** Profiles indicate the probability of each comparable regimen being ranked from first to last on overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and grade ≥ 3 adverse events (≥ 3AEs). **B** Number in each cell indicates the probability of each regimen being ranked from first to last on overall PFS, ORR, ≥3AEs, and PFS for subgroups according to the surface under the cumulative ranking curve (SUCRA) presented in Figure S13A. **C** Number in each cell indicates the probability of each treatment being ranked from first to last on overall OS, ORR, ≥3AEs, and OS for subgroups according to the SUCRA value presented in Figure S13B

A



B

				Mutation subtype		Sex		Smoking		Age		ECOG		Brain metastasis		Ethnicity		Sensitivity analysis				
	PFS	ORR	≥3AEs	19DEL	21L858R	Male	Female	Yes	No	<65	≥65	PS=0	PS=1	Yes	No	Asian	Non-asian	PFS	ORR	≥3AEs	19DEL	21L858R
OSI_RAM	1	15	14	5	3	14	1	15	6	3	2			2	3	1	2					
OSI_PB	2	3	7	1	1	1	2	2	1	2	3	2	1	1	2	2	1	1	3	5	1	1
AMI_LAZ	3	9	8	2	2	4	3	4	2	1	5	1	2	3	1	3	3	2	7	7	2	2
AUM_APA	4	5														4		3	5			
OSI_BEV	5	18	16	3	14	5	6	1	10			5	3	6	5	7						
FUR	6	7	18	4	5	2	8	7	4	4	8	3	5	9	4	5		4	6	15	3	5
AUM	7	17	15	6	10	9	4	10	3	6	6	4	6	4	9	6		6	14	13	4	7
OSI	8	10	19	8	4	11	5	6	5	7	4	6	7	8	6	12	4	5	9	16	6	3
GEF_PB	9	2	6	9	7	12	10	9	9	8	7	8	9	5	8	9		8	2	6	7	4
BEF	10	14	11	7	12	7	7	8	7	5	13	7	8	7	7	8		7	12	11	5	9
ERL_RAM	11	16	10	12	11	6	14	11	13	10	12	10	13			14	5	9	13	10	10	8
ICO_PB	12	4		13	8	3	12	3	12	14	1	11	4			13						
DAC	13	12	9	10	13	15	9	13	8	9	10	12	10			10	8	10	11	8	8	10
ERL_BEV	14	8	3	11	9	8	11	5	11	11	9	9	11	10	10	11	7	11	4	3	11	6
ERL_PF	15	1	5													15		12	1	4		
GEF_APA	16	11	1	14	15	13	13	16	14	12	15	13	12	12	11	16		13	10	1	12	11
AFA_CET	17	13	2	16	6	10	16	12	16	15	11											
AFA	18	6	13	15	16	16	15	14	15	13	14	14	14	11	12	17	6	14	8	12	9	12
F_TKI	19	19	17	17	17	17	17	18	17	16	16	15	15	13	13	18	10	15	15	14	13	13
PB	20	20	12	18	18	18	18	17	18	17	17	16	16			19	9	16	16	9	14	14
PF	21	21	4	19	19	19	19	19	19	18	18	17	17			20	11	17	17	2	15	15

C

				Mutation subtype		Sex		Smoking		Age		ECOG		Brain metastasis		Ethnicity		Sensitivity analysis				
	OS	ORR	≥3AEs	19DEL	21L858R	Male	Female	Yes	No	<65	≥65	PS=0	PS=1	Yes	No	Asian	Non-asian	OS	ORR	≥3AEs	19DEL	21L858R
OSI_RAM		15	14																			
OSI_PB	4	3	7															4	3	5		
AMI_LAZ	3	9	8															3	7	7		
AUM_APA		5																	5			
OSI_BEV	7	18	16													8						
FUR	13	7	18													7		10	6	15		
AUM		17	15																14	13		
OSI	8	10	19	3	7	5	2	2	4	3	3	3	3	3	1	10	1	6	9	16	2	6
GEF_PB	2	2	6	4	5	2	7	3	5	5	4	2	1	2	2	2		2	2	6	3	4
BEF		14	11																12	11		
ERL_RAM	10	16	10															7	13	10		
ICO_PB	9	4														4						
DAC	6	12	9	6	1	7	1	6	3	4	6	5	4			3	2	5	11	8	5	2
ERL_BEV	12	8	3	5	2	3	3	1	9	2	2	1	2	1	5	6	4	8	4	3	6	1
ERL_PF	1	1	5													1		1	1	4		
GEF_APA	16	11	1													12		14	10	1		
AFA_CET	5	13	2	1	4	1	5	4	1	6	1											
AFA	11	6	13	2	9	4	4	5	2	1	5	6	5	5	3	5	3	9	8	12	1	8
F_TKI	15	19	17	8	8	8	9	8	7	9	7	4	8	4	4	11	6	12	15	14	7	7
PB	17	20	12	9	3	9	8	9	8	8	9	7	7			13	7	13	16	9	8	3
PF	14	21	4	7	6	6	6	7	6	7	8	8	6			9	5	11	17	2	4	5

Fig. 5 (See legend on previous page.)

3G-TKI combination regimens, especially OSI_RAM, could be the optimal. To the best of our knowledge, to date, not only did this NMA include the most comprehensive RCTs, but it also involved the largest number of regimens. Besides, our NMA for the first time included 3G-TKI combination regimens.

The development of TKI resistance critically impairs the efficacy of the drug and has emerged as the largest challenge for EGFR-mutated NSCLC [62]. "TKI + X" combination therapy is one of the major strategies to overcome or delay TKI resistance, which mainly includes "TKI + chemotherapy" and "TKI + angiogenesis inhibitor" [63, 64]. Indeed, synergistic antitumor effects were observed in the 1G-TKI from multiple RCTs. In our NMA, it was found that the GEF_PB could be the best option among all regimens of 1/2G-TKI monotherapy or combination therapy, which is in line with previous studies [22, 23]. The findings that the inhibition of T790M mutation-derived resistance by pemetrexed from basic experiments provide more robust evidence for the rationality of the combination regimen [65]. However, adverse effects significantly increased as well. In contrast, the combination pattern of ERL_RAM enhances TKI efficacy with a manageable safety profile.

Modification of the molecular structure of TKIs is another strategy to overcome TKI resistance [64]. Encouragingly, the 3G-TKIs were successfully developed, which irreversibly and selectively inhibit both EGFR sensitizing (19DEL/21L858R) and resistance (T790M) mutations [66]. Subsequently, the 3G-TKIs of AUM, FUR, LAZ, and BEF were developed [67]. Our NMA revealed that the 3G-TKI monotherapy was superior to the 1/2G-TKIs in prolonging PFS and the safety profile was favorable. Although there was no statistical difference in PFS among all 3G-TKI monotherapy, the SUCRA-based rankings indicated that FUR was the most effective not only in PFS but also in ORR. Therefore, FUR is preferred if choosing TKI monotherapy.

Based on the fact that the addition of other agents to the 1G-TKIs has increased anti-tumor effect [44], the hypothesis that "new wine in old bottles" (the combination of chemotherapy or angiogenesis inhibitors with the 3G-TKIs) could also provide superior survival benefit to the patient has been logically proposed. In terms of combined with chemotherapy, the FLAURA2 successfully proved the superiority of OSI combined with chemotherapy over OSI alone [19]. Consequently, OSI_PB was recommended as the first-line treatment for EGFR-mutated NSCLC in the 2024 NCCN guideline. Similarly, our NMA showed that OSI_PB provided excellent PFS (ranked 2nd) and ORR (ranked 3rd) benefits among 21 regimens, with an increase in adverse events, but generally manageable. In terms of combined with angiogenesis inhibitors, OSIRAM-1 and RAMOSE are two representative RCTs, which have explored the efficacy of OSI combined with RAM versus OSI [17, 40]. However, the conclusions of the two trials were completely different, with a significant PFS benefit being obtained for OSI_RAM compared with OSI alone in RAMOSE but no difference was observed in OSIRAM-1 [17, 40]. Potential contributors to the difference between two RCTs are as follows: The first is the dosing interval for RAM. In RAMOSE, RAM was dosed every 3 weeks, whereas every 2 weeks in OSIRAM-1 [17, 40]. Another key factor is the maintenance time of RAM, with 14.4 months in RAMOSE versus 4.7 months in OSIRAM-1 [17, 40]. Surprisingly, nevertheless, our NMA showed that OSI_RAM was optimal among 21 regimens (including OSI combined with chemotherapy) with favorable safety profiles (≥ 3AEs ranked 14th). Although the current lung cancer guidelines have not included OSI_RAM as a standard of care for EGFR-mutated NSCLC, OSI_RAM is a highly potential and promising new first-line regimen. More high-quality RCTs with larger numbers of NSCLC patients are warranted to explore the optimal combination strategy of OSI and RAM and advance the inclusion of OSI_RAM in lung cancer guidelines. Among angiogenesis inhibitors, apart from include RAM/BEV, a class of intravenously administered large-molecule agents, also include APA, an oral small-molecule TKI targeting VEGFR2 [68]. In the NMA, AUM combined with APA provided a relatively favorable PFS benefit (ranked 4th). Although inferior to OSI_RAM (1st), OSI_PB (2nd), and AMI_LAZ (3rd) in terms of ranking, all agents in the AUM_APA regimen are orally administered, making it a strength of the regimen. Questionnaires have found that a proportion of patients preferred simple regimens even at the cost of decreased benefits to highly effective but complicated regimens, making doctors increasingly aware of the importance of the patient's feelings [69]. In 2023, experts proposed that precise, pragmatic, and inclusive are three key factors for the modern era of oncology clinical trials, which emphasizes the crucial role of a patient-centered pattern in advancing modern cancer care [69]. AUM_APA, an orally administered regimen, can liberate patients from the hospital and return them to a normal life, which exactly caters to the aforementioned patient-centered model pattern. If a patient prefers simplicity, AUM_APA is a potentially available option, but evidence from high-quality RCTs is still required.

Apart from the conventional combination regimens (TKI + chemotherapy/angiogenesis inhibitors), emerging novel combination strategies are being explored, with AMI plus LAZ being the most representative. AMI is a bispecific EGFR/MET antibody approved for patients with advanced NSCLC with EGFR exon 20 insertion

mutations [70]. Intriguingly, a real-world study from Wang et al. revealed that AMI is a potentially effective option for patients with EGFR mutations outside of exon 20 insertion mutations and the combination of OSI with AMI is safe and feasible [71]. Another trial of MARIPOSA-2, which has investigated the synergistic antitumor effect of 3G-TKI (LAZ) plus AMI in patients with refractory EGFR-mutated advanced NSCLC, provided stronger evidence for the hypothesis of combining AMI with a third-generation TKI [72]. MARIPOSA, a phase III RCT evaluating AMI + LAZ versus OSI in the first-line setting, revealed that AMI plus LAZ was statistically superior to OSI, which further validated the hypothesis above [41]. In our NMA, significant superiority of the AMI_LAZ regimen (ranked 3rd) in PFS was observed compared to the others and it presented an acceptable safety profile. Therefore, AMI_LAZ could be a new potential option for EGFR-mutated NSCLC in the first-line setting and, and further trials are warranted.

Of note, a growing body of evidence indicates that specific clinicopathologic characteristics, such as EGFR mutation subtypes, brain metastasis status, ECOG score, sex, smoking history, and ethnicity, could influence the efficacy of treatments and warrant attention [73–75]. Therefore, it will facilitate precise and individualized therapy if comprehensively evaluating clinicopathologic characteristics during clinical decision-making. In our NMA, the PFS benefit influenced by clinicopathologic characteristics were found, including EGFR mutation type for OSI_BEV (19DEL vs. 21L858R: 3rd vs. 14th), sex for OSI_RAM (male vs. female: 14th vs. 1st) and ICO_PB (male vs. female: 3rd vs. 12th), smoking history for OSI_RAM (smoker vs. non-smoker: 15th vs. 6th) and ICO_PB (smoker vs. non-smoker: 3rd vs. 12th), age for ICO_PB (<65 vs. ≥65: 14th vs. 1st), and ECOG for ICO_PB (PS = 0 vs. PS = 1: 11th vs. 4th). With regard to sex, there is indeed a growing body of evidence suggesting that gender plays a crucial role in tumor development and treatment. Differential responses to immunotherapy between males and females have been observed in a variety of tumors [76–78]. At present, the influence of gender on targeted therapy for EGFR-mutated NSCLC remains elusive. We hypothesize that the observed sex-based differences in PFS for OSI + RAM may be influenced by such factors. Nevertheless, the potential for bias introduced by the limited sample size cannot be discounted, emphasizing the need for further investigation in future studies. Our study further confirmed that clinicopathologic characteristics are critical factors influencing the treatment efficacy of EGFR-mutated NSCLC, which requires high attention from clinicians. Encouraging, the combination regimen based on 3G-TKIs was generally stable and superior to other regimens in terms of PFS prolongation, making them more preferable options for EGFR-mutated NSCLC in the first-line setting.

Based on the result of our NMA, as well as the current medical literature, we have developed a prioritization scheme for treatment options as a guiding tool for the patient management pathway (Figure S42), yet it necessitates additional clinical trial validation.

The limitations of this study warrant consideration. Firstly, since the primary endpoint for all RCTs enrolled in this study was PFS, while OS was a secondary endpoint and the OS data of multiple RCTs was not available. Therefore, the analysis and comparison of the effectiveness of the various regimens in this NMA is mainly based on the NMA result of PFS. However, OS benefit is the ultimate objective and the most concerning indicator either for the clinician or the patient. Therefore, in-depth and updated NMA for OS is warranted in the future. Secondly, multiple RCTs from conference abstract reports were enrolled in this NMA, with some data in terms of adverse events or subgroup analyses not reported, which emerged as potential sources of bias, thereby weakening the reliability of the NMA. Thirdly, with few RCTs being available for some regimens, the robustness and reliability of the NMA results will be influenced, which requires further validation by including more RCTs in the future.

Conclusion

Combination regimens based on third-generation TKIs, especially OSI_RAM, showed superior efficacy compared with third-generation TKIs monotherapy or other regimens in the first-line setting for EGFR-mutated advanced NSCLC in overall and most of the subgroup analyses, along with manageable safety profiles. Taken together, our study concluded that combination regimens based on third-generation TKIs (OSI_RAM, OSI_PB, AMI_LAZ, AUM_APA, and OSI_BEV) are potentially new and clinically preferable first-line, standard of care for EGFR-mutated advanced NSCLC. These findings could complement the current standard of care and provide clues for the design of future clinical trials.

Abbreviations

PFS	progression-free survival
≥3AEs	grade 3 or higher adverse events
19DEL	19 deletion mutation
1G-TKI	first-generation TKI
21L858R	21Leu858Arg point mutation
2G-TKI	second-generation TKI
3G-TKI	third-generation TKI
95% CI	95% credible intervals
AFA	afatinib
AMI	amivantamab
APA	apatinib
ASCO	American Society of Clinical Oncology
AUC	area under the concentration-time curve
AUM	aumolertinib
BEF	befotertinib

BEV	bevacizumab
CET	cetuximab
DAC	dacomitinib
DIC	deviance information criteria
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
ERL	erlotinib
ESMO	European Society of Medical Oncology
F_TKI	first-generation TKI
FUR	furmonertinib
GEF	gefitinib
HR	hazard ratio
ICO	icotinib
LAZ	lazertinib
NG	not given
NMA	network meta-analysis
NSCLC	non-small cell lung cancer
OR	odds ratio
ORR	objective response rate
OS	overall survival
OSI	osimertinib
PB	pemetrexed based chemotherapy
PF	pemetrexed free chemotherapy
RAM	ramucirumab
RCT	randomized controlled trial
SUCRA	surface under the cumulative ranking curve
TKI	tyrosine kinase inhibitors
WCLC	World Conference on Lung Cancer

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Zhang W: Writing - Original Draft, Conceptualization, Methodology, Formal analysis, Data Curation, Visualization. Zhang X: Writing - Original Draft, Data Curation, Software, Formal analysis. Guo Z: Conceptualization, Methodology, Formal analysis, Data Curation. Liu X: Software, Investigation. Ye L: Methodology, Resources. Chen Z: Methodology, Formal analysis. Xu K: Methodology, Investigation. Liu Y: Resources, Software. Wang H: Formal analysis, Validation. Zhao L: Data Curation, Validation. Zhao W: Conceptualization. Zhang Q: Conceptualization, Methodology. Li Y: Software, Investigation. Chen C: Resources, Software. He Y: Writing - Review & Editing, Conceptualization, Supervision, Project administration.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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