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Meta-Analysis

EGFR-TKI Plus Anti-Angiogenic Drugs in EGFR-Mutated Non–Small Cell Lung Cancer: A Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: Results of several randomized clinical trials (RCTs) testing the combination of an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) plus an anti-angiogenic drug in advanced EGFR-mutated non–small cell lung cancer were reported. **Methods:** We first report a systematic review and meta-analysis of all RCTs to estimate effectiveness and toxicity of this new therapeutic approach compared with first-generation EGFR-TKI monotherapy. Subsequently, we present a network meta-analysis comparing the combination of an EGFR-TKI plus an anti-angiogenic drug with 2 new treatment options: combination of an EGFR-TKI plus chemotherapy or new EGFR-TKIs of second or third generation as monotherapy. **Results:** Five RCTs were included in the first meta-analysis. The progression-free survival (PFS) was statistically significantly larger in patients treated with an EGFR-TKI plus an anti-angiogenic drug compared with EGFR-TKI monotherapy: the pooled PFS–hazard ratio (HR) was 0.59 (95% confidence interval [CI] = 0.51 to 0.69). The pooled median-PFS was 17.8 months (95% CI = 16.5 to 19.3 months) for the combination vs 11.7 months (95% CI = 11.1 to 12.7 months) for EGFR-TKI as monotherapy. No statistically significant differences between the 2 treatment arms were observed in overall survival or objective response rate. The rate of grade equal or higher than 3 adverse events was statistically significantly higher in patients treated with EGFR-TKI plus an anti-angiogenic drug: the pooled-relative risk was 1.72 (95% CI = 1.43 to 2.06). Ten RCTs were included in the network meta-analysis. All 3 experimental treatments were associated with a statistically significant improvement in PFS compared with first-generation EGFR-TKIs. When compared to each other, none of the 3 experimental treatments were statistically significantly associated with larger PFS or lower rate of grade 3 or higher adverse events. **Conclusion:** Patients with EGFR-mutated non small-cell lung cancer derived clinically meaningful larger PFS benefit from the addition of an anti-angiogenic drug to a first-generation EGFR-TKI at the cost of an increase of toxicities.

In the last 10 years, therapy with an EGFR-TKI of first or second generation (ie, erlotinib, gefitinib, or afatinib) has become the standard first-line treatment choice for patients with advanced epidermal growth factor receptor (EGFR)–mutated non–small cell lung cancer (NSCLC) (1–5) in which several pivotal randomized clinical trials (RCTs) showed a statistically significantly longer progression-free survival (PFS) when treated with an EGFR-TKI instead of platinum-based chemotherapy (1–5).

Recently, results have been reported from several RCTs comparing the effectiveness of new therapeutic strategies vs standard EGFR-TKIs, including second and third generation EGFR-TKIs as monotherapy as well as the combination of EGFR-TKIs with chemotherapy or with anti-angiogenic drugs (6–16). Positive results have been reported for both second- and third-generation EGFR-TKIs and for the combination of EGFR-TKIs with chemotherapy in a few large RCTs (6–16). Several lines of preclinical and clinical evidence suggests a potential synergistic antitumor activity for the

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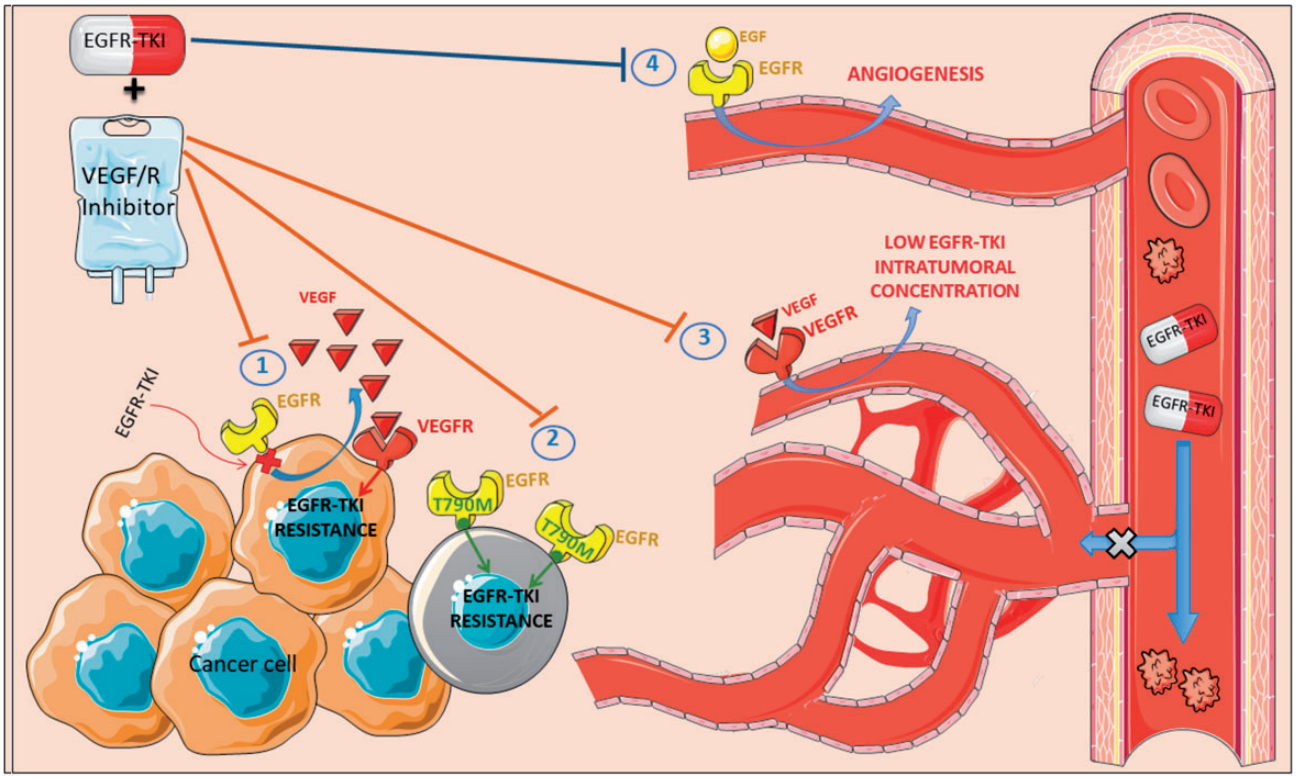

Figure 1. Potential molecular mechanisms leading to synergistic antitumor activity of estimated epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) inhibition shows 4 potential molecular mechanisms leading to synergistic antitumor activity through the concomitant EGFR and VEGFR inhibition: 1) EGFR inhibition can result in compensatory increase in stroma and tumor-derived VEGF levels that fosters disease progression and that could be prevented by the concomitant VEGFR blockade (17–19); 2) VEGFR inhibition could delay the emergence of acquired resistance to first-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) mediated by the T790M EGFR mutation (17); 3) anti-angiogenic drug can improve EGFR-TKI delivery and penetration into the tumor tissue through the normalization of both the vessel wall by reducing leakiness and the structure of the vascular network by pruning immature vessels and making the remaining vessels better organized (20); 4) EGFR is expressed on tumor-associated endothelium, and its inhibition can exert a synergistic anti-angiogenic activity in combination with VEGFR blockade (18, 21). GFR-TKI = (epidermal growth factor receptor-thyrosine kinase inhibitor); VEGFR = vascular endothelial growth factor receptor.

combination of an EGFR-TKI plus an anti-angiogenic drug (see Figure 1) (17–22). For these reasons, several phase 2 and 3 RCTs comparing such new combination therapy vs an EGFR-TKI alone have been conducted in comparable patient populations and with similar study design. However, the majority of such trials enrolled a limited number of patients (6–10).

Here, we report the results of a systematic review and meta-analysis to better estimate the effectiveness and toxicity of the combination of an EGFR-TKI plus an anti-angiogenic drug, as well as to more reliably explore heterogeneity of results across relevant subgroups. We also performed a network meta-analysis to indirectly compare such therapeutic options with other new experimental treatments that have been recently tested in RCTs vs standard first-generation EGFR-TKIs, as a first-line treatment option for advanced EGFR-mutated NSCLC.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for the systematic review and meta-analyses in this study (23).

Meta-Analysis of All RCTs Testing the Combination of an EGFR-TKI Plus an Anti-Angiogenic Drug

We searched PubMed, MEDLINE, Embase, and Scopus for phase 2 and 3 RCTs testing an EGFR-TKI administered alone or in combination with an anti-angiogenic drug in patients with advanced NSCLC, published from the inception of each database to September 2019. We also reviewed abstracts and presentations from all major conference proceedings, including the American Society of Clinical Oncology, the International Association for the Study of Lung Cancer, and the European Society for Medical Oncology, from January 1, 2010, to September 2019.

Two investigators (AM and LP) independently searched the databases. The search terms were as follows: "non small cell lung cancer," "NSCLC," "EGFR TKI," "epidermal growth factor receptor tyrosine kinase inhibitor," "erlotinib," "gefitinib," "afatinib," "dacomitinib," "osimertinib," "anti-angiogenic drug," "bevacizumab," "sunitinib," "sorafenib," "regorafenib," "vandetanib," "aflibercept," "axitinib," "cabozantinib," "pazopanib," "ramucirumab," and "levantinib." We also reviewed the references of articles included in the final selection. The following inclusion criteria were used: randomized clinical trials evaluating an EGFR-TKI of first generation (ie, gefitinib, erlotinib), second (ie, afatinib, dacomitinib,) or third generation (ie, osimertinib) vs their combination with an anti-angiogenic drug (both TKI or monoclonal antibody) in patients with advanced EGFR-mutated NSCLC and data available on hazard ratio (HR) for PFS. We excluded single-arm phase 1 and 2 trials (ie, nonrandomized trials). Two investigators (AM and LP) independently reviewed the list of retrieved articles to choose potentially relevant articles, and disagreements about particular studies were discussed and resolved with the consensus of all investigators.

From each study, the following data were extracted: name of study, first author and year of publication, study design and blinding, study phase, number of patients, age distribution, sex distribution, patients' smoking status distribution, patients' performance status distribution, type of EGFR-TKI and anti-angiogenic drug used, hazard ratio for PFS and/or overall survival (OS) in overall population, PFS hazard ratios according to EGFR-mutation type subgroups, objective response rate according to Response evaluation criteria in solid tumors (RECIST) 1.1 criteria, and rate of grade 3 or higher adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) criteria version 4. We included only the most recent and complete report of controlled trials when duplicate publications were identified.

Study methodological quality was assessed by using the 5-point Jadad ranking system that evaluates quality of randomization, double-blinding, and the flow of patients (withdrawals and dropouts)—a practice in agreement with other meta-analyses done in this context (23). A clinical trial could receive a Jadad score of between 0 (poor methodological quality) and 5 (optimal methodological quality) (24).

The primary endpoint was the difference in efficacy of the experimental arm as compared with control arm, measured in terms of hazard ratio for progression or death (PFS-HR). Secondary endpoints were the differences between the experimental arm and control arm expressed as follows: hazard ratio for death (OS-HR); relative risk of achieving an overall response rate (ORR) as defined by RECIST 1.1 criteria; relative risk of having grade 3 or higher toxicities (adverse event [AE] ≥ 3) as defined by CTCAE 4.0 criteria.

The hazard ratios for PFS and OS in the intervention arm compared with those in the control arm, along with their 95% confidence intervals (CIs), were derived from each included study. Hazard ratios and confidence intervals were translated into log-hazard ratios and the corresponding variances. The pooled hazard ratios of PFS and OS were calculated using random-effects model. Each study log(HR) was weighted by the inverse of its variance. Weights were taken equal to the inverse of the reported within-study variance plus the between-study variance component τ (2). The moment estimator of the between-study variance was used. The Q test was performed to assess between-study heterogeneity, and the I^2 statistics, which express the percentage of the total observed variability due to heterogeneity, were also calculated (25,26). The null hypothesis that the PFS-HR and OS-HR between intervention and control arms is 1 was tested using a z test.

For each study, the percentage of objective responses (ie, complete or partial response according to RECIST 1.1 criteria) and toxicities (ie, grade 3, 4, or 5 toxicities according to CTCAE 4.0 criteria) were collected along with their 95% confidence intervals, separately for each treatment arm. The pooled relative risks for objective response and toxicities were calculated using random-effects model. The null hypothesis that the relative risk between intervention and control arms is 1 was tested using a z test. A subgroup analysis was conducted to explore the variation of the treatments' effect according to the EGFR mutation type (ie, Exon 19 deletions vs Exon 21 L858R mutation).

To avoid the risk of ecological bias, the null hypothesis that the interaction between EGFR-mutation status and treatments efficacy is equal across subgroups was tested using the following approach: firstly, for each trial an interaction trial-specific hazard ratio was calculated from the ratio of the reported PFS-HRs in the 2 different EGFR-mutation type subgroups; secondly, these trial-specific interaction hazard ratios were combined across trials using a random-effects model (27). A pooled hazard ratio estimate lower than 1 indicates a greater treatment effect in Exon21 L858R mutation subgroup and higher than 1 indicates a greater effect in Exon19 deletions subgroup. The null hypothesis that the interaction between EGFR-mutation type and treatments efficacy is equal across subgroups was tested using a χ^2 test.

Finally, the Kaplan-Meier survival curves for PFS from each included publication were digitized using WebPlotDigitizer (28), and individual patient data (IPD) were recovered from digitized curves using the techniques described in Guyot et al. (29) The proportions of patients free from progression at prespecified time points (ie, 6-, 12-, 18- and 24-month) and restricted mean PFS time at 24 months were calculated from IPD (30).

All reported *P* values are 2-sided. A *P* value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the R-software (version 3.4.0) (31).

Network Meta-Analysis

We searched PubMed, MEDLINE, Embase, and Scopus from the inception of each database to September 2019 for all phase 2 and 3 RCTs testing a standard first-generation EGFR-TKIs vs one of the following therapeutic strategies: combination of a first-generation EGFR-TKI plus an antiangiogenic drug; combination of a first-generation EGFR-TKI plus chemotherapy; an EGFR-TKI of second (ie, dacomitinib) or third generation (ie, osimertinib) as monotherapy. Two investigators (AM and LP) independently searched the databases. The search terms were as follows: "non small cell lung cancer," "NSCLC," "EGFR TKI," "epidermal growth factor receptor tyrosine kinase inhibitor," "erlotinib," "gefitinib," "afatinib," "dacomitinib," "osimertinib," "anti-angiogenic drug," "bevacizumab," "ramucirumab," and "chemotherapy."

The following inclusion criteria were used: randomized trials comparing 1 of the 3 experimental treatments vs standard first-generation EGFR-TKIs, as first-line treatment option for patients with advanced EGFR-mutated NSCLC and data available on hazard ratio for PFS and/or on rate of grade 3 or higher AEs as defined by CTCAE 4.0 criteria. Study methodological quality was assessed by using the 5-point Jadad ranking system (24).

The coprimary endpoints were the difference in efficacy of the experimental arm as compared with control arm, measured in terms of PFS-HR and the difference in toxicity measured in terms of relative risk of having grade 3 or higher toxicities (relative risk AE $\geq$ 3) as defined by CTCAE 4.0 criteria. For each endpoint, a network meta-analysis with a frequentist approach was performed. Therapies were ranked based on *P*-scores, measuring the extent of certainty that a treatment is better than another, averaged over all competing therapies (32).

Because there were no head-to-head comparisons between treatment of interest (ie, combination of a first-generation EGFR-TKI plus an antiangiogenic drug, combination of a first-generation EGFR-TKI plus chemotherapy, and an EGFR-TKI of second [ie, dacomitinib] or third generation [ie, osimertinib] as monotherapy), it was not possible to assess the network consistency and to estimate the correlation between direct and indirect evidence (33).

Results

Systematic review and meta-analysis of all RCTs are testing the combination of an EGFR-TKI plus an anti-angiogenic drug.

We found 5 eligible RCTs reporting results of the combination of an EGFR-TKI plus an anti-angiogenic drug vs an EGFR-TKI alone in patients with advanced EGFR-mutated NSCLC (Supplementary Figure 1, available online). All 5 trials had available data on PFS and were included in the analysis for such endpoint (Table 1 reports mean features of the RCTs) (6–10). Four trials (JO25567, NEJ026, ACCRU-RC1126, and ARTEMIS-CTONG 1509 trial) tested the combination of erlotinib plus the anti–vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab vs erlotinib alone (6–10). The RELAY trial tested the combination of erlotinib plus the anti-VEGF receptor (VEGFR)-2 monoclonal antibody ramucirumab (Table 1) (6–10).

Risk of bias assessment through Jadad score for each trial is reported in the Supplementary Table 1 (available online). The Jadad mean score was 3 (range = 3-5). No trial received a low-quality score (ie, Jadad score = 1-2). All of the included studies had a low risk of reporting bias, attrition bias, and other biases (Supplementary Table 1, available online).

The analysis for PFS included 1224 patients of whom 447 (36.5%) were males with Eastern Cooperative Oncology Group performance status of 0 in 536 (43.7%) patients and 1 in 686 (56.0%); 654 (53.4%) patients had a tumor harboring an Exon 19 deletion of the EGFR gene and 567 (46.3%) the L858R point mutation in Exon 21; specifically, 613 (50.0%) patients received erlotinib alone, 387 (31.6%) erlotinib plus bevacizumab, and 224 (18.3%) erlotinib plus ramucirumab (Table 1).

The median follow-up ranged between 12.4 and 20.7 months across the 4 trials, and 749 of 1224 patients (61.2%) experienced a PFS event. Of the patients, 27 (2.2%) had tumors in stage IIIB, 170 (13.8%) had a postoperative recurrence, and 1027 had tumors in stage IV (83.9%). Among these, the presence of brain metastases was an exclusion criteria in 2 trials (ie, JO25567 and RELAY trial); thus, only 188 (15.3%) of the 1224 patients included in the analysis had brain metastases at baseline.

Results showed that patients treated with erlotinib plus an anti-angiogenic drug had a statistically significant reduced risk of progression or death as compared with patients treated with erlotinib alone: the pooled PFS-HR was 0.59 (95% CI = 0.51 to 0.69; Figure 2,A). No heterogeneity among single study estimates was observed (I^2= 0%; P = .73; Figure 2,A). Supplementary Figure 2 (available online) shows the pooled Kaplan-Meier (KM)-PFS curves based on the reconstructed IPD from the 5 RCTs, and Supplementary Table 2 (available online) reports the restricted mean survival times (RMSTs) at 24 months of follow-up and PFS-rate estimates at 6, 12, 18, and 24 months obtained from reconstructed IPD. The pooled median-PFS was 17.8 months (95% CI = 16.5 to 19.3 months) for the combination vs 11.7 months (95% CI = 11.1 to 12.7 months) for EGFR-TKI as monotherapy. The meta-analytic–pooled RMST difference between the 2 treatment arms was 3.2 months (95% CI = 2.2 to 4.2 months); Supplementary Table 2, available online). A larger percentage of patients treated with the combination of a EGFR-TKI plus an anti-angiogenic drug obtained a long-lasting PFS as compared with patients receiving an EGFR-TKI alone: the pooled PFS rates at 18 and 24 months were 48.9% (95% CI = 44.3% to 53.3%) and 29.9% (95% CI = 25.2% to 34.9%) with EGFR-TKI plus an anti-angiogenic drug and 33.1% (95% CI = 28.9% to 37.3%) and 20.3% (95% CI = 16.4% to 24.6%) with EGFR-TKI alone, respectively (Supplementary Table 2, available online).

Of the 5 RCTS, 3 (JO25567, ACCRU-RC1126, and RELAY trial) had available data on OS and were included in the analysis for an OS endpoint (6–10). The analysis for OS included 689 patients of whom 345 (50.0%) received erlotinib alone, 120 (17.4%) received erlotinib plus bevacizumab, and 224 (32.5%) received erlotinib plus ramucirumab. Only 206 of 689 patients (29.8%) experienced an OS event.

The risk of death of patients treated in the combination arms was not statistically different compared with patients treated in EGFR-TKI monotherapy arm: pooled OS-HR of 0.90 (95% CI = 0.67 to 1.19; Figure 2,B). No heterogeneity among single-study estimates was observed (I^2 = 0%; P=.38; Figure 2,B).

All 5 trials had available data on the ORR according to RECIST 1.1 criteria and on rate of grade 3 or higher AEs according to CTCAE 4.0 criteria and were included in the analyses for such endpoints. In the 5 trials, the ORR ranged from 69% to 86.3% in the combination arm and from 64% to 84.7% in the EGFR-TKI monotherapy arm. The pooled relative risk for ORR was 1.03 (95% CI = 0.97 to 1.09; Figure 2,C). No heterogeneity among single-study estimates was observed (I^2 = 0%; P = .91; Figure 2,C).

The rate of grade 3 or higher AEs ranged from 53.5% to 100% for the combination of EGFR-TKI plus an antiangiogenic drug arm and from 25.5% to 54% for EGFR-TKI alone. The pooled estimates of AEs of at least grade 3 (G3) rates were 0.81 (95% CI = 0.65 to 0.96) in patients treated with the combination vs 0.53 (95% CI = 0.49 to 0.57) in patients treated with EGFR-TKIs alone. The pooled estimate for grade 3 or higher AEs was 1.72 (95% CI = 1.43 to 2.06; Figure 2,D), indicating a statistically significant higher risk of toxicities for patients treated in the combination arm. Substantial heterogeneity among single-study estimates was observed (I^2 = 69%; P = .01; Figure 2,D). For this reason, we performed a subgroup analysis to assess the interaction between the risk of experiencing grade 3 or higher AEs and treatment arm, according to the type of anti-angiogenic drug used. Results revealed that, compared with erlotinib alone, the relative risk of experiencing grade 3 or higher AEs was statistically significantly higher in patients treated with bevacizumab (RR = 1.84, 95% CI = 1.59 to 2.13) as compared with those treated with ramucirumab (RR= 1.33, 95% CI = 1.15 to 1.53; $P_{interaction}$ = .01).

Finally, we performed a subgroup analysis to assess the heterogeneity of treatment efficacy according to the EGFR mutation type (ie, Exon19 deletions vs Exon21 L858R mutation), using PFS as an endpoint. Patients treated in the combination arm had a statistically significant reduced risk of progression or death compared with patients treated in EGFR-TKI monotherapy arm in both subgroups explored: the pooled PFS-HRs were 0.59 (95% CI = 0.47 to 0.73; Supplementary Figure 3,A, available online) in the Exon21 L858R mutation subgroup and 0.61 (95% CI = 0.49 to 0.75; Supplementary Figure 3,A, available online) in the Exon19 deletions subgroup, respectively. The pooled ratio of PFS-HRs reported in Exon21 L858R mutation subgroup vs those reported in Exon19 deletions subgroup in each trial was 0.97 (95% CI = 0.71 to 1.31; Supplementary Figure 3,B, available online).

Network Meta-Analysis

We performed a network meta-analysis to indirectly compare the efficacy and toxicity of the combination of an EGFR-TKI plus an anti-angiogenic drug with 2 other therapeutic strategies: the combination of a first-generation EGFR-TKI plus chemotherapy and a new EGFR-TKI of second (ie, dacomitinib) or third generation (ie, osimertinib) as monotherapy.

We found and included in this analysis 10 eligible RCTs: 5 RCTs tested the combination of an EGFR-TKI plus an antiangiogenic drug, 3 tested the combination of an EGFR-TKI plus chemotherapy, and 2 trials tested respectively one-trial-tested-dacomitinib-and-one-trial-tested-osimertinib (6–16). Table 1 reports mean features of the RCTs

Table 1. Mean features of RCTs included in the analyses[a]

References	Phase	Median follow-up, mo	Primary endpoint	Treatment groups	Patients	Median age, y	ECOG PS 0, N (%)	Sex, N (%)	Negative smoking history, N (%)	EGFR mutation type, N (%)	Median PFS, mo (95% CI)	PFS-HR, (95% CI)	ORR, %	P	Median OS, mo	OS-HR (95% CI)
Nakagawa, ASCO 2019 (RELAY trial) (6)	3	20.7	PFS	Erlotinib + Ramucirumab	224	65	116 (52)	F 141 (63)	134 (60)	Exon 19 del 123 (55) Exon 21 (L858R) mut 101 (45)	19.4 (15.4 to 21.6)	0.591 (0.46 to 0.76)	76	.741	NA	0.832 (0.53 to 1.30)
				Erlotinib	225	64	119 (53%)	F 142 (63%)	139 (62%)	Exon 19 del 121 (54%) Exon 21 (L858R) mut 104 (46%)	12.4 (11.0 to 13.5)		75		NA	
Seto, 2014 Kato, 2018 Yamamoto, 2018 (JO25567 trial) (7)	2	20.4	PFS	Erlotinib + Bevacizumab	75	67	43 (57%)	F 45 (60%)	42 (56%)	Exon 19 del 40 (53%) Exon 21 (L858R) mut 35 (47%)	16.0 (13.9 to 18.1)	0.54 (0.36 to 0.79)	69	·495	47.0 (NA-NA)	0.81 (0.53 to 1.23)
				Erlotinib	77	67	41 (53%)	F 51 (66%)	45 (58%)	Exon 19 del 40 (52%) Exon 21 (L858R) mut 37 (48%)	9.7 (5.7 to 11.1)		64		47.4 (NA-NA)	
Stinchombe, 2019 (ACCRU RC1126) (8)	2	33	PFS	Erlotinib + Bevacizumab	43	65	24 (56%)	F 31 (72%)	25 (60%)	Exon 19 del 29 (67%) Exon 21 (L858R) mut 14 (33%)	17.9 (NA-NA)	0.81 (0.50 to 1.31)	81	.81	32.4 (NA-NA)	1.4 (0.71 to 2.81)
				Erlotinib	45	63	29 (42%)	F 31 (69%)	23 (51%)	Exon 19 del 30 (67%) Exon 21 (L858R) mut 15 (33%)	13.5 (NA-NA)		83		50.6 (NA-NA)	
Saito, 2019 (NEJ026 trial) (9)	3	12.4	PFS	Erlotinib + Bevacizumab	112	67	64 (57%)	F 71 (63%)	65 (58%)	Exon 19 del 56 (50%) Exon 21 (L858R) mut 56 (50%)	16.9 (14.2 to 21.0)	0.605 (0.42 to 0.88)	72	.31	NA	NA
				Erlotinib	112	68	68 (61%)	F 73 (65%)	64 (57%)	Exon 19 del 55 (49%) Exon 21 (L858R) mut 57 (51%)	13.3 (11.1 to 15.3)		66		NA	
Zhou, ESMO 2019 (ARTEMIS/CTONG 1509) (10)	3	22.0	PFS	Erlotinib + Bevacizumab	157	57	25 (16%)	F 97 (62%)	NA	Exon 19 del 82 (52%) Exon 21 (L858R) mut 75 (48%)	18.0 (15.2-20.7)	0.55 (0.41 to 0.75)	86.3	.741	NA	NA
				Erlotinib	154	59	17 (11%)	F 96 (62%)	NA	Exon 19 del 79 (51%) Exon 21 (L858R) mut 75 (49%)	11.3 (9.8 to 13.8)		84.7		NA	
Cheng, 2016 Yang, ESMO 2018 (11) (NCT01469000)	2	18	PFS	Gefitinib + Pemetrexed	126	62	39 (31%)	F 82 (65%)	81 (64%)	Exon 19 del 65 (52%) Exon 21 (L858R) mut 52 (41%) Other 9 (7%)	15.8 (12.6 to 18.3)	0.68 (0.48 to 0.96)	80	.38	43.4 (33.4 to 50.8)	0.77 (0.5 to 1.2)
				Gefitinib	65	62	21 (32%)	F 41 (63%)	47 (72%)	Exon 19 del 40 (62%) Exon 21 (L858R) mut 23 (35%) Other 2 (3%)	10.9 (9.7 to 13.8)		74		36.8 (26.7 to 42.6)	
Noronha V, ASCO 2019 (CTRI/2016/08/007149) (12)	3	17	PFS	Gefitinib + Pemetrexed + Carboplatin	174	54	1 (1%)	F 86 (49%)	145 (83%)	Exon 19 del 107 (62%) Exon 21 (L858R) mut 60 (35%) Other 7 (4%)	16 (13.5 to 18.5)	0.51 (0.39 to 0.66)	75.3	.01	NA	0.45 (0.31 to 0.65)
				Gefitinib	176	56	7 (4%)	F 83 (47%)	150 (85%)	Exon 19 del 109 (62%) Exon 21 (L858R) mut 60 (34%) Other 7 (4%)	8 (7.0 to 9.0)		62.5		17 (13.5 to 20.5)	
Nakamura, ASCO, 2018 Seike, ESMO, 2018 (NEJ009) (14)	3	NA	OS	Gefitinib + Pemetrexed + Carboplatin	170	65	98 (58%)	F 114 (67%)	97 (57%)	Exon 19 del NA Exon 21 (L858R) mut NA	20.9 (18.0 to 24.0)	0.49 (0.39 to 0.63)	84	NA	52.2 (44.0 to NR)	0.695 (0.5 to 0.93)
				Gefitinib	172	64	107 (62%)	F 108 (63%)	97 (57%)	Exon 19 del NA Exon 21 (L858R) mut NA	11.2 (9.0 to 13.4)		67.4		38.8 (31.1 to 50.8)	
Soria, 2017 Ramalingam, ESMO, 2019 (FLAURA) (15)	3	15.0	PFS	Osimertinib	279	64	112 (40%)	F 178 (64%)	182 (65%)	Exon 19 del 175 (63%) Exon 21 (L858R) mut 104 (37%)	18.9(15.2 to 21.4)	0.46 (0.37 to 0.57)	80	.24	38.6 (34.5, 41.8)	0.799 (0.64 to 0.997)
				Gefitinib 66%; Erlotinib 34%)	277	64	116 (42%)	F 172 (62%)	175 (63%)	Exon 19 del 174 (63%) Exon 21 (L858R) mut 103 (37%)	10.2(9.6 to 11.1)		76		31.8 (26.6, 36.0)	
Wu, 2017 Mok, 2018 (ARCHER-1050) (16)	3	22.1 Analysis	PFS	Dacomitinib	227	62	75 (33%)	F 146 (64%)	147 (65%)	Exon 19 del 134 (59%) Exon 21 (L858R) mut 93 (41%)	14.7 (11.1 to 16.6)	0.59 (0.47 to 0.74)	75	.42	34.1 (29.5 to 37.7)	0.76 (0.58 to 0.99)
				Gefitinib	225	61	62 (28%)	F 125 (56%)	144 (64%)	Exon 19 del 133 (59%) Exon 21 (L858R) mut 92 (41%)	9.2 (9.1–11.0)		72		26.8 (23.7 to 32.1)	

[a]CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; F = female; HR = hazard ratio; NA = not available; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS 0 = performance status 0; RCT = randomized clinical trials.

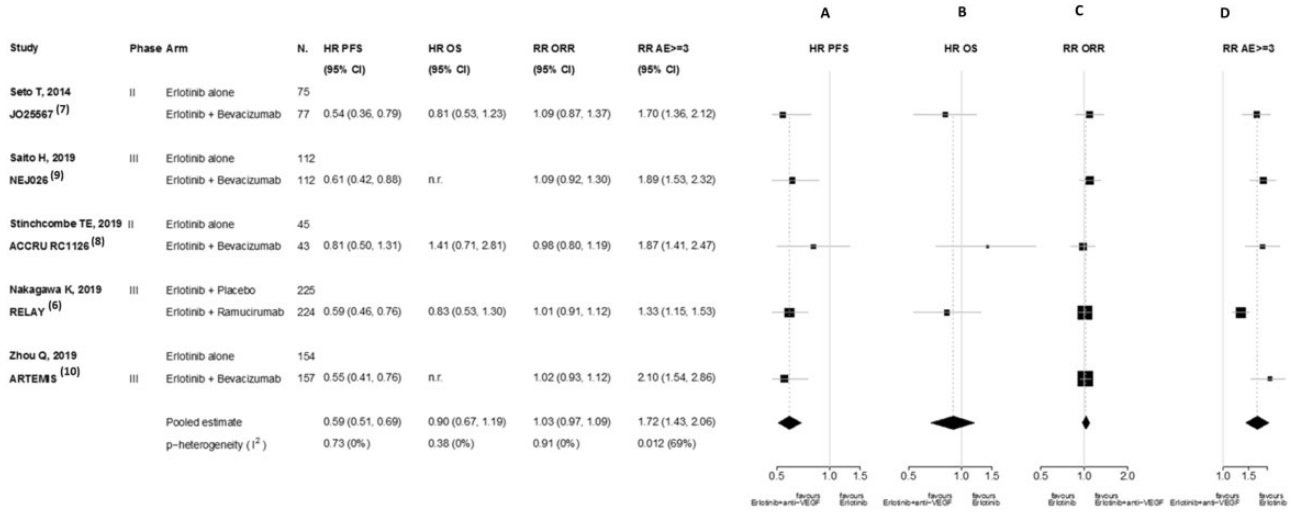

Figure 2. Meta-analytic pooled estimates of progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and risk of grade 3 or higher adverse events (AEs) in patients treated in experimental vs control arm. **A)** and **(B)** show respectively the hazard ratios of PFS and OS for patients assigned to intervention treatment (ie, epidermal growth factor receptor [EGFR]-TKI plus anti-angiogenic drug) as compared with those assigned to control treatment (ie, EGFR-TKI alone). **Squares** indicate study-specific hazard ratios (HRs). Values less than 1 indicate intervention is better than control. Size of the square is proportional to the precision of the estimate (ie, the inverse of the variance). **Horizontal lines** indicate the 95% confidence interval (CI). **Diamonds** indicate the meta-analytic pooled hazard ratios, with their corresponding 95% confidence intervals. The **dashed vertical lines** indicate the pooled hazard ratios, and the **solid vertical lines** indicate a hazard ratio of 1, which is the null-hypothesis value (ie, no association between type of treatment and risk of PFS or OS). **C)** and **(D)** show respectively the relative risk (RR) to obtain an objective response (complete or partial response, according to RECIST 1.1 criteria) or to experience a grade 3 or higher AE according to Common Terminology Criteria for Adverse Events v4 for patients assigned to intervention treatment (ie, EGFR-TKI plus anti-angiogenic drug) as compared with those assigned to control treatment (ie, EGFR-TKI alone). **Squares** indicate study-specific relative risks relative. Values higher than 1 indicate intervention has higher objective responses or toxicities than control. Size of the square is proportional to the precision of the estimate (ie, the inverse of the variance). **Horizontal lines** indicate the 95% confidence interval. **Diamonds** indicate the meta-analytic pooled relative risks, with their corresponding 95% confidence intervals. The **dashed vertical lines** indicate the pooled, relative risks and the **solid vertical lines** indicate a of relative risk 1, which is the null-hypothesis value (ie, no association between type of treatment and chance of objective response or toxicity). Pts: patients.

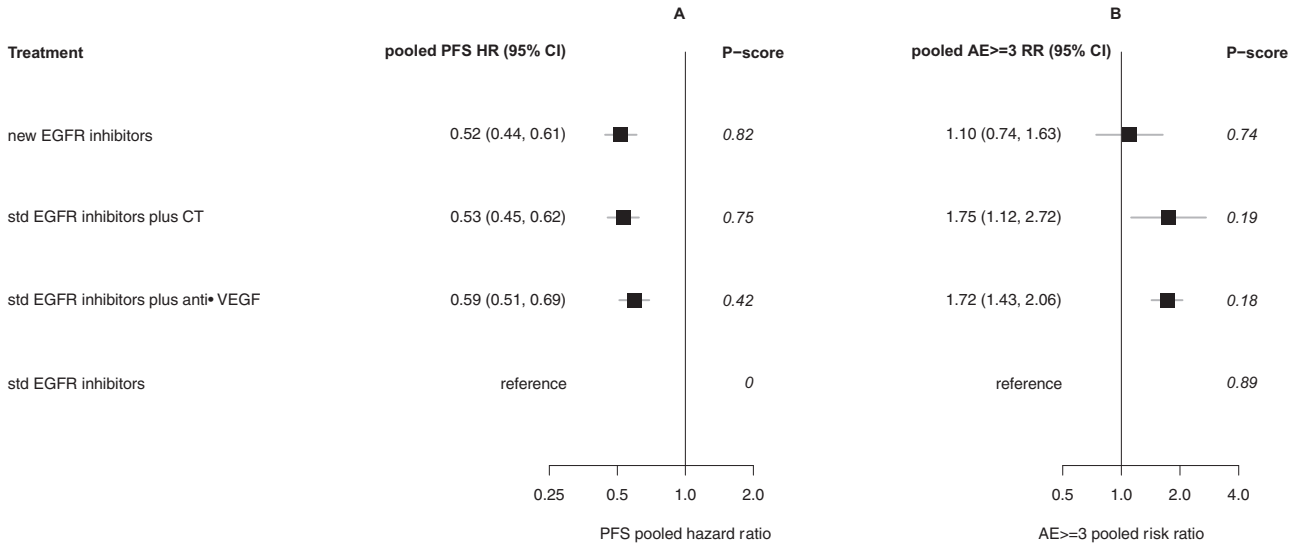

Figure 3. Network meta-analysis for hazard ratio (HR)–progression-free survival (PFS) and relative risk (RR) of grade 3 or higher adverse events (AEs). **A)** and **(B)** show respectively the meta-analytic hazard ratio of PFS and to experience a grade 3 or higher AE according to Common Terminology Criteria for Adverse Events v4 for patients assigned to intervention treatments (ie, epidermal growth factor receptor [EGFR]-TKI plus anti-angiogenic drug or EFGR-TKI plus chemotherapy or new EGFR-TKIs of second or third generation alone) as compared with those assigned to control treatment (ie, first-generation EGFR-TKI alone). **Squares** indicate, respectively, the meta-analytic pooled PFS-HRs **(A)** and pooled s hazard ratios of grade 3 or higher AEs **(B)** with their corresponding 95% confidence intervals. The **solid vertical lines** indicate, respectively, a hazard ratio and a relative risk of 1, which is the null-hypothesis value (ie, no association between type of treatment and risk of PFS or grade 3 or higher AEs). For each different treatment approach, the associated P-score value for PFS-HR **(A)** and of grade 3 or higher AEs **(B)** is reported. CT = chemotherapy; new EGFR inhibitors = dacomitinib and osimertinib; Std EGFR inhibitors = first-generation EGFR inhibitors; VEGFR = vascular endothelial growth factor.

included in the analysis. The Jadad mean score was 3 (range = 3-5). No trial received a low-quality score (ie, Jadad score received 1-2; Supplementary Table 1, available online). All trials had a first-generation EGFR-TKI monotherapy as a control arm.

Supplementary Figure 4 (available online) shows the KM-PFS curves of the control arms of each of the RCTs included in this NMA, based on the reconstructed IPD. Results of the NMA showed that all the 3 experimental treatments were associated with a statistically significant improvement of PFS as compared with standard EGFR-TKI (Figure 3,A; Supplementary Table 3, available online). However, when compared to each other, none of the 3 experimental treatments were associated with a statistically significant improvement of PFS in any of the indirect comparisons (Supplementary Table 3, available online).

Figure 3,A reported the P-score associated with each treatment: the higher the P-score, the larger the extent of certainty that the associated treatment is more effective than any other treatment evaluated, allowing us to rank the treatments according to their comparative effectiveness in a frequentist network meta-analysis. The treatment efficacy ranking according to P-scores was EFGR-TKI of second or third generation or combination of a first-generation EGFR-TKI plus chemotherapy; combination of a first-generation EGFR-TKI plus an anti-angiogenic drug; and first-generation EGFR-TKIs monotherapy (Figure 3,A). A sensitivity analysis, performed analyzing the EGFR-TKI of second (ie, dacomitinib) and third generation (ie, osimertinib) separately confirmed similar results (data not shown).

Compared with first-generation EGFR-TKIs, the pooled relative risk of grade 3 or higher AEs was statistically significantly higher in patients treated with the combination of an EGFR-TKI plus an anti-angiogenic drug or an EGFR-TKI plus chemotherapy but not in patients treated with dacomitinib or osimertinib (Figure 3,B; Supplementary Table 4, available online). In indirect comparisons, there was a non-statistically significant higher relative risk of grade 3 or higher AEs in patients treated with an EGFR-TKI plus an antiangiogenic drug (RR= 1.52, 95% CI= 0.93 to 2.48) or an EGFR-TKI plus chemotherapy (RR= 1.49, 95% CI= 0.87 to 2.90) compared with those receiving an EGFR-TKI of second or third generation in monotherapy (Figure 3,B; Supplementary Table 4, available online).

Figure 3,B reported the P-scores for each treatment related to its toxicity profile: the higher the P-score, the larger the extent of certainty to have a lower risk of grade 3 or higher AEs compared with any other treatment. The treatments' tolerability ranking according to P-scores was first-generation EGFR-TKIs; EGFR-TKIs of second or third generation; combination of a first-generation EGFR-TKI plus an anti-angiogenic drug; and combination of a first-generation EGFR-TKI plus chemotherapy (Figure 3,B). However, a sensitivity analysis assessing the EGFR-TKIs of second (ie, dacomitinib) and third generation (ie, osimertinib) separately showed statistically significant heterogeneity in terms of risk of grade 3 or higher AEs.

Indeed, as compared with first-generation EGFR-TKIs, osimertinib was associated with a statistically significantly lower relative risk of grade 3 or higher AEs (RR= 0.76, 95% CI = 0.62 to 0.94), whereas daconitinib was associated with a statistically significantly higher relative risk (RR = 1.53, 95% CI = 1.27 to 1.85). In the NMA, osimertinib was the treatment option associated with the lowest risk of grade 3 or higher AEs among all treatments (*P* score = 0.97), whereas dacomitinib ranked third, below both osimertinib and first-generation TKIs (P-score = 0.34; Supplementary Table 5, available online).

Discussion

In the last few years, results from 5 RCTs comparing the efficacy of an EGFR-TKI plus an anti-angiogenic drug vs a first-generation EGFR-TKI in monotherapy in patients with EGFR-mutated advanced NSCLC have been reported (6–10). This new therapeutic strategy is supported by a strong and multifactorial rationale: VEGF or VEGFR pathway blockade could overcome some primary and acquired resistance mechanisms to EGFR inhibitors, including resistance mediated by the Thr790Met *EGFR* mutation, whereas EGFR inhibition on tumor-associated endothelium cells could exert synergistic anti-angiogenic activity in combination with VEGF/VEGFR blockade (Figure 1) (17–22). However, results across the 5 RCTs were not entirely consistent, because the 4 largest RCTs reported a statistically significant improvement of the primary endpoint PFS, but the smallest one did not (6–10).

For this reason, as well as to better estimate the magnitude of the clinical benefit of such a new therapeutic approach compared with standard first-generation EGFR-TKI, we performed a meta-analysis. Using both published data of PFS-HRs and reconstructed individual patient-level data, we obtained a meta-analytic estimate not only of the relative PFS benefit achievable with the combination treatment but also of the absolute benefit, as evaluated by gain in median PFS and differences in RMSTs and in the PFS rates at relevant milestone time points, which are essential to assess the clinical benefit of a new treatment, as specified by the European School of Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS) v1.1 (34). Results reported clearly demonstrated that patients with advanced EGFR-mutated NSCLC obtain a statistically significant larger PFS benefit from the addition of an anti-angiogenic drug to a first-generation EGFR-TKI, independently from the type of activating EGFR mutations harbored by tumors. The magnitude of such benefit is clinically meaningful: assessed through the ESMO-MCBS v1.1, such therapeutic strategy obtains a score of 3 on a scale that ranges from 1 to 4 (34).

Indeed, the lower limit of the 95% confidence interval of the meta-analytic PFS-HR was no more than 0.65, there was a gain in the median-PFS larger than 3 months for the experimental compared with the control arm, and there was nearly a 10% improvement in the PFS rate at 2 years, without an increase in the percentage of the serious adverse events specified by the ESMO-MCBS. Analysis of the KM-PFS curves derived from IPD showed that the PFS-benefit for patients treated with the combination compared with EGFR-TKI as monotherapy started early and persisted during follow-up (Supplementary Figure 2, available online).

RMSTs calculated at 12 and 24 months further confirmed that the PFS benefit of patients treated with the combination increases over time (the RMST difference between the 2 treatment arms was 1.2 months at 12 months and 3.2 months at 24 months of follow-up, (respectively). However, it is also evident that the tail of the IPD PFS curve of patients treated with the combination did not reach a plateau, as instead was observed, for example, in trials testing immunotherapy (Supplementary Figure 2, available online). This indicates that the combination of EGFR-TKIs plus antiangiogenic drugs statistically significantly delays PFS events compared with first-generation EGFR-TKIs, but its ability to obtain long-lasting disease responses is limited. A more reliable assessment of the long-term benefit of such treatment option needs longer follow-up and mature data on overall survival.

The PFS improvement is obtained at the cost of a statistically significant increase of the rate of grade 3 or higher AEs, which was higher in patients treated with bevacizumab compared with those receiving ramucirumab. To date, PFS improvement over first-generation EGFR-TKI in patients with EGFR-mutated

NSCLC has been reported with 2 different therapeutic strategies that, however, have never been compared face-to-face in RCTs with the combination of an EGFR-TKI plus an anti-angiogenic drug. We therefore performed an NMA that allowed to indirectly compare the efficacy and tolerability profiles of the 3 new available therapeutic options.

All 3 experimental treatments were associated with a statistically significant improvement of PFS when compared with first-generation EGFR-TKIs. Albeit, none of the 3 approaches were associated with a statistically significant improvement of PFS when compared with each other. The EGFR-TKIs of third generation appeared to be associated with the best efficacy to toxicity ratio, as confirmed by the highest P-scores for both, indicating a higher chance to be the most effective and also the less toxic therapeutic option among those evaluated. Moreover, mature OS results from ARCHER-1050 (35) and FLAURA (15) trials were recently reported: both dacomitinib and osimertinib statistically significantly improved patient overall survival vs first-generation EGFR-TKIs. Data available are still not mature to assess the impact of the combination of an EGFR-TKI plus an anti-angiogenic drug on patient OS, because only 30% of patients experienced an OS event.

The results of our NMA provided some evidence to put in the context and compare all the available therapeutic options for EGFR-mutated NSCLC patients, but they should not be interpreted as definitive. Indeed, they only relied on indirect cross-trials comparisons. Furthermore, there was a relevant heterogeneity of the outcome of patients treated in the control arms in the different trials, which further limits the conclusion of our NMA (Supplementary Figure 4, available online). The PFS rate at 12 months ranged from 29.6% (95% CI = 22.7% to 36.8%) to 49.6% (95% CI = 33.7% to 63.7%) in the control arms of the RCTs included in the NMA.

Our analysis did not take into account differences between treatment options in terms of low-grade adverse events, which could have a relevant impact on patients' quality of life, because TKIs often cause long-lasting, low-grade toxicities. We also did not assess OS as an endpoint in NMA because of the limited follow-up and several studies did not include mature OS data, preventing the possibility to draw reliable conclusions.

Results of our NMA strongly showed the need for face-to-face comparison of 3 such promising therapeutic strategies in RCTs, because data available do not allow to conclude which is the best therapeutic option.

Of note, ongoing trials are testing osimertinib monotherapy vs its combination with an anti-angiogenic drug (NCT03909334) or its combination with platinum-based chemotherapy (FLAURA2 trial-NCT04035486). Such trials will provide further data on the activity and tolerability of combinations in first-line and, if positive, could substantially change the treatment landscape of patients with EGFR-mutated NSCLC, potentially making current treatment options out of date.

In conclusion, our results clearly showed that first-generation EGFR-TKIs in monotherapy should no longer be considered a proper therapeutic option for patients with advanced EGFR-mutated NSCLC. Patients treated with the combination of an EGFR-TKI plus an anti-angiogenic drug obtain a meaningful clinical benefit at a cost of an acceptable increase of toxicity. The new therapeutic options available for EGFR-mutated NSCLC are not associated with a statistically significant improvement of PFS or reduction of grade 3 or higher AEs. Face-to-face comparisons in RCTs as well as cost-benefit analyses are therefore needed to identify the most effective therapeutic option for patients and the most sustainable choice for health care systems.

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Data availability

The data underlying this article are available in the article and in its online Supplementary Material (available online).

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