Real-Life Use of First-Generation EGFR-TKI with Chemotherapy in EGFR-sensitive Mutations in Non-Small-Cell Lung Cancer: A Single-Center Analysis and Meta-Analysis

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Abstract

Background: Recently,epidermal growth factor receptor (EGFR) -targeting drugs have benefited thousands of patients with EGFR mutation-positive (EGFR MUT+) non-small-cell lung cancer (NSCLC). Nevertheless, nearly all patients with NSCLC who were sensitive to first- or second-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs), finally developed resistance. Therefore, numerous clinicians have focused on improving the clinical effect of first-generation EGFR-TKIs (1st-gen EGFR-TKIs). Methods: To analyze the therapeutic outcomes of individuals with progressive NSCLC, a retroactive assessment was performed on 86 patients who were medicated with only icotinib or combined with pemetrexed and platinum-based chemotherapy at The First Affiliated Hospital of Henan University of Science and Technology (HAUST). Results: Eighty-six patients with NSCLC-bearing EGFR-sensitive mutations were retroactively analyzed. The results showed statistical significance in PFS (P = 0.049) and disease control rate DCR (P = 0.031) between icotinib + chemotherapy and icotinib alone, especially in the brain metastases (P = 0.021) and L-858R mutation subgroups (P = 0.05). According to the findings of the multivariate analysis, treatment (P = 0.033) and EGFR mutation status (P = 0.019) were significant predictive variables. The OS comparison between icotinib + chemotherapy and icotinib alone were not significantly different. The study included a total of 1242 patients, of which 648 obtained combined treatment and 594 obtained first-generation EGFR-TKI monotherapy. Analyzing the relevant data from multiple studies, the results showed significant improvements in ORR (RR: 0.63, 95% CI: 0.49–0.82, P = 0.0006), PFS (RR: 0.61, 95% CI: 0.47–0.79, P = 0.0002), and OS (RR: 0.67, 95% CI: 0.51–0.88, P = 0.004) for those on combination therapy. However, there was also an increase in treatment-emergent AEs among these patients. Conclusion: In summary, administering first-generation EGFR-TKI concurrently with chemotherapy provides an edge in the therapeutic management of locally or severely advanced NSCLC that is EGFR-positive. Therefore, EGFR mutation-positive NSCLC (EGFR MUT+ NSCLC) patients in this condition may find it advantageous to consider using 1st-gen EGFR-TKIs in conjunction with chemotherapy (1st-gen EGFR-TKIs + Chemo).

Title

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Abstract

Background: Lung cancer patients' survival is currently not improved by the platinum-based two-drug combination regimen used as first-line chemotherapy (FLC). In contrast, epidermal growth factor receptor (EGFR) -targeting drugs have benefited thousands of patients with EGFR mutation-positive (EGFR MUT+) non-small-cell lung cancer (NSCLC). Nevertheless, nearly all patients with NSCLC who were sensitive to first- or second-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs), finally developed resistance. Therefore, numerous clinicians have focused on improving the clinical effect of first-generation EGFR-TKIs (1^{st}-gen EGFR-TKIs).

Methods: To analyze the therapeutic outcomes of individuals with progressive NSCLC, a retroactive assessment was performed on 86 patients who were medicated with only icotinib or combined with pemetrexed and platinum-based chemotherapy at The First Affiliated Hospital of Henan University of Science and Technology (HAUST). The study also included a thorough review and meta-analysis to determine the correlation between survival findings, progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events (AEs) in NSCLC patients with EGFR-sensitive mutations who were treated with 1^{st}-gen EGFR-TKIs alone or in conjunction with chemotherapy.

Results: Eighty-six patients with NSCLC-bearing EGFR-sensitive mutations were retroactively analyzed. The results showed statistical significance in PFS *(*$P = 0.049$) and disease control rate DCR ($P = 0.031$) between icotinib + chemotherapy and icotinib alone, especially in the brain metastases ($P = 0.021$) and L-858R mutation subgroups ($P = 0.05$). According to the findings of the multivariate analysis, treatment ($P = 0.033$) and EGFR mutation status ($P = 0.019$) were significant predictive variables. The OS comparison between icotinib + chemotherapy and icotinib alone were not significantly different. The study included a total of 1242 patients, of which 648 obtained combined treatment and 594 obtained first-generation EGFR-TKI monotherapy. Analyzing the relevant data from multiple studies, the results showed significant improvements in ORR (RR: 0.63, 95% CI: 0.49–0.82, $P = 0.0006$), PFS (RR: 0.61, 95% CI: 0.47–0.79,$P = 0.0002$), and

OS (RR: 0.67, 95% CI: 0.51–0.88, $P = 0.004$) for those on combination therapy. However, there was also an increase in treatment-emergent AEs among these patients.

Conclusion: In summary, administering first-generation EGFR-TKI concurrently with chemotherapy provides an edge in the therapeutic management of locally or severely advanced NSCLC that is EGFR-positive. Therefore, EGFR mutation-positive NSCLC (EGFR MUT+ NSCLC) patients in this condition may find it advantageous to consider using 1^{st}-gen EGFR-TKIs in conjunction with chemotherapy (1^{st}-gen EGFR-TKIs + Chemo).

Keywords

Keywords: Combination therapy, Epidermal growth factor receptor Tyrosine kinase inhibitors, First-line treatment, Meta-Analysis, Non-small cell lung cancer

Introduction

Lung carcinoma represents a major threat. According to the global cancer morbidity and mortality estimation by the Global Cancer Epidemiology Database (GLOBOCAN), there would be 2.2 million additional instances and 1.8 million fatalities projected in 2020 (1). NSCLC is the most prevalent type, and its five-year survival rate is below 15%. Unfortunately, it's usually identified at an advanced stage, eliminating the possibility of radical surgery or radiotherapy and often leading to unfavorable results [2]. Chemotherapy remains the preferred treatment for individuals with locally and advanced NSCLC. The efficacy of platinum-based drugs has been difficult to improve. However, with the development and application of modern molecular biology techniques, NSCLC-associated driver genes have been discovered, and targeted drugs for such driver genes have been applied, enabling a new era of targeted therapy for NSCLC (2, 3).

The EGFR mutation is prevalent amongst NSCLC patients, particularly among Asians with lung cancer. Approximately 40-60% of Asian NSCLC patients carry EGFR mutations, with 45% of cases resulting from in-frame deletion (Ex19del) in EGFR exon 19, 40-45% from missense mutation (L858R) in EGFR exon 21, and the remaining 10% from other variations [5]. EGFR-TKIs show great effectiveness in patients with advanced EGFR MUT+ NSCLC, leading to significant improvements in PFS and ORR. The first generation of small molecule TKIs, such as gefitinib, erlotinib, and icotinib, which can bind to the HER1 receptor reversibly to block EGFR signaling pathways, are highly effective against wild-type and sensitive mutant EGFR [6, 7, 8]. Despite their advantages over chemotherapy in bettering PFS and quality of life (QoL), the majority of NSCLC patients who reinforce resistance to 1^{st}-gen EGFR-TKIs ultimately experience complex mechanisms of resistance [9, 10]. Furthermore, less than 50% of patients experience EGFR-T790M mutation after resistance to 1^{st}-gen EGFR-TKIs, which can affect their suitability for third-generation EGFR-TKIs [11]. Consequently, medical professionals have increasingly focused their efforts on enhancing the clinical advantages of first-generation TKIs.

This study aimed a meta-analysis of data from 6 clinical trials to estimate the effectiveness of combining 1^{st}-gen EGFR-TKIs + Chemo in comparison to 1^{st}-gen EGFR-TKIs alone in the first-line treatment (FLT) of EGFR MUT+ patients. The findings show the best results of the combination. Additionally, an 86-patient retrospective analysis of our center's use of icotinib, either as monotherapy or in conjunction with pemetrexed and platinum-based chemotherapy, was conducted from January 2013 to January 2022. The aim was to explore the real-world efficacy and safety of using 1^{st}-gen EGFR-TKIs in conjunction with chemotherapy in EGFR MUT+ NSCLC patients. The results demonstrated that patients receiving the combined treatment had improved PFS and DCR in comparison to those who obtained first-generation TKIs alone, and experienced a low occurrence of treatment-related AEs.

Methods

A single-center retrospective study

This retrospective investigation organized at HAUST, focused on patients with a confirmed history of NSCLC (stage IIIB or IV) in January 2013 and January 2022. Due to the investigation's retroactive nature, the local

Research Committee accepted it and waived the need for permission. Patients were identified through an extensive search of the cancer registry at the hospital, resulting in the inclusion of 86 suitable patients for the retroactive study. To be eligible, Patients required to be at least 18 years old, have an ECOG PS score of 2 or less, have advanced NSCLC diagnosed by pathology, have EGFR Mutation-activated NSCLC (usually exon 21 L858R point mutation or exon 19 deletion), have radiologically assessable disease, have no other cancers, and have obtained FLT using either icotinib (125 mg tid) + chemotherapy or icotinib alone (125 mg tid). Although prior treatment of early NSCLC was allowed, the main exception was previous or concurrent cancer treatment for advanced NSCLC. Additional information gathered from patients' therapeutic records is age, gender, smoking history, EGFR mutation type, best feedback, adverse effects, and mortality information.

Efficacy and safety assessment

The study primarily focused on PFS as its main objective. However, other secondary endpoints such as overall ORR, DCR, OS, and safety were also considered. OS was described as the duration between random assignment and either death or the patient's last contact. Tumors were evaluated utilizing the response evaluation criteria in solid tumors 1.1 (RECIST 1.1) [12].

The safety evaluation included registration of AEs and serious AEs (SAEs). The severity of AEs and SAEs was classified using the National Cancer Institute Adverse Events Common Terminology Criteria Version 4.0 [13].

Statistical analysis

Kaplan-Meier method was utilized to estimate PFS and OS. The significance of the groups was assessed by the log-rank test. Hazards were estimated by multivariate Cox regression model. Statistical significance was defined as a P -value < 0.05 ($P< 0.05$). The chi-squared (χ 2) test was employed to compare ORR, DCR, and toxicities at a significance level of 5% (a = 0.05, two-sided). All statistical analyses were conducted utilizing SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA).

Meta-analysis

Literature search strategy

Extensive research was executed on PubMed, Cochrane Register of Controlled Trials (CENTRAL), and Embase, covering the period from inception through February 24, 2022 (2022.02.24). The search specifically targeted "human studies and clinical trials," with no constraints imposed on publication time, language, or format (abstract or full text). The literature search employed keywords such as "Gefitinib and lung cancer," "Erlotinib and lung cancer," and "Icotinib and lung cancer." It should be noted that Gefitinib is also referred to as Iressa, Erlotinib as Tarceva, and Icotinib as Conmana, and variations or synonyms of these terms were included in the subject heading or title during the search process.

Eligibility criteria

To be participated in a meta-analysis, studies must satisfy the stipulated requirements: (1) publication in English and available up until February 2022, (2) inclusion of only patients with NSCLC, (3) provision of data on PFS, ORR - defined as the combination of complete response and partial response, OS, and safety measures including treatment tolerability and AEs, (4) implementation of first-generation TKI combined chemotherapy treatment as the intervention, and (5) comparison with first-generation TKI therapy as the control. Clinical trials focusing on second-line therapy and sequential TKI therapy following chemotherapy for advanced NSCLC were excluded. If there are different reports on the same study, only the most recent reports are considered. Two independent investigators (JSR and DJK) reviewed all potentially relevant articles to determine their suitability for inclusion.

Risk of bias assessment

As mentioned earlier, cohort research and randomized controlled trials were considered in this comprehensive review. Utilizing the Cochrane Collaboration's approach, the risk of bias in the randomized controlled trials

was assessed and categorized as either "low" or "others" to aid in analysis [14]. The Newcastle-Ottawa scale was employed to assign a score from 0 to 9 to each study, with a higher score signifying a lower risk of bias. To simplify the analysis, research findings with scores between 7 to 9 were referred to as the low-risk-of-bias group. Bias risk was separately determined by two reviewers, and any discrepancies were settled by conversation and a study of the original manuscript. If any disagreements remained unresolved, a third researcher was consulted to make a final decision.

Data extraction

The main focus of this investigation was the assessment of PFS, with OS, ORR, and safety serving as secondary outcomes. The comparative impact of EGFR TKIs on PFS, OS, ORR, and safety was evaluated using the risk ratio (RR) accompanied by a 95% confidence interval (CI). In terms of ORR and DCR, a RR < 1 indicates that the intervention group exhibits greater efficacy compared to the reference group, while a RR > 1 suggests the opposite. Regarding safety, a RR > 1 signifies that the intervention group has a greater risk profile in comparison to the reference group, whereas a RR < 1 indicates the opposite.

Statistical analysis

The meta-analysis was executed by utilizing STATA 14.0 software (Stata Corp, College Station, TX, USA). To assess the heterogeneity among the studies included, Cochran's Q test and the I2 statistic were employed [15]. A fixed-effects model was utilized if no substantial heterogeneity was seen ($P > 0.05$; I2 $< 50\%$). Conversely, a random-effects model was used if there was significant heterogeneity ($P < 0.05$; I2 $> 50\%$). When statistical heterogeneity ($P < 0.05$; I2 $> 50\%$) was found, efforts were made to determine its cause and subgroup or sensitivity analyses were carried out as necessary. A funnel plot was utilized to evaluate the presence of publication bias. Statistical significance was defined as a P -value < 0.05.

Single-center retrospective study

The study comprised of 30 male individuals (34.8%) and 56 female individuals (63.2%). The population has an age range from 32 to 90 with an average age of 63. 42 of the 86 patients who were a part of the trial obtained icotinib in conjunction with chemotherapy (group A), while 44 obtained icotinib alone (group B). Table 1 presents the patients' characteristics, including age, gender, smoking history and presence of EGFR mutations. The two groups exhibited similar demographic and disease-related features. Lung cancer was found in every patient. The majority of patients were nonsmokers and had a favorable Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1. Approximately 48.8% of the patients (n = 42) had an EGFR exon 19 deletion, while 51.2% (n = 44) had an EGFR exon 21 L858R point mutation in the EGFR gene.

Table 1 Characteristics of all patients

Characteristics	Group A (n = 42)	Group B (n = 44)	Total
Median age (years)	62.5	66.5	64
Sex	Sex	Sex	Sex
Female	14 (33.3%)	16 (36.4%)	30 (34.9%)
Male	28 (66.7%)	28 (63.6%)	56 (65.1%)
Age			?¿?
65 years	24 (57.1%)	20 (45.5%)	44 (51.1%)
> 65 years	18 (42.9%)	24 (54.5%)	42 (48.8%)
Smoking History	8		
Nonsmoker	30 (71.4%)	31 (70.5%)	61 (70.9%)
Smoker	12 (28.6%)	13 (29.5%)	25 (29.1%)
Brain Metastases			
Metastases	11 (26.2%)	13 (29.5%)	24 (27.9%)
No Metastases	31 (73.8%)	31 (70.5%)	62 (72.1%)

Characteristics	Group A (n = 42)	Group B (n = 44)	Total
Type of EGFR Mutation			
19-del	20 (47.6%)	22 (50.0%)	42 (48.8%)
21-858R	22 (52.4%)	22 (50.0%)	44 (51.2%)

In terms of the immediate treatment outcomes, the data presented in Table 2 indicate that group A exhibited a higher DCR in comparison to group B (97.6% vs. 84.1%, $P = 0.031$). Nevertheless, the overall response rate (ORR) did not differ between group A and group B (78.6% vs. 65.9%, $P = 0.191$) (Table 2).

Table 2 Short-term curative effects of all patients

Curative effects	Group A	Group B	Total
Best response	Best response	Best response	Best response
PD	1 (2.4%)	7 (15.9%)	8 (9.3%)
PR	33 (78.6%)	29 (65.9%)	62 (72.1%)
SD	8 (19.0%)	8 (18.2%)	16 (18.6%)
ORR	78.6%	65.9%	72.1%
DCR	97.6%	82.2%	89.7%

Abbreviations: DCR: Disease control rate, ORR: Overall response rate, PD: Progression disease, PR: Partial disease, SD: Stable disease.

Survival analysis

By January 2022, a total of 60 patients (69.7%) had reached the final stage of the disease or had died. Median progression-free survival (mPFS) of patients in group A and group B are 16 months (95% CI, 9,926-22.074) and 9 months (95% CI, 6. 461-11.539) respectively. These findings indicate a significant upgrade in PFS in patients obtaining icotinib plus chemotherapy in comparison to patients receiving icotinib alone ($P = 0.049$, Fig. 1a). In addition, multivariate investigation revealed that EGFR mutation ($P = 0.019$) and treatment method ($P = 0.033$) were independent factors of the study. At the final analysis, 66.3% (n = 57) of patients were alive, 28 in group A and 29 in group B. The average OS was 47.218 months (95% CI, 28.815-65.621) for group A and 35.383 months (95% CI, 28.693-42.074) for group B. Although the OS findings are still uncertain, the OS comparison between groups A and B did not yield significance ($P = 0.380$, Fig. 1b).

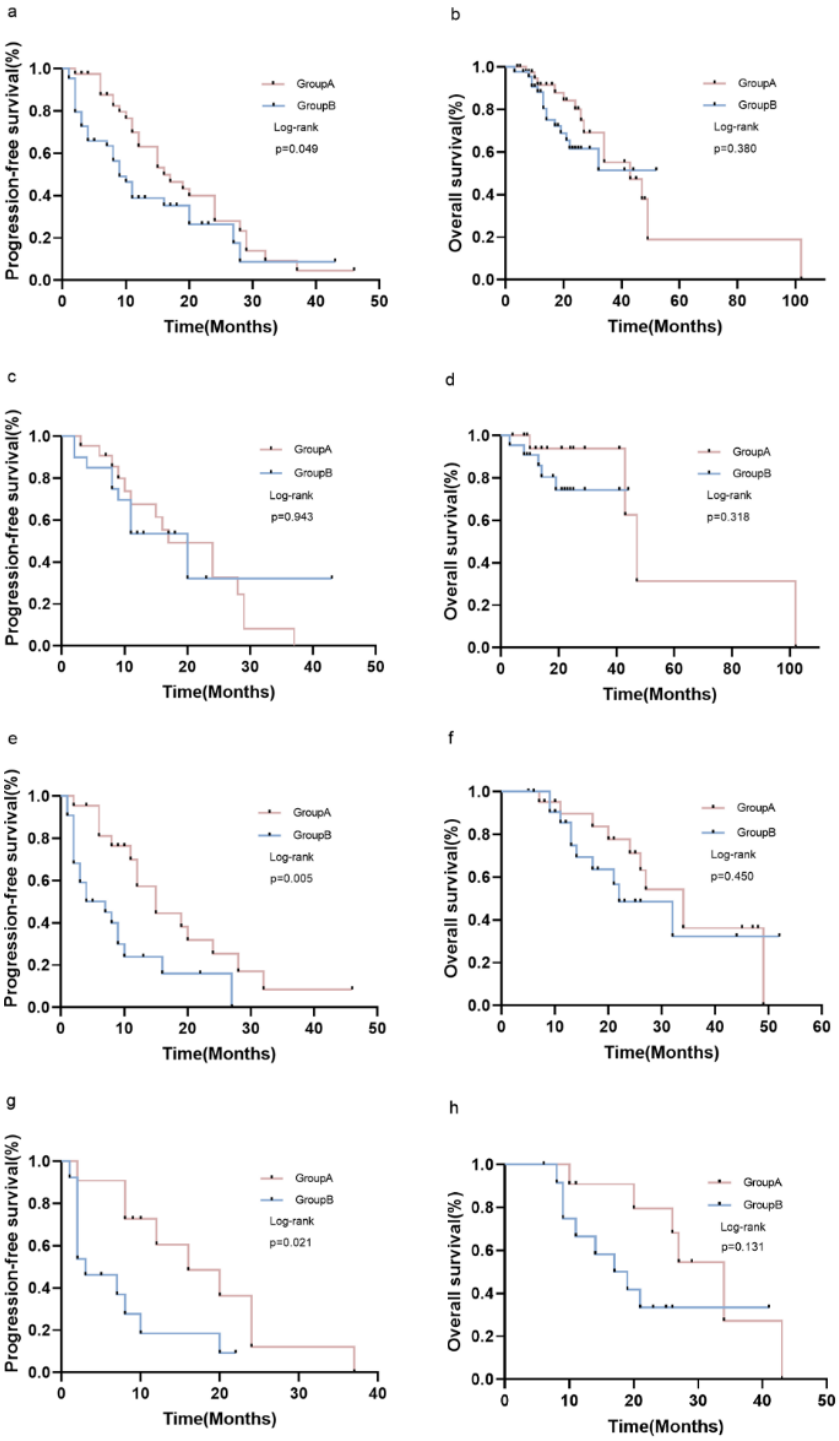
Among the individuals identified with an EGFR exon 19 deletion, a total of 42 individuals were identified. Among them, 20 patients obtained icotinib + chemotherapy (group A1), while 22 patients obtained icotinib alone (group B1). The mPFS for patients in groups A1 and B1 was 17 months (95% CI, 8.557-25.443) and 20 months (95% CI, 12.191-27.809), respectively ($P = 0.943$, Fig. 1c). The average OS was 60.625 months (95% CI, 26.829-94.421) in group A1 and 35.777 months (95% CI, 29.477-42.076) in group B1. The results indicate that there was no significant difference in terms of PFS or OS between group A1 and group B1 ($P = 0.318$, Fig. 1d).

Among the patients with the L858R point mutation in the EGFR gene, a total of 44 individuals were identified. Among them, 22 patients obtained icotinib + chemotherapy (group A2), while 22 patients obtained icotinib alone (group B2). The mPFS for patients in groups A2 and B2 was 15 months (95% CI, 9.395-20.605) and 4 months (95% CI, 0.000-9.931), respectively. The average OS was 34 months (95% CI, 26.041-41.959) in group A2 and 22 months (95% CI, 10.758-33.242) in group B2. Although no significant OS benefit was observed, patients in group A2 demonstrated clear advantages in terms of PFS (Fig. 1e, f).

Among the patients diagnosed with brain metastases, a total of 24 individuals were identified. Among them, 11 patients obtained icotinib + chemotherapy (group A3), while 13 patients obtained icotinib alone (group

B3). The median PFS for patients in groups A3 and B3 was 16 months (95% CI, 5.254-26.746) and 3 months (95% CI, 0.064-5.936), respectively. The median OS was 34 months (95% CI, 25.898-42.102) in group A3 and 17 months (95% CI, 8.531-25.487) in group B3. The PFS of patients in group A3 demonstrated excellent results (Fig. 1g, h).

Fig.1 Kaplan–Meier (KM) plots.**a, b**KM plots of progression-free survival (PFS) and overall survival (OS) comparing patients receiving icotinib + chemotherapy and icotinib alone strategies. **c, d** KM plots of progression-free survival (PFS)and overall survival (OS) in the EGFR exon 19 deletion group comparing patients receiving icotinib + chemotherapy and icotinib alone strategies.**e, f** KM plots of progression-free survival (PFS)and overall survival (OS) in EGFR exon 21 L858R point mutation group comparing patients receiving icotinib + chemotherapy and icotinib alone strategies. **g, h** KM plots of progression-free survival (PFS)and overall survival (OS) comparing patients in the brain metastases group receiving icotinib + chemotherapy and icotinib alone strategies.



Adverse events

As indicated in Table 3, the prevalent AEs observed in groups A and B included hematologic toxicities (88.1%, 4.5%, $P = 0.00$), gastrointestinal reactions (nausea/vomiting 66.7%, 22.7%, $P = 0.00$; diarrhea 35.7%, 38.6%, $P = 0.779$), skin reactions (rash 45.2%, 45.5%, $P = 0.984$), and hepatic dysfunction (elevation of aspartate

transaminase [AST] and alanine transaminase [ALT]) (52.4%, 11.4%, $P = 0.00$).

Table 3 Characteristics of all included studies

Study	Country	Issue date	Design	Control	Patients	Median age (year)	Median follow-up time (month)	Stage	Adeno-carci-noma (%)	EGFR muta-tions (%)	Risk of bias	A
NEJ009	Japan	2020.01.10	GCP	G	169/172	64	45	III/IV	98.8	95	Other	Y H
CTRI/2015/08/007120	India	2020.01.10	GCP	G	174/176	56	17	III B/IV	98	100	Other	V N
NCT01469000	East Asia	2020.01.01	GP	G	126/65	62	NR	IV or EGFR mutations	100	100	Other	J C H Y
NCT02148380	China	2017.07.15	GCP	G	40/41	NR	NR	IIIB or IV	100	100	Other	H H
NCT00283244	America	2011.09.01	GE	E	51/51	76	12.3	IIIb/IV	64	NR	Other	T H S
NCT02031601	China	2019.07.01	ICP	I	90/89	59	NR	III/IV	100	100	Other	L X

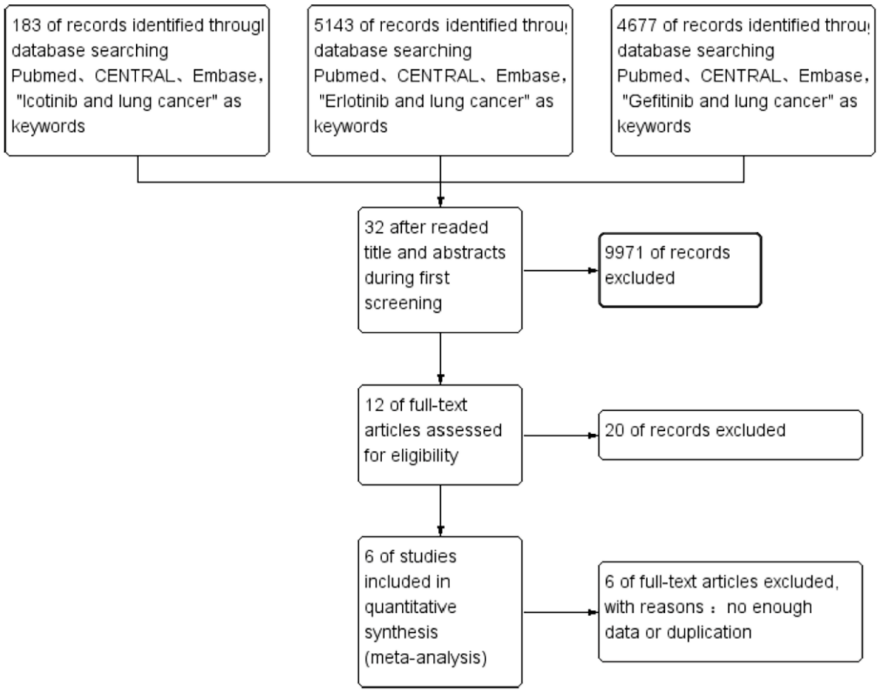
Abbreviations: GCP, Gefitinib+ Pemetrexed carboplatin; G, Gefitinib;GP, Gefitinib+ Pemetrexed; GE, Gemcitabine+ Erlotinib; E, Erlotinib ;ICP, Icotinib + Pemetrexed carboplatin;I, Icotinib.

Meta-analysis

Literature search results

Initially, a total of 10,003 possible articles were reviewed. 9,971 records were removed by the first filter of the title and summary. After a thorough examination of the complete articles, 20 articles were further excluded based on criteria such as repetition, non-randomized controlled trials, trials focusing on a single agent, and insufficient data on efficacy and safety for analysis. Among these exclusions, only six articles provided hazard ratios and were thus deemed eligible for the analysis of survival outcomes [16, 17, 18, 19, 20, 21]. The study flow based on the PRISMA guidelines for the article search is depicted in Figure 2.

Fig. 2 Flow chart of study selection



Study characteristics

Table 3 describes the characteristics of specific studies. Most of the investigations were carried out in Asia, with the exception of one clinical trial in the United States. Four studies compared gefitinib with chemotherapy (4-7), and one compared erlotinib with chemotherapy (8). Only two studies accurately described blindness (4, 5), and the data on adverse reactions were incomplete for most of the articles

Outcome analysis: Efficacy and OS

Data from six independent studies, excluding our retrospective cohort, were subjected to analysis. The study pool comprised a total of 1,242 patients, with 648 patients receiving combined treatment and 594 patients receiving first-generation EGFR-TKI monotherapy. The average age of the patients participated in the analysis was over 60 years, and the majority of them had adenocarcinoma with EGFR mutations.

Efficacy

The article and appendix compile the results of all comparisons, with variations in the availability of outcomes across studies. All studies reported on ORR, PFS, and OS. The combined analysis revealed that the combination therapy group had a substantially greater ORR than the monotherapy group (RR: 0.63, 95% CI: 0.53–0.74, $P < 0.00001$). There was diversity (I2 = 59%, $P = 0.03$), indicating variation among the studies. Hence, a random effects model was employed (RR: 0.63, 95% CI: 0.49–0.82, $P = 0.0006$) (Fig.3a).

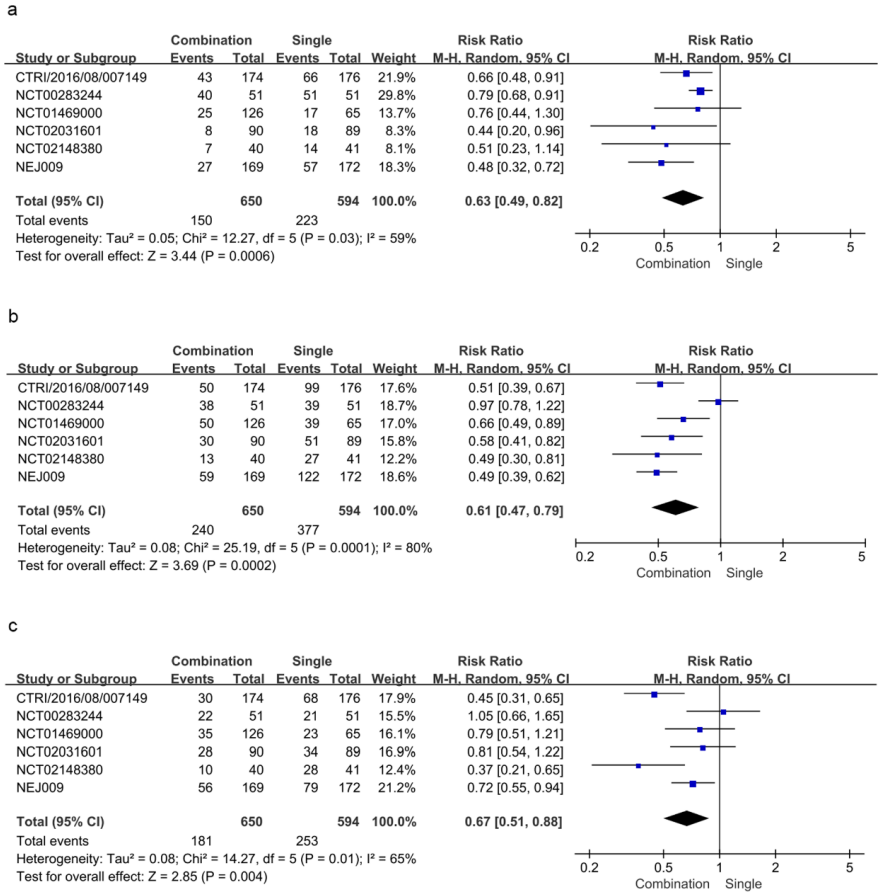
In the subgroup evaluation, the Asian group also benefited from combination therapy (RR: 0.58, 95% CI: 0.47–0.72, $P < 0.00001$), with no varience noticed (I2 = 0%, $P = 0.57$). This suggests that Asians may derive greater benefit from combination therapy compared to Europeans and Americans (RR: 0.79, 95% CI: 0.68–0.91,$P = 0.001$) (Supplementary Fig. 1).

The combined data suggested that combination therapy prolongs PFS compared to monotherapy (RR: 0.61, 95% CI: 0.47–0.79, $P = 0.0002$). Heterogeneity was present, and thus the random effects model was utilized (I2 = 80%, $P = 0.0001$) (Fig.3b). The advantages of combination treatment were also evident in various subgroups, including brain metastases (RR: 0.39, 95% CI: 0.26–0.57, $P < 0.00001$), non-brain metastases

(RR: 0.50, 95% CI: 0.41–0.62, $P< 0.00001$), smoking (RR: 0.40, 95% CI: 0.31–0.53, $P< 0.00001$), non-smoking (RR: 0.59, 95% CI: 0.46–0.75,$P < 0.0001$), EGFR mutation (RR: 0.51, 95% CI: 0.42–0.63, $P < 0.00001$), male (RR: 0.49, 95% CI: 0.39–0.62, $P < 0.00001$), female (RR: 0.54, 95% CI: 0.44–0.66, $P < 0.00001$), Asian (RR: 0.54, 95% CI: 0.47–0.61, $P < 0.00001$), with no heterogeneity observed. The results for the Euro-American subgroup were not statistically significant (RR: 0.97, 95% CI: 0.78–1.22, $P = 0.82$) (Supplementary Fig. 2).

OS was significantly increased in the combination therapy group contrary to monotherapy (RR: 0.67, 95% CI: 0.51–0.88, $P = 0.004$). Heterogeneity was present, and hence the random effects model was utilized (I2 = 65%, $P = 0.01$) (Fig.3c). A significant increase in OS was also observed in the Asian group (RR: 0.62, 95% CI: 0.46–0.82, $P = 0.0008$). The Euro-American subgroup did not show a significant difference (RR: 1.05, 95% CI: 0.66–1.65, $P = 0.84$) (Supplementary Fig. 3).

Fig. 3 Meta-analysis of Overall response rate (ORR), the progression-free survival (PFS)and overall survival (OS).



Safety

Table 4 presents the findings from the evaluation of combined data for all grades of treatment-emergent adverse events (TEAEs). The results indicated that the inclusion of chemotherapy alongside first-generation TKI therapy led to higher occurrence rates of various TEAEs, including decreased appetite, increase of aspartate aminotransferase/alanine aminotransferase (AST/ALT), leukopenia, neutropenia, anemia, thrombocytopenia, stomatitis, and nausea across all grades. Moreover, the occurrence of neutropenia was particularly increased with the addition of chemotherapy.

Table 4 Meta-analysis of all grade's treatment-emergent adverse events

	RR	[95% CI]	*p*
Leukopenia	4.58	2.33 ,9.02	<0.0001
Neutropenia	10.04	3.98, 25.35	<0.00001
Anemia	2.8	1.38, 5.65	0.004
Thrombocytopenia	5.33	2.73, 10.40	<0.00001
Elevated aminotransferase	1.33	1.05, 1.68	0.02
Diarrhea	1.15	1.00, 1.33	0.05
Nausea and vomiting	4.06	2.23, 7.38	<0.00001
Oral/mucositis	1.67	1.33, 2.11	<0.0001
Constipation	3.48	2.48, 4.87	<0.00001
Fatigue	2.79	1.48, 5.28	0.002
Anorexia	2.37	1.72, 3.26	<0.00001
Rash	0.93	0.71, 1.24	0.64

Abbreviations: RR, risk ratio; CI, confidence interval

Discussion

Lung carcinoma is the most dominant form of carcinoma globally, with the most of cases being NSCLC, often detected at an late stage (9). The FLC regimen based on a platinum-based two-drug combination fails to improve patient survival (10). Recently, several molecular targeted drugs, especially EGFR-TKIs, have been applied, which have extended the median PFS of patients with NSCLC, showing broad application prospects. Nevertheless, molecular targeted drugs' benefits are still limited, and resistance cannot be avoided (11, 12). Therefore, some scholars have proposed using chemotherapy and molecularly targeted medicines in advanced NSCLC patients to improve their QoL, prolong their median PFS, and extend their survival (13-15).

To examine the effectiveness and safety of combining EGFR-TKIs with chemotherapy as the initial therapy for progressive EGFR MUT+ NSCLC, a comprehensive meta-analysis was conducted based on available literature. The results of our analysis revealed that when used as FLT, combining 1st-gen EGFR-TKIs with chemotherapy led to improved PFS, ORR, and other efficacy measures in patients with EGFR MUT+ NSCLC compared to using 1st-gen EGFR-TKIs alone. Furthermore, our safety analysis demonstrated a greater frequency of neutropenia, thrombocytopenia, and diarrhea in the group receiving EGFR-TKIs in conjunction with chemotherapy compared to the group receiving EGFR-TKI monotherapy. These findings align with those of Chen et al. [29], who also observed that the incidence of adverse reactions associated with TKIs combined with chemotherapy remained manageable for patients.

All six studies including the meta-analysis, were written in English with high quality and reliable results. However, these studies still had the following limitations: 1. Among these studies, two explicitly described blindness and six detailed distributional concealments, but none of them described other sources of bias; 2. the variation in outcome indicators among studies could have potentially impacted the combined results; 3. the baseline of the studies were inconsistent, which may have caused bias; and 4. the data included in these studies were still limited, so it was impossible to conduct subgroup analysis for different patient types, and there might be confounding factors in the merged results. In conclusion, compared to EGFR-TKIs alone, EGFR-TKIs along with chemotherapy can prolong patients' median PFS, improve their ORR, and can be utilized in progressive NSCLC patients. However, due to the restricted number and quality of the included studies, this conclusion should be interpreted with caution and further validated by better studies.

Gefitinib, erlotinib, and icotinib were successively released onto the market in China in 2004, 2007, and 2011, respectively, offering advantages to EGFR MUT+ NSCLC patients [30, 31]. The mPFS for patients

with progressed or locally advanced EGFR MUT+ NSCLC who obtained 1st-gen EGFR-TKIs as primary treatment ranged from 9 to 14 months, although the development of resistance was inevitable. To delay the onset of resistance, researchers conducted several notable studies with positive outcomes. As indicated by the aforementioned meta-analysis, 1st-gen EGFR-TKIs + Chemo led to improved ORR and significantly prolonged PFS. While none of the included studies demonstrated a substantial enhancement in OS when comparing 1st-gen EGFR-TKIs + Chemo to EGFR-TKI monotherapy, the comprehensive analysis of these studies suggested an overall trend toward OS benefit for 1st-gen EGFR-TKIs + Chemo compared to EGFR-TKIs alone.

Due to the limitations imposed by the inclusion and exclusion criteria of clinical trials, the aforementioned research may not fully reflect the real-world benefits of targeted therapy for with EGFR MUT+ NSCLC patients. To elucidate the therapeutic effectiveness and safety of 1st-gen EGFR-TKIs + Chemo in EGFR gene mutations patients, compared to EGFR-TKIs alone, we performed an observational investigation at our hospital from January 2013 to January 2022. The analysis focused on EGFR mutations patients who obtained either icotinib combined with pemetrexed and platinum-based chemotherapy or icotinib monotherapy. The findings revealed that improvement in PFS and DCR in patients who obtained icotinib plus pemetrexed and platinum-based chemotherapy as FLT compared to patients who obtained icotinib alone. However, there were no statistically significant differences in ORR and OS. Notably, among the 86 patients included in the study, 24 had brain metastases at the time of diagnosis, and subgroup analysis indicated that this subgroup derived greater benefits from combination therapy. Furthermore, in the subgroup analysis based on EGFR mutation status, patients with EGFR-L858R mutation showed significant PFS advantages when receiving icotinib combined with pemetrexed and platinum chemotherapy compared to those who underwent icotinib monotherapy. Regarding safety evaluation, although the combined treatment group experienced higher incidences of bone marrow suppression and liver dysfunction in comparison to the monotherapy group, no patients in the combined treatment group stopped receiving their medication as a result of these adverse effects. Thus, the treatment of the disease was not compromised. The prevalence of other therapy-related AEs, such as rash and diarrhea, did not differ between the two groups.

Our center's meta-analysis and retrospective analysis provide compelling evidence for the significant clinical benefits of combining first-generation EGFR-TKI with chemotherapy as a FLT for patients with locally progressed or advanced NSCLC harboring EGFR-positive mutations. Notably, in the subgroup analysis of patients with EGFR-L858R mutation and brain metastases, although no OS benefit was observed, all patients derived benefits in terms of PFS. Several factors may contribute to these findings: Firstly, the OS data of the patients included in this study might not have reached full maturity. Secondly, the complexity of second-line therapy following disease development from FLT, whether with EGFR-TKI alone or in conjunction with chemotherapy, could impact patients' overall survival. Lastly, it is essential to acknowledge the limited sample size of only 86 patients in this study, which might not fully reflect the treatment outcomes for all patients. In conclusion, the integration of 1st-gen EGFR-TKI with chemotherapy demonstrates clear advantages as a FLT option for locally progressed or advanced NSCLC with EGFR-positive mutations patients.

In conclusion, the availability of EGFR-targeting drugs has brought significant benefits to numerous patients diagnosed with EGFR MUT+ NSCLC, pointing towards improved medical utilization of EGFR-TKIs through extensive large-scale multi-center prospective, randomized, and monitored clinical studies. The findings from this retrospective analysis highlight the advantages of 1st-gen EGFR-TKIs + Chemo as a FLT approach for EGFR MUT+ NSCLC patients. Therefore, considering the evidence presented, opting for the 1st-gen EGFR-TKIs + Chemo may represent a more favorable choice for this specific group of patients.

Declarations

Ethical Approval The experimental research conducted in this study was approved by the ethics committee of the First Affiliated Hospital of Henan University of Science and Technology, and the approval number provided by the Institutional Review Board (IRB) is 2022-03-B075. All research involving human subjects adhered to the principles outlined in the Helsinki Declaration.**Competing interests**The author(s) have stated that they have no conflicts of interest regarding the research, authorship, and publication of this

article.**Authors' contributions**Each author contributed significantly to concept and development of the present paper. Guoqiang Miao and Shegan Gao designed the research process. Jiachun Sun, Jingya Li and Junshuai Rui searched the database for corresponding articles and extracted useful information from the articles above. Haolin Shi and Zihan Yang used statistical software for analysis. Dejiu Kong , Zhiyi Jiang and Xinyang Li drafted the meta-analysis. All authors had read and approved the manuscript and ensured that this was the case. (applicable for submissions with multiple authors) **Funding**This study was supported by the National Science Foundation of China (81872500).

Availability of data and materials Data availability The authors state that they have full control of all primary data and agree to allow the journal to review this data if requested. Code availability N/A.

DeclarationsConsent to participate N/A

Consent for publication N/A

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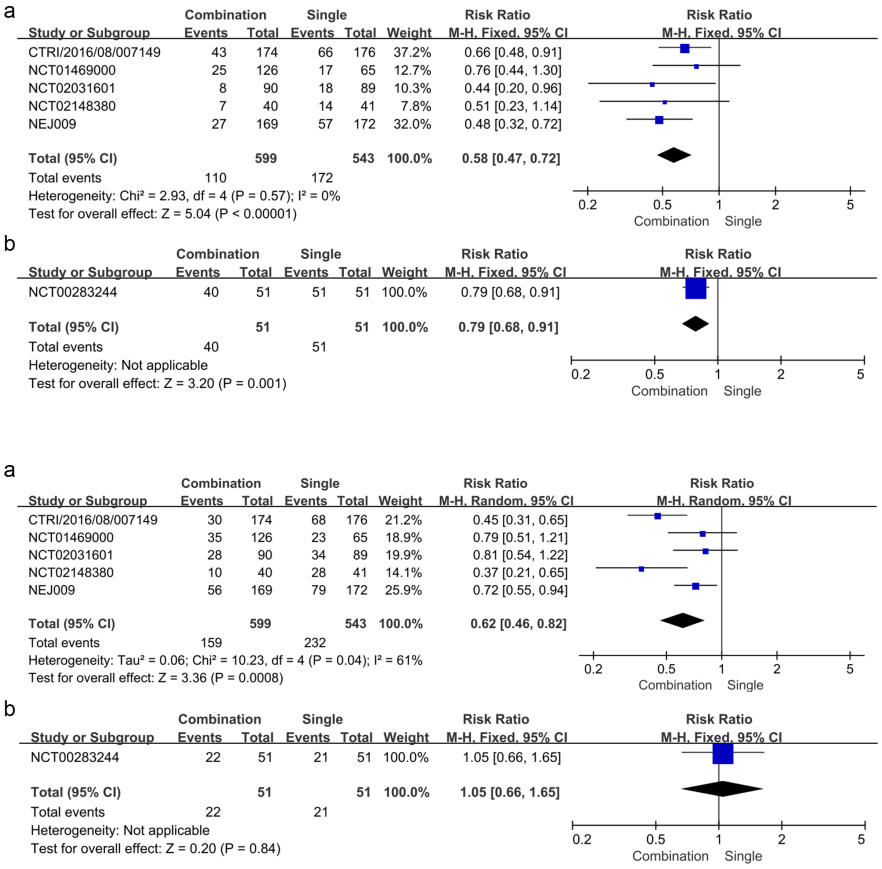


a

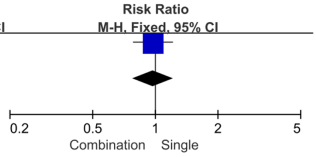
Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CTRI/2016/08/007149	50	174	99	176	28.2%	0.51 [0.39, 0.67]
NCT01469000	50	126	39	65	14.8%	0.66 [0.49, 0.89]
NCT02031601	30	90	51	89	14.7%	0.58 [0.41, 0.82]
NCT02148380	13	40	27	41	7.6%	0.49 [0.30, 0.81]
NEJ009	59	169	122	172	34.7%	0.49 [0.39, 0.62]
Total (95% CI)		**599**		**543**	**100.0%**	**0.54 [0.47, 0.61]**
Total events	202		338			

Heterogeneity: Chi² = 2.97, df = 4 (P = 0.56); I² = 0%
Test for overall effect: Z = 9.24 (P < 0.00001)

b

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT00283244	38	51	39	51	100.0%	0.97 [0.78, 1.22]
Total (95% CI)		**51**		**51**	**100.0%**	**0.97 [0.78, 1.22]**
Total events	38		39			

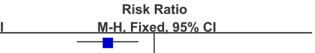
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



c

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CTRI/2016/08/007149	30	88	53	93	43.3%	0.60 [0.43, 0.84]
NCT02031601	10	33	16	23	15.9%	0.44 [0.24, 0.78]
NEJ009	18	56	52	64	40.8%	0.40 [0.27, 0.59]
Total (95% CI)		**177**		**180**	**100.0%**	**0.49 [0.39, 0.62]**
Total events	58		121			

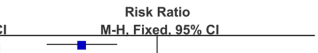
Heterogeneity: Chi² = 2.59, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 5.94 (P < 0.00001)



d

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CTRI/2016/08/007149	23	86	51	83	33.9%	0.44 [0.29, 0.64]
NCT02031601	21	57	35	66	21.2%	0.69 [0.46, 1.05]
NEJ009	39	114	67	108	44.9%	0.55 [0.41, 0.74]
Total (95% CI)		**257**		**257**	**100.0%**	**0.54 [0.44, 0.66]**
Total events	83		153			

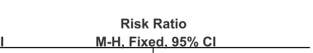
Heterogeneity: Chi² = 2.65, df = 2 (P = 0.27); I² = 25%
Test for overall effect: Z = 5.90 (P < 0.00001)



e

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT02031601	7	26	16	20	21.2%	0.34 [0.17, 0.66]
NEJ009	28	73	68	75	78.8%	0.42 [0.31, 0.57]
Total (95% CI)		**99**		**95**	**100.0%**	**0.40 [0.31, 0.53]**
Total events	35		84			

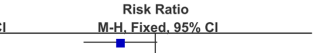
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 6.47 (P < 0.00001)



f

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT02031601	22	64	35	69	34.6%	0.68 [0.45, 1.02]
NEJ009	34	96	64	97	65.4%	0.54 [0.40, 0.73]
Total (95% CI)		**160**		**166**	**100.0%**	**0.59 [0.46, 0.75]**
Total events	56		99			

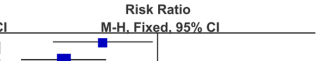
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 4.28 (P < 0.0001)



g

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CTRI/2016/08/007149	9	30	20	34	36.3%	0.51 [0.28, 0.94]
NEJ009	12	50	29	38	63.7%	0.31 [0.19, 0.53]
Total (95% CI)		**80**		**72**	**100.0%**	**0.39 [0.26, 0.57]**
Total events	21		49			

Heterogeneity: Chi² = 1.38, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 4.72 (P < 0.00001)



h

Study or Subgroup	Combination Events	Total	Single Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CTRI/2016/08/007149	37	114	90	142	48.5%	0.51 [0.38, 0.69]
NEJ009	40	120	90	134	51.5%	0.50 [0.38, 0.66]
Total (95% CI)		**234**		**276**	**100.0%**	**0.50 [0.41, 0.62]**
Total events	77		180			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 6.64 (P < 0.00001)