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Molecular heterogeneity and treatment outcome of EGFR exon 20 insertion mutations in Chinese patients with advanced non-small cell lung cancer: insights from a large-scale real-world study

Weirui Wu[1,2†], Silin Yu[1,3†], Jinsheng Huang[1†], Qi Qi[1,2], Yongyi Wu[1,2] and Jun Dong[1*]

Abstract

Introduction This retrospective study aimed to investigate treatment patterns and outcomes in patients with NSCLC harboring EGFR20ins in China. EGFR20ins mutations are associated with poor responses to EGFR-TKIs, and limited real-world data exist regarding the efficacy of various treatment modalities.

Methods In this retrospective, single-center study, treatment outcomes, including PFS and ORR, were evaluated for different treatment regimens based on imaging assessments. The impact of mutation heterogeneity on treatment efficacy was also explored.

Results Data from 302 patients diagnosed with NSCLC with EGFR20ins were analyzed. EGFR-TKI monotherapy demonstrated suboptimal PFS compared to platinum-based chemotherapy in the first-line setting (3.00 m vs. 6.83 m, HR = 3.674, 95%CI = 2.48–5.44, $p < 0.001$). Platinum plus pemetrexed plus bevacizumab combination therapy showed improved PFS and ORR compared to platinum plus pemetrexed (7.50m vs. 5.43 m, HR = 0.593, 95%CI = 0.383–0.918, $p = 0.019$). In later-line treatments, monotherapy with EGFR-TKIs or ICIs exhibited suboptimal efficacy. The specific EGFR20ins subtype, A763_Y764insFQEA, showed favorable responses to EGFR-TKIs in real-world settings.

Conclusions This large-scale real-world study provides valuable insights into the treatment patterns and outcomes of NSCLC patients with EGFR20ins mutations in China. These findings contribute to the understanding of EGFR20ins treatment and provide real-world benchmark for future clinical trials and drug development.

Keywords Non-small cell lung cancer, Advanced lung cancer, EGFR mutations, EGFR exon 20 insertions

†Weirui Wu, Silin Yu and Jinsheng Huang these authors contributed equally to this work.

*Correspondence:
Jun Dong
dongjun1@sysucc.org.cn
Full list of author information is available at the end of the article

Introduction

Lung cancer stands as one of the most prevalent malignancies worldwide, with a staggering incidence of approximately 1.06 million new cases annually in China [1]. In the realm of non-small cell lung cancer (NSCLC), patients harboring actionable driver mutations have entered a new era dominated by molecular targeted therapies. Among these, deletions in exon 19 or missense mutations in exon 21 of the Epidermal Growth Factor Receptor (EGFR) gene are the most common oncogenic drivers, accounting for 85% to 90% of all EGFR mutations [2]. These classical mutations are recognized as strong predictors of sensitivity to existing EGFR tyrosine kinase inhibitors (EGFR-TKIs) [2, 3].

Within the spectrum of EGFR mutations, insertions in EGFR exon 20 (EGFR20ins) constitute approximately 4% to 12% of all EGFR mutations [4, 5]. These insertion mutations are generally associated with poor responses to EGFR-TKIs, exhibiting resistance to first, second or third-generation EGFR-TKIs in most cases [2]. Patients carrying these mutations typically have a significantly worse prognosis and limited therapeutic options. Recognizing the challenging nature of these mutations, recent advances have sought to expand the arsenal of treatments specifically targeting EGFR20ins. Among the scarce treatment alternatives, mobocertinib, amivantamab have demonstrated some efficacy in the second-line or beyond treatment settings [6, 7]. However, in clinical research, the scarcity of EGFR20ins mutations contributes to the paucity of real-world data regarding the efficacy of various treatment modalities. Consequently, the establishment of first-line standard treatment strategies for EGFR20ins is fraught with challenges, leaving a considerable void in terms of comprehensive, large-scale real-world studies.

In addition to investigating therapeutic measures targeting the entire EGFR20ins cohort, the heterogeneity present within exon 20 itself also warrants further exploration. The specific subtype with EGFR exon 20 A763_Y764insFQEA has been demonstrated to be sensitive to first and second-generation EGFR-TKIs in both in vitro and in vivo experiments, as well as in case reports [8–10]. Furthermore, the G770 equivalent variant has similarly been reported to exhibit sensitivity to first and second-generation TKIs, findings supported by computational simulations and a limited number of case reports [8, 11]. Given the limited clinical real-world data and contentious efficacy of existing treatments, a substantial gap exists in large-scale real-world studies in this field, necessitating further discussion.

This study endeavors to provide more precise clinical reference data for NSCLC patients with EGFR20ins, and to offer valuable insights for future drug development and clinical trial design, providing an essential real-world benchmark for ongoing clinical trials. This retrospective analysis represents the largest study to date, assessing real-world patient characteristics, treatment patterns, and clinical outcome of NSCLC patients with EGFR20ins mutations in China.

Method

This study is a retrospective, single-center study focusing on patients with advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertions. Data Extraction Criteria: (1) histological diagnosis of NSCLC; (2) Confirmation of EGFR20ins via Polymerase Chain Reaction (PCR) or Next-Generation Sequencing (NGS); (3) diagnosis of advanced or metastatic cancer. Cases that were unable to be evaluated for treatment outcomes owing to incomplete data by imaging assessments were excluded. Criteria for data exclusion include: (1) Absence of baseline imaging assessments at the initiation of therapy to confirm treatment efficacy; (2) Images such as CT scans or MRIs that do not have sufficient quality to clearly identify tumor characteristics. Medical records including PCR or NGS sequencing results, treatment history and imaging examination reports was collected via Sun Yat-Sen University Cancer Center hospital information system, online questionnaires and long-time telephone follow-up. The study received approval from the Ethics Committee of Sun Yat-Sen University Cancer Center. All patients voluntarily participated in this study and provided informed consent for data collection.

In this study, progression-free survival (PFS) was defined as the time from the initiation of a specified treatment regimen to the first documented evidence of disease progression or death from any cause. Treatment response was evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) to identify a response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). For the calculation of the 95% confidence intervals (CIs) for the Objective Response Rate (ORR) across different generations of TKIs, owing to the limited sample sizes, we employed the Wilson procedure with a continuity correction. Cases that had not experienced progression at the data cutoff date (August 1, 2023) or missing at follow-up were censored. For a small subset of patients who transitioned to a different treatment regimen without clear radiological confirmation of disease progression, PFS was censored at the time of the last radiological assessment prior to the change in treatment, minimizing the confounding effects of subsequent therapies.

Statistical analyses were conducted using R software, version 4.2.1. The chi-square test was employed to assess statistical differences in ORR among groups.

Survival differences, specifically PFS across various subgroups, were estimated using the Kaplan–Meier method. To ensure statistical rigor, Bonferroni adjustment was employed for multiple comparisons. Hazard factors affecting PFS of patients were assessed using Cox proportional hazards models. Variables that achieved a *p*-value of less than 0.10 in univariate analyses, along with those factors of clinical significance, were subjected to subsequent multivariate Cox regression analysis to identify independent risk factors. *P* values < 0.05 at two-sided were considered statistically significant.

Results

General characters and mutation map

Data from a total of 302 patients with EGFR20ins were incorporated into the analysis, yielding 856 treatment regimens across various lines of therapy, along with detailed information on treatment outcomes. Patients who with incomplete data by imaging assessments were excluded ($n=63$). The initial diagnosis of these patients ranged from November 2008 to February 2023, with a follow-up cut-off date of August 1, 2023. The cohort had an average age of 57.35 years (range, 23 to 83 years), with 178 females (58.9%) and 124 males (41.1%). All patients were initially diagnosed with advanced or metastatic cancer (stage III, $n=53$; stage IV, $n=249$ patients). Among them, 74 patients (24.5%) presented with brain metastasis at the time of diagnosis. The histological diagnoses included 293 patients (97.0%) with adenocarcinoma, 6 patients (2.0%) with adenosquamous carcinoma, and 3 patients (1.0%) with squamous carcinoma. Detailed baseline characteristics are shown in Table 1. Among 257 patients with detailed insertion site information for EGFR20ins, 62 distinct insertion subtypes were identified. Classified by the relative insertion location within EGFR exon 20 [12], there were 14 patients with insertions in the helical (D761-M766) region, 198 in the near loop region (A767-P722), and 45 in the far loop region (H773-C775). The four most common insertion variants, based on frequency, were V769_D770insASV, D770_N771insSVD, A763_Y764insFQEA, and H773_V774insNPH, with 91, 27, 14, and 11 patients, respectively. A comprehensive display of all mutations is shown in Fig. 1.

Table 1 Characteristics of study patients

Characteristics	Value(%)
Age	57.35±10.76
CNS Metastasis at diagnosis	
Yes	74 (24.5)
No	228 (75.5)
stage	
IIIA	19 (6.3)
IIIB/IIIC	34 (11.3)
IV	249 (82.5)
Histology	
Adenocarcinoma	293 (97.0)
Adenosquamous carcinoma	6 (2.0)
Squamous carcinoma	3 (1.0)
Sex	
Female	178 (59.0)
Male	124 (41.0)
ECOG PS	
0	57
1	237
2	4
3	4
Site of Metastasis	
Bone	110 (36.4)
Central nervous system	74 (24.5)
Pleura	39 (12.9)
Liver	20 (6.6)
Adrenal	12 (4.0)
Pericardium	3 (1.0)
Kidney	3 (1.0)
Spleen	1 (0.3)
Co-existing Genetic Alterations	
TP53	58 (19.2)
EGFR G719R	1 (0.3)
EGFR S768I	4 (1.3)
EGFR T790M	3 (1.0)
EGFR L858R	3 (1.0)
KI67	13 (4.3)
KRASG12V	1 (0.3)
ROS 1	2 (0.67)
ALK	2 (0.67)
Insertion subsites	
Helix	14 (4.6)
Near loop	198 (65.6)
Far loop	45 (14.9)
Unknown	45 (14.9)

First-line treatment outcomes

After omitting cases undergoing clinical trial treatments ($n=23$), a cohort of 279 patients harboring EGFR20ins received the following treatment regimens: EGFR-TKIs monotherapy ($n=53$), platinum combined with pemetrexed and bevacizumab ($n=66$), platinum in conjunction with immunotherapy agents ($n=20$), platinum plus pemetrexed ($n=80$), other platinum-based chemotherapy regimens ($n=35$), and other less common regimens ($n=25$). Detailed treatment patterns are presented in Table 2.

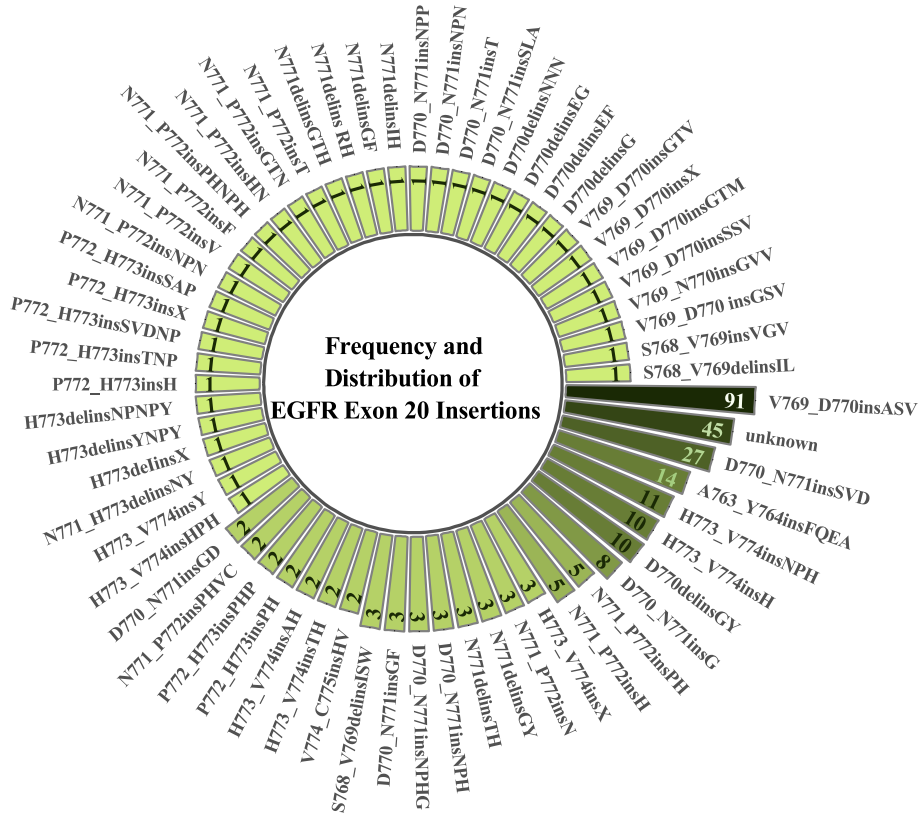

Fig. 1 Frequency and distribution of EGFR 20 insertions among all patients in this study($n=302$). The numerical values beneath the columnar diagram represent the count of individuals associated with each specific insertion variant

We observed that patients receiving platinum-based chemotherapy ($n=201$) exhibited superior PFS compared to those treated with single-agent EGFR-TKIs ($n=53$), with a median PFS of 6.83 (95%CI = 6.00–7.50) months versus 3.00 (95%CI = 2.10–4.07) months, respectively ($p<0.001$), and an ORR of 34.3% (69/201) versus 24.5% (13/53). (Fig. 2A) The univariate analysis included covariates such as sex, age, the presence of central nervous system metastases at diagnosis, disease stage at diagnosis, specific amino acid insertion sites in EGFR exon 20, TP53 mutation status, ECOG PS scores and specific regimen used. Figure 2C provides a detailed presentation of the results of both univariate and multivariate analyses. Multivariate analysis indicated that, compared to patients treated with platinum-based chemotherapy, those receiving EGFR-TKI monotherapy had a significantly increased risk of progression or death (HR = 3.674, 95% CI = 2.480–5.442, $p<0.001$).

We delved into the efficacy of various platinum-based regimens in the first-line treatment setting, including platinum plus pemetrexed plus bevacizumab, platinum-based chemotherapy plus immune oncology agents, and platinum plus pemetrexed. Their respective median PFS were 7.50(95%CI = 5.87–9.50) months, 6.50(95%CI = 6.00-NA) months, and 5.43(95%CI = 4.63–8.00) months, with corresponding ORRs of 45.5%(30/66), 45.0%(9/20), and 21.2%(17/80). Notably, in multiple comparisons among the three chemotherapy groups, only the combination of platinum with pemetrexed and bevacizumab showed statistically significant improvements in both median PFS (7.50 months vs. 5.43 months, $p=0.016$) and ORR (45.6% vs. 21.3%, $p=0.0018$) compared to platinum-based chemotherapy with pemetrexed alone (Fig. 2B). Additional baseline information of patients treated with or without bevacizumab can be found in Supplement Table 1. The effects of immunotherapy in both first-line and subsequent lines of therapy will be elaborated in subsequent sections. Similar univariate and multivariate analyses were performed for both the combination of platinum with pemetrexed and bevacizumab group and the platinum-based chemotherapy with pemetrexed group (Fig. 2D). The incorporation of bevacizumab into platinum-based chemotherapy with pemetrexed was significantly associated with improved PFS (HR = 0.593, 95%CI = 0.383–0.918, $p=0.019$). Additionally, subgroup comparisons were conducted between two groups (platinum-based chemotherapy vs. TKI monotherapy, Platinum + Pemetrexed with Bevacizumab

Table 2 Treatment pattern of EGFR20ins patients

Regimen in various lines of treatment	Count
1L	
Platinum + Pemetrexed	80
Platinum + Pemetrexed + Bevacizumab	66
EGFR-TKIs monotherapy	53
other Platinum based chemotherapy	35
other less common regimens	25
Platinum-based chemotherapy + IO	20
2L	
EGFR-TKI monotherapy	49
Platinum + Pemetrexed + Bevacizumab	21
IO monotherapy	10
Platinum + Paclitaxel	10
Platinum + Pemetrexed	9
Paclitaxel + Bevacizumab	9
Platinum + Paclitaxel + Bevacizumab	8
Bevacizumab + EGFR-TKI	7
Paclitaxel + IO	6
other less common regimens	44
≥ 3L	
EGFR-TKI monotherapy	47
nonEGFR-TKI monotherapy	12
Platinum + Pemetrexed + Bevacizumab	10
Paclitaxel + Bevacizumab	7
Bevacizumab + EGFR-TKI	6
Platinum + Paclitaxel + Bevacizumab	5
IO monotherapy	5
other less common regimens	67

vs. without Bevacizumab). Details of the results can be found in Supplementary Fig. 1. Treatment outcomes of other platinum-based chemotherapy regimens ($n=35$), and other less common regimens ($n=25$) in firstline treatment can be found in Supplement Table 2.

Treatment outcomes for second-line and subsequent therapies

In the cohort, second ($n=173$) and third-line or beyond treatments ($n=159$) predominantly comprised monotherapy with traditional TKIs. In the second-line setting, monotherapy TKIs ($n=49$) demonstrated a median PFS of 3.07(95%CI = 2.13–4.87) months and an ORR of 24.5% (12/49). Similarly, in the third-line or beyond setting, monotherapy TKIs ($n=47$) exhibited a lower median PFS of 2.5 months (95%CI = 2.03–4.07) and a reduced ORR of 8.5% (4/47). Other treatment strategies in the second and third-line or beyond settings include immune checkpoint inhibitors monotherapy, platinum-based chemotherapy, albumin-bound paclitaxel-based systemic chemotherapy, and maintenance therapies. Variations in survival outcomes were assessed among these different treatment approaches, generally associated with poor outcomes. Given the heterogeneity of treatment modalities in real-world clinical practice among patients with EGFR20ins, the analysis was concentrated on treatments received by five or more patients, with comprehensive PFS and ORR data detailed in Table 3. Among these, platinum-based chemotherapy was associated with the longest median PFS.

Real-world effectiveness of EGFR-TKIs in patients with EGFR exon 20 insertions

The real-world efficacy of first-, second-, and third-generation EGFR-TKIs was objectively reported across various lines of therapy in terms of PFS and ORR. In the first-line (1L) setting, the data suggest that monotherapy with EGFR-TKIs exhibits inferior efficacy compared with platinum-based chemotherapy regimens. Moving to second-line (2L) and third-line (3L) therapies, evidence outlined in Table 4 reinforces the view that monotherapy with EGFR-TKIs continues to be suboptimal.

Furthermore, we explored the real-world effects of various drugs in combination with EGFR-TKIs. Detailed reports on the efficacy of these combination therapies in treating NSCLC patients with EGFR20ins mutations are currently scarce. Herein is a comprehensive analysis of different therapeutic combinations and their outcomes in a real-world setting. The combination treatment regimens in our cohort included chemotherapy regimens alternated with targeted therapy ($n=22$), combination therapy of EGFR-TKI with bevacizumab ($n=16$), concurrent TKIs treatment($n=7$) and other combination therapies ($n=4$). Intriguingly, supplementing EGFR-TKI treatment with bevacizumab, in contrast to TKI monotherapy, resulted in a numerical improvement in both PFS 6.27 months (95%CI = 4.67-NA) and ORR 18.8%(3/16), respectively. The PFS and ORR of these regimens are presented in Supplement Table 3.

The role of immuno-oncology treatment in the management of EGFR20ins patients

The roles of immune checkpoint inhibitors (ICIs) across various therapeutic regimens were evaluated. Our analysis encompassed 71 patients who received ICIs as part of their treatment strategy. The most commonly used ICI was Pembrolizumab ($n=45$), followed by other immunotherapeutic agents such as sintilimab ($n=11$), nivolumab ($n=8$), among others. For the purposes of this analysis, all immunotherapeutic agents targeting the PD-1/PD-L1 axis were categorized together, with a detailed list of the specific immunotherapeutic agents provided in Supplement Table 4. The majority of findings are summarized as follows: ICIs Monotherapy($n=18$): median PFS = 5.13

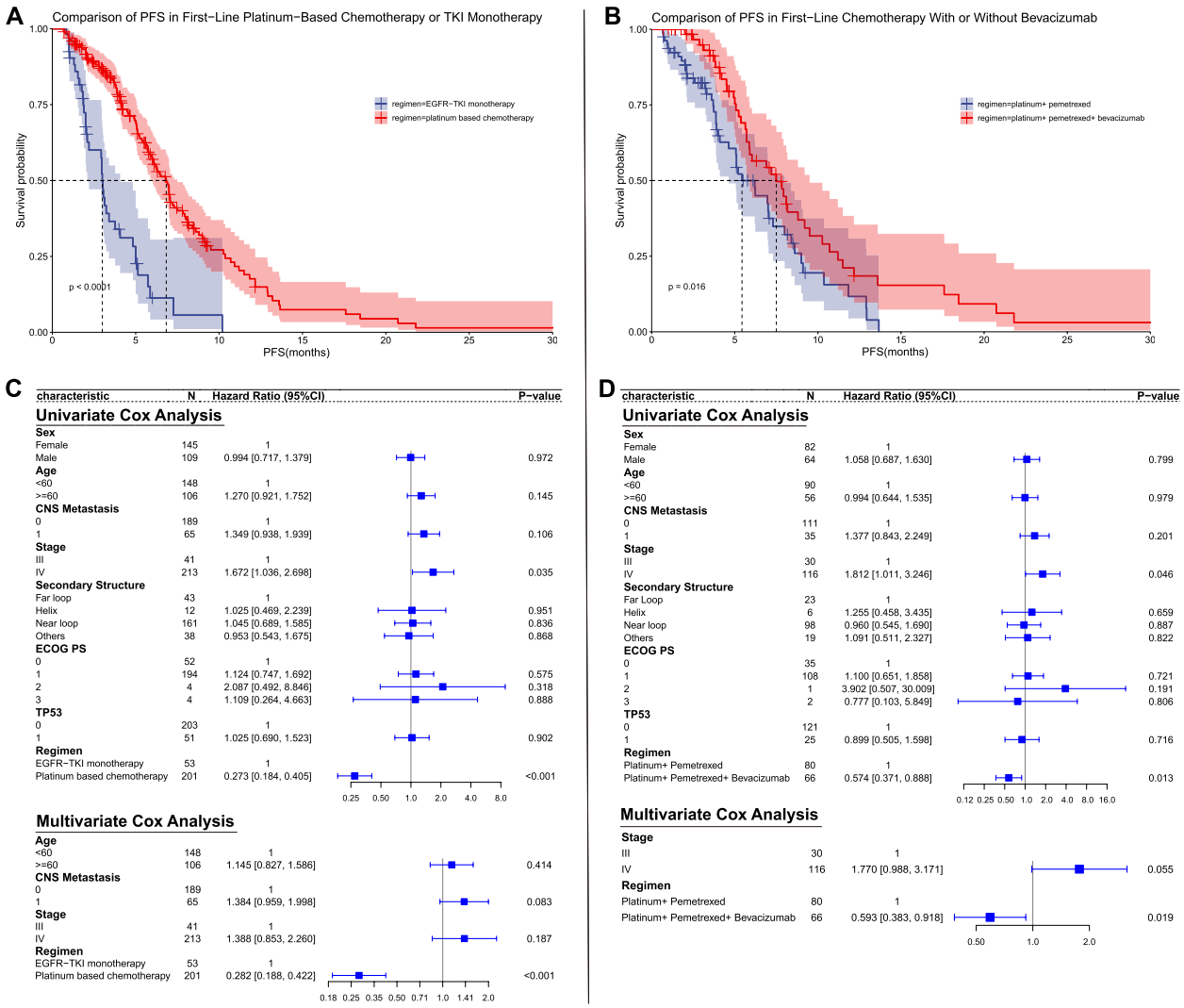

Fig. 2 **A** Kaplan–Meier Survival Curves for Progression-Free Survival among Patients Treated with First-Line Platinum-Based Chemotherapy or EGFR-TKI Monotherapy. **B** Median Progression-Free Survival Comparison between Patients Receiving First-Line Chemotherapy with and without Bevacizumab. **C** Univariate and Multivariate Cox Proportional Hazards Analyses for Patients Undergoing First Line Platinum-Based Chemotherapy or EGFR-TKI Monotherapy. **D** Univariate and Multivariate Cox Proportional Hazards Analyses for Patients receiving First-Line chemotherapy, comparing those with and without Bevacizumab Administration. In this figure, CNS denotes the central nervous system

months (95%CI = 2.63-NA), ORR = 22.2% (4/18); Paclitaxel + ICI combination(n = 10): median PFS = 9.40 months (95%CI = 2.97-NA), ORR = 50% (5/10); Platinum + Pemetrexed + Bevacizumab + ICI (n = 5): median PFS = 4.70 months (95%CI = 4.70-NA), ORR = 40% (2/5). Platinum + Pemetrexed + ICI(n = 12): median PFS = 10.90 months (95%CI = 5.03-NA), ORR = 41.7% (5/12). The concurrent use of platinum and pemetrexed with ICIs demonstrated modestly encouraging results in terms of median PFS. In first-line treatment, 11 patients utilized a regimen of platinum + pemetrexed + ICIs (9 pembrolizumab, 1 sintilimab, 1 nivolumab), exhibiting a median PFS of 10.9 months (95%CI = 5.03-NA) and an ORR of 45.5% (5/11). This regimen is numerically superior to the outcomes of platinum + pemetrexed + bevacizumab, albeit without statistical significance (univariate Cox, HR = 0.942, 95% CI = 0.397–2.236, p = 0.892).

Heterogeneity in the secondary structure of EGFR exon 20 insertions

For patients who had insertions in the loop region of EGFR exon 20 (A767-C775) treated with TKI monotherapy (n = 109), we analyzed the impact of secondary structure of EGFR exon 20 on TKI monotherapy outcomes, as well as the differences in PFS associated with specific insertion sites and targeted therapy strategies. Among

Table 3 Effectiveness of Various Therapeutic Strategies in Second-Line and Beyond Treatments

Regimen	Count	median PFS(95%CI) months	ORR(95%CI) %
Secondline Treatment			
Platinum + Pemetrexed	9	6.13 (4.70-NA)	11.1 (0.5–49.3)
Platinum + Paclitaxel + Bevacizumab	8	6.03 (3.90-NA)	25.0 (4.5–64.4)
Bevacizumab + EGFR-TKI	7	5.33 (4.67-NA)	28.6 (5.1–29.7)
Platinum + Pemetrexed + Bevacizumab	21	5.27 (3.43–16.27)	14.3 (3.8–37.4)
Paclitaxel + Bevacizumab	9	5.13 (2.80-NA)	22.2 (4.0–59.8)
IO monotherapy	10	4.20 (2.30-NA)	40.0 (13.7–72.6)
EGFR-TKI monotherapy	49	3.07 (2.13–4.87)	24.5 (13.8–39.2)
Platinum + Paclitaxel	10	2.80 (1.00-NA)	30.0 (8.1–64.6)
Paclitaxel + IO	6	NA[a]	66.7 (24.1–94.0)
Thirdine or beyond Treatment			
Platinum + Pemetrexed + Bevacizumab	10	8.00 (2.57-NA)	10.0 (0.5–45.9)
Paclitaxel + Bevacizumab	7	5.10 (1.33-NA)	14.3 (0.8–58.0)
Bevacizumab + EGFR-TKI	6	5.03 (3.00-NA)	0
nonEGFR-TKI monotherapy	12	4.17 (1.93-NA)	41.7 (16.5–71.4)
Platinum + Paclitaxel + Bevacizumab	5	4.03 (1.50-NA)	0
IO monotherapy	5	2.97 (1.20-NA)	0
EGFR-TKI monotherapy	47	2.50 (2.03–4.07)	8.5 (2.8–21.3)

[a] Median PFS is not available (NA) due to a limited number of events observed

patients treated with TKI monotherapy, two achieved a best response of complete response (CR), both of whom had EGFR 20ins at the D770_N771 site in the near loop, one with D770_N771insG, and the other with D770_N771insSVD, treated with erlotinib and osimertinib, respectively. The D770_N771insX site ($n=27$) showed numerically better effectiveness compared to other loop region EGFR20ins patients (n = 82), with median PFS of [3.73 m, 2.93 m, $p=0.52$] and ORR of [25.9% (7/27), 15.9% (13/82), $p=0.50$], albeit without statistical significance.

Among the collected data, a total of 29 patients harbored the unique A763_Y764insFQEA insertion subtype and G770 equivalent variants, ($n=14$ and $n=15$, respectively), with 14 of these patients receiving EGFR-TKIs therapies. Given the demonstrated efficacy of first or second-generation EGFR-TKIs against these particular EGFR20ins subtypes in both in vitro experiments and real world case reports [9, 11], we outlined real-world treatment strategies, corresponding real-world PFS, and other relevant data for patients carrying this specific insertion type, as detailed in Table 5. Patients with the A763_Y764insFQEA variant treated with EGFR-TKI based therapies showed an ORR of 50% (8/16), whereas those with the G770 equivalent variant demonstrated an ORR of 0% (0/6).

In regards to the efficacy heterogeneity between patients using EGFR-TKIs monotherapy for the near loop (A767-P722, $n=93$) and far loop mutations(H773-C775, $n=16$), a statistically significant difference in PFS (2.93m vs. 3.03m, $p=0.85$) and ORR (19.4% vs. 12.5%, $p=0.73$) was not observed.

Discussion

Following the report by Ou [13] on the real-world treatment outcomes of 237 American patients with EGFR20ins and the identification of 263 EGFR20ins patients among 14,483 NSCLC patients by Riess [14], herein we present the largest real-world data concerning NSCLCs harboring EGFR exon 20 insertions in China. This cohort is notably characterized by its limited responsiveness to conventional EGFR-TKI therapy. Our findings further highlight the heterogeneity of EGFR20ins mutations and their impact on treatment efficacy on a larger scale. This provides a comprehensive analysis of the characteristics and responses to treatment modalities currently available.

In the realm of NSCLC treatment, established treatment protocols exist for targeted therapy against EGFR mutations, including exon 19 deletions and the L858R point mutation in exon 21, leading to favorable therapeutic results based on EGFR-TKIs [2–4]. In contrast, EGFR20ins mutations typically exhibit poor responsiveness to existing EGFR-TKIs, and patients with these mutations have poorer prognoses, with effective first-line treatment options still under exploration [4].

For first-line treatment of patients with EGFR20ins mutations, our real-world study, through multivariate

Table 4 Efficacy of EGFR-TKI Monotherapy Across Different Lines of Therapy

TKI Generation		Count	median PFS (95%CI) months	ORR (95%CI) %
any line EGFR-TKI monotherapy				
Gen1:	Gefitinib	18	2.10 (0.80-3.40)	11.1 (2.0 -36.1)
	Icotinib	11	2.50 (1.54-3.46)	18.2 (3.2 -52.2)
Gen2:	Afatinib	48	3.67 (2.85-4.48)	25.0 (14.1-40.0)
	Dacomitinib	2	NA^	0
Gen3:	Osimertinib	60	3.00 (2.14-3.86)	16.7 (8.7 -29.0)
	Almonertinib	3	2.10 (NA -NA)	33.3 (1.8 -87.5)
1L EGFR-TKI monotherapy				
Gen1:	Gefitinib	12	3.13 (0.94-5.33)	8.3 (0.4 -40.2)
	Icotinib	9	2.03 (1.55-2.52)	22.2 (4.0 -59.8)
Gen2:	Afatinib	13	4.07 (1.17-6.96)	38.5 (15.1-67.7)
	Dacomitinib	0	-	-
Gen3:	Osimertinib	17	3.00 (1.56-4.44)	23.5 (7.8 -50.2)
	Almonertinib	2	NA^	50.0 (2.7 -97.3)
2L EGFR-TKI monotherapy				
Gen1:	Gefitinib	2	NA^	50.0 (2.7 -97.3)
	Icotinib	1	NA^	0
Gen2:	Afatinib	20	2.80 (1.37-4.23)	25.0 (9.6 -49.4)
	Dacomitinib	1	0.60 (NA -NA)	0
Gen3:	Osimertinib	20	3.20 (1.62-4.79)	20.0 (6.6 -44.3)
	Almonertinib	0	-	-
≥3L EGFR-TKI monotherapy				
Gen1:	Gefitinib	4	2.02 (0.53-NA)	0
	Icotinib	1	2.50 (NA -NA)	0
Gen2:	Afatinib	15	3.73 (2.03-5.83)	13.3 (2.3 -41.6)
	Dacomitinib	1	NA^	0
Gen3:	Osimertinib	23	2.50 (2.00-5.73)	8.7 (1.5 -29.5)
	Almonertinib	1	NA^	0

^Median PFS is not available (NA) due to a limited number of events observed

Cox proportional hazards regression analysis, confirmed that platinum-based chemotherapy significantly prolonged the median PFS in comparison to conventional EGFR-TKIs monotherapy. This study provides real-world evidence supporting the use of platinum-based chemotherapy over traditional EGFR-TKIs as a first-line treatment option for patients with EGFR20ins mutations [15]. For the role of bevacizumab in platinum based chemotherapy, consistent with Yang's real-world study on first-line chemotherapy [16], which showed that adding bevacizumab to platinum-based chemotherapy could numerically extend the PFS of patients with EGFR20ins mutations (7.5 m vs 5.6 m), our study verified that the combination of bevacizumab with platinum and pemetrexed significantly extends PFS (median PFS = 7.50 months, HR = 0.593, 95% CI = 0.383–0.918, $p = 0.019$), offering a new direction for future standard first-line treatment strategies.

The role of immunotherapy in patients with NSCLC harboring EGFR driver mutations remains contentious [17–21], with few reports specifically addressing its efficacy in those with EGFR20ins. A real-world study in 2020 documented the outcomes of immunotherapy in ten patients with EGFR20ins, noting that only two individuals received pembrolizumab as monotherapy in a second-line setting, both demonstrating very short PFS [16]. In addition to the limited data previously reported, more recent studies further illuminate the real-world effectiveness of immunochemotherapy in patients harboring EGFR20ins. One study involved a total of 31 patients (EGFR20ins, $n = 15$; ERBB2ex20ins, $n = 16$), comparing their outcomes to a cohort of 141 patients without targetable mutations (EGFR or ALK aberrations) [20]. Notably, despite a similar ORR between the two cohorts (48.4% for the EGFR20ins group versus 53.2%, $p = 0.628$), the DCR was significantly lower in the EGFR20ins group (77.4% compared to 91.5%, $p = 0.024$). Furthermore, the PFS was markedly poorer in the Ex20ins group, with a median PFS of only 5.0 months (95% CI: 4.4–5.6) compared to 11.2 months (95% CI: 8.9–13.7, $p < 0.001$) in the non-mutated cohort when receiving immunochemotherapy. Focusing on patients harboring EGFR20ins, another study reported on 39 patients treated with ICI monotherapy or immunochemotherapy compared to 183 patients receiving non-immunotherapy treatments [21]. The median overall survival (OS) was 29.0 months (95% CI: 19.3–44.3) for the immunotherapy group, versus 14.6 months (95% CI: 10.1–18.4) for those receiving non-immunotherapy. Both univariate and multivariate analyses indicated statistically significant favorable outcomes for patients undergoing immunotherapy.

In our retrospective cohort, while the efficacy of single ICI treatment appears limited, combination immunotherapy has shown more favorable outcomes. The regimen combining platinum, pemetrexed, and an IO agent ($n = 11$) in the first-line setting demonstrated a median PFS of 10.9 months (95%CI = 5.03-NA) and an ORR of 45.5% (5/11). However, given the relatively small sample size, outliers may significantly impact the results, necessitating cautious interpretation of the aforementioned findings. Moreover, the potential synergistic effects of such treatment combinations must be balanced against their toxicity to avoid compromising the overall treatment outcomes. Besides, within our cohort, the expression levels of PD-L1 in patients were largely absent. Whether the EGFR20ins subgroup could indeed benefit from ICI-based combination therapy as a first-line treatment remains an area for further investigation.

Table 5 Effectiveness of EGFR-TKIs in patients with EGFR20ins special variants

ID	Exon 20 insertion variant	EGFR-TKI	Regimen	PFS(months)	Lines of Treatment	Best Response
FEQA variant						
1	A763_Y764insFQEA	Afatinib	Bevacizumab + EGFR-TKI	11.70	2	PR
2	A763_Y764insFQEA	Afatinib	Bevacizumab + EGFR-TKI	11.57	2	PR
3[a]	A763_Y764insFQEA	Icotinib	Platinum + Paclitaxel + Bevacizumab + EGFR-TKI	8.47 +	1	PR
3[a]	A763_Y764insFQEA	Afatinib	EGFR-TKI monotherapy	1.23 +	2	PR
4	A763_Y764insFQEA	Afatinib	EGFR-TKI monotherapy	7.27	1	PR
5[a]	A763_Y764insFQEA	Afatinib	EGFR-TKI monotherapy	5.83	3	PR
5[a]	A763_Y764insFQEA	Icotinib	EGFR-TKI monotherapy	1.87	1	PD
5[a]	A763_Y764insFQEA	Osimertinib	EGFR-TKI monotherapy	1.17	5	PD
6[a]	A763_Y764insFQEA	Osimertinib	EGFR-TKI monotherapy	5.73	1	PR
6[a]	A763_Y764insFQEA	Osimertinib	Platinum + Pemetrexed + Bevacizumab + EGFR-TKI	2.53	4	PR
6[a]	A763_Y764insFQEA	Osimertinib	Pemetrexed + Bevacizumab + EGFR-TKI	2.13	2	SD
7[a]	A763_Y764insFQEA	Osimertinib	EGFR-TKI monotherapy	5.00	5	SD
7[a]	A763_Y764insFQEA	Gefitinib	EGFR-TKI monotherapy	2.03	3	PD
8	A763_Y764insFQEA	Afatinib	EGFR-TKI monotherapy	3.77 +	2	SD
9	A763_Y764insFQEA	Gefitinib	EGFR-TKI monotherapy	2.10	6	PD
10	A763_Y764insFQEA	Gefitinib	EGFR-TKI monotherapy	2.00 +	1	SD
G770 equivalent variant						
11	D770delinsGY	Afatinib	EGFR-TKI monotherapy	3.93	3	SD
12[a]	V769_D770insGTM	Afatinib	EGFR-TKI monotherapy	2.13	2	PD
12[a]	V769_D770insGTM	Osimertinib	EGFR-TKI monotherapy	1.40	5	PD
13[a]	D770delinsGY	Almonertinib	EGFR-TKI monotherapy	1.67 +	1	SD
13[a]	D770delinsGY	Afatinib	EGFR-TKI monotherapy	0.80 +	2	SD
14	V769_D770insGSV	Icotinib	EGFR-TKI monotherapy	1.53	1	PD

[a] The same patients who received EGFR-TKIs treatment across different lines of treatment

+ Censored PFS values

In our observations, the majority of patients derived minimal clinical benefits from first-, second-, and third-generation EGFR-TKIs, with all median PFSs of less than four months. However, the impact of adding bevacizumab to EGFR-TKI therapy on clinical outcomes warrants further discussion. In contrast to the poor efficacy of EGFR-TKIs monotherapy, the addition of bevacizumab to the treatment regimen resulted in a numerical improvement in both PFS and ORR, achieving outcomes of 6.27 months (95%CI = 4.67-NA) and 18.8% (3/16), respectively. These findings underscore the potential advantages of incorporating bevacizumab into the treatment protocols for patients with NSCLC harboring EGFR20 insertions, suggesting a promising strategy that may offer increased clinical benefit.

Moreover, it is noteworthy to mention the third-generation EGFR-TKI osimertinib in the context of EGFR20ins. In a preclinical study, osimertinib was observed to effectively inhibit the growth of the Ba/F3 cell line harboring the EGFR20ins [22]. However, recent retrospective analyses present a contrasting picture. In real world retrospective studies, NSCLC patients with EGFR20ins treated with osimertinib monotherapy showed ORRs of 5% to 6.5% and median PFS ranging from 2.3 to 3.6 months, including an early retrospective study in China [23, 24]. The ECOG-ACRIN EA5162 (NCT03191149) phase II trial tested osimertinib at 160 mg daily, twice the usual dose, in NSCLC patients with EGFR20ins mutations. It fell short of its primary goal of 30% ORR, with early findings showing a 24% ORR and a median PFS of 9.6 months [25]. In our cohort, regardless of the line of treatment, osimertinib monotherapy did not demonstrate favorable outcomes, with a median PFS of 3.00 months (95% CI = 2.85–4.48) and an ORR of 25% (15/60). It is important to acknowledge that for the majority of our cohort, the exact dosages of osimertinib administered (either 80 mg or 160 mg) remained unspecified. The suboptimal real-world efficacy suggests that osimertinib may have limited effectiveness in patients with EGFR20ins mutations.

Considering the poor responses and unsatisfied outcomes of typically used therapies for NSCLC with

EGFRex20ins, there is a need for more effective treatment options. The evolving landscape of targeted therapies for patients harboring EGFR20ins has been marked by both advancements and setbacks. A notable event in this journey was Takeda's decision to voluntarily withdraw mobocertinib, prompted by the less-than-expected outcomes of the EXCLAIM-2 phase III confirmatory trial. The results revealed that mobocertinib's effectiveness was comparable to, but did not surpass, that of first-line platinum-based chemotherapy, with median PFS being 9.59 months for mobocertinib versus 9.63 months for chemotherapy (platinum + pemetrexed) group [26]. The objective response rates were 32% for mobocertinib compared to 30% for chemotherapy, further highlighting the need for more effective first-line treatment options.

Among the recent developments in drug research, amivantamab stands out as a novel, fully humanized bispecific monoclonal antibody targeting both EGFR and c-MET. Encouraged by promising preclinical data, the CHRYSALIS study (NCT02609776), a phase I clinical trial, was conducted in patients with NSCLC harboring EGFR20ins mutations who had received prior treatments. This study reported an ORR of 40% with a median PFS of 8.3 months [6]. Furthermore, recent results in 2023 have shown that amivantamab, in combination with chemotherapy as a first-line treatment, demonstrated a PFS of 11.4 months [27]. Another EGFR-TKI, DZD9008 (sunvozertinib), demonstrated significant efficacy in the WU-KONG6 pivotal study (CTR20211009), showing a confirmed ORR of 60.8% in Chinese patients with NSCLC harboring EGFR20ins mutations [28]. Furmonertinib also showed promising efficacy in treatment- naïve patients with an ORR of 69.0%. Similarly, poziotinib, a novel EGFR-TKI, has shown promising efficacy, with a blinded independent review confirming an ORR of 31% and a median PFS of 5.5 months in a phase II clinical trial [29]. Notably, the efficacy of poziotinib varied among patients with different amino acid insertions in the near loop and far loop-region of EGFR exon 20, with ORRs of 46% and 0%, respectively. Also, there have been additional reports regarding the efficacy of Osimertinib across different loop regions. As documented in the study by Okahisa M, et al., patients with near-loop EGFR Exon 20 insertions who received Osimertinib, a third-generation TKI, exhibited a significantly longer PFS compared to those with far-loop insertions (median PFS: 5.6 vs. 2.0 months; Hazard Ratio [HR] [95% CI], 0.22 [0.07–0.64]; $P < 0.01$) [30].

In our analysis, the secondary loop structure of EGFR exon 20 (near loop:A767-P722, far loop:H773-C775) did not serve as a predictive biomarker for the efficacy of first-, second- or third-generation EGFR-TKIs monotherapy. Despite the absence of observed differences in efficacy between the near loop and far loop for EGFR-TKIs, heterogeneity within the entire exon cannot be overlooked. According to recent research, the specific subtype occurring in the αC-helix of exon 20, A763_Y764insFQEA, is considered sensitive to first and second-generation EGFR-TKIs treatment [9]. Furthermore, G770 equivalent variants are believed to demonstrate certain sensitivity [11].The detailed treatment outcomes of patients with these two specific insertion subtypes for EGFR-TKIs are presented in Table 5. Notably, among our patients, two individuals with amino acid insertions at D770_N771 exhibited a complete response (CR), one with D770_N771insG and the other with D770_N771insSVD, treated with erlotinib and osimertinib, respectively. These singular outcomes, while encouraging, highlight the need for cautious interpretation and further research into the efficacy of TKIs at this specific insertion site D770_N771. We compared the treatment outcomes of EGFR-TKIs between the two types of insertion mutations, D770_N771insX and others occurring in the loop region. Although the results were numerically better [PFS: 3.73 m, 2.93 m, $p = 0.52$] [ORR: 25.9% (7/27), 15.9% (13/82), $p = 0.50$], there was no statistically significant difference. We believe that different amino acid insertions at different sites by various EGFR-TKIs may represent a possible breakthrough in EGFR20ins treatment.

Besides, it is imperative to evaluate the role of TP53 co-mutations within the context of EGFR20ins. Previous research, notably that conducted by Janning et al., has highlighted the prognostic importance of genetic variations in determining the outcomes of targeted therapy [31]. Janning's findings indicate that TP53 act as a predictor of poor prognosis in patients with EGFR20ins mutations when treated with EGFR-TKIs. Our investigation aimed to explore whether TP53 co-mutations similarly influence the therapeutic efficacy of EGFR-TKI monotherapy in 58 out of 302 patients harboring EGFR20ins. However, a significant impact of TP53 co-mutations on the response to EGFR-TKI monotherapy was not observed ($p = 0.66$). Neither PFS analysis nor multivariate Cox regression analysis revealed a statistically significant correlation between the TP53 mutation status and therapeutic outcomes. Although co-occurring TP53 mutations exerted a non-significant impact on EGFR-TKI therapies in our cohort, acknowledging the specific context of each co-mutation and its potential interactions with different treatment regimens remains crucial.

This research is subject to the inherent limitations of any retrospective analysis conducted in a real-world setting, where data collection is reliant on online questionnaires and telephone follow-ups, potentially introducing

selection bias. Despite adherence to stringent protocols to define real-world outcomes, the integrity and accuracy of the data may still be compromised due to reliance on available information. Nevertheless, the value of this study lies in providing invaluable real-world data on the efficacy of treatments for patients with EGFR exon 20 insertions mutations.

Conclusions

In this comprehensive retrospective study, we explored the intricacies of treating NSCLC patients with EGFR20ins, a challenging and under-researched subset of lung cancer. By analyzing data from 302 patients and 856 treatment regimens, we provided a granular look into the real-world effectiveness of various therapeutic strategies. Our research stands out as the largest study to date in this domain within China, filling a significant gap in the literature by offering detailed insights into treatment patterns, outcomes, and the impact of mutation heterogeneity on therapeutic efficacy. Our findings reveal that platinum-based chemotherapy, particularly when combined with pemetrexed and bevacizumab, offers superior PFS compared to monotherapy with EGFR-TKIs. Additionally, we identified promising results with immuno-oncology treatments and the nuanced benefits of targeted therapies in later-line treatment, highlighting the potential for personalized treatment plans based on specific mutation subtypes and patient characteristics. Ultimately, the insights garnered from this study are poised to substantially contribute to the evolving therapeutic landscape of EGFR20ins in NSCLC, laying the groundwork for future clinical trials and drug development efforts.

Abbreviations

NSCLC	Non-small cell lung cancer
EGFR	Epidermal Growth Factor Receptor
EGFR20ins	EGFR Exon 20 Insertion
ICI	Immune Checkpoint Inhibitor
TKI	Tyrosine Kinase Inhibitor
HR	Hazard Ratio
CI	Complete Response
PR	Partial Response
SD	Stable Disease
PD	Progressive Disease
CI	Confidence intervals
ORR	Objective Response Rate
PFS	Progression Free Survival
OS	Overall Survival

Supplementary Information

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Supplementary Material 1: Supplement Figure 1. Subgroup analysis of first line treatment.

Supplementary Material 2: Supplement Table 1. Characteristics of patients who received first-line chemotherapy with or without bevacizumab.

Supplementary Material 3: Supplement Table 2. Treatment outcomes of other less common regimens in firstline treatment.

Supplementary Material 4: Supplement Table 3. EGFR-TKIs Combination Treatment Regimens.

Supplementary Material 5: Supplement Table 4. Treatment Outcome of Immune Oncology agents in patients harboring EGFR20ins.

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Authors' contributions

W.W. performed formal analysis, visualized Fig. 2, Supplement figure 1 and wrote the original draft. S.Y. performed formal analysis and contributed to the writing of the original draft. J.H. performed formal analysis and curated data. Q.Q. curated data. Y.W. visualized Fig. 1. J.D. developed the methodology and conceptualized the study. All authors reviewed the manuscript.

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Availability of data and materials

Original data related to this article can be found online at www.researchdata.org.cn/. All data in the manuscript is available through the responsible corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Sun Yat-Sen University Cancer Center, under the consent number B2024-174–01. Information regarding participation requirements and the right to refuse was clearly communicated to all participants. All research activities were performed in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Intergrated Therapy in Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, No. 651, East Dong Feng Road, Guangzhou, Guangdong 510060, China. [2]Zhongshan School of Medicine, Sun Yat-Sen University, No. 74, Zhong Shan Er Lu, Guangzhou, Guangdong 510060, China. [3]Otorhinolaryngology Hospital, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510060, China.

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References

1. Han B, Zheng R, Zeng H, Wang S, Sun K, Chen R, Li L, Wei W, He J. Cancer incidence and mortality in China, 2022. Journal of the National Cancer Center. 2024. https://doi.org/10.3760/cma.j.cn112152-20240119-00035.

2. Ke EE, Wu YL. EGFR as a Pharmacological Target in EGFR-Mutant Non-Small-Cell Lung Cancer: Where Do We Stand Now? Trends Pharmacol Sci. 2016;37(11):887–903. https://doi.org/10.1016/j.tips.2016.09.003.
3. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(5):497–530. https://doi.org/10.6004/jnccn.2022.0025.
4. Bai Q, Wang J, Zhou X. EGFR exon20 insertion mutations in non-small cell lung cancer: Clinical implications and recent advances in targeted therapies. Cancer Treat Rev. 2023;120:102605. https://doi.org/10.1016/j.ctrv.2023.102605.
5. Sabari JK, Heymach JV, Sandy B. Hitting the Right Spot: Advances in the Treatment of NSCLC With Uncommon EGFR Mutations. J Natl Compr Canc Netw. 2021;19(Suppl_2):S1-s11.
6. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, Viteri S, Han JY, Kim SW, Lee CK, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021;39(30):3391–402. https://doi.org/10.1200/JCO.21.00662.
7. Zhou C, Ramalingam SS, Kim TM, Kim SW, Yang JC, Riely GJ, Mekhail T, Nguyen D, Garcia Campelo MR, Felip E, et al. Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial. JAMA Oncol. 2021;7(12):e214761. https://doi.org/10.1001/jamaoncol.2021.4761.
8. Yang G, Yang Y, Hu J, Xu H, Zhang S, Wang Y. EGFR exon 20 insertion variants A763_Y764insFQEA and D770delinsGY confer favorable sensitivity to currently approved EGFR-specific tyrosine kinase inhibitors. Front Pharmacol. 2022;13:984503. https://doi.org/10.3389/fphar.2022.984503.
9. Vasconcelos P, Gergis C, Viray H, Varkaris A, Fujii M, Rangachari D, VanderLaan PA, Kobayashi IS, Kobayashi SS, Costa DB. EGFR-A763_Y764insFQEA Is a Unique Exon 20 Insertion Mutation That Displays Sensitivity to Approved and In-Development Lung Cancer EGFR Tyrosine Kinase Inhibitors. JTO Clin Res Rep. 2020;1(3). https://doi.org/10.1016/j.jtocrr.2020.100051.
10. Voon PJ, Tsui DW, Rosenfeld N, Chin TM. EGFR exon 20 insertion A763–Y764insFQEA and response to erlotinib–Letter. Mol Cancer Ther. 2013;12(11):2614–5. https://doi.org/10.1158/1535-7163.MCT-13-0192.
11. Kobayashi IS, Viray H, Rangachari D, Kobayashi SS, Costa DB. EGFR-D770>GY and Other Rare EGFR Exon 20 Insertion Mutations with a G770 Equivalence Are Sensitive to Dacomitinib or Afatinib and Responsive to EGFR Exon 20 Insertion Mutant-Active Inhibitors in Preclinical Models and Clinical Scenarios. Cells. 2021;10(12). https://doi.org/10.3390/cells10123561.
12. Robichaux JP, Le X, Vijayan RSK, Hicks JK, Heeke S, Elamin YY, Lin HY, Udagawa H, Skoulidis F, Tran H, et al. Structure-based classification predicts drug response in EGFR-mutant NSCLC. Nature. 2021;597(7878):732–7. https://doi.org/10.1038/s41586-021-03898-1.
13. Ou SI, Lin HM, Hong JL, Yin Y, Jin S, Lin J, Mehta M, Nguyen D, Neal JW. Real-World Response and Outcomes in Patients With NSCLC With EGFR Exon 20 Insertion Mutations. JTO Clin Res Rep. 2023;4(10):100558. https://doi.org/10.1016/j.jtocrr.2023.100558.
14. Riess JW, Gandara DR, Frampton GM, Madison R, Peled N, Bufill JA, Dy GK, Ou SI, Stephens PJ, McPherson JD, et al. Diverse EGFR Exon 20 Insertions and Co-Occurring Molecular Alterations Identified by Comprehensive Genomic Profiling of NSCLC. J Thorac Oncol. 2018;13(10):1560–8. https://doi.org/10.1016/j.jtho.2018.06.019.
15. ZHOU C. [Chinese Expert Consensus on Non-small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations (2023 Edition)]. Chin J Lung Cancer. 2023;26(5):325–337. https://doi.org/10.3779/j.issn.1009-3419.2023.106.10.
16. Yang G, Li J, Xu H, Yang Y, Yang L, Xu F, Xia B, Zhu VW, Nagasaka M, Yang Y, et al. EGFR exon 20 insertion mutations in Chinese advanced non-small cell lung cancer patients: Molecular heterogeneity and treatment outcome from nationwide real-world study. Lung Cancer. 2020;145:186–94. https://doi.org/10.1016/j.lungcan.2020.03.014.
17. Gainor JF, Shaw AT, Sequist LV, Fu X, Azzoli CG, Piotrowska Z, Huynh TG, Zhao L, Fulton L, Schultz KR, et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. Clin Cancer Res. 2016;22(18):4585–93. https://doi.org/10.1158/1078-0432.CCR-15-3101.
18. Qiao M, Jiang T, Liu X, Mao S, Zhou F, Li X, Zhao C, Chen X, Su C, Ren S, et al. Immune Checkpoint Inhibitors in EGFR-Mutated NSCLC: Dusk or Dawn? J Thorac Oncol. 2021;16(8):1267–88. https://doi.org/10.1016/j.jtho.2021.04.003.
19. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–65. https://doi.org/10.1016/S0140-6736(16)32517-X.
20. Zheng Y, Fu Y, Chen Y, Li Q, Liu T, Ding Z. Poor Efficacy of Immune Checkpoint Inhibitors Plus Chemotherapy in Lung Cancer Patients with EGFR/ERBB2 Exon 20 Insertion. Curr Oncol. 2023;30(11):9929–39. https://doi.org/10.3390/curroncol30110721.
21. Behera M, Jiang R, Huang Z, Bunn B, Wynes MW, Switchenko J, Scagliotti GV, Belani CP, Ramalingam SS. Natural History and Real-World Treatment Outcomes for Patients With NSCLC Having EGFR Exon 20 Insertion Mutation: An International Association for the Study of Lung Cancer-American Society of Clinical Oncology CancerLinQ Study. JTO Clin Res Rep. 2024;5(6):100592. https://doi.org/10.1016/j.jtocrr.2023.100592.
22. Hirano T, Yasuda H, Tani T, Hamamoto J, Oashi A, Ishioka K, Arai D, Nukaga S, Miyawaki M, Kawada I, et al. In vitro modeling to determine mutation specificity of EGFR tyrosine kinase inhibitors against clinically relevant EGFR mutants in non-small-cell lung cancer. Oncotarget. 2015;6(36):38789–38803. https://doi.org/10.18632/oncotarget.5887.
23. van Veggel B, Madeira RSJFV, Hashemi SMS, Paats MS, Monkhorst K, Heideman DAM, Groves M, Radonic T, Smit EF, Schuuring E, et al. Osimertinib treatment for patients with EGFR exon 20 mutation positive non-small cell lung cancer. Lung Cancer. 2020;141:9–13. https://doi.org/10.1016/j.lungcan.2019.12.013.
24. Yang GJ, Li J, Xu HY, Sun Y, Liu L, Li HS, Yang L, Zhang Y, Li GH, Wang Y. Osimertinib for Chinese advanced non-small cell lung cancer patients harboring diverse EGFR exon 20 insertion mutations. Lung Cancer. 2021;152:39–48. https://doi.org/10.1016/j.lungcan.2020.11.027.
25. Piotrowska Z, Wang Y, Sequist LV, Ramalingam SS. ECOG-ACRIN 5162: A phase II study of osimertinib 160 mg in NSCLC with EGFR exon 20 insertions. J Clin Oncol. 2020;38(15_suppl):9513–9513. https://doi.org/10.1200/JCO.2020.38.15_suppl.9513.
26. Jänne PA, Wang BC, Cho BC, Zhao J, Li J, Hochmair MJ, Peters S, Besse B, Kato T, Wu YL, et al. 507O EXCLAIM-2: Phase III trial of first-line (1L) mobocertinib versus platinum-based chemotherapy in patients (pts) with epidermal growth factor receptor (EGFR) exon 20 insertion (ex20ins)+ locally advanced/metastatic NSCLC. Ann Oncol. 2023;34:S1663–4. https://doi.org/10.1016/j.annonc.2023.10.586.
27. Zhou C, Tang KJ, Cho BC, Liu B, Paz-Ares L, Cheng S, Kitazono S, Thiagarajan M, Goldman JW, Sabari JK, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med. 2023;389(22):2039–51. https://doi.org/10.1056/NEJMoa2306441.
28. Wang M, Fan Y, Sun M, Wang Y, Zhao Y, Jin B, Hu Y, Han Z, Song X, Liu A, et al. Sunvozertinib for patients in China with platinum-pretreated locally advanced or metastatic non-small-cell lung cancer and EGFR exon 20 insertion mutation (WU-KONG6): single-arm, open-label, multicentre, phase 2 trial. Lancet Respir Med. 2023. https://doi.org/10.1016/S2213-2600(23)00379-X.
29. Elamin YY, Robichaux JP, Carter BW, Altan M, Tran H, Gibbons DL, Heeke S, Fossella FV, Lam VK, Le X, et al. Poziotinib for EGFR exon 20-mutant NSCLC: Clinical efficacy, resistance mechanisms, and impact of insertion location on drug sensitivity. Cancer Cell. 2022;40(7):754-767.e756. https://doi.org/10.1016/j.ccell.2022.06.006.
30. Okahisa M, Udagawa H, Matsumoto S, Kato T, Yokouchi H, Furuya N, Kanemaru R, Toyozawa R, Nishiyama A, Ohashi K, et al. Clinical outcomes in patients with non-small cell lung cancer harboring EGFR Exon20 inframe insertions in the near-loop and far-loop: Results from LC-SCRUM-Asia. Lung Cancer. 2024;191:107798. https://doi.org/10.1016/j.lungcan.2024.107798.
31. Janning M, Süptitz J, Albers-Leischner C, Delpy P, Tufman A, Velthaus-Rusik JL, Reck M, Jung A, Kauffmann-Guerrero D, Bonzheim I, et al. Treatment outcome of atypical EGFR mutations in the German National Network Genomic Medicine Lung Cancer (nNGM). Ann Oncol. 2022;33(6):602–15. https://doi.org/10.1016/j.annonc.2022.02.225.

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