Review Article

EGFR exon 20 insertion mutation and *MET* exon 14 skipping mutation in non-small cell lung cancer: a scoping review in the Chinese population

Xiao-Rong Yang[1,2#], Si-Min Zhong[3#], Zhen-Yi Jin[4], Xīn Gào[5], Ying Wu[5], Qing Zhou[2], Yang-Qiu Li[3], Si-Yang Maggie Liu[3], Yi-Long Wu[2]

[1]School of Medicine South China University of Technology, Guangzhou, China; [2]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; [3]Key Laboratory for Regenerative Medicine of Ministry of Education, Institute of Hematology, School of Medicine, Jinan University, Guangzhou, China; [4]Key Laboratory of Viral Pathogenesis and Infection Prevention and Control, Department of Pathology, School of Medicine, Jinan University, Guangzhou, China; [5]Medical Affairs Department, Xi'an Janssen Pharmaceutical Ltd., Beijing, China

Contributions: (I) Conception and design: XR Yang, SM Zhong, ZY Jin, Q Zhou, YQ Li, SYM Liu, YL Wu, X Gào, Y Wu; (II) Administrative support: XR Yang, SM Zhong, ZY Jin, Q Zhou, YQ Li; (III) Provision of study materials or patients: XR Yang, SM Zhong, ZY Jin, Q Zhou, YQ Li; (IV) Collection and assembly of data: SY Maggie Liu, YL Wu, X Gào, Y Wu; (V) Data analysis and interpretation: ZY Jin, Q Zhou, YQ Li, SYM Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yi-Long Wu, MD. Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences) of Southern Medical University. No. 123 Huifu West Rd, Guangzhou 510080, China. Email: syylwu@live.cn; Si-Yang Maggie Liu, MD, PhD. Key Laboratory for Regenerative Medicine of Ministry of Education, Institute of Hematology, School of Medicine, Jinan University, 601 West Huangpu Avenue, Guangzhou 510632, China. Email: siyangliu2020@outlook.com.

Background: Epidermal growth factor receptor (*EGFR*) and mesenchymal-epithelial transition (*MET*) gene mutations are well established in the pathogenesis of non-small cell lung cancer (NSCLC). However, there is limited understanding about the impact of rare variants, such as *EGFR* exon 20 insertion mutation (*EGFR*ex20ins) and *MET* exon 14 skipping mutation (*MET*ex14) in the Chinese population even though targeted therapies have been approved in China. We conducted a scoping review to assess the current available evidence of these two mutations in NSCLC in the Chinese population.

Methods: Electronic searches were performed before November 2023. Two investigators independently collected data. Any discrepancies were resolved through discussion with a senior investigator.

Results: We identified 111 studies, involving a total of 159,993 NSCLC Chinese patients. Of the 111 studies, 76 studies reported on *EGFR*ex20ins and 45 reported on *MET*ex14. When we evaluated the frequency from studies with at least 1,000 patients, the frequency of *EGFR*ex20ins ranged from 0.02–2.85% of all NSCLC patients and 0.56–6.90% of all *EGFR* mutations. The frequency of *MET*ex14 ranged from 0.08–1.38% of all NSCLC patients and 8.33–56.60% of all MET mutations. The treatments for NSCLC with *EGFR*ex20ins varied depending on the study, and all available treatments have limited therapeutic efficacy and a relatively poor prognosis, and fewer studies have examined the efficacy and effectiveness of treatments for NSCLC with *MET*ex14 mutation in the Chinese population.

Conclusions: Despite the recent approval of three targeted therapies in China, there is still insufficient evidence regarding their optimal treatment and therapeutic efficacy for Chinese patients. Further large-scale studies are needed to establish links between these mutations and clinical features at baseline and following treatment. Furthermore, moving forward, the development of novel drugs will be essential to fulfill the clinical unmet needs.

Keywords: *EGFR* exon 20 insertion mutation (*EGFR*ex20ins); *MET* exon 14 skipping mutation (*MET*ex14); non-small cell lung cancer (NSCLC); Chinese population

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Introduction

Lung cancer is a leading cause of cancer deaths worldwide. In China, it accounted for approximately 710,000 deaths in 2020, with around 80% being non-small cell lung cancers (NSCLCs) (1). NSCLC is associated with a poor 5-year survival rate, with a large proportion of patients (67.5%) having advanced disease at diagnosis (2). Over the past decades, the discovery of targetable driver mutations in NSCLC has transformed the management of patients with these mutations (3).

The epidermal growth factor receptor (*EGFR*) gene aberrations lead to over-activation of various downstream oncogenic pathways (4), such as the phosphoinositide 3-kinase/AKT pathway. Mutations in *EGFR* are presented in a considerable proportion of patients with NSCLC, especially in Asian patients (30–35%) (5). There are several types of *EGFR* mutations, of which in-frame insertion mutations in *EGFR* exon 20 (*EGFR*exon20ins) account for 4–10%, making it the third-most frequent subtype of *EGFR* mutation after *EGFR* L858R point mutation or exon 19 deletions (6). *EGFR*exon20ins NSCLC has poor prognosis. It has been shown that patients carrying *EGFR*exon20ins have a 75% increased risk of death compared to patients who have common *EGFR* mutations (7).

The mesenchymal-epithelial transition *(MET)* mutations are another group of NSCLC driver mutations. The *MET* proto-oncogene can be activated by *MET* exon 14 skipping mutation (*MET*ex14) and is also involved in cell proliferation that plays a critical role in cancer development (8). They present in approximately 3% to 4% of Western patients with NSCLC (9). However, Western NSCLC patients with *MET*ex14 mutation exhibit molecular characteristics that differ from those of Asian patients, particularly in Chinese patients as reported by previous study (10).

The presence of these mutations enables the application of precision medicine through the use of targeted therapies, rather than basing treatment options on crude histological subtypes. Recently, new targeted therapies which have recently been approved include amivantamab (1) and mobocertinib (2) that target *EGFR*ex20ins, and capmatinib (11), tepotinib (12), glumetinib (13), savolitinib (14,15), and vebreltinib (16) that target *MET*ex14 (9). Although *EGFR*ex20ins and *MET*ex14 mutations in NSCLC have attracted considerable interest from the scientific community (5,9,17), there remains limited information on the clinical relevance and impact of these mutations in Chinese patients. Some studies investigated epidemiological and clinical burden of *MET*ex14 in lung cancer in Chinese population (9,10,18,19), but there is no systematic summary. Therefore, we conducted a scoping review to assess the currently available evidence of these two rare mutations of NSCLC in the Chinese population. The scoping review is a type of knowledge synthesis that uses a systematic and iterative approach to identify and synthesize an existing or emerging body of literature on a given topic. We present this article in accordance with the PRISMA-ScR reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-528/rc) (20).

Highlight box

Key findings

- This study provides a comprehensive overview of the prevalence of *EGFR* exon 20 insertion mutation (*EGFR*ex20ins) and *MET* exon 14 skipping mutation (*MET*ex14) mutations in non-small cell lung cancer (NSCLC) in the Chinese population.
- The evidence on the prognostic effect of these mutations was limited to reliably assess the impact on overall survival.
- The treatments for NSCLC with *EGFR*ex20ins or *MET*ex14 mutation varied depending on the study, and no clear evidence has indicated the optimal treatment regimen during our study period.

What is known and what is new?

- Some studies have investigated the epidemiological and clinical burden of *MET*ex14 in lung cancer in the Chinese population, but there is no systematic summary. The optimal treatment regimen for Chinese NSCLC patients with *EGFR*ex20ins and *MET*ex14 remains unclear.
- This study provides a comprehensive overview of the prevalence of *EGFR*ex20ins and *MET*ex14 mutations in the Chinese population and shows that the optimal treatment regimen for Chinese patients still remains unclear given the heterogeneity of published studies.

What is the implication, and what should change now?

- Further large-scale studies will be needed to improve patient management and enhance overall clinical care. The development of novel drugs will be essential to fulfill the clinical requirements.

Methods

Literature searches and identification

We identified relevant studies through systematic searches of eight databases from inception to 14 November 2023: PubMed, EMBASE, The Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical (CBM), Wanfang and Chinese Scientific Journals (VIP) databases. Search terms included those related to *EGFR*ex20ins, *MET*ex14, NSCLC and Chinese (see Appendix 1). There were no restrictions on publication language or study design. After removing duplicates, two reviewers independently determined whether articles were eligible for inclusion based on their titles and abstracts. To avoid missing studies, studies that include at least one Chinese authors also were reconfirmed in the full text to ensure the reporting of data from the Chinese population. We included studies that met the eligibility criteria, which involved examining the therapeutic effectiveness in Chinese patients with NSCLC harbouring *EGFR*ex20ins or *MET*ex14 mutations or reporting the prevalence of *EGFR*ex20ins or *MET*ex14 mutations in Chinese NSCLC patients, including Chinese cohorts or arms reported in multi-national studies. Case reports, reviews and abstracts were excluded. Furthermore, we were interested in examining the proportion of mutations among Chinese patients with NSCLC in the subgroup analysis such as smoking statuses and age groups. Discrepancies in data collection were resolved through discussion with a third senior author.

Data extraction

We extracted data from each study in a standardized manner, including information on age, gender, diagnosis, disease stage, family history, smoking status, frequency of mutations, interventions (treatment regimens, description, frequency, dosage, duration, combination of drugs), and outcomes including mutation proportion as defined by the number of NSCLC patients harboring mutation within the total number of NSCLC patients, and therapeutic effectiveness as defined by original studies such as overall survival (OS), progression-free survival (PFS), disease control rate (DCR), complete response (CR), and partial response (PR). Additional information on study design, clinical, biochemical, and pathological parameters was also collected from identified articles. If appropriate, authors of included studies were contacted to request missing or additional data.

Statistical analyses

Data were narratively summarized and presented in text and tables. For categorical variables, we summarized data in proportions as reported in original studies. For continuous variables, we summarized data in different outcome measures as reported in original studies using such as median OS or PFS and their 95% confidence interval (CI).

Results

A total of 111 studies were identified (see the list of included studies in Appendix 2), reporting on *EGFR*ex20ins and *MET*ex14 mutations in 159,993 NSCLC Chinese patients (*Figure 1*). One study was based in Northeast China, 41 in Eastern China, 22 in North China, 9 in South China, 6 in Southwest China, 5 in Northwest China, and 13 in mixed regions (Figure S1). Of the 111 studies, 78 studies were single-center, 24 studies were multi-center, and this information was not available for 9 studies (*Table 1*). Only 8 studies were known to be funded by industry.

Of the 111 studies included, 76 studies reported on *EGFR*ex20ins and 45 studies reported on *MET*ex14. Thirty-two studies had sample sizes of more than 1,000 patients (28.8%; *Table 1*). The most common method to detect the mutations was next-generation sequencing (N=35 studies), followed by reverse transcription polymerase chain reaction (RT-PCR) (N=27 studies; Table S1). Stage IV was the most reported stage (34.2%) and adenocarcinoma was the most reported subtype (52.3%) among patients with NSCLC (Table S2). Seventy-five studies were written in English, whereas 36 studies were written in Chinese (*Table 1*). None of the included studies reported the presence of both *EGFR*ex20ins and *MET*ex14 mutations concurrently in NSCLC patients. However, individually these mutations have been reported to co-occur with other uncommon mutations (Table S3).

EGFRex20ins

Among the 76 included studies (Table S4) that reported on *EGFR*ex20ins, the frequency of *EGFR*ex20ins ranged from 0.02–6.56% of all NSCLC patients and 0.56–100% of all *EGFR* mutations in China. When we evaluated the frequency from studies with at least 1,000 patients, there were 32 studies in China; and the frequency of *EGFR*ex20ins ranged from

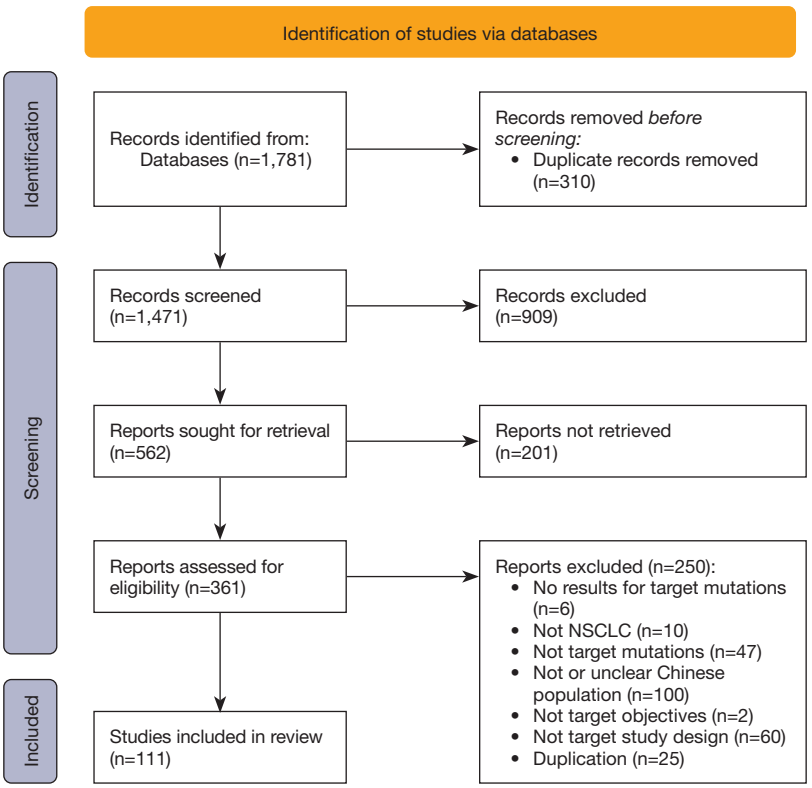

Figure 1 The PRISMA flow diagram for studies included in the scoping review. NSCLC, non-small cell lung cancer.

0.02–2.85% of all NSCLC patients and 0.56–6.90% of all *EGFR* mutations (*Table 2*). The frequency of *EGFR*ex20ins varied between the different regions in China, where North China reported the highest frequency and South China reported the lowest (Table S5).

Twenty-eight studies reported smoking status (N=1,798 patients), in which 70.6% of patients were non-smokers (N=1,270 patients) (Table S6). Six studies perform subgroup analyses by age group (21-26). Compared to younger patients (age <60 years), the frequency of *EGFR*ex20ins was slightly higher in older patients (age ≥60 years), with 0–14.29% versus 1.68–17.39% (Table S7).

Sixteen studies evaluated the first-line treatment regimens for NSCLC patients with *EGFR*ex20ins (*Table 3*). Among these studies, fourteen (N=338 patients) investigated the effectiveness of tyrosine kinase inhibitors (TKIs), with median PFS ranged from 2.0 to 9.97 months. Seven studies (N=735 patients) examined chemotherapy, with median PFS ranged from 3.4 to 15.43 months. Three studies (N=21 patients) investigated immune checkpoint therapy, with median PFS ranged from 1.7 to 2.8 months. Two studies (N=104 patients) explored the use of chemotherapy and TKI but only one study report PFS and OS. Another study (N=55 patients) explored the use of platinum and TKIs but did not report PFS or OS. Additionally, one study (N=49 patients) did not specify the examined intervention but reported a median PFS of 7.6 months (95% CI: 5.7–9.6).

Nine studies evaluated the second-line treatment regimens (*Table 3*). Among them, eight studies (N=159 patients in total) examined TKIs, with a median PFS ranged from 2.0 to 6.77 months. Two studies (N=83 patients in total) examined chemotherapy, reporting median PFS ranged from 2.4 to 6.0 months. Two studies (N=6 patients in total) investigated immune checkpoint therapy, with one of them reporting a median PFS of 2.3 months. One study (N=4 patients) investigated the third-line treatment, reporting a median PFS of 8.5 months. Another study (N=1 patient) investigated the fourth-line treatment, with a PFS of 6.6 months.

The treatments used varied depending on the study, and there was limited evidence on whether any one treatment was superior compared to the rest in terms of clinical efficacy and safety for patients with *EGFR*ex20ins. Patients were usually treated with *EGFR* TKIs and chemotherapy.

Table 1 Summary of general study characteristics (total number of studies =111)

Study characteristics	Number	Proportion (%)
Language		
English	75	67.6
Chinese	36	32.4
Funding sources		
Industry	8	7.2
Non-industry	69	62.2
Not-reported*	25	22.5
None#	9	8.1
Objectives of study		
Frequency of uncommon mutations	101	91.0
Clinical outcomes	54	48.6
Prognostic factors	13	11.7
Study types (by number of centre)		
Single	78	70.3
Multi-centre	24	21.6
Not report	9	8.1
Number of NSCLC patients		
≤1,000	79	71.2
>1,000	32	28.8

*, not-reported: the study did not report any information on funding; #, none: no funding reported in the study. NSCLC, non-small cell lung cancer.

Notably, the presence of *EGFR*ex20ins was generally associated with a shorter PFS time. Eight studies involving 11,009 patients delved into prognostic factors to predict PFS or OS outcomes. Among these factors, histological type of NSCLC, patient age, and smoking status were identified as potential elements associated with PFS or OS outcomes (Table S8).

Additionally, seven studies (27-33) involving 673 patients reported adverse events (AEs). Any grade AE ranged from 41.5% to 99.1%. These studies predominantly detailed grade 1–2 AEs, with common occurrences such as rash (15.4–57.3%), diarrhea (12.5–54.7%), dry skin (54.00%), decreased appetite (54.00%), and paronychia (12.0–52.00%). Moreover, three studies (27, 28, 31) documented grade 3 AEs, with incidence rates ranging from 38.0% to 62.0%. Grade ≥3 events that occurred in ≥10% of patients were rash (21.3%) and diarrhea (10.7%).

MET exon 14 skipping mutation

Among the 45 studies reported on *MET*ex14, the frequency of *MET*ex14 ranged from 0–26.7% of all NSCLC patients and 0–100% of all *MET* mutations in China (Table S9). When we evaluated the frequency from studies with at least 1,000 patients, there were 8 studies in China. The frequency of *MET*ex14 ranged from 0.08–1.38% of all NSCLC patients and 8.33–56.6% of all *MET* mutations (*Table 2*). The frequency of *MET*ex14 varied between different regions in China (Table S5), where the highest and lowest frequencies of *MET*ex14 were typically in Eastern and South China, respectively.

Nineteen studies, involving 34,107 patients, reported smoking status (N=571 patients), of which 63.9% patients were non-smokers (N=365 patients) (Table S10). Nine studies perform subgroup analyses by age groups (31,34-41) (Table S11). In general, compared to younger patients (age <60 years), the frequency of *MET*ex14 was higher in older patients (age ≥60 years), with 0–4.35% versus 0.43–27.78% (Table S11). Thus far, no studies included in the scoping review evaluated treatment regimen for NSCLC patients with *MET*ex14 in China such as tepotinib and capmatinib.

Eight studies evaluated first-line treatment regimens or more for NSCLC patients with *METex14* (*Table 4*). They investigated the effectiveness of TKIs, reporting median PFS ranging from 3.4 to 11.5 months and median OS ranging from 10.9 to 35.8 months. Additionally, one study explored the use of Amivantamab, reporting a PFS of 0.8 months and OS of 0.9 months. Furthermore, three studies (14,42,43) involving 137 patients reported AEs. The incidence of AEs of any grade ranged from 36.8% to 100.0%. These studies primarily documented grade 1–2 AEs, including nausea (52.9%), edema peripheral (48.6%), rash (37.9%), decreased appetite (34.3%), vomiting (32.9%), elevated alanine aminotransferase (ALT) (28.8–36.8%), and elevated aspartate aminotransferase (AST) (20.7–28.9%), and dysgeusia (21.1%). Moreover, they reported grade 3 AEs, with incidence rates ranging from 28.0% to 45.7%. Grade ≥3 events occurring in ≥10% of patients included elevated AST (12.9%), elevated ALT (10.0%), and palmar-plantar erythrodysesthesia (PPE) (10.5%).

Discussion

This scoping review consists of 111 studies that report

Table 2 Frequency of *EGFR*ex20ins & *MET*ex14 mutation for larger studies (patients n>1,000) by different regions of China

Regions of China	*EGFR* exon 20 insertion mutation				*MET* exon 14 skipping			
	NSCLC		EGFR positive		NSCLC		MET positive	
	No. of studies	% in NSCLC	No. of studies	% in EGFR positive	No. of studies	% in NSCLC	No. of studies	% in MET positive
Northeast China	0	NR	0	NR	0	NR	0	NR
Eastern China	11	0.70–2.85%	8	1.90–6.90%	2	0.91–1.30%	NR	NR
North China	1	2.0%	1	3.87%	1	0.49%	1	8.70%
Central China	1	1.60%	1	3.50%	2	0.71–0.98%	2	30.00–56.60%
South China	2	0.26–1.20%	2	0.56–3.60%	1	0.08%	1	8.33%
Southwest China	2	0.64–0.70%	2	1.44–2.46%	0	NR	0	NR
Northwest region	0	NR	0	NR	0	NR	0	NR
Mixed or NR	4	0.02–2.10%	4	3.15–5.12%	4	0.42–1.38%	1	12.20%

Northeast China: Heilongjiang Province, Jilin Province and Liaoning Province; Eastern China: Shanghai, Jiangsu Province, Zhejiang Province, Anhui Province, Fujian Province, Jiangxi Province, Shandong Province, and Taiwan; North China: Beijing, Tianjin, Shanxi Province, Hebei Province, Inner Mongolia Autonomous Region; Central China: Henan Province, Hubei Province, Hunan Province; South China: Guangdong Province, Guangxi Zhuang Autonomous Region, Hainan Province, Hong Kong Special Administrative Region, Macao Special Administrative Region; Southwest China: Sichuan Province, Guizhou Province, Yunnan Province, Chongqing Municipality, Tibet Autonomous Region; Northwest region: Shaanxi Province, Gansu Province, Qinghai Province, Ningxia Hui Autonomous Region, Xinjiang Uygur Autonomous Region. NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; NR, not reported.

on a total of 159,993 patients and provides the most comprehensive assessment of *EGFR*ex20ins and *MET*ex14 mutations in Chinese NSCLC patients to date. Most of the studies were non-comparative studies. We found that the frequency of these two mutations varied between different regions in China, with the lowest frequency in the South. Forty-eight studies (76.2%) were published in the last five years since these two mutations have attracted more attention in China. Patients with these mutations were more likely to have advanced NSCLC compared to those without. The most common histological subtype was adenocarcinoma.

Findings of a previous systematic review indicated that the frequency of *EGFR*ex20ins ranged from 0.1–4% of all NSCLC patients and 1.0–12% of all *EGFR* mutations globally (9). In the present review, the frequency of *EGFR*ex20ins ranged from 0.02–2.85% of all NSCLC patients and 0.56–6.90% of all *EGFR* mutations when we focus on the larger studies with at least 1,000 Chinese patients. The frequency of *EGFR*ex20ins found in our study is similar to the reported data among Caucasian patients with NSCLC, although the upper range is lower in Chinese patients. The frequency of *MET*ex14 is much lower in Chinese patients (0.08–1.38%) with NSCLC than in Caucasian patients (~3%). Both mutations also account for a smaller proportion of all *EGFR* and *MET* mutations in Chinese patients with NSCLC. Therefore, the frequency of these mutations may be relatively low in Chinese patients with NSCLC. However, the frequency of these two mutations may have been underestimated since various genotyping methods were used (Table S1). Among the methodologies employed, RT-PCR, utilized in 27 studies (24.32%), was an earlier-published genotyping technique. In contrast, a more recent trend, observed in 35 studies (31.5%), involved the use of next-generation sequencing for identifying both known and novel variants (Table S1). Therefore, further large-scale studies using the next-generation sequencing are warranted to understand the frequency of these mutations in Chinese patients.

The treatment regimens were assessed in NSCLC patients with *EGFR*ex20ins mutation. The treatments used varied depending on the study, with the most common treatment regimens consisting of *EGFR*-specific TKIs and chemotherapy (*Table 3*). There was limited evidence on whether any one treatment was superior compared to the rest in terms of clinical efficacy and safety for NSCLC patients with these mutations. In general, the presence of these mutations was associated with a shorter PFS time. In

Table 3 Summary of studies reporting the line of therapy and drug class in the target population (all in EGFRex20ins)

Author, year	Prospective or retrospective	Sample size (target population description)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
First-line treatment											
EGFR TKIs											
Chao Shi, 2022	Retrospective	15	–	NR	NR	NR	NR	NR	NR	5.5 (2.537–8.463)	NR
Chao Shi, 2022	Retrospective	6 (EGFRex20ins near loop[a])	1st-generation EGFR TKIs	NR	NR	NR	NR	NR	NR	3.9 (2.380–5.420)	11.68 (0–24.692)
Chao Shi, 2022	Retrospective	5 (EGFRex20ins near loop[a])	2nd or 3rd-generation EGFR TKIs	NR	NR	NR	NR	NR	NR	8.9 (0–18.311)	23.233 (14.029–32.438)
Chihsien Huang, 2021	Retrospective	13	Afatinib	NR	NR	NR	NR	NR	NR	2.6	NR
Cheng He, 2020	Retrospective	1	Gefitinib	NR	NR	NR	NR	NR	NR	NR	NR
DYL Chow, 2022	Retrospective	5	Afatinib	NR	NR	NR	NR	NR	NR	4.5 (0–13.2)	10.4 (0.4–28.5)
Guangjian Yang, 2022	Retrospective	16 (patients with V769_D770insASV and D770_N771insSVD mutants)	–	0	0	8	8	0	50.0	2.07 (0–6.25)	NR
Guangjian Yang, 2022	Retrospective	12 (patients with A763_Y764insFQEA and D770delinsGY mutants)	–	4		6	2	33.3	83.3	9.97 (4.75–15.19)	NR
Guangjian Yang, 2022	Retrospective	7 (less common ex20ins subtypes[b])	–	0	0	3	4	0	42.9	2.03 (0–4.86)	NR
Guangjian Yang, 2020	Retrospective	23	–	NR	NR	0	NR	8.7	8.7	2.9 (1.5–4.3)	NR
Guangjian Yang, 2020	Retrospective	14	1st-generation EGFR TKIs	NR	NR	NR	NR	0	NR	2.0 (0.2–3.8)	NR
Guangjian Yang, 2020	Retrospective	16	–	NR	NR	NR	NR	NR	NR	2.9 (2.1–3.7)	NR
Guangjian Yang, 2020	Retrospective	7	–	NR	NR	NR	NR	NR	NR	2.0 (0.8–3.2)	NR
Guangjian Yang, 2020	Retrospective	1	Gefitinib	NR	NR	NR	NR	NR	NR	3.2	NR
Guangjian Yang, 2020	Retrospective	1	Icotinib	NR	NR	NR	NR	NR	NR	1	NR
Huanlan Sa, 2023	Retrospective	19	Furmonertinib	NR	NR	NR	NR	26.3	89.5	NR	NR
Jianchun Duan, 2023	Prospective	26	YK-029A	0	19	5	2	73.1	92.3	9.3 (5.85–NE)	NR
Jie Qian, 2022	Retrospective	4	Afatinib	0	0	3	1	0	75.0	2.37 (0.00–5.11)	NR
John Wen-Cheng Chang, 2022	Retrospective	32	Gefitinib/erlotinib	3		5	24	9.4	25.0	2.3 (1.5–3.1)	7.3 (0.1–16.0)
John Wen-Cheng Chang, 2022	Retrospective	23	Afatinib	6		3	14	26.1	39.1	2.5 (2.2–2.9)	6.9 (0.1–17.2)
Jennyu Wu, 2019	Retrospective	16	TKI-containing	0	1	0	15	6.25	6.25	1.8	16.8
Shen Zhao, 2023	Prospective	52	JMT101[c] plus afatinib/osimertinib	NR	NR	NR	NR	42.3	NR	NR	NR
Ying-Ting Liao, 2023	Retrospective	22	–	NR	NR	NR	NR	9.1	18.2	3.13 (1.03–5.4)	12.4 (1.87–118.1)
Yicheng Shen, 2017	Retrospective	2	Gefitinib/erlotinib	0	0	2	0	0	100	NR	NR

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Prospective or retrospective	Sample size (target population description)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
Chemotherapy											
Chao Shi, 2022	Retrospective	39	–	NR	NR	NR	NR	NR	NR	9.2 (5.218–13.115)	NR
Chao Shi, 2022	Retrospective	37 (EGFRex20ins near loop[a])	Chemotherapy/ICIs	NR	NR	NR	NR	NR	NR	7.2 (3.625–10.775)	NR
Chao Shi, 2022	Retrospective	27 (EGFRex20ins near loop[a])	–	NR	NR	NR	NR	NR	NR	7.2 (2.611–11.789)	NR
Chao Shi, 2022	Retrospective	8 (EGFRex20ins far loop[d])	–	NR	NR	NR	NR	NR	NR	15.43 (4.402–26.465)	NR
Chao Shi, 2022	Retrospective	5 (EGFRex20ins far loop[d])	Chemotherapy alone	NR	NR	NR	NR	NR	NR	15.43 (6.702–24.165)	NR
Chao Shi, 2022	Retrospective	3 (EGFRex20ins far loop[d])	Chemotherapy plus anti-angiogenesis	NR	NR	NR	NR	NR	NR	6.8 (0–14.428)	NR
Chao Shi, 2022	Retrospective	NR	Chemotherapy/EGFR-TKI	NR	NR	NR	NR	NR	NR	NR	14.0 (9.872–18.128)
Chao Shi, 2022	Retrospective	NR (EGFRex20ins near loop[a])	Chemotherapy/EGFR-TKI	NR	NR	NR	NR	NR	NR	NR	13.87 (7.398–20.335)
Chao Shi, 2022	Retrospective	NR	Chemotherapy plus anti-angiogenesis/EGFR-TKI plus anti-angiogenesis	NR	NR	NR	NR	NR	NR	NR	28.7 (21.384–36.016)
Chao Shi, 2022	Retrospective	NR (EGFRex20ins near loop[a])	Chemotherapy plus anti-angiogenesis/EGFR-TKI plus anti-angiogenesis	NR	NR	NR	NR	NR	NR	NR	26.27 (17.732–34.802)
Chunwei Xu, 2020	Retrospective	77	Pemetrexed/platinum	NR	NR	NR	NR	41.56	75.32	5.5	NR
Guangjian Yang, 2022	Retrospective	44	Chemotherapy alone	8		29	7	18.2	84.1	5.93 (2.70–9.17)	32.03 (17.55–46.52)
Guangjian Yang, 2022	Retrospective	63	Chemotherapy plus angiogenesis inhibitors	24		37	2	38.1	96.8	7.73 (6.40–9.06)	30.57 (19.90–41.23)
Guangjian Yang, 2020	Retrospective	105	Platinum-based chemotherapy	NR	NR	13	NR	19.2	41.3	6.4 (5.7–7.1)	NR
Guangjian Yang, 2020	Retrospective	84	Platinum-based chemotherapy	NR	NR	NR	NR	NR	NR	6.5 (4.9–8.1)	NR
Guangjian Yang, 2020	Retrospective	20	Platinum-based chemotherapy	NR	NR	NR	NR	NR	NR	3.6 (0.0–8.0)	NR
Guangjian Yang, 2020	Retrospective	39	Platinum-based chemotherapy with bevacizumab	NR	NR	NR	NR	NR	NR	7.5 (5.6–9.4)	NR
Guangjian Yang, 2020	Retrospective	66	Platinum-based chemotherapy without bevacizumab	NR	NR	NR	NR	NR	NR	5.6 (2.8–8.4)	NR
Jiahui Zhang, 2022	Retrospective	31	Pemetrexed and platinum-based chemotherapy plus bevacizumab	0	13	15	3	41.9	90.3	8.3 (6.6–10.0)	17.9 (8.9–26.9)
Jennyu Wu, 2019	Retrospective	24	Pemetrexed-containing	0	7	11	6	29.2	75	6.2	28

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Prospective or retrospective	Sample size (target population description)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
Jennyu Wu, 2019	Retrospective	7	Taxane-containing	0	1	0	6	14.29	14.29	3.4	15.9
Jennyu Wu, 2019	Retrospective	10	Gemcitabine-containing	0	1	2	7	10	30	3.4	6.3
Qingyue Lin, 2022	Retrospective	8	Chemotherapy with/without bevacizumab	0	3	4	1	37.5	87.5	7.2 (range, 1.7–13.6)	NR (range, 6.1–27.5)
Ying-Ting Liao, 2023	Retrospective	38	Platinum-based chemotherapy	NR	NR	NR	NR	26.3	60.5	5.37 (0.5–23.2)	21.37 (2.77–62.5)
Chemotherapy plus EGFR-TKI											
Yue Wang, 2020	Retrospective	55	–	NR	8	23	3	23.5	91.2	NR	NR
Yue Wang, 2020-3	Retrospective	49	–	NR	NR	NR	NR	NR	NR	7.6 (5.7–9.6)	19.9 (15.9–24.0)
ICIs											
Chao Shi, 2022	Retrospective	10	PD-1 or single-agent PD-L1 inhibitors: 3	0	4	6	0	40	100	NR	NR
			ICI plus pemetrexed/platinum: 7								
Chao Shi, 2022	Retrospective	1 (one patient with D770_P772dup)	Sintilimab	NR	NR	NR	NR	NR	NR	1.7	NR
Chao Shi, 2022	Retrospective	1 (another patient with D770_P772dup)	Sintilimab	NR	NR	NR	NR	NR	NR	2.5	NR
Guangjian Yang, 2020	Retrospective	5	–	0	3	2	0	60	100	2.8	NR
Ying-Ting Liao, 2023	Retrospective	4	–	0	0	1	3	0	25.0	2.43 (0.967–12.467)	NR
Chemotherapy plus ICI											
Guangjian Yang, 2022	Retrospective	15	–	6		6	3	40.0	80.0	6.53 (5.06–8.01)	Immature[e]
Jiahui Zhang, 2022	Retrospective	29	–	0	20	8	1	69.0	96.6	13.0 (11.9–14.1)	22.7 (20.4–25.0)
Qingyue Lin, 2022	Retrospective	3	–	0	1	2	0	33.3	100	6 (range, 3.8–9.9)	NR (range, 12.8–28.1)
Other drugs											
Qingyue Lin, 2022	Retrospective	4	Amivantamab-vmjw/Sutent/vemurafenib	0	2	2	0	50	100	11.3 (range, 6.0–11.5)	15.5 (range, 7.8–15.5)

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Prospective or retrospective	Sample size (target population description)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
Second-line treatment											
EGFR TKIs											
Chia-I Shen, 2022	Retrospective	1	Erlotinib	–	–	1	–	–	–	NR	19.9
Cheng He, 2020	Retrospective	1	Afatinib	NR	NR	NR	NR	NR	NR	NR	NR
Guangjian Yang, 2022	Retrospective	13 (patients with A763_Y764insFQEA and D770delinsGY mutants)	–	5		7	1	38.5	92.3	6.77 (5.48–8.06)	NR
Guangjian Yang, 2022	Retrospective	11 (patients without A763_Y764insFQEA and D770delinsGY mutants)	–	1		6	4	9.1	63.6	2.23 (1.19–3.28)	NR
Guangjian Yang, 2020	Retrospective	18	–	NR	NR	1	NR	5.9	11.8	2.0 (1.1–2.9)	NR
Guangjian Yang, 2020	Retrospective	1	Afatinib	NR	NR	NR	NR	NR	NR	8.2	NR
Guangjian Yang, 2020	Retrospective	1	Erlotinib	NR	NR	NR	NR	NR	NR	14.3	NR
Huanlan Sa, 2023	Retrospective	25	Furmonertinib	NR	NR	NR	NR	40.0	100.0	NR	NR
Shen Zhao, 2023	Prospective	69	JMT10[c] plus afatinib/osimertinib	NR	NR	NR	NR	31.9	NR	NR	NR
Ying-Ting Liao, 2023	Retrospective	16	–	0	0	NR	NR	0	25	2.25	NR
Yicheng Shen, 2017	Retrospective	3	Afatinib	0	1	0	2	33.3	33.3	NR	NR
Chemotherapy											
Guangjian, Yang, 2020	Retrospective	35	–	NR	NR	15	NR	17.1	60	4.0 (3.2–4.8)	NR
Guangjian, Yang, 2020	Retrospective	20	Chemotherapy plus bevacizumab	NR	NR	NR	NR	NR	NR	6.0 (4.0–8.0)	NR
Guangjian, Yang, 2020	Retrospective	15	Chemotherapy alone	NR	NR	NR	NR	NR	NR	2.4 (1.8–3.0)	NR
Ying-Ting Liao, 2023	Retrospective	13	Platinum-based chemotherapy	NR	NR	6	NR	7.7	53.8	4.73	NR
Ying-Ting Liao, 2023	Retrospective	13	Patients with single-agent chemotherapy	0	1	0	12	7.7	7.7	2.57 (range, 1.5–29.27)	NR
ICIs											
Guangjian, Yang, 2020	Retrospective	4	–	0	0	2	2	0	50	2.25	NR
Qi Gui, 2018	Retrospective	2	–	NR	NR	NR	NR	NR	NR	NR	NR
Chemotherapy plus EGFR-TKI											
Shen Zhao, 2023	Prospective	53	Platinum-based chemotherapy with JMT101[c] and osimertinib	NR	NR	NR	NR	34	96.2	9.2 (5.5–14.3)	NR

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Prospective or retrospective	Sample size (target population description)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
Other drugs											
Qingyue Lin, 2022	Retrospective	6	Amivantamab-vmjw/Sutent/vemurafenib	NR	NR	NR	NR	NR	NR	12.3 (range, 2.0–12.3)	NR (range, 2.0–21.6)
Third-line treatment											
Chemotherapy											
Yenting Lin, 2017	Retrospective	4	–	0	1	3	0	25	100	8.5	31
Fourth-line treatment											
ICIs											
Guangjian Yang, 2020	Retrospective	1	–	0	1	0	0	100	100	6.6	NR
≥1 line treatment											
EGFR TKIs											
Huanlan Sa, 2023	Retrospective	53	Furmonertinib	0	20	29	4	37.7	92.5	Not reached	NR
Jie Qian, 2022	Retrospective	7	Afatinib	0	0	6	1	0	6	3.78 (1.93–5.64)	NR
Jingjing Wang, 2022	Retrospective	4	Amivantamab plus lazertinib	0	1	3	0	25.0	100.0	NC	NC
Kaiyan Chen, 2020	Retrospective	15	–	NR	NR	NR	NR	13.3	NR	2.6	23.3
Shen Zhao, 2023	Prospective	11 (radiological review based on independent review committee assessment)	JMT101[c] plus afatinib 30 mg/d	0	3	7	1	27.3	90.9	NR	NR
Shen Zhao, 2023	Prospective	6 (radiological review based on independent review committee assessment)	JMT101[c] plus afatinib 40 mg/d	0	2	4	0	33.3	100	NR	NR
Shen Zhao, 2023	Prospective	12 (radiological review based on independent review committee assessment)	JMT101[c] plus osimertinib 80 mg/d	0	4	7	0	33.3	91.7	NR	NR
Shen Zhao, 2023	Prospective	121 (radiological review based on independent review committee assessment)	JMT101[c] plus osimertinib 160 mg/d	0	42	73	3	34.7	95	NR	NR
Shen Zhao, 2023	Prospective	11 (radiological review based on investigator assessment)	JMT101[c] plus afatinib 30 mg/d	0	2	8	1	18.2	90.9	NR	NR
Shen Zhao, 2023	Prospective	6 (radiological review based on investigator assessment)	JMT101[c] plus afatinib 40 mg/d	0	2	4	0	33.3	100	NR	NR

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Prospective or retrospective	Sample size (target population description)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
Shen Zhao, 2023	Prospective	12 (radiological review based on investigator assessment)	JMT101[c] plus osimertinib 80 mg/d	0	5	6	0	41.7	91.7	NR	NR
Shen Zhao, 2023	Prospective	121 (radiological review based on investigator assessment)	JMT101[c] plus osimertinib 160 mg/d	0	44	71	1	36.4	95	NR	NR
EGFR-TKI plus ICI											
Kaiyan Chen, 2023	Prospective	12	Sintilimab plus anlotinib	NR	NR	NR	NR	41.7	NR	4.3	NR
Other drugs											
Jingjing Wang, 2022	Retrospective	3	Amivantamab	0	1	2	0	33.33	100.00	NC	NC
≥3 line treatment											
EGFR TKIs											
Huanlan Sa, 2023	Retrospective	9	Furmonertinib	NR	NR	NR	NR	55.6	77.8	NR	NR
ICIs											
Ying-Ting Liao, 2023	Retrospective	3	–	0	0	0	3	0	0	2.2 (1.667–2.733)	NR

[a], *EGFR* ex20ins near loop was defined as the site on the loop following the C-helix (A767–P772) of *EGFR* exon 20; [b], less common ex20ins subtypes including P772_H773insGHP, D770_N771insGD, N771_P772insH, P772_H773insH, H773_V774insAH, and H773delinsRY; [c], JMT101 is an anti-EGFR IgG1 monoclonal antibody developed using cetuximab as a prototype; [d], *EGFR* ex20ins far loop was defined as the site on the loop following the C-helix (H773–C775) of *EGFR* exon 20; [e], immature (at the cutoff time, the median OS of C+I (chemotherapy plus immune checkpoint inhibitor) was immature because of this treatment pattern was used in more recent times with only three events of deaths, but not for better efficacy). EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progress free survival; CI, confidence interval; OS, overall survival; TKI, tyrosine kinase inhibitors; NR, not reported; NE, not estimable; ICIs, immune checkpoint inhibitors; NC, not calculable.

Table 4 Summary of studies reporting the line of therapy and drug class in the target population (all in METex14 skipping)

Author, year	Prospective or retrospective	Target population description (sample size)	Treatments received	CR	PR	SD	PD	ORR (%)	DCR (%)	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
First-line treatment											
MET TKIs											
Hanmin Wang, 2021	Retrospective	6	Bozitinib or crizotinib	NR	NR	NR	NR	NR	NR	4	18.3
≥1 lines treatment											
MET TKIs											
Hanmin Wang, 2021	Retrospective	12	Bozitinib or crizotinib	NR	NR	NR	NR	33.3	NR	6.1	17.3
Hanmin Wang, 2021	Retrospective	5	Bozitinib	NR	NR	NR	NR	NR	NR	19.6	23.6
Hanmin Wang, 2021	Retrospective	7	Crizotinib	NR	NR	NR	NR	NR	NR	1.6	14.2
Kang Miao 2023	Retrospective	17	Crizotinib or savolitinib	0	5	10	2	29.41	88.24	10.7 (5.2, 17.3)	NR
Kang Miao 2023	Retrospective	9	Savolitinib	NR	NR	NR	NR	NR	NR	10.1 (4.4, 19.6)	NR
Kang Miao 2023	Retrospective	8	Crizotinib	NR	NR	NR	NR	NR	NR	7.2 (3.6, 19.5)	NR
Shun Lu, 2022	Prospective	70	Savolitinib	33		24	13	47.1	81.4	6.9 (4.6, 8.3)	12.5 (10.5, 21.4)
Xingsheng Hu 2023	Prospective	4	BPI-9016M	0	0	3	1	0	75.0	3.4 (3.2, 3.7)	NR
Xiaorong Dong 2022	Prospective	1	HS-10241	–	–	1	–	–	–	4.2	7.7
Xinghao Ai, 2022	Retrospective	14	Crizotinib or savolitinib	NR	NR	NR	NR	NR	NR	11.5	NR
Yang Xia 2023	Prospective	29	Ensartinib	1	19	7	2	69	93	6.1 (4.5, 7.8)	NR
Yongfeng Yu, 2022	Prospective	46[a]	Savolitinib	24		NR	NR	52.2	NR	5.6 (4.14, 6.93)	10.9 (9.2, 13.96)
Yongfeng Yu, 2022	Prospective	13[b]	Savolitinib	12		NR	NR	92.3	NR	11.0 (5.5, NC)	35.8 (9.7, NC)
≥2 lines treatment											
MET TKIs											
Hanmin Wang, 2021	Retrospective	6	Bozitinib or crizotinib	NR	NR	NR	NR	NR	NR	6.1	17.3
Five-line treatment											
Other treatment											
Jingjing Wang, 2022	Retrospective	1	Amivantamab	–	–	–	1	–	–	0.8	0.9

[a], patients with the detectable baseline *MET*ex14 skipping; [b], patients with *MET*ex14 skipping clearance post-treatment. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progress free survival; CI, confidence interval; OS, overall survival; TKI, tyrosine kinase inhibitors; NR, not reported; NC, not calculable.

recent years, emerging real-world studies are focusing on EGFR-TKIs in the treatment of *EGFR*-mutant NSCLC (23,44-50) in Chinese population. However, EGFR-TKIs show controversial effectiveness in *EGFR*ex20ins. Furmonertinib has shown encouraging antitumor activity and a good safety profile in advanced NSCLC patients with *EGFR*ex20ins and the 6-month PFS rate was 69.4% (95% CI: 53.7–85.1%) (29), whereas afatinib has not shown favorable efficacy and tolerability in the treatment of advanced lung adenocarcinomas with *EGFR*ex20ins comparing to other *EGFR* mutations (23) (median PFS =2.4 months, 95% CI: 0.0–5.1 months). The similar situation was found in the treatment with Gefitinib and Erlotinib (median PFS =2.3 months, 95% CI: 1.5–3.1) (51). Moreover, the *EGFR-MET* bispecific antibody amivantamab showed effectiveness in the treatment of *EGFR*ex20ins-positive NSCLC with osimertinib resistant, which is similar to the findings from other study populations (52,53).

Fewer studies have examined the efficacy and effectiveness of treatments for NSCLC with *METex14* mutation in the Chinese population, as indicated in *Table 4*. It has been shown that the median PFS was 3.4–11.5 months, and the median OS was 10.9–35.8 months in NSCLC patients with *MET*ex14 mutation who received bozitinib, savolitinib, or crizotinib treatment. In addition, the median PFS and OS were 1.9 months (95% CI: 1.9–3.7) and 10.3 months [95% CI: 7.3–not evaluable (NE)] in all 38 NSCLC patients with c-*MET* overexpression (n=34) or *MET*ex14 mutation (n=4) (42).

The evidence on the prognostic effect of these mutations was little to assess the impact on OS time. In terms of age group and smoking status, limited evidence was available to give a clear picture for the *EGFR*ex20ins and *MET*ex14 mutations in Chinese patients with NSCLC.

There was also some evidence to assess the treatment regimens in other ethnic groups with *EGFR*ex20ins mutation or with *MET*ex14 mutation (5). For the first-line treatment, the most common treatment regimens were chemotherapy for patients with *EGFR*ex20ins mutation. Median OS ranged from 6.3 to 28.0 months. Median PFS and objective response rates (ORRs) were 3.4–6.9 months and 23–29%, respectively (5). For *MET*ex14 mutation, the efficacy and safety of two MET-TKIs capmatinib and tepotinib, have been previously assessed (5). These drugs yielded PFS of 5.6–12.4 months in clinical trials. However, it has been reported that one-third to half of patients showed inherent resistance to MET-TKIs. Given the evidence indicating inherent resistance to MET-TKIs in up to half of patients with *METex14* mutation, future clinical trials should prioritize investigating novel therapeutic approaches or combination therapies to address this challenge. Additionally, it would be crucial to explore the efficacy and safety of these treatment regimens specifically in diverse ethnic groups to ensure a comprehensive understanding of their impact across different populations. This will not only enhance the precision of treatment but also contribute valuable insights into optimizing therapeutic strategies for patients with *METex14* mutation.

Our study has several strengths. We conducted systematic searches on eight databases and identified 111 studies with nearly 160,000 Chinese patients with NSCLC. The assessment of mutation frequency in larger studies should be less prone to selective reporting than in smaller studies. Furthermore, evaluation of the current literature has allowed the identification of gaps in our current knowledge, which may help direct future research in Chinese NSCLC patients. For example, there is limited evidence on which treatment option is more beneficial when considering clinical efficacy and the safety of NSCLC patients with these mutations. Additionally, the frequency of *EGFR*ex20ins and *MET*ex14 mutations and their correlation with gender, smoking status, stage, and histological grade remains unclear, especially when considering the presence of other co-occurring genomic mutations in these patients.

Limitations of our study include the possible underestimation in the frequency of *EGFR*ex20ins and *MET*ex14 mutations in Chinese NSCLC patients, as the earlier genotyping method to detect the mutations in the included studies was RT-PCR. Mutation detection using next-generation sequencing, which focuses on large-scale studies, could potentially improve this. Further large-scale studies, including epidemiological studies and real-world data, are required to identify the association between the presence of these mutations, clinical characteristics at baseline, and treatment efficacy. Due to limited data on NSCLC patients with these mutations, we are unable to perform a meta-analysis.

At present, the optimal treatment regimen for Chinese NSCLC patients with *EGFR*ex20ins and *MET*ex14 remains unclear. In the present review, we focused on evaluating the efficacy and safety of treatment regimens for Chinese patients with *EGFR*ex20ins or *MET*ex14 mutations, based on non-comparative studies. Among these studies, the treatment regimens of *EGFR*ex20ins varied depending on the specific study. For NSCLC patients with MET exon 14 skipping mutations, targeted therapies such as capmatinib, tepotinib, glumetinib, savolitinib, and vebreltinib have

shown efficacy and have been approved for use. In contrast, MET amplification represents a distinct alteration that may respond differently to treatment, typically requiring more comprehensive therapeutic approaches. While MET exon 14 skipping mutations directly confer sensitivity to MET inhibitors, further research is required to optimize treatment regimens, particularly for cases involving MET amplification.

Conclusions

Our review highlights that both *EGFR*ex20ins and *MET*ex14 mutations account for a smaller proportion of all *EGFR* and *MET* mutations in Chinese patients with NSCLC; while several targeted therapies have been approved in China, there is still insufficient evidence regarding the optimal treatment and therapeutic efficacy for Chinese patients with NSCLC. Further large-scale studies are required to identify associations between the presence of these mutations and clinical characteristics at baseline and outcome following treatment.

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Footnote

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