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Current clinical practice and physicians' insights on Chinese patients with advanced non-small cell lung cancer habouring epidermal growth factor receptor 20 insertion mutation

Yuequan Shi[1,2], Yan Xu[1*] and Mengzhao Wang[1*]

Abstract

Background The present study aimed to investigate physicians' perspectives on the diagnosis and treatment decisions for patients with non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) exon 20 insertion (exon20ins) mutations in a real-world setting in China using an online questionnaire.

Methods This study was performed via the CAPTRA-Lung collaboration between December 9, 2022 and March 6, 2023. The questionnaire was distributed digitally to physicians around China and was comprised of three sections: basic characteristics of surveyed physicians, diagnosis and treatment status of NSCLC patients with the EGFR exon20ins-mutation, and physicians' perspectives on treatment options. Physicians who treat more than 10 patients with advanced NSCLC every month and who have treated patients with advanced EGFR exon20ins-mutant NSCLC in the past six months were involved in this study.

Results A total of 53,729 questionnaires were distributed and 390 valid ones were collected. The EGFR mutation test was performed in 80.9% and 59.9% of patients receiving first-line or second-line therapy and beyond (hereinafter "second-line")therapy, respectively. In terms of treatment options, chemotherapy plus antiangiogenic therapy was the most common treatment option (30.0% of patients in first-line settings; 25.0% of patients in second-line settings), and a certain proportion of patients received novel EGFR exon20ins-targeted agents (including tyrosine kinase inhibitors [TKIs] and bispecific antibodies) in first- or second-line settings, which accounted for 11.9% and 15.7% of all treated patients, respectively. Additionally, physicians reported the highest satisfaction score for the efficacy and safety of targeted agents. Most physicians believed that EGFR exon20ins-targeted TKIs represented the most promising treatment option (80.2% in first-line treatment and 73.3% in second-line treatment). Among several novel agents under study, sunvozertinib has received the highest recognition for efficacy and safety.

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Conclusions This study investigated the current diagnosis and treatment status and physicians' perspective, of patients with EGFR exon20ins-mutant NSCLC. The results highlight significant unmet clinical needs in this subgroup of patients. EGFR exon20ins-targeted TKIs were recognized as the most promising treatment regimen and may benefit more patients considering their awareness and acceptance of targeted therapy.

Keywords EGFR exon20ins, Real-world clinical practice, Targeted agents, Questionnaire

Introduction

Due to its high incidence and mortality rates [1], lung cancer is one of the most prevalent malignancies affecting the world population. Therapies that act on various molecular targets of lung cancer have progressed because of scientific and technological advances [2, 3]. Among these mutations, epidermal growth factor receptor (EGFR) mutation is a common driver mutation detected in 45% of Chinese non-small cell lung cancer (NSCLC) patients and 20% of western NSCLC patients [4, 5]. The most common EGFR mutations include exon 19 deletions and exon 21 L858R, which are two subtypes that have demonstrated promising sensitivity to 1st -3rd generation EGFR tyrosine kinase inhibitors (TKIs) and account for 80-85% of all EGFR mutations [6–9].

Among the atypical EGFR mutations, exon 20 insertion (exon20ins) mutations are the most common and account for approximately 4-12% of all EGFR mutations in NSCLC patients [10–12]. EGFR exon20ins occurs in two basic domains, the αC-helix and the αC-helix adjacent loop, and greater than 90% of insertion mutations occur in the loop [13, 14]. This mutation causes steric hindrance in the binding position of conventional EGFR-TKIs, and patients with EGFR exon20ins generally respond poorly to EGFR-TKIs [15, 16]. However, insertion mutations that occur in the αC-helix, such as A763_Y764insFQEA, may be sensitive to 1st -3rd generation EGFR-TKIs [11, 13, 17]. EGFR exon20ins exhibits high heterogeneity, with more than 100 mutation subtypes identified to date [18, 19], which has posed an additional challenge to testing technologies and targeted therapies.

The standard of care for patients with advanced EGFR exon20ins-mutant NSCLC primarily includes platinum-based doublet chemotherapies and chemotherapy-based combination regimens, but many studies have shown that these treatments offer only limited benefits [20, 21]. These results indicate the demand for more effective therapies. Targeted therapies are under evaluation for the treatment of this subtype of NSCLC [22–27].Sunvozertinib has been approved by China National Medical Products Administration (NMPA) for patients with EGFR exon20ins-mutant NSCLC who have experienced disease progression from or intolerant to platinum-based chemotherapy on August 23, 2023. However, there is a lack of study on the current status of the diagnosis and whole process management treatment of patients with EGFR exon20ins-mutant NSCLC, and we need a clearer picture for physicians' understanding of the disease characteristics of EGFR exon20ins-mutant NSCLC and recent advances in this field. Therefore, we performed the present study to assess the current status of the diagnosis and treatment of patients with EGFR exon20ins-mutant NSCLC as well as physicians' understanding of the structure, function, and research progress of EGFR exon20ins mutations to promote standardised diagnosis and treatment for this condition.

Methods

Procedures and participants

This study was initiated by the CAPTRA-Lung collaboration. Physicians across China participated in this survey by completing an online questionnaire. To be eligible for participation, physicians met the following inclusion criteria: (1) practicing at a tertiary hospital; (2) specializing in thoracic surgery, oncology, or respiratory medicine; (3) holding an attending doctor or higher title; (4) treating more than 15 NSCLC patients per month, including more than 10 patients with advanced disease; and (5) having treated patients with advanced EGFR exon20ins-mutant NSCLC in the past six months.

The questionnaire consisted of three parts: (1) basic information of the participant, including the level of the hospital, city, department, and number of patients treated; (2) current status of the diagnosis and treatment of EGFR exon20ins-mutant NSCLC patients, including the EGFR mutation test rate and methodology, the physician's understanding of the characteristics and common treatment options for EGFR exon20ins-positive patients; and (3) physicians' perceptions of treatment options, including levels of satisfaction with existing treatment options and views on novel EGFR exon20ins-targeted therapies.

On the basis of the preliminary survey results, treatment options in the questionnaire were further categorised into the following choices: chemotherapy alone, chemotherapy plus antiangiogenic therapy, immune checkpoint inhibitors (ICIs) plus chemotherapy, other ICI-based combination therapies, and 1st -3rd generation EGFR-TKI monotherapy or EGFR-TKI-based combination therapies. We also added novel EGFR exon20ins-targeted agents as options (including TKIs and bispecific antibodies). In addition, we added a question to investigate the factors influencing physicians' decision to not perform NGS testing and followed up with respondents

on the surveyed items from February 19, 2023 to March 6, 2023.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 21 (SPSS Inc., Chicago, IL, USA). Categorical variables, such as the reasons for not performing genetic tests or performing genetic tests using non-NGS methods, the most promising treatment strategies, and perspectives on novel EGFR exon20ins-targeted agents were quantified as percentages in all samples, and the statistical significance was determined using the chi-squared test. Continuous variables, such as the proportion of EGFR gene-tested samples, applied testing technologies, selected treatment options for EGFR exon20ins-mutant patients, and the satisfaction score for these therapies, are presented as the mean values, and statistical significance was determined using the F test. At the 95% confidence interval (CI), $p<0.05$ was considered statistically significant.

Results

General information

A total of 53,729 questionnaires were distributed and 390 valid questionnaires from 319 hospitals located in 124 cities around China were collected between December 9, 2022 and March 6, 2023. 94.1% ($n=367$) of the surveyed physicians were from grade A tertiary hospital and 82.3% ($n=321$) of them were from general hospital. 59.0% ($n=230$) were from department of oncology and 32.6% ($n=127$) were from department of respiratory medicine. The characteristics of participating physicians including city tier, hospital type and departments are shown in Table 1.

Table 1 Basic characteristics of 390 physicians with valid questionnaires

Characteristics	Number (percentage)
Hospital level	
Grade A tertiary hospital	367(94.1%)
Grade B tertiary and other tertiary hospitals	23(5.9%)
Hospital class[a]	
General hospital	321(82.3%)
Cancer hospital	41(10.5%)
Unknow	28 (7.2%)
Department	
Department of Thoracic Surgery	33 (8.5%)
Department of Oncology	230(59.0%)
Department of Respiratory Medicine	127(32.6%)
City tier[b]	
First-tier and new first-tier city	167(42.8%)
Second-tier city	91(23.3%)
Third and lower-tier city	132(33.8%)

(a) Only including the information of 362 physicians who provide the institutional details

(b) The location of the hospital where the doctor practices. The classification of city tiers refers to the ranking system published by Yi Magazine in 2022 [28], which is primarily based on five criteria: commercial resources index, city as a hub index, urban residents' activity index, lifestyle diversity index, and future potential index

Among the 124 cities, 18 were first-tier/ new first-tier cities, accounting for 95% of all 19 first-tier/ new first-tier cities; 28 were second-tier cities, accounting for 93% of all 30 second-tier cities; and 78 were third or lower-tier cities, accounting for 27% (78/288) of all such cities [28]. Detailed region distribution of the 390 questionnaires is shown in Fig. 1.

The survey outcome revealed that the 390 participants on average treated approximately 10 patients with advanced EGFR exon20ins-mutant disease every 6 months, which accounted for 3.8% of all advanced NSCLC patients they were treating during the same period, and there was no significant difference between departments (data not shown).

Overall status of the diagnosis and treatment of patients with EGFR exon20ins-mutant NSCLC

The rate of EGFR mutation tests and testing methods

Physicians reported that among patients with advanced NSCLC receiving first- or second-line treatment, 80.9% and 59.9% underwent EGFR mutation tests, respectively, and there was no significant difference in the testing rate across different departments (data not shown). In the first-line setting, 25.0% (98/390) of the surveyed physicians reported a 100% EGFR testing rate. Among the remaining physicians (292/390, 75.0%) who did not reach a 100% EGFR testing rate, the reasons for not performing EGFR testing (based on a multiple-choice question) included patient-related factors (financial considerations and personal willingness, 224/292, 76.7%), patients who were pathologically confirmed to have squamous cell carcinoma (185/292, 63.4%), patients who had already undergone an EGFR mutation test elsewhere prior to the current hospital visit (115/292, 39.4%), and patients with insufficient tumour tissue samples (112/292, 38.4%) (Figure S1A).

With respect to EGFR mutation test methods in first-line setting, NGS was performed for 75.0% of the patients, including 62.0% performed NGS test only and 13.0% performed NGS plus PCR dual test. For the additional question concerning EGFR mutation test methods in first-line that 270 physicians answered, 21.9% (59/270) reported using the NGS method exclusively for EGFR testing. Among the remaining 78.1% (211/270) who did not achieve a 100% NGS testing rate, the following reasons for not performing NGS testing (based on a multiple-choice question) were provided: patient-related factors (financial consideration or personal willingness) (184/211, 87.2%), insufficient/low-quality tumour tissue samples (112/211, 53.1%), unavailability of in-house NGS

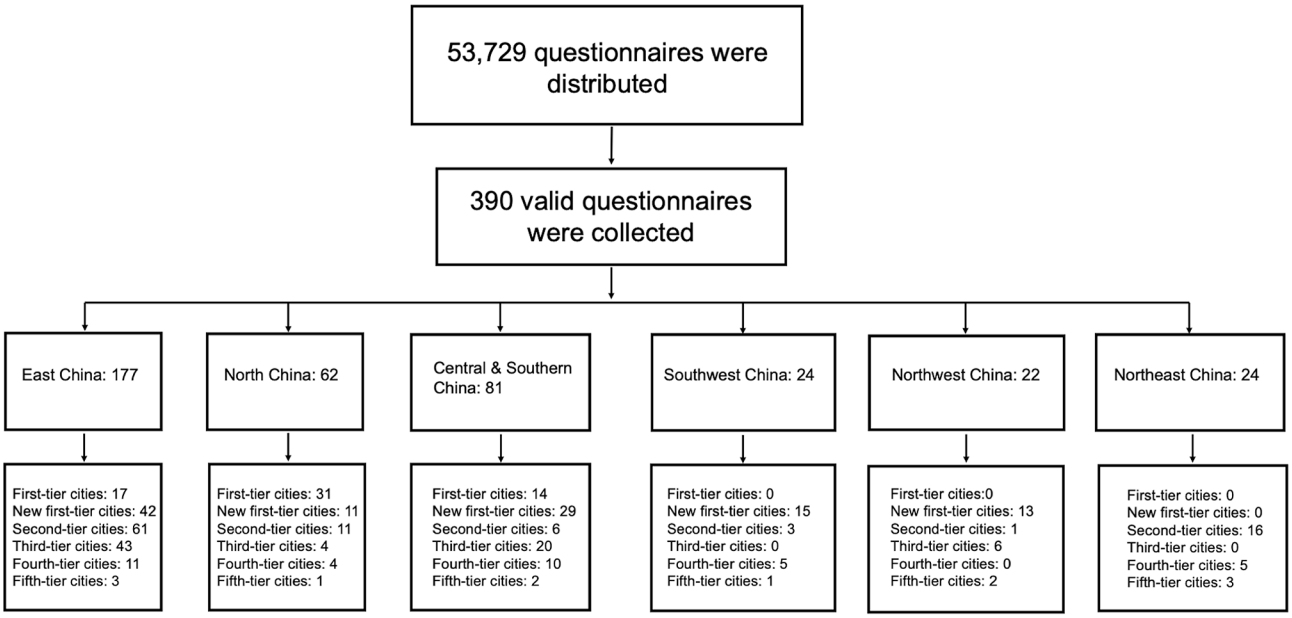

Fig. 1 Region distribution of the 390 questionnaires collected in this study. Note: **The first-tier cities**: Beijing, Shanghai, Guangzhou, Shenzhen; **The new first-tier cities**: Tianjin, Chongqing, Hefei, Foshan, Zhengzhou, Wuhan, Changsha, Nanjing, Suzhou, Qingdao, Xi'an, Chengdu, Hangzhou, Ningbo; **The second-tier cities**: Fuzhou, Quanzhou, Xiamen, Lanzhou, Huizhou, Zhongshan, Nanning, Guiyang, Baoding, Shijiazhuang, Harbin, Changchun, Changzhou, Nantong, Wuxi, Xuzhou, Nanchang, Dalian, Shenyang, Jinan, Linyi, Weifang, Yantai, Taiyuan, Kunming, Jinhua, Shaoxing, Wenzhou; **The third-tier cities**: Anqing, Fuyang, Wuhu, Ningde, Putian, Zhangzhou, Chaozhou, Qingyuan, Shantou, Zhanjiang, Guilin, Liuzhou, Haikou, Lang fang, Tangshan, Kaifeng, Luoyang, Nanyang, Xinxiang, Jingzhou, Yueyang, Zhuzhou, Huai'an, Taizhou, Yancheng, Zhenjiang, Ganzhou, Jiujiang, Shangrao, Hohhot, Yinchuan, Heze, Jining, Liaocheng, Weihai, Zibo, Xianyang, Urumqi, Huzhou, Taizhou; **The fourth-tier cities**: Bozhou, Huaibei, Huangshan, Tongling, Maoming, Baise, Chengde, Jiaozuo, Pingdingshan, Shiyan, Xiaogan, Huaihua, Loudi, Yiyang, Jilin, Dandong, Jinzhou, Baotou, Binzhou, Dongying, Zaozhuang, Jinzhong, Linfen, Dazhou, Leshan, Neijiang, Yibin; **The fifth-tier cities**: Wuwei, Qinzhou, Jingmen, Siping, Pingxiang, Xinyu, HuLudao, Liaoyang, Hulunbuir, Zigong, Shihezi

tests (75/211, 35.5%), and long NGS testing duration (64/211, 30.3%) (Figure S1B). The proportion of patients who did not receive the NGS test due to the unavailability of the test was greater in third- or lower-tier cities than first-tier cities (27.2% in first-tier cities vs. 49.3% in third- or lower-tier cities, $p<0.05$) (data not shown).

Physicians' general understanding of the EGFR exon20ins mutation

Physicians' comprehension of the EGFR exon20ins mutation was assessed via a series of questions related to the characteristics of the EGFR exon20ins mutation, subtypes of the mutation, mutation insertion locations, and the effectiveness of 1st -3rd generation EGFR-TKIs.

Among 390 surveyed physicians, 85.9% ($n=335$) were aware that EGFR exon20ins was a primary driver mutation, but 14.1% ($n=55$) of the surveyed physicians considered EGFR exon20ins a secondary drug-resistant mutation (Fig. 2A). The percentages of surveyed physicians who knew that EGFR exon20ins mutations occurred in the αC-helix and postαC-helix loops were 77.9% (304/390) and 80.3% (313/390), respectively (Fig. 2B). Regarding the subtypes of the mutation, 70.0% (273/390) and 67.4% (263/390) of the surveyed physicians correctly identified p.767_V769dup and H773_V774insNPH as subtypes of the EGFR exon20ins mutation (Fig. 2C). Furthermore, 37.4% (146/390) of the surveyed physicians knew that the 1st -3rd–generation EGFR TKIs were effective against the A763_Y764insFQEA subtype (Fig. 2D).

Current clinical practices in the treatment of patients with EGFR exon20ins-mutant NSCLC

In the case of patients with EGFR exon20ins-mutation undergoing first-line treatment, the three most commonly used regimens included chemotherapy combined with antiangiogenic therapy (30.0%), 1st -3rd -generation EGFR-TKI monotherapies or EGFR-TKI-based combinations (18.3%), and chemotherapy alone (16.8%). For patients receiving second-line therapies, the three most commonly used regimens were chemotherapy combined with antiangiogenic therapy (25.0%), chemotherapy alone (18.5%), and chemotherapy combined with ICIs (16.4%). In addition, 11.9% and 15.7% of patients on first-line or second-line treatment, respectively, received novel EGFR exon20ins-targeted therapies (including TKIs and bispecific antibodies) (Fig. 3A).

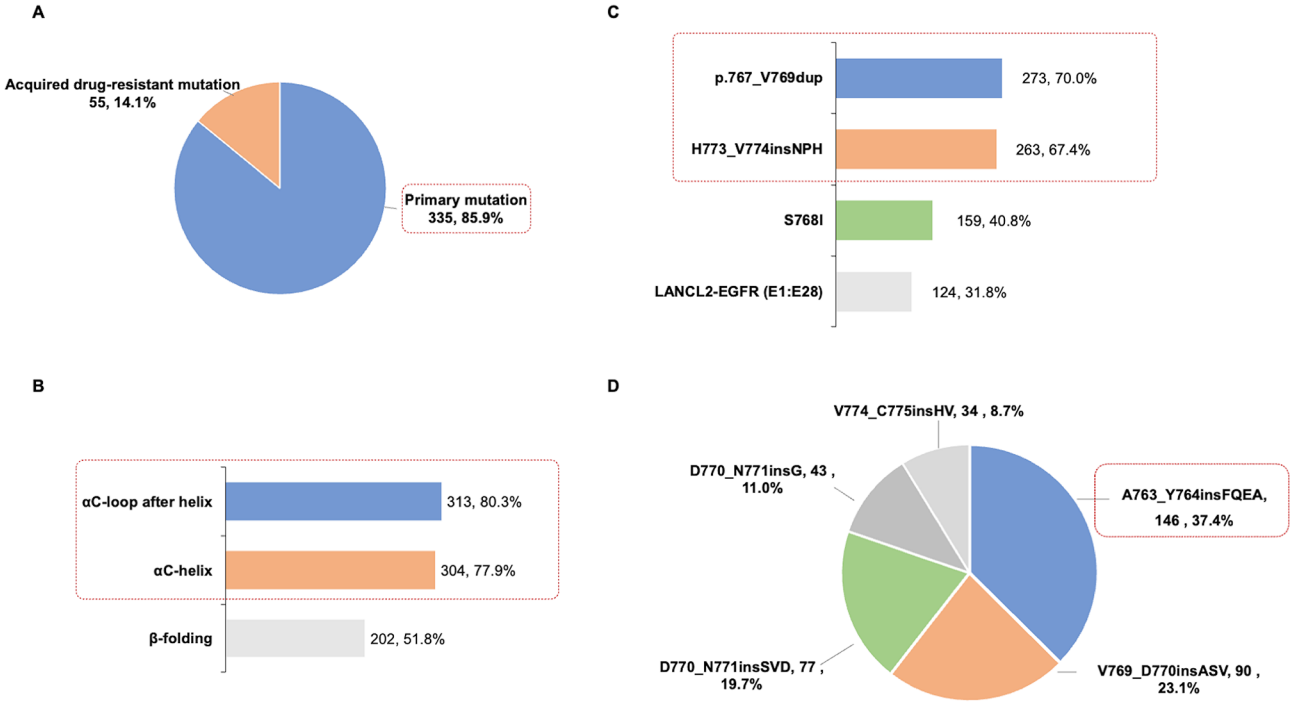

Fig. 2 The results of questions concerning physicians' understanding of EGFR exon20-ins mutations ($n=390$). **A**. Is EGFR exon20ins mutation a primary mutation or an acquired drug-resistance mutation? (single-choice); **B**. Where do EGFR exon20in mutations occur? (multiple-choice); **C**. Which are EGFR exon20ins mutations? (multiple-choice); **D**. Which one of the following subtype is sensitive to 1st -3rd generation EGFR TKIs? (single-choice). EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor

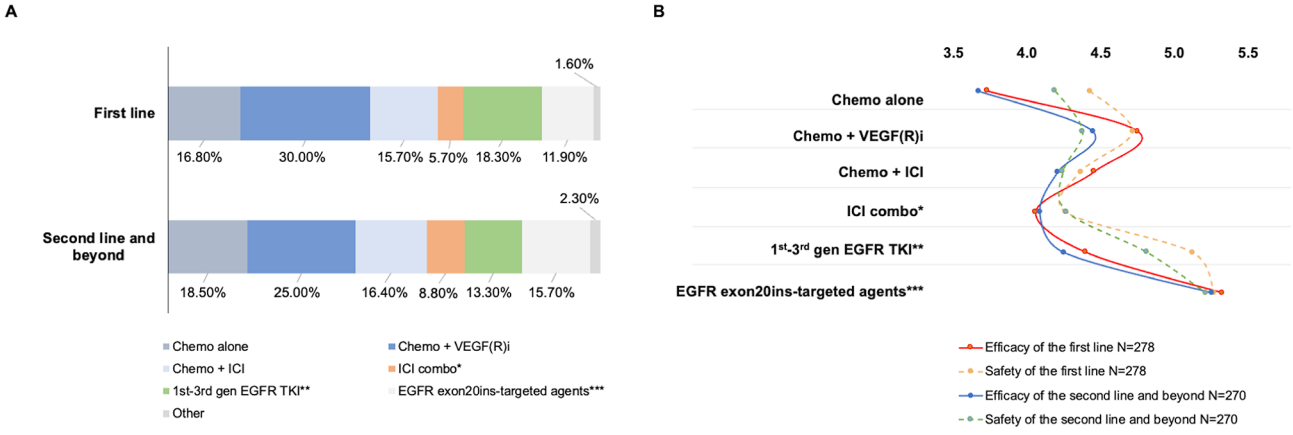

Fig. 3 **A**. Proportions of physicians using first-line and second-line therapy in EGFR exon20ins-mutant patients. **B**. Physicians' scaling scores for the efficacy and safety of each therapy. *Notes* On a scale of 1–7, a score of 1 indicates the lowest level of satisfaction, and a score of 7 indicates the highest level of satisfaction. * ICI-based combination therapies, including ICI + chemo + VEGF(R)i, ICI + VEGF(R)i, etc. **1st -3rd generation TKI alone or in combination. *** EGFR exon20ins-targeted agents include TKIs and bispecific antibodies. Chemo, chemotherapy; VEGF(R)i, vascular endothelial growth factor (receptor)-targeted inhibitor; ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; Gen, generation; TKI, tyrosine kinase inhibitor

Physicians' overall perspectives on treatment options

Physicians' views on existing treatment options

A total of 278 physicians answered additional questions on first-line treatment, with 74.8% (208/278) had prescribed novel targeted agents. 270 physicians answered questions on second-line treatments, with 76.7% ($n=207$) prescribed novel targeted agents.

To further understand the unmet need in the treatment of patients with the EGFR exon20ins mutation, this study assessed physicians' views on the overall efficacy and safety of existing treatment options. Regardless of the line of treatment, novel EGFR exon20ins-targeted agents (including TKIs and bispecific antibodies) received the highest score in terms of satisfaction (first-line: 5.3/7; second-line: 5.3/7), followed by the most commonly used

chemotherapy plus antiangiogenic therapy (first-line: 4.8/7; second-line: 4.4/7) (Fig. 3B).

Compared to physicians who had never prescribed novel targeted therapies, those physicians who had ever prescribed novel targeted therapies had higher satisfaction scores (first-line: 5.5/7 vs. 4.8/7; second-line: 5.4/7 vs. 4.6/7) (Figure S2A). Moreover, EGFR exon20ins-targeted TKI ranked the most promising therapy both in first line and second-line and beyond setting in the future regardless of the prescription history of physicians. (Figure S2B)

With respect to the safety profile, regardless of the treatment line, the three highest satisfaction scores were given to novel EGFR exon20ins-targeted agents (including TKIs and bispecific antibodies) (first-line: 5.3/7; second-line: 5.2/7), 1st -3rd generation EGFR TKIs as monotherapies or in combination (first-line: 5.1/7; second-line: 4.8/7), and chemotherapy plus antiangiogenic therapy (first-line: 4.7/7; second-line: 4.4/7) (Fig. 3B).

Physicians' views on targeted therapy for the treatment of patients with EGFR exon20ins-mutant NSCLC

Most physicians, regardless of their experience in prescribing novel targeted therapies, considered EGFR exon20ins-targeted TKIs the most promising treatment strategy for patients with EGFR exon20ins-mutant NSCLC (first-line: 223/278, 80.2%; second-line: 198/270, 73.3%) (Fig. 4A). When all of the given novel EGFR exon20ins-targeted agents were considered, sunvozertinib received the highest recognition for efficacy and safety (126/390, 33.2% and 126/390, 33.2%), followed by mobocertinib (110/390, 28.9%) and 109/390, 28.7%) (Fig. 4B).

The most important indicators for physicians

This study revealed that overall survival (OS) (297/390, 76.2%), progression-free survival (PFS) (225/390, 57.7%), and safety (214/390, 54.9%) were regarded by physicians as the most important clinical indicators for evaluating novel targeted agents. In comparison, the convenience of drug administration (64/390, 16.4%) and mechanism of action (72/390, 18.5%) were considered less important (Fig. 5).

Discussion

The present study included surveyed physicians from a diverse range of healthcare institutions. This study revealed that approximately 3.8% of all patients with advanced NSCLC harboured EGFR exon20ins mutation. In a prospective molecular epidemiology study of Asian patients with advanced NSCLC of adenocarcinoma histology, the incidence of the EGFR exon20ins mutation was 4.0% of the EGFR mutations in the Chinese subset [29, 30].

Our findings indicated that 80.9% and 59.9% of patients with advanced NSCLC receiving first-line and second-line treatment, respectively, underwent EGFR mutation testing. A portion of patients with NSCLC did not undergo the EGFR mutation test, primarily because they had already been diagnosed with squamous cell carcinoma or had undergone genetic testing prior to their visit. In terms of detection methods, physicians reported that 75% of patients in the first-line setting were performed NGS, which is similar to the data from a study performed in the United States [31]. There was no difference in the testing rate between cities, which indicates a high level of acceptance of the EGFR mutation test by Chinese physicians.

Nevertheless, a small portion of patients with NSCLC did not undergo the EGFR mutation test or only underwent PCR. Therefore, patient-related factors were the most important, followed by the long turnaround time of the NGS test, high requirements for the quality of tumour tissue samples, and the unavailability of in-house NGS tests. EGFR exon20ins exhibits high heterogeneity with greater than 100 subtypes. Although PCR offers advantages, such as high sensitivity and easy implementation,

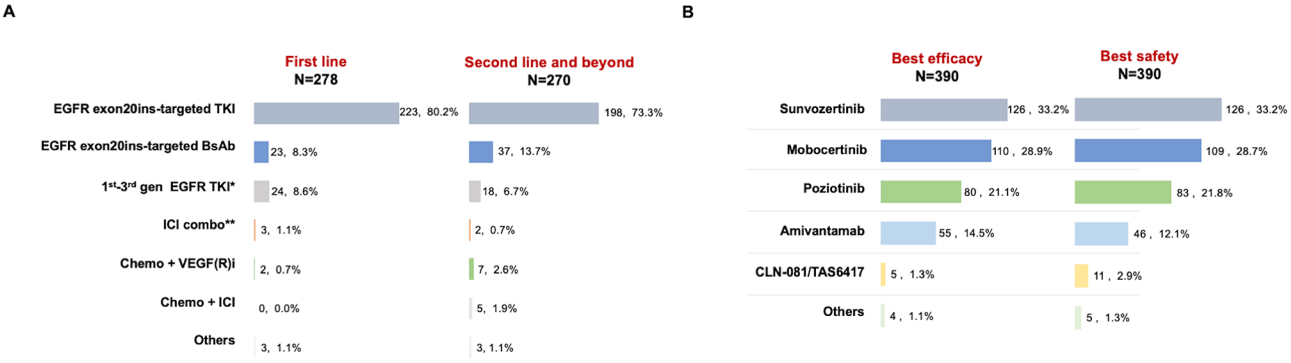

Fig. 4 Physicians' views on the most promising therapy for EGFR exon20ins-positive patients (**A**), and the novel targeted agents with the highest efficacy and best safety (**B**). *1st -3rd generation TKI alone or in combination. ** ICI-based combination therapies, including ICI + chemo + VEGF(R)i, ICI + VEGF(R)i, etc. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; BsAb, bispecific antibody; ICI, immune checkpoint inhibitor; Combo, combination; Chemo, chemotherapy; VEGF(R)i, vascular endothelial growth factor (receptor)-targeted inhibitor

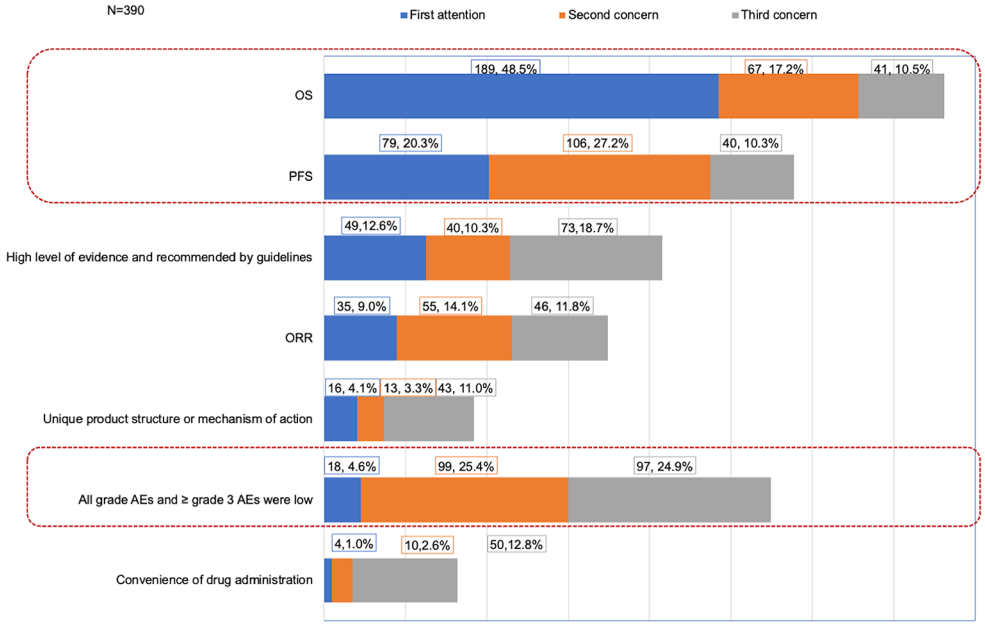

Fig. 5 The most important indicators for physicians in choosing novel targeted agents. OS, overall survival; PFS, progression-free survival; ORR, objective response rate; AEs, adverse events

it may miss the detection of certain EGFR exon20ins subtypes. Comparatively, NGS is capable of detecting a broader range of subtype mutations, which results in a higher detection rate for these patients. To further improve the detection rate of the EGFR exon20ins mutation, we recommend expanding patient education and improving accessibility to in-house NGS testing.

Platinum-based doublet chemotherapy and chemotherapy-based combination regimens are the standard of care for patients with EGFR exon20ins mutation. The present study suggests that the most common treatment choices are chemotherapy and chemotherapy-based combination regimens, including chemotherapy plus antiangiogenic therapy and chemotherapy plus ICIs. Although 1st -3rd -generation EGFR-TKIs as monotherapies or in combination are commonly used in clinical practice, this study revealed that most physicians considered the use of chemotherapy plus antiangiogenic therapy/ICI regimens. Several previous studies showed that, compared with traditional EGFR-TKIs, chemotherapy and chemotherapy-based combination regimens benefited NSCLC patients harbouring EGFR exon20ins mutations [21, 32]. However, the OS benefit from chemotherapy and chemotherapy-based combinations is limited. Although double-dosed 3rd -generation EGFR-TKIs are under evaluation in patients with EGFR exon20ins mutations, only a few of these studies exist, and their results remain controversial [33–35]. Patients with advanced NSCLC harbouring the EGFR exon20ins mutation represent an urgent unmet need for new treatment options. This study revealed that 34.1% of physicians have ever participated in clinical trials of novel agents targeting EGFR exon20ins mutations, which indicates the need for active exploration of new treatment strategies.

In terms of efficacy and safety, the satisfaction scores given by the participating physicians for novel targeted therapy were the highest, especially among the physicians who had prescribed EGFR exon20ins-targeted agents. A total of 88.5% (246/278) and 87.0% (235/270) of the physicians considered targeted therapies (including TKIs and bispecific antibodies) as the most promising treatment for patients in first-line and second-line settings, respectively, and the proportion was even greater among physicians who had not prescribed novel targeted agents, 95.7% and 98.4% in first-line and second-line settings, respectively, which reveals a stronger demand for novel EGFR exon20ins-targeted agents. Despite the absence of clinical data from pivotal studies supporting the use of new targeted agents in the first-line treatment of EGFR exon20ins-mutant NSCLC patients, more physicians believe that TKIs hold greater clinical potential in first-line treatment than in second-line treatment.

Several novel agents targeting the EGFR exon20ins mutation are currently under clinical development, and some of the results have been published [22–25, 36, 37]. Poziotinib is among the first agents to be investigated for the treatment of EGFR exon20ins-mutant NSCLC [15]. Although preclinical and early-stage studies suggest that poziotinib has favourable antitumour activity [36, 38], the limited efficacy and high incidence of adverse events [37] led to the discontinuation of the development of poziotinib. Amivantamab is a bispecific antibody that targets

EGFR/MET, and it was the first FDA-approved agent for the second-line treatment of EGFR exon20ins-positive patients [39]. The phase II CHRYSALIS study enrolled 114 patients with locally advanced or metastatic NSCLC that harboured EGFR exon20ins mutations [22]. These patients had previously received platinum-based chemotherapies and were treated with amivantamab in the study. The overall response rate (ORR), median PFS, and median OS were 36.8%, 6.9 months, and 22.8 months, respectively [22]. Mobocertinib was approved by the U.S. FDA on September 15, 2021 and by the China NMPA on January 1, 2023 for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon20ins mutations who had progressed on platinum-based chemotherapies. The latest data demonstrated that 114 patients were treated with mobocertinib at 160 mg QD after prior platinum-based chemotherapies, and the ORR was 28%, the disease control rate (DCR) was 78%, the duration of response was 15.8 months, the median PFS was 7.3 months, and the median OS was 20.2 months, as assessed by the Independent Review Committee. However, the incidence of Grade 3 or higher treatment-related adverse events was as high as 52% [40]. Moreover, due to the unachieved phase 3 clinical (EXCLAIM-2) study outcome, FDA revoked the indication for Mobocertinib on Oct 2 2023.

Sunvozertinib demonstrated encouraging antitumour activity in a pivotal phase II clinical study (WU-KONG6) [24]. In this study, 97 patients with locally advanced or metastatic NSCLC harbouring EGFR exon20ins mutations who had failed or were intolerant to platinum-based chemotherapies were enrolled and administered sunvozertinib at 300 mg QD. The ORR and DCR, as assessed by a blinded independent review committee, were 60.8% and 87.6%, respectively. Neither the median PFS nor the median OS has been reached, but these results are highly anticipated. Sunvozertinib has received Breakthrough Therapy Designations from the China NMPA and the U.S. FDA, and it has been approved by China NMPA on August 23, 2023.

This study also reveals the current understanding of EGFR exon20ins-mutant NSCLC. This understanding may be attributable to the limited portion of patients with the EGFR exon20ins mutation in the overall population of patients with NSCLC and the slow progress of earlier studies. It is necessary to increase physicians' awareness and update their knowledge to improve physicians' understanding of EGFR exon 20ins mutations.

This study has several limitations. First, the questionnaires were collected from September 2022 to March 2023, which reflects the diagnosis and treatment status at that period. With the development of novel targeted drug on exon20 insertion mutation, physicians' perspective may evolve consistently. Therefore, novel agents are awaited to provide best therapeutic strategy for such patients. Second, this study presented the results gathered via a questionnaire, a format that is subjective to a certain extent, and real-world data are required to further validate the analysis of the current status of diagnosis and treatment.

Conclusion

In clinical practice, chemotherapy and chemotherapy-based combination regimens are the primary treatment options for patients with the EGFR exon20ins mutation. However, these therapies often fail to achieve the satisfactory clinical outcome desired by physicians. In contrast, novel EGFR exon20ins-targeted agents that are currently under rapid development have been widely recognized and are regarded as the most promising treatment modality. Among agents undergoing clinical investigations, sunvozertinib has gained increasing interest and recognition because of its impressive clinical data. In addition, physicians' high awareness of genetic testing provides important data that will allow more EGFR exon20ins-positive patients to benefit from personalised and precision-targeted therapies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12797-3.

Supplementary Material 1

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Author contributions

Yan Xu and Mengzhao Wang conceived this study. All authors designed the questionnaire. Yuequan Shi led the statistical analysis and wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participants

The ethics committee of Peking Union Medical College Hospital approved all experimental protocols. Informed consent was obtained from all of the physicians who participated in this survey.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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