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Evolution of treatment strategies for solid tumors with RET rearrangement in China and real-world treatment status of Non-small Cell Lung Cancer (NSCLC)

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Abstract

Objective The present study endeavors to furnish an exhaustive review of the research advancements on solid tumors harboring RET rearrangement within the Chinese context, particularly emphasizing the examination of real-world therapeutic strategies and clinical outcomes observed in individuals diagnosed with advanced non-small cell lung cancer (NSCLC). The review delves into a critical assessment of the therapeutic efficacy of targeted RET inhibitors, while also scrutinizing the diverse array of treatment modalities employed in the Chinese patient population.

Methods The study conducted a comprehensive review of the advancements made by Chinese scholars in the realm of RET driver genes. It delved into the analysis of the incidence of RET rearrangements in solid tumors, alongside an examination of the varied treatment paradigms and their current status within China. Utilizing the RECIST 1.1 criteria, the study evaluated the therapeutic efficacy achieved in RET-positive NSCLC patients undergoing diverse treatment modalities. Furthermore, treatment-related adverse events (TRAEs) were meticulously graded following the Common Terminology Criteria for Adverse Events (CTCAE).

Results A retrospective, multi-center, real-world analysis was conducted, encompassing 64 patients diagnosed with pathologically confirmed RET rearrangement advanced non-small cell lung cancer (NSCLC) between December 2015 and November 2023. Notably, KIF5B-RET emerged as the most prevalent RET fusion partner, accounting for 59.4% of cases. Therapeutic interventions among these patients included specific targeted inhibitors such as Pralsetinib (48.4%), chemotherapy (34.3%), multi-target inhibitors (15.6%), and one case (1.6%) involving immunotherapy combined with anti-angiogenic therapy. In terms of progression-free survival (PFS), Pralsetinib monotherapy demonstrated a median PFS of 16.03 months, outperforming chemotherapy (2.87 months; $p < 0.0001$), chemotherapy combined with anti-angiogenic therapy (6.90 months; $p = 0.048$), and multi-target inhibitors (2.50 months; $p < 0.0001$). Furthermore, the one-year and two-year overall survival (OS) rates for Pralsetinib monotherapy were 64.3%

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and 46.4%, respectively. Regarding safety, 71.0% of patients receiving Pralsetinib experienced at least one adverse event, with 45.2% classified as grade 3–4 in severity. Notably, no fatalities were attributed to adverse events. Common adverse events included hemoglobin reduction (35.5%) and neutropenia (32.3%), indicative of an overall favorable safety profile for Pralsetinib in this patient population.

Conclusion This study encapsulates the research endeavors and treatment advancements of RET rearrangement solid tumors within the Chinese healthcare landscape, specifically highlighting the diverse real-world therapeutic approaches and their effectiveness in managing advanced RET rearrangement NSCLC among Chinese patients. Notably, targeted RET inhibitors like Pralsetinib have emerged as potent therapeutic agents, exhibiting remarkable efficacy and a manageable safety profile in this patient cohort. These findings underscore the potential of Pralsetinib and similar targeted therapies as novel treatment options for individuals with RET fusion-positive NSCLC.

Keywords RET Fusion, Non-small Cell Lung Cancer (NSCLC), Real-world treatment patterns, Pralsetinib

In 1985, a pivotal discovery was made by scholars, notably Takahashi M, who identified a novel gene in the context of transformed NIH/3T3 mouse cells. This gene, arising from the unique recombination of two non-contiguous DNA segments during the metastatic process, was subsequently designated as the RET proto-oncogene [1]. Subsequent in-depth research has unveiled that the RET proto-oncogene, prone to rearrangement or fusion events during transfection procedures, plays a pivotal role in the initiation and progression of a diverse array of malignancies. Specifically, its aberrant activation has been intricately linked to the pathogenesis and progression of multiple tumor types [2]. Mutations in the RET gene are varied, encompassing deletions, point mutations, amplifications, and rearrangements [3]. Specifically, RET gene rearrangement involves the reorganization or fusion of its nucleotide sequence with those of other genes under specific circumstances, leading to the formation of unique fusion transcripts and proteins. These collaborating genes, known as "partner genes," confer a dependence on RET kinase activation, which subsequently propels the proliferation and survival of tumor cells. This state of dependency is coined as "oncogene addiction," where the cancer cells become addicted to the continuous activation of RET for their growth and survival. Predominantly observed in papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), and non-small cell lung cancer (NSCLC), RET rearrangements have also been identified in a spectrum of malignancies, including colorectal, breast, and ovarian cancers, highlighting its broad oncogenic potential [4, 5].

Advancements in Chinese treatment strategies for solid tumors with RET rearrangement

Before the emergence of targeted RET inhibitors, the therapeutic landscape for Chinese tumor patients harboring RET fusion mutations was essentially congruent with that of patients devoid of identifiable driver genes. While Chinese researchers have achieved profound insights into the RET driver gene, their investigations have primarily concentrated on non-small cell lung cancer (NSCLC), underscoring the urgent need to broaden the scope of exploration to encompass other RET-driven malignancies.

In 2019, Chinese researchers intensified their scrutiny of the RET driver gene within the context of non-small cell lung cancer (NSCLC), conducting a Next-Generation Sequencing (NGS) analysis of 6,125 Chinese NSCLC patients. Their findings unveiled that 84 patients (1.4%) harbored RET rearrangements, predominantly affecting female patients with lung adenocarcinoma and no history of smoking. Among these RET rearrangements, the KIF5B-RET fusion emerged as the most prevalent type, accounting for 53.8% of cases. Furthermore, TP53 mutations were identified as the most common co-occurring genetic alterations, highlighting the complex mutational landscape and potential therapeutic implications for this patient subgroup [6]. Expanding upon the previous findings, subsequent pathological tissue analysis of 9,431 Chinese NSCLC patients revealed 167 cases (1.77%) of RET fusion, again predominantly occurring in non-smoking female patients with lung adenocarcinoma. Within this cohort, the most prevalent RET fusion patterns were KIF5B (68.3%), CCDC6 (16.8%), and NCOA4 (1.2%), reinforcing the notion of specific fusion partners associated with RET rearrangements in NSCLC. Notably, the concordance rate between Fluorescence In Situ Hybridization (FISH) and Next-Generation Sequencing (NGS) in detecting RET fusions was high, at 83.3% (25/30), whereas the agreement between Immunohistochemistry (IHC) and NGS was considerably lower, at only 28.1% (16/57), underscoring the importance of selecting appropriate diagnostic modalities to accurately identify RET-driven NSCLC [7]. Follow-up reports included a statistical analysis of 39 Chinese NSCLC patients with RET-Rearranged, finding KIF5B-RET as the most common fusion type (52%), with a PFS of 4.0 months (95%CI, 3.2 ~ 4.8) and median overall survival (OS) of 25 months

(95%CI, 1.5 ~ 48.5), showing no significant differences [8]. A review of real-world data from 75 patients with RET fusion showed that 73.3% (55/75) carried the KIF5B-RET driver gene. Among 15 patients treated with Pralsetinib or Selpercatinib, the objective response rate(ORR) was 53.3% (8/15), with progression-free survival(PFS) of 10.0 months (95% CI 5.2 ~ 14.9) [9]. Another multicenter Chinese study exploring the relationship between NSCLC with RET fusion and pemetrexed efficacy found that among 62 patients, 40 treated with first-line Chemotherapy based on pemetrexed had a mPFS of 9.2 months compared to 5.2 months with other regimens ($P=0.007$), and OS was 35.2 months and 22.6 months, respectively ($P=0.052$) [10]. This stage represents the initial understanding and therapeutic exploration of the driver gene RET in NSCLC patients by Chinese scholars, confirming the incidence and prognosis of this target, but with limited exploration beyond NSCLC.

In 2022, NGS technology was utilized to identify RET fusion patterns in Chinese cancer patients across various cancer types. A total of 44 fusion patterns were identified in the study cohort, with KIF5B, CCDC6, and ERC1 being the most common RET fusion partners [11]. The study also reported for the first time 17 novel fusions. The prevalence rates were 1.05% in lung cancer, 6.03% in thyroid cancer, 0.39% in colorectal cancer, and less than 0.1% in gastric and liver cancers. The analysis revealed preferences for fusion partners among different tumor types, with KIF5B being a common type in lung cancer, CCDC6 in thyroid cancer, and NCOA4 in colorectal cancer. Subsequent research further explored the relationship between somatic RET mutations and clinical and genetic characteristics in patients with metastatic colorectal cancer, finding a RET mutation rate of 2.7% [12]. The LIBRETTO-321 study [13], an open-label, multicenter Phase II clinical trial conducted across 15 research centers in China, investigated the anti-tumor activity of Selpercatinib in Chinese advanced solid tumors patients with RET fusion alterations. Cohort 1 ($n=30$) included patients with RET^+ NSCLC ($n=29$) and RET^+ thyroid cancer(TC)($n=1$). Cohort 2 ($n=26$) enrolled patients with RET^+ medullary thyroid carcinoma (MTC), with or without prior systemic treatment. Cohort 3 ($n=21$) included patients with advanced solid tumors with RET alterations, including three patients with RET^+ MTC. Among all RET^+ MTC ($n=29$), the ORR assessed by IRC was 58.6% (95%CI: 38.9-76.5%), with a clinical benefit rate of 65.5%, including three patients achieving CR, 14 PR, and 11 SD. A patient with RET^+TC in Cohort 1, who was treatment-naïve, received 23 weeks of treatment and achieved confirmed PR at week 8. In terms of safety, among the 77 patients treated with Selpercatinib, the median treatment duration was 40 weeks, with 40 patients (51.9%) experiencing Grade 3 AEs, the most common of which were hypertension (19.5%), aspartate aminotransferase elevation (15.6%), and alanine aminotransferase elevation (14.3%). The dosage was reduced in 32.5% of patients due to treatment-related adverse events, and four patients (5.2%) experienced TEAEs that led to the discontinuation of Selpercatinib. The previous LIBRETTO-001 study did not include Chinese patients [14], whereas this study provided strong evidence for drug application.

In the realm of case reports, Chinese scholars have, for the first time, documented a mutation involving the ERC1-RET fusion in pancreatic ductal adenocarcinoma (PDAC) [15]. This mutation is not only a novel finding within this type of tumor but is also exceedingly rare, and the treatment with Pralsetinib has achieved remarkably satisfactory outcomes [16]. In pulmonary sarcomatoid carcinoma (PSC), which is highly aggressive and associated with RET mutations, Pralsetinib has also demonstrated promising therapeutic efficacy [17]. Even in triple-negative breast cancer(TNBC), where patients have received multiple lines of treatment and carried the CCDC6-RET mutation, Pralsetinib has shown gratifying therapeutic responses [18]. Furthermore, a novel PIBF1-RET fusion has been identified in tissue samples post-surgery from stage IA lung adenocarcinoma, marking a discovery in this field [19].

With the availability of specific targeted drugs such as Pralsetinib and Selpercatinib, Chinese scholars have shifted their focus from purely retrospective studies to more prospective explorations of therapeutic approaches and drug efficacy research. A pivotal milestone was reached in 2022 when Chinese scholars reported the inaugural successful application of Pralsetinib in a neoadjuvant setting. This case involved a patient who manifested an optimal therapeutic response, achieving a partial response (PR) following one month of targeted intervention, which facilitated a subsequent successful surgical procedure. Adding to this momentum, Professor Cai-cun Zhou, Shanghai Chest Hospital of Shanghai Jiao Tong University, spearheads the LIBRETTO-432 study (NCT04819100) as the principal investigator. This Phase III clinical trial assesses Selpercatinib as an adjuvant therapy for early-stage RET fusion-positive NSCLC patients. It specifically reviews the efficacy of Selpercatinib following curative-intent treatments for patients with stages IB to IIIA of RET^+ NSCLC. Chinese research centers participated from the study's initiation, marking a significant contribution by administering the first global dose to an enrolled patient. The study's outcomes, published in 2023 in the <New England Journal of Medicine> [20], revealed that Selpercatinib significantly enhanced mPFS to a degree that surpassed that of platinum-based

Chemotherapy, both with and without pembrolizumab (24.8 months versus 11.2 months; HR = 0.46; 95%CI, 0.31 ~ 0.70; $p < 0.001$).

We acknowledge the significant contributions of Chinese researchers to the field of RET-driven malignancies. Their work has expanded the global understanding of the incidence, clinical characteristics, and treatment responses in patients with RET rearrangements. The findings from Chinese studies have enriched the international database and provided valuable insights into the management of RET$^+$ NSCLC within the unique context of the Chinese healthcare system. This comprehensive approach underscores the commitment of the Chinese research community to advancing the understanding and management of RET-positive tumors, ultimately aiming to improve patient outcomes.

The real-world treatment patterns for advanced RET+ NSCLC in China

Before the advent of specific RET inhibitors, the main treatment options for NSCLC patients with RET fusion mutations were largely consistent with those for NSCLC patients with driver gene-negative status, but the therapeutic efficacy was very limited [10, 21, 22]. With the emergence of multi-target drugs (MKIs) such as cabozantinib, vandetanib, and immune checkpoint inhibitors, some activity against RET kinase has been demonstrated. However, their clinical application was limited due to high adverse effects and short duration of therapeutic efficacy [23, 24]. As medical science has progressed, the development of specific drugs targeting rare genetic mutation sites has become increasingly common, mainly because they bring revolutionary breakthroughs, even disruptions, to existing treatment regimens. Although the incidence of RET gene fusion in NSCLC is only 1.4 ~ 2.5% [25], given the large number of NSCLC patients in China, the annual number of new patients with RET gene fusion is not insubstantial.

Specific RET-TKIs have demonstrated durable efficacy and manageable safety profiles in recent years in clinical trials, offering new hope for treating NSCLC patients with RET fusion-positive mutations. The specific RET inhibitors Selpercatinib [26] (LOXO-292) and Pralsetinib [27] (BLU-667) have shown broad and sustained anticancer activity in tumors with RET fusion-positive mutations based on the ARROW and LIBRETTO series of clinical studies, respectively. Both drugs were approved for marketing by the US FDA in 2020 and have been given a Level 1 recommendation (evidence level 1 A) by the National Comprehensive Cancer Network (NCCN) guidelines. Pralsetinib was first approved for marketing in China in March 2021, ahead of Selpercatinib, which was approved in September 2022. Despite the approval and initial treatment consensus for these targeted drugs for this target point, the clinical application in China spans a maximum of only three years, and the efficacy and safety of Chinese patients urgently require corroboration by real-world data. Therefore, this section aims to explore the diversified treatment patterns and therapeutic effects of real-world treatment for Chinese patients with advanced NSCLC driven by the RET gene.

Methods

Study design and patient selection

The described study is a retrospective, multi-center, real-world investigation that involved the compilation of data from patients meeting specific inclusion criteria. The study cohort comprised 64 individuals aged 18 years or older who were initially diagnosed with NSCLC and subsequently confirmed to have a RET$^+$ status between December 1, 2015, and November 30, 2023. Importantly, patients with histologically verified small cell lung cancer (SCLC) or those with incomplete information were excluded from the analysis, ensuring the accuracy and relevance of the collected data for the intended research objectives.

Baseline assessments

Before the commencement of treatment, all patients enrolled in the study underwent comprehensive baseline assessments to establish their medical status and document the extent of their disease. These evaluations encompassed a complete blood count to assess hematological parameters, biochemical profiles to monitor organ function, and measurements of tumor marker levels to track disease activity. Additionally, imaging studies including chest computed tomography (CT), abdominal CT, and brain magnetic resonance imaging (MRI) were performed to precisely determine the size and location of measurable lesions, providing a baseline for subsequent disease monitoring. Throughout treatment, any clinical symptoms suggestive of disease progression or metastasis were promptly evaluated using additional imaging modalities such as brain MRI, chest and abdominal CT, or Emission Computed Tomography (ECT), ensuring timely detection of any changes in disease status.

Efficacy and safety evaluation

The study's efficacy evaluation adhered to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a widely accepted standard for assessing tumor response to treatment in clinical trials. For patients with target lesions, the best overall response was recorded, encompassing complete response (CR), partial response (PR), and stable disease (SD). Notably, the duration of the imaging response had to exceed six weeks to be

considered valid, ensuring the reliability of the observed responses. Key survival outcomes, including progression-free survival (PFS), overall survival (OS), and time to treatment failure (TTF), were defined and calculated as previously described, providing valuable insights into the long-term efficacy of the treatment. Furthermore, the disease control rate (DCR) and objective response rate (ORR) were determined, offering additional metrics to assess the treatment's impact on disease status. All patients were closely monitored until August 20, 2024, or until their demise, ensuring a comprehensive follow-up period for the analysis.

Adverse events assessment

The study's safety assessment protocol meticulously tracked adverse events (AEs) experienced by patients, both at baseline and during each subsequent visit or clinical evaluation. The attending physician carefully evaluated the relationship of each AE to the treatment, ensuring accurate attribution. Of particular interest were treatment-related adverse events (TRAEs), which, if severe enough, could necessitate dose adjustments, treatment interruptions, or even complete discontinuation of therapy. These TRAEs were meticulously documented and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, a standardized system that facilitates the reporting, assessment, and comparison of AEs across different studies and treatments. This rigorous approach to safety monitoring and reporting provided valuable insights into the tolerability of the treatment and informed decisions regarding patient management.

Statistical analysis

Data were statistically analyzed using SPSS 26.0 software. Categorical data were presented as numbers and percentages, while continuous data were expressed as medians with ranges or means with standard deviations. The reverse Kaplan-Meier method was used to calculate the median follow-up time, and the Kaplan-Meier method was employed to estimate the median values for OS, PFS, and TTF. A p-value of less than 0.05 was considered to indicate statistical significance.

Data privacy and confidentiality

All patient data were managed in compliance with data protection regulations, ensuring the privacy and confidentiality of participants. Personal identifiers were removed from the dataset to maintain anonymity. The final dataset was securely stored and accessible only to authorized studies. Ethical approval for this retrospective study was granted by the institutional review boards (IRBs) of all participating centers, with the understanding that the study poses minimal risk to patients and involves the analysis of existing data. Given the study's retrospective nature and the use of de-identified data, the IRBs provided a waiver for the requirement of written informed consent (Ethical Approval Number: [S2023-121-01]).

Results

Patient demographics and baseline characteristics

This study included 64 patients with RET^{+} advanced NSCLC (Table 1). The age range was from 34 to 81, with a median age of 57. Female patients accounted for 53.1%. Regarding ECOG-PS scores, 70.3% of patients scored 0 or 1, indicating that most were in relatively good general

Table 1 Patient demographics and baseline characteristics

Variables	Total ($n=64$)	no-RETi ($n=33$)	RETi ($n=31$)	*P*
Female, n(%)	35 (54.69)	17 (51.52)	18 (58.06)	0.599
Age, y, Median[RG]	57(34–81)	54(39–81)	59(34–76)	0.220
< 65y, n(%)	40 (62.50)	23 (69.70)	17 (54.84)	
≥ 65y, n(%)	24 (37.50)	10 (30.30)	14 (45.16)	
Smoking, n(%)				0.510
Never	45 (70.31)	22 (66.67)	23 (74.19)	
Former/Current	19 (29.69)	11 (33.33)	8 (25.81)	
ECOG PS, n(%)				0.228
≤1, n(%)	45 (70.31)	21 (63.64)	24 (77.42)	
≥2, n(%)	19 (29.69)	12 (36.36)	7 (22.58)	
Adenocarcinoma, n(%)	60 (93.75)	31 (93.94)	29 (93.55)	1.000
RET fusion partner, n(%)				0.067
no-KIF5B	13 (24.53)	4 (14.29)	9 (36.00)	
KIF5B	40 (75.47)	24 (85.71)	16 (64.00)	
TP53, n(%)	14 (45.16)	7 (77.78)	7 (31.82)	**0.044**
Stage, n(%)				0.698
IIIC	3 (4.69)	1 (3.03)	2 (6.45)	
IVA	23 (35.94)	11 (33.33)	12 (38.71)	
IVB	38 (59.38)	21 (63.64)	17 (54.84)	
Pleural effusion metastasis, n(%)	41 (64.06)	25 (75.76)	16 (51.61)	**0.044**
Hepatic metastases, n(%)	11 (17.19)	5 (15.15)	6 (19.35)	0.656
Bone metastasis, n(%)	30 (46.88)	13 (39.39)	17 (54.84)	0.216
CNS metastasis, n(%)	19 (29.69)	9 (27.27)	10 (32.26)	0.663
Basic lung disease, n(%)	27 (42.19)	14 (42.42)	13 (41.94)	0.968
Hypertension, n(%)	17 (26.56)	7 (21.21)	10 (32.26)	0.317
Diabetes, n(%)	9 (14.06)	7 (21.21)	2 (6.45)	0.181
Cerebrovascular disease, n(%)	7 (10.94)	3 (9.09)	4 (12.90)	0.930
Radiotherapy, n(%)	18 (28.12)	12 (36.36)	6 (19.35)	0.130
Thoracic radiotherapy, n(%)	10 (15.62)	8 (24.24)	2 (6.45)	0.106
Surgery, n(%)	13 (20.31)	5 (15.15)	8 (25.81)	0.290

health. 70.3% of the patients had no smoking history, 95.3% were diagnosed with adenocarcinoma, and 59.4% of the patients were at stage IVB. Additionally, 64.1% of the patients had pleural or pericardial effusions, with liver, brain, and bone metastases occurring in 17.2%, 29.7%, and 48.4% of the cases, respectively. The distribution of RET fusion partners showed that KIF5B-RET was the most common fusion type (59.4%) (Figs. 1 and 2). Other types of RET fusions included CCDC6-RET, NCOA4-RET, KIF13A-RET, etc. Notably, three patients had two RET fusion partners, including SIRT1-RET/KIF5B-RET, KIF5B-RET/TRIML1-RET, and MIR4299-RET/MIR8070-RET, and the RET fusion partners were unknown in 13 patients.

Treatment landscape and efficacy

This retrospective study encompassed a variety of treatment modalities, analyzing the impact of different historical therapeutic regimens on the PFS and OS of patients with RET fusion-positive advanced NSCLC. The treatment modalities included (Table 2; Fig. 2): ①The monotherapy uses Pralsetinib only, a specific RET inhibitor: 28 cases, accounting for 43.8%; ② Pralsetinib combined with anti-angiogenic therapy, bevacizumab: 3 cases, 4.7%; ③ Chemotherapy: 11 cases, 17.2%; ④Chemotherapy combined with bevacizumab: 8 cases, 12.5%; ⑤Chemotherapy combined with immunotherapy and anti-angiogenic therapy: 3 cases, 4.7%; ⑥ Immunotherapy combined with anti-angiogenic therapy: 1 case, 1.6%; ⑦ Multi-targeted kinase inhibitor therapy (MKIs): 10 cases, 15.6%, including Cabozantinib 6 cases, Alectinib 2 cases, Vandetanib 1 case, Sunitinib 1 case.

Among the 28 patients treated with Pralsetinib monotherapy, 15 (53.6%) achieved PR, and 13 (46.4%) had SD. In the three patients treated with Pralsetinib combined with bevacizumab, 2 cases (66.7%) achieved PR, and 1 (33.3%) had SD. Among the 11 patients treated with Chemotherapy, 4 cases (36.4%) achieved PR, 3 cases (27.3%) had SD, and 4 cases (36.4%) had PD. In the eight patients treated with Chemotherapy combined with bevacizumab, 2 cases (25.0%) achieved PR, and 6 cases (75.0%) had SD. Among the ten patients treated with MKIs, 6 cases (60.0%) had PD (Table 3; Fig. 3). The mPFS for Pralsetinib monotherapy was 16.03 months, which was superior to 2.87 months for Chemotherapy ($p < 0.0001$), and the mPFS for Chemotherapy combined with bevacizumab was 6.90 months ($p = 0.048$), and mPFS for MKIs was 2.50 months ($p < 0.0001$). Furthermore, the mTTF for Pralsetinib monotherapy was 12.93 (95%CI, 6.745 ~ 19.115) months. The survival analysis showed that the one-year OS rate for Pralsetinib monotherapy was 64.3%, and the two-year OS rate was 46.4% (Fig. 4).

Exploration of prognostic biomarkers

In addition to RET fusions, we also observed mutations in accompanying genes such as TP53, MDM2, RELN, RICTOR, CTNNB1, FGFR3, and CDK4, with the TP53 gene being the most common accompanying mutation (21.9%)

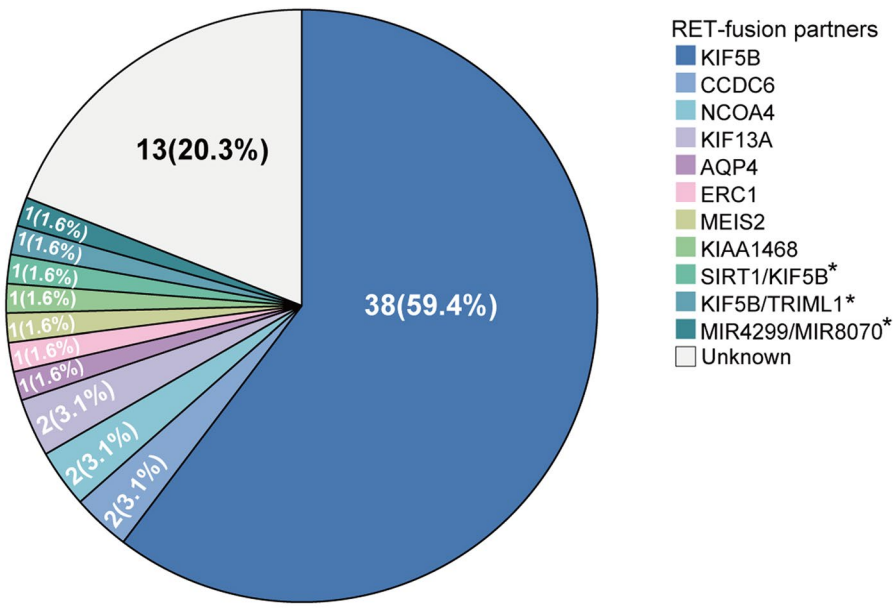

Fig. 1 RET-fusion partners

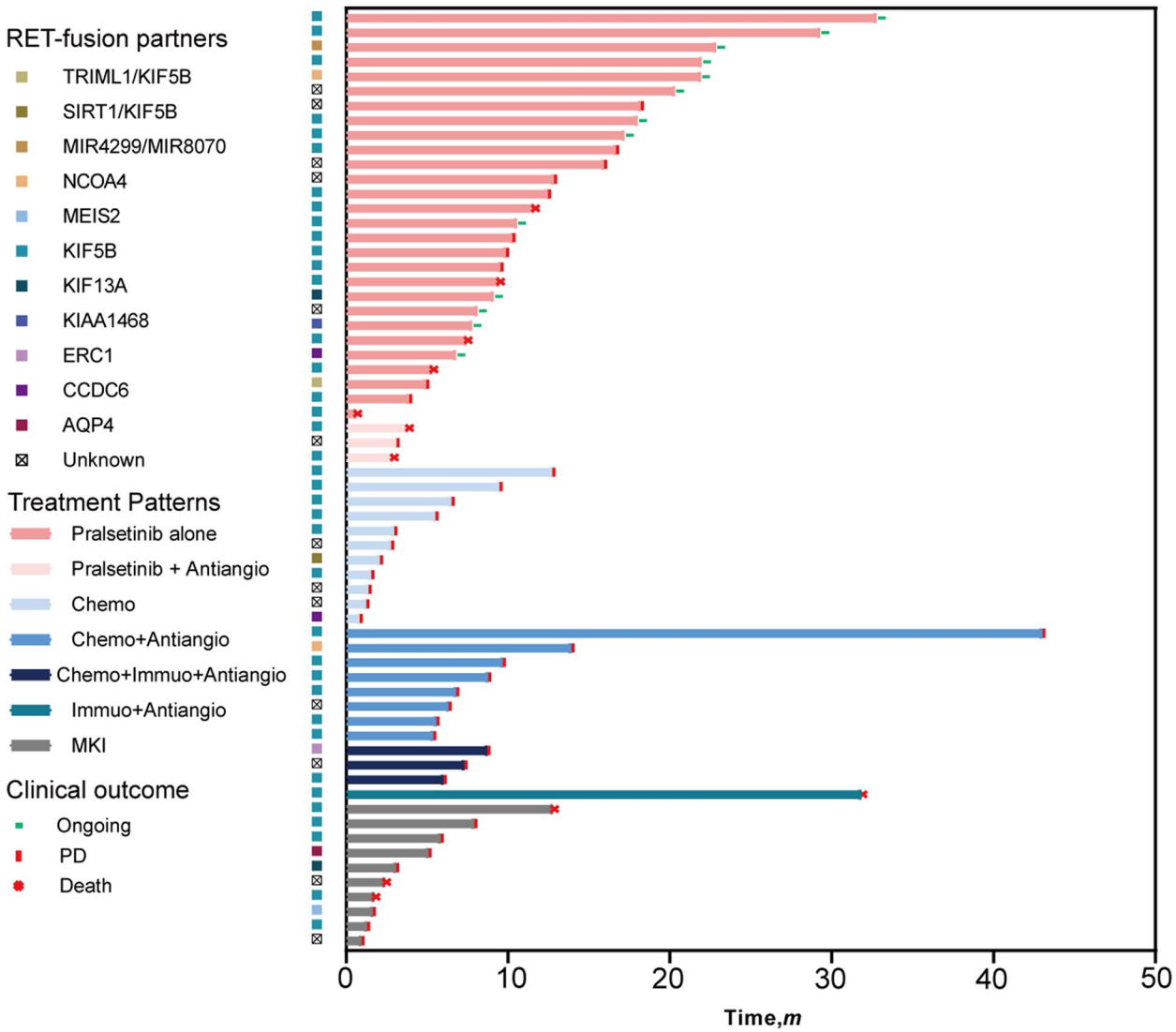

Fig. 2 A swimming plot of PFS in 64 patients

(Fig. 5). A high lymphocyte-to-monocyte ratio (LMR) was significantly correlated with longer PFS ($p=0.017$), and in further multivariate Cox regression analysis, the HR for LMR was 3.740 (95%CI, 1.167 ~ 11.987). The systemic immune-inflammation index (SII) and the ratio of lactate dehydrogenase to albumin (LAR) also showed trends related to PFS. However, both the Kaplan-Meier curve and Cox regression analysis of TP53 did not achieve statistical significance (Table 4).

Safety

Among the 31 patients who received Pralsetinib-based treatment, 71.0% experienced at least one AE, with 45.2% of these being Grade 3–4 AEs. There were no deaths among the patients due to adverse events. Common adverse events included a decrease in hemoglobin (35.5%), a reduction in neutrophil count (32.3%), an increase in aspartate aminotransferase (AST) levels (25.8%), and a decrease in lymphocyte count (25.8%). Hypertension (22.6%) and an increase in alanine aminotransferase (ALT) levels (22.6%) were also frequently observed adverse events. (Table 5)

Among them, our attention was drawn to the Pralsetinib Monotherapy Group, where 4 cases (14.3%) of grade 3 to 4 pneumonia were observed out of a total of 28 patients. We further conducted a comprehensive analysis of the pneumonia incidence among all treatment groups. Chemotherapy Group: Out of 11 patients, 1 case (9.1%) of grade 2 pneumonia was reported. MKIsGroup: Out of 10 patients, 2 cases (20%) of pneumonia were noted, with

Table 2 Treatment landscape

Therapy, *n* (%)	
Pralsetinib alone	28(43.8%)
Pralsetinib + Antiangio	3
Pralsetinib + Bevacizumab	2
Pralsetinib + Anlotinib	1
Chemo	11(17.2%)
Carboplatin + Pemetrexed	4
Cisplatin + Pemetrexed	2
Nedaplatin + Pemetrexed	1
Pemetrexed	1
Nedaplatin + Docetaxel	1
Lobaplatin + Docetaxel	1
Gemcitabine + Carboplatin	1
Chemo + Antiangio	8(12.5%)
Cisplatin + Pemetrexed + Bevacizumab	5
Carboplatin + Pemetrexed + Bevacizumab	3
Immuo + Antiangio	1(1.6%)
Penpulimab + Anlotinib	1
Chemo + Immuno + Antiangio	3(4.7%)
Carboplatin + Pemetrexed + Bevacizumab + Pembrolizumab	2
Cisplatin + Abraxane + Bevacizumab + Sintilimab	1
MKI	10(15.6%)
Cabozantinib	6
Alectinib	2
Vandetanib	1
Sufatinib	1
Patients treated with lung surgeries, n (%)	13(20.3%)
Patients treated with radiotherapy, n (%)	10(15.6%)

1 being grade 3. Combined Therapies Group: Out of 14 patients receiving combination therapies (including Pralsetinib with anti-angiogenic therapy, chemotherapy with bevacizumab, and immunotherapy with anti-angiogenic therapy), 3 cases (21.4%) of pneumonia were observed, with 1 case being grade 3. It is important to note that the incidence of pneumonia in the Pralsetinib group appears to be higher compared to other treatment groups. However, the numbers are small, and the differences in incidence across groups are not statistically significant due to the limited sample size.

Discussion

The Pralsetinib real-world study (RWS) presented here represents, to the best of our knowledge, the first reported cohort to date. It has been discovered that the abnormal activation of the RET gene is closely associated with the occurrence and development of various types of cancer [2, 28]. The recurrent rearrangement of the RET gene with its fusion partner genes (KIF5B-RET, CCDC6-RET, NCOA4-RET) is primarily observed in non-squamous NSCLC, where patients are typically younger, female, and non-smokers [29], consistent with the characteristics of the population in this study. Although most of our patients had adenocarcinoma, 6.25% had other histologic types. In our cohort, 19 (29.69%) of the patients had central nervous system metastases at diagnosis of advanced disease, coherent with published data.

Regarding treatment, before the advent of specific RET inhibitors, the therapeutic options for RET^{+}

Table 3 Best overall response

	Pralsetinib (***n*** **= 28**)	**Pralsetinib + Antiangio** (***n*** **= 3**)	**Chemo** (***n*** **= 11**)	**Chemo + Antiangio** (***n*** **= 8**)	**Chemo + Immuno + Antiangio** (***n*** **= 3**)	**Immuo + Antiangio** (***n*** **= 1**)	**MKIs** (***n*** **= 10**)
Best response, n (%)							
CR	0	0	0	0	0	0	0
PR	15	2	4	2	0	1	0
SD	13	0	3	6	3	0	4
PD	0	1	4	0	0	0	6
ORR, %	53.6%	66.7%	36.4%	25.0%	0	1(1/1)	0
DCR, %	100.0%	66.7%	63.6%	100.0%	3(3/3)	1(1/1)	40.0%
PFS							
Events, n (%)	15	3	11	8	3	1	10
Median, months (95% CI)	16.03	3.20	2.87	6.90	7.40	NA	2.50
	(9.861–22.199)	(2.827–3.573)	(0.793–4.424)	(3.528–10.272)	(5.32-10.272)		(0.434–4.566)
One-year survival rate, %	18 (64.3%)	0	1 (9.1%)	2 (25%)	0	1 (1/1)	1 (10%)
Two-year survival rate, %	13 (46.4%)	0	0	1 (12.5%)	0	1 (1/1)	0

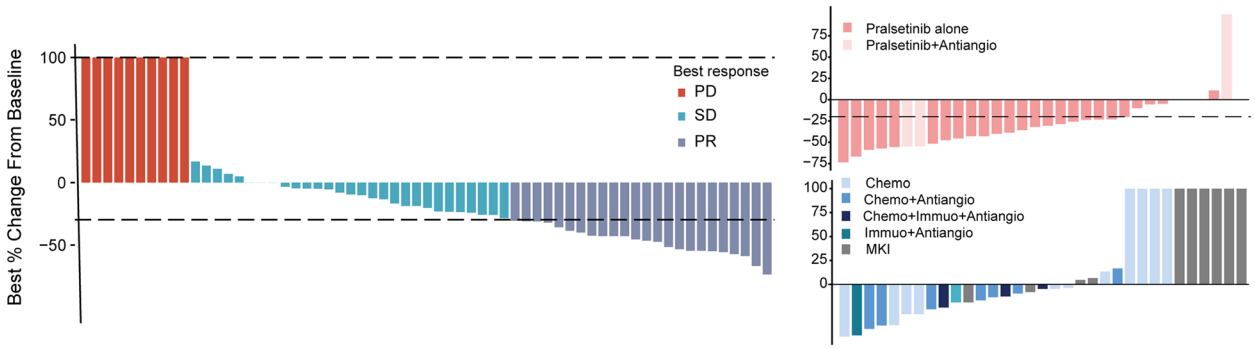

Fig. 3 Cancer response waterfall

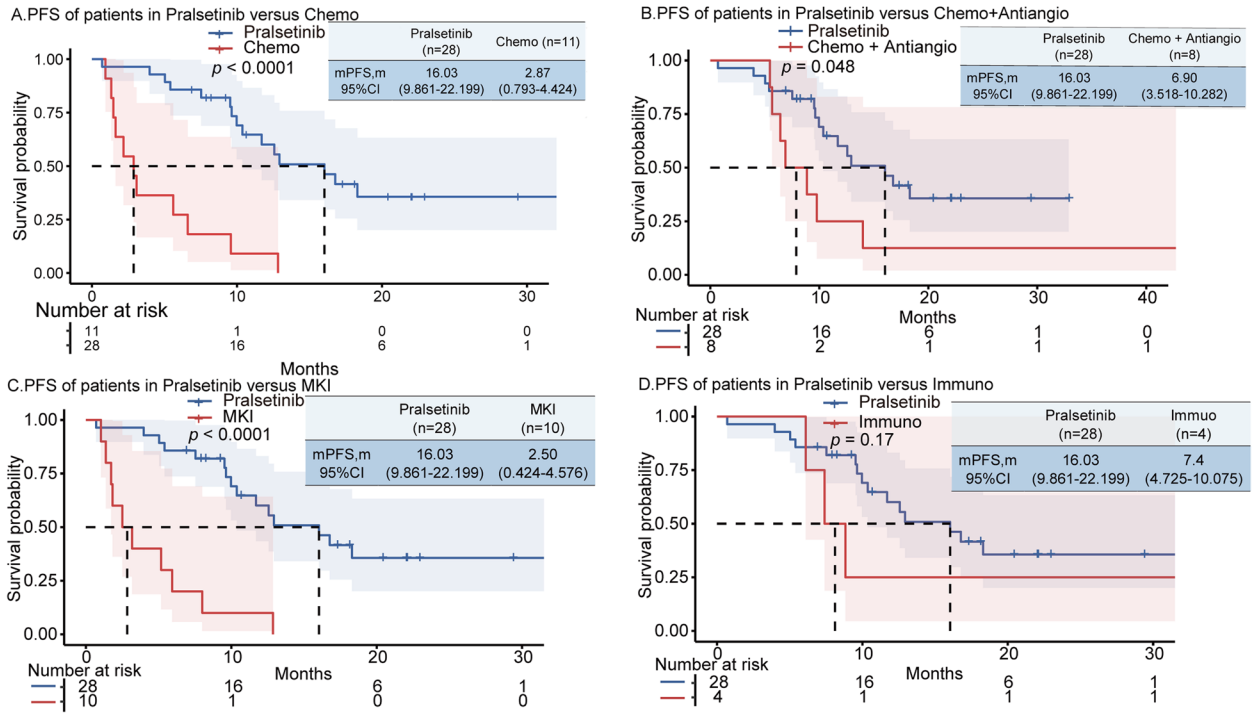

Fig. 4 Kaplan-Meier plot of PFS

NSCLC patients were quite limited and lacked specificity. The main first-line treatment plan was Chemotherapy with platinum in combination with pemetrexed, which was almost identical to the treatment for NSCLC patients with driver gene-negative status. In this study, the median PFS ranged from 2.87 to 6.90 months with Chemotherapy, with or without anti-angiogenic therapy. A multi-center retrospective study in China showed that the first-line PFS for RET^{+} NSCLC patients treated with chemotherapy-based comprehensive therapy was between 5.2 and 9.2 months [10]. Over the past decade, the treatment for RET^{+} NSCLC patients has evolved from Chemotherapy alone to MKIs and selective RET-TKIs. However, MTKIs did not ideally serve the role of efficient, low-toxicity precision-targeted therapy. In this study, the mPFS was 2.50 months. A Phase II clinical study of cabozantinib showed that TRAEs occurred in 96.2% of patients (25 out of 26), and 73% required dose reduction [23]. In 2017, Gautschi O and others summarized the efficacy of multi-kinase inhibitors such as Cabozantinib, Alectinib, Vandetanib, Sunitinib, Sorafenib, and Lenvatinib, with mPFS was only 2.3 months and mOS was 6.8 months [24].

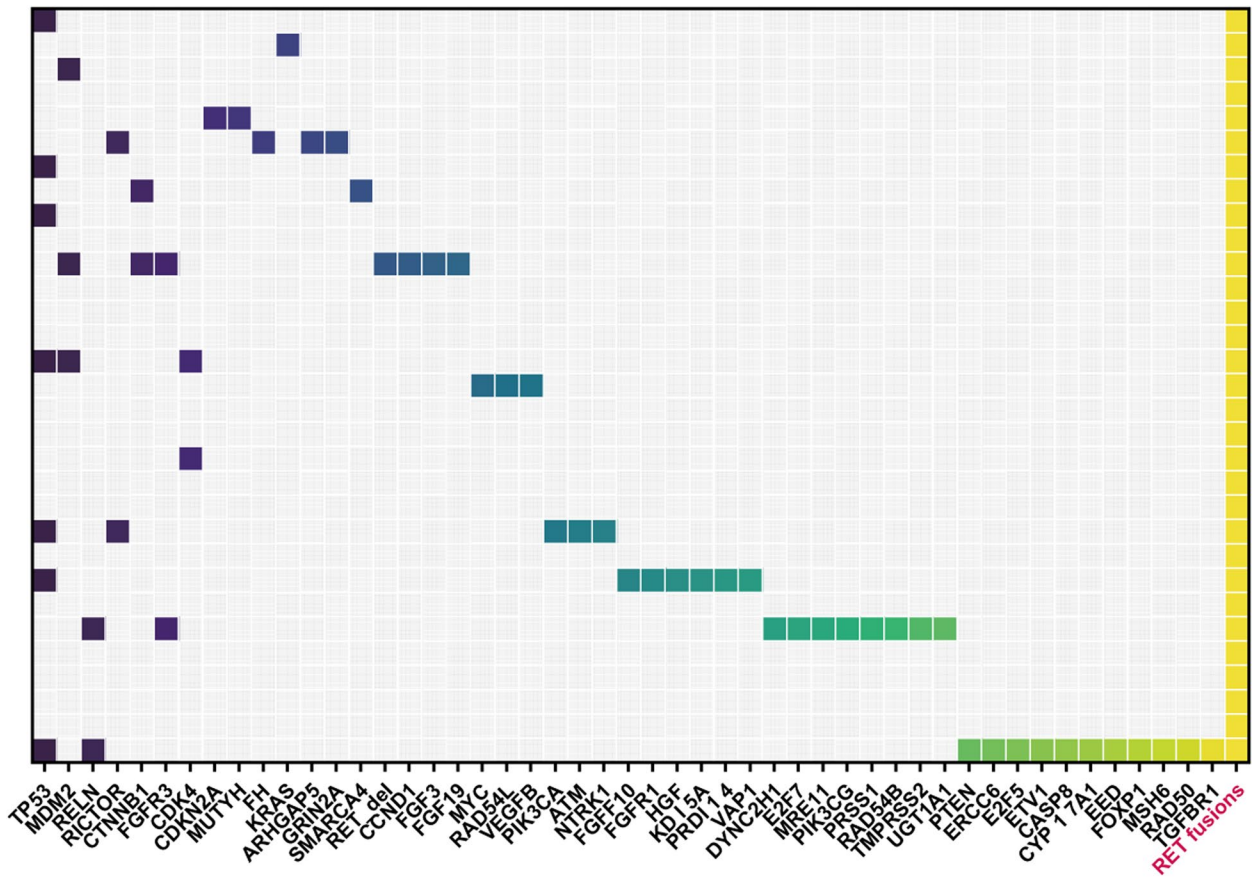

Fig. 5 Genomic alterations of patients with RET-positive NSCLC at the time they were diagnosed

Table 4 Kaplan-Meier curve and Cox regression analysis of biomarkers

	K-M *p*-value	Univariate *p*-value, HR (95%CI)	Multivariate *p*-value, HR (95%CI)
NLR (≻2.1214)	0.146	0.156, 2.156 (0.747–6.222)	
dNLR (≻2.0234)	0.169	0.177, 1.991 (0.732–5.414)	
PLR (≻314.1468)	0.463	0.467, 1.602 (0.449–5.711)	
LMR (≻6.0795)	**0.017**	**0.026**, 3.740 (1.167–11.987)	**0.045**, 3.393 (1.030-11.182)
NPS (score≻1)	0.133	0.203, 1.725 (0.746–3.989)	
NAR (≻0.0843)	0.101	0.113, 2.513 (0.805–7.844)	
SII (≻369.7022)	**0.036**	0.069, 6.596 (0.865–50.293)	
LAR (≻4.9606)	0.18	0.189, 2.037 (0.705–5.884)	
TP53(Yes/No)	0.294	0.303, 1.965 (0.544-7.100)	
Histologic type(Non-/Adenocarcinoma)	**0.012**	**0.029**, 6.290 (1.207–32.786)	**0.025**, 8.640(1.307–57.119)
RET-fusion partners(Non-/KIF5B)	0.867	0.868, 1.111 (0.322–3.831)	
Histological differentiation(G1-2/G3)	0.679	0.681, 0.714 (0.143–3.560)	

As drug development and therapeutic strategies have been progressively refined, the highly selective RET inhibitor Pralsetinib was approved by the FDA in September 2020 and received conditional approval from the China National Medical Products Administration (NMPA) in March 2021. The approval of Pralsetinib was

Table 5 Summary of TEAEs for Pralsetinib-based therapy ($n=31$)

Patients with ≥ 1 event, *n* (%)	***N*=31**		
	Any adverse event, $N=22$(71.0%)	Grade 3–4 Aes, $N=14$(45.2%)	Death, $N=0$
Hemoglobin decreased	11(35.5%)	1	0
Neutrophil count decreased	10(32.3%)	1	0
AST increased	8(25.8%)	1	0
Lymphocyte count decreased	8(25.8%)	1	0
Hypertension	7(22.6%)	1	0
ALT increased	7(22.6%)	1	0
Musculoskeletal pain	4(12.9%)	0	0
Infectious pneumonia	4(12.9%)	4	0
Creatine phosphokinase increased	4(12.9%)	2	0
Platelet counts decreased	3(9.7%)	1	0
Fatigue	3(9.7%)	0	0
Interstitial pneumonia	3(9.7%)	1	0
Edema	3(9.7%)	0	0
Oral mucositis	2(6.5%)	0	0

based on the results of the ARROW (NCT03037385) clinical study, a pivotal multi-center, multi-cohort, open-label research [30], which enrolled patients with advanced RET^+ NSCLC who had disease progression after platinum-based Chemotherapy. The results showed ORR was 61% (95%CI, 50 ~ 71) for previously treated patients and ORR was 70% (95%CI, 50 ~ 86) for untreated patients (not eligible for platinum chemotherapy), with mPFS were 17.1 months (95%CI, 8.3 ~ 22.1) and 9.1 months (95%CI, 6.1 ~ 13), respectively. The intracranial ORR was 53.3% (95%CI, 26.6 ~ 78.7). In the latest clinical study results, which included untreated patients eligible for platinum chemotherapy [31], the ORR for previously treated patients in this cohort was 66.7% (95%CI, 48.2 ~ 82.0), and the ORR for untreated patients (meeting the conditions for platinum chemotherapy) was 83.3% (95%CI, 65.3 ~ 94.4), with mPFS of 11.7 months (95%CI, 8.7 ~ inestimable) and 12.7 months (95%CI, 8.9 ~ inestimable), respectively.

Since its market launch, two international real-world studies have also demonstrated the good efficacy of selective RET inhibitors. In the largest real-world study involving multiple international centers [32], 218 patients with RET^+ NSCLC of various stages from 31 cancer centers were included, including those who participated in clinical trials. Of these, 131 patients received Pralsetinib or Selpercatinib as first- or second-line treatment, with a treatment ORR of 76% (99 out of 133 cases), mPFS was 16.2 months (95%CI, 11.9 ~ 26.1), and mOS was 50.6 months (95%CI, 37.7 ~ 72.1). Another Italian multi-center real-world study [33] showed that among 61 cases [48 previously treated patients and 13 untreated patients (not eligible for platinum chemotherapy)], the ORR was 66% (95%CI, 53 ~ 81), the DCR was 79%, and mPFS was 8.9 months (95%CI, 4.7 ~ inestimable).

Similar to the studies above, this study also observed the benefits of Pralsetinib in RET^+ NSCLC patients. We conducted an efficacy evaluation of Pralsetinib monotherapy in 28 patients. The results showed that the ORR of this treatment approach reached 53.6%, indicating that more than half of the patients achieved partial or complete tumor responses. Although no patients achieved CR, 15 patients (53.6%) achieved PR, and another 13 (46.4%) achieved SD, resulting in a DCR of 100%. This means all patients treated with Pralsetinib monotherapy had their disease controlled or responded to. Nearly one-third of the patients included in this study had an ECOG PS score of ≥ 2, and 45.16% were aged 65 or older, exhibiting poorer tolerance due to their poorer baseline conditions and older age. In addition, more than half of the patients (17, 54.84%) had already reached TNM stage IVB at the time of Pralsetinib application, indicating a heavier tumor burden.

In this study, for the patient population receiving pralsetinib treatment, some cases discontinued medication due to treatment-related factors. Therefore, we specifically considered the TTF as an indicator that not only encompasses disease progression but also includes drug discontinuation due to treatment toxicity. As a measure reflecting drug tolerability and persistence, TTF may be more representative of the actual situations faced by patients in real-world studies. In our study, the mTTF for pralsetinib monotherapy was 12.93 months. The administration of pralsetinib-based therapy resulted in adverse reactions, leading to the suspension or adjustment of drug dosage in 6 cases (23.1%). Among these cases, three

patients discontinued pralsetinib-based therapy due to adverse events or personal preference.

Additionally, in the patients treated with the Pralsetinib group, we observed four cases of grade 3 to 4 pneumonia. Although the incidence of this pneumonia is low, it still requires high vigilance. Based on the ARROW study [30], 17% of patients developed pneumonia, with 8% being grade 3 or higher events, including bacterial pneumonia, fungal pneumonia, viral pneumonia, and atypical pneumonia. In this study, two cases showed cytomegalovirus, Pneumocystis jirovecii, Aspergillus fumigatus, and human herpesvirus infection by NGS one to two months after Pralsetinib administration, which improved after active anti-infective treatment. There have been previous reports of opportunistic infections related to Pralsetinib. This indicates that opportunistic infections may be a specific adverse reaction of Pralsetinib, and early detection along with timely application of anti-infective drugs is key to treatment. The mechanism by which Pralsetinib causes pneumonia is currently unclear and may be related to the downstream pathways of the RET gene. Abnormal fusion of the RET gene can activate downstream signaling pathways such as RAS/ERK/MAPK, PI3K/AKT/mTOR, JAK/STAT, etc. Pralsetinib selectively inhibits RET kinase activity, thereby inhibiting the phosphorylation of RET and its downstream molecules in a dose-dependent manner [25]. Studies have shown that the phosphoinositol-3 kinase (PI3K) signaling pathway is a key route for regulating immune responses, and inhibiting the PI3K pathway can reduce the number and function of regulatory T cells and suppress the inflammatory response of NK cells and neutrophils [34]. Similarly, the JAK/STAT signaling pathway is involved in differentiating CD4+T cells and the maturation of CD8+T cells [35]. JAK1/JAK2 kinase inhibitors reduce the Th1 response and cause downregulation of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α), affecting the adaptive immune system [36]. They can also inhibit the activation and maturation of NK cells, leading to immunosuppression and an increased risk of infection [37]. There have been case reports of opportunistic infections such as progressive multifocal leukoencephalopathy caused by JC virus reactivation, toxoplasma retinochoroiditis, fungal infections, Pneumocystis pneumonia, mycobacterial infections (including tuberculosis), and reactivation of hepatitis B virus, etc [38]. Therefore, Pralsetinib may affect cellular immunity by inhibiting the downstream pathways of RET, suppressing immune function, and increasing the risk of infection, which is incredibly opportunistic.

TP53 mutations are known to be associated with poor prognosis in various cancers due to the loss of TP53's tumor suppressor function. In the context of RET^+NSCLC, the presence of TP53 mutations may indicate a more aggressive disease phenotype, with potential implications for disease progression and survival outcomes. In our study, TP53 was the most common co-occurring mutation in patients with RET^+NSCLC; however, both the Kaplan-Meier curve and Cox regression analysis of TP53 did not achieve statistical significance. Reviewing previous studies, co-occurring mutations were identified in approximately 41–73% of RET fusion NSCLC cases. The most prevalent co-occurring mutation was TP53 [6, 39], with an occurrence rate ranging from 37.7 to 42.5%. Co-occurrence with driver genes such as EGFR, KRAS, HER2, BRAF, ALK, and ROS1 mutations was less frequent. Chang Lu et al. [39] demonstrated that patients harboring TP53 mutations exhibited significantly shorter overall survival compared to those without TP53 mutations, with median OS of 18.4 months and 24.8 months, respectively. J. Feng et al. [40] observed similar trends in ORR (67% for TP53 mutation vs. 88% for TP53 wild type, $p=0.11$), PFS (aHR 2.83, CI 1.52–5.27; $p=0.001$), and OS (aHR 5.00, CI 2.42–10.33; $p<0.001$) among fusion mutations in ALK, ROS1, RET, and NRG1 genes. This suggests that co-mutations of TP53 with various rare driver genes indicate poor efficacy of targeted therapy for NSCLC and shorter OS and PFS durations. However, in our study, TP53(21.9%) was identified as the most common co-occurring mutation alongside RET rearrangements. This genetic profile is particularly intriguing due to the potential synergistic effects of these mutations on tumor behavior and response to therapy. The survival analysis of TP53 did not reach statistical significance due to several reasons. Firstly, the PCR analysis revealed RET fusion mutations in nine out of 31 pralsetinib cases; however, limitations in the detection method made it inconclusive whether TP53 mutations were present. Secondly, our study's small sample size and retrospective nature hindered achieving statistical significance based on TP53 mutations. Nonetheless, we acknowledge that certain fusion partners may exhibit differential responses to therapies. Therefore, future studies with larger cohorts are imperative for a more comprehensive exploration of this phenomenon.

In our study, Pralsetinib has shown promising efficacy and safety in treating RET^+NSCLC. However, several limitations should be acknowledged. The retrospective design may introduce biases due to variations in treatment practices, follow-up, and data documentation across centers. The small sample size may limit our ability to detect significant differences in treatment outcomes and could affect the generalizability of our results. Additionally, the limited number of patients with specific RET

fusion partners constrains our ability to draw definitive conclusions about treatment efficacy within these subgroups. The study's focus on Chinese patients may also limit the applicability of our findings to other populations with different genetic profiles, as the prevalence of RET rearrangements and response to targeted therapies may vary. Lastly, while we adjusted for known confounders, there may be residual confounding factors that were not accounted for in our analysis. To mitigate these limitations, future studies should aim to include larger and more diverse patient populations, with longer follow-up periods to assess long-term treatment effects. International multicenter collaborations could help validate our findings and explore the impact of different healthcare systems and treatment patterns on patient outcomes. Despite these limitations, our study provides valuable real-world data on the treatment of RET^+ NSCLC in China and contributes to the growing body of evidence on the management of this disease.

Moreover, following the approval of Selpercatinib in China, this will significantly transform the treatment landscape for Chinese patients with RET^+ NSCLC. The inclusion of Selpercatinib offers a novel therapeutic option within the regimen of RET inhibitors, potentially reshaping the current treatment paradigm. However, there remains limited real-world data on Selpercatinib in China. Hence, we emphasize the imperative need for continuous collection and analysis of data to assess its efficacy and safety among Chinese patients. This endeavor will aid physicians in formulating more personalized treatment plans while uncovering new patterns of therapeutic response or adverse reactions. Nonetheless, due to factors such as the timeline of Selpercatinib's approval, data availability, and accumulation of real-world evidence, our study solely encompasses treatment outcomes related to Pralsetinib. As the first approved RET inhibitor in China, Pralsetinib has provided valuable preliminary insights into the potential effectiveness of RET inhibitors against RET^+ NSCLC. Nevertheless, we acknowledge that future research must encompass data on Selpercatinib as well as other emerging treatment options to gain a comprehensive understanding of the treatment landscape involving RET inhibitors among Chinese patients. We eagerly anticipate these additional datasets complementing our existing findings and offering further guidance for clinical practice.

Conclusions

This study analyzes the real-world treatment patterns of Chinese patients with RET^+ solid tumors. A retrospective exploration of the treatment patterns for first-line advanced RET^+ NSCLC patients in China ranged from Chemotherapy alone to combinations with Chemotherapy and from MTKIs to specific TKI drugs. This demonstrates the diverse approaches Chinese physicians have explored in treating this target. Pralsetinib has shown well clinical efficacy and sustained response in the first-line treatment of advanced Chinese RET^+ NSCLC patients, along with a relatively controllable safety profile. These findings provide new scientific evidence for the personalized treatment of RET^+ advanced NSCLC patients and signify an important step for China in transitioning from a follower to a leader in global oncology treatment research. In the future, we look forward to further validating the efficacy and safety of these target-specific drugs through larger-sample and multi-center studies, offering patients more precise and effective treatment strategies.

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Clinical trial number
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Authors' contributions
Conceptualization and design: WANG A, LI T, and MAO YY; data collection and analysis: WANG A, SHENG S, XIA CH, and LIU M; manuscript drafting: LI T, WANG A, and DONG Y; critical revision of the article for important intellectual content: WANG JL and MA JX; study supervision: HU Y. All authors have approved the final version of the article.

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Data availability
All data supporting this study's findings are included in this manuscript and its supplementary information files.

Declarations

Ethics approval and consent to participate
Ethical approval for this retrospective study was granted by the institutional review boards (IRBs) of all participating Medical Centers of PLA General Hospital, with the understanding that the study poses minimal risk to patients and involves the analysis of existing data. Given the study's retrospective nature and the use of de-identified data, the IRBs of PLA General Hospital provided a waiver for the requirement of written informed consent (Ethical Approval Number: [S2023-121-01]).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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