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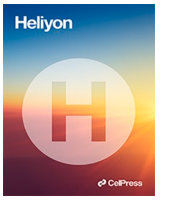

Research article

Real-world outcomes of chemoimmunotherapy and selective RET inhibitors in Chinese patients with RET fusion-positive non-small cell lung cancer

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ABSTRACT

Background: Rearranged during transfection (*RET*) gene fusion is a target for non-small cell lung cancer (NSCLC) treatment, and RET inhibitors are approved for advanced NSCLC. The role of immune checkpoint inhibitors (ICIs) in *RET* fusion-positive NSCLC remains controversial. This retrospective study analyzed the efficacy of ICIs and RET inhibitors in Chinese patients with *RET* fusion-positive NSCLC.

Methods: Data from patients diagnosed with advanced NSCLC harboring *RET* fusion from Jan 2017 to Sep 2021 were analyzed. Clinicopathological characteristics and outcomes of ICIs and RET inhibitors treatments were collected.

Results: Seventy-five patients with *RET* fusion-positive advanced NSCLC were identified. The median age of patients was 57 years, half of the patients were female (50.3%), and most were non-smokers or light smokers (72%). Of the cancer types diagnosed in study patients, the *KIF5B-RET* fusion subtype accounted for 73.3% (55/75), twelve patients (16%) had *CCDC6-RET* fusion, and three (4%) had *NCOA4-RET* fusion. Sixteen patients were treated with ICIs. In previously untreated patients, we observed an objective response rate (ORR) of 71.4% and median progression free survival (PFS) of 7.5 months in seven assessable patients. Of four patients with PD-L1 overexpression (>50%) one received pembrolizumab and the other three patients received pemetrexed, carboplatin, and pembrolizumab or camrelizumab. In these patients, the ORR was 75% and disease control rate was 100%. Fifteen patients received selective RET inhibitors (pralsetinib and selpercatinib), resulting in an ORR of 53.3% (8/15) and median PFS of 10.0 months (95% CI 5.2–14.9).

Conclusions: ICIs for PD-L overexpression and treatment naive patients offer comparable benefits for *RET* fusion-positive NSCLC, warranting further investigation.

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1. Introduction

Targeted therapy for driver mutation-positive metastatic non-small cell lung cancer (NSCLC) has dramatically improved overall survival. Approximately 1%–2% of patients with NSCLC are diagnosed with rearranged during transfection (*RET*) gene fusion especially younger patients, non-smokers, and patients diagnosed with adenocarcinoma [1,2]. Multiple fusion partners have been identified, the most common *RET* fusion partners include *KIF5B, CCDC6*, and *NCOA4* [3,4].

RET fusion is defined as a unique subtype of NSCLC that may benefit from precision medicine. Multi-kinase inhibitors (MKIs) such as cabozantinib and vandetanib showed modest clinical activity but are associated with off-target toxicity [5,6]. The limitations of MKIs prompted the development of more selective target therapy for *RET* fusion. Selpercatinib and pralsetinib are highly selective RET inhibitors. In early phase studies involving *RET* fusion-positive NSCLC, both agents demonstrated robust efficacy and favorable tolerability [7,8]. Selpercatinib and pralsetinib were later approved for patients with *RET* fusion-positive advanced NSCLC.

Immune checkpoint inhibitors (ICIs) have become the standard of care for patients with advanced NSCLC without driver mutations [9–11]. The use of ICIs in *RET* fusion-positive advanced NSCLC remains controversial. The IMMUNOTARGET study reported a poor response of *RET* fusion-positive NSCLC to ICIs, with a 6.3% overall response rate (ORR) and a median of 2.1 months progression-free survival (PFS) [12]. However, data from real-world databases in the US showed good efficacy in patients with *RET* fusion-positive NSCLC who received ICI-based therapy, with a 53.8% ORR and 4.2 months median PFS [13].

Owing to the limited and conflicting reports on the efficacy of ICIs in *RET* fusion-positive NSCLC, the use of ICIs is still uncertain. However, the low prevalence of this subtype (approximately 1%–2% in NSCLC) means data pertaining to ICI therapy in this cancer type is scarce. In this study, we collected and analyzed the clinicopathological data of Chinese patients with *RET* fusion-positive NSCLC and examined the clinical efficacy of their treatment with RET inhibitors.

2. Materials and methods

2.1. Patients

In this retrospective study, patients diagnosed with *RET* fusion-positive lung cancer in our center between Jan 2017 and Sep 2021 were identified. Clinical, pathological, and molecular data were extract from electronic health records. Patients receiving RET inhibitors or ICIs were included in the efficacy analysis. Clinical response was evaluated according to the Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1. Progression -free survival was measured from initiation of the therapy to disease progression or

Table 1
Patients baseline characteristics.

Characteristic	N (%)
Age, median (years)	57 (51, 65)
Age (years)	
≤65	56 (74.7%)
>65	19 (25.3%)
Sex	
male	37 (49.3%)
female	38 (50.7%)
Smoking status	
never or light smoking	54 (72%)
heavy smoking	21 (28%)
ECOG	
0	36 (48%)
1	39 (52%)
Histological subtype	
adenocarcinoma	71 (94.6%)
non-adenocarcinoma	4 (5.4%)
Brain metastasis	
no	58 (77.3%)
yes	17 (22.7%)
Liver metastasis	
no	67 (89.3%)
yes	8 (10.3%)
Pleural metastasis	
no	48 (64%)
yes	27 (36%)
Immune checkpoint inhibitors (ICIs)	
Pembrolizumab	1 (1.3%)
chemotherapy and ICIs	15 (20%)
RET inhibitors	
Pralsetinib	11 (14.7%)
Selpercatinib	4 (5.3%)
Cabozantinib	6 (8%)

death. Patients who continued therapy were censored at the last follow-up. All data were updated as of 3 Dec 2021. The study was approved by the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences. Written informed consent was obtained from every patient.

2.2. Detection of RET fusion partners

RET fusion was identified using DNA based targeted next generation sequencing (NGS). A 56-gene panel sequencing was performed with genomic DNA as previously reported [14]. For some uncommon *RET* fusion variants, targeted RNA NGS was performed as previously reported [15].

2.3. PD-L1 immunohistochemistry

Tumor tissue sections were stained with the 22C3 pharmDx kit (Agilent, Santa Clara, CA, USA) using the Dako Autostainer Link 48 platform (Agilent). Expression of PD-L1 was evaluated by tumor proportion score (TPS) which was defined as the percentage of tumor cells with partial or complete membrane staining.

2.4. Statistical analysis

Descriptive statistics were used to summarize patient characteristics. RECIST 1.1 guidelines were used to evaluate treatment efficacy. Patients who were alive without disease progression were censored at the initiation of a new therapy or the last follow-up. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was

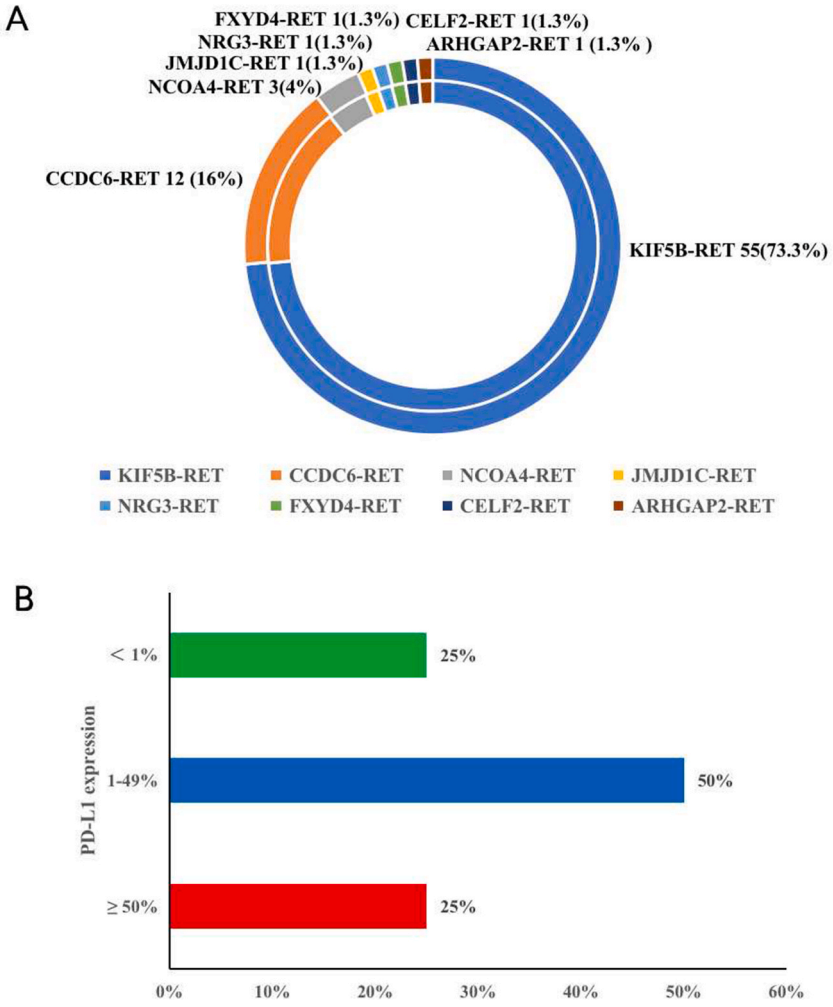

Fig. 1. Genotype and PD-L1 expression in *RET* fusion NSCLC. A: *RET* upstream fusion partners. B: PD-L1 expression in *RET* fusion NSCLC. Abbreviations: PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; NSCLC: non-small cell lung cancer.

set at $p < 0.05$. All analyses were performed using the IBM SPSS® Statistics version 23.

3. Results

3.1. Patient characteristics

From Jan 2017 to Sep 2021, data from seventy-five patients with *RET* fusion-positive advanced lung cancer were retrospectively analyzed. Patient baseline characteristics are summarized in Table 1. The median age of patients was 57 years (range 51–65), half of the patients were female (50.7%), and most patients were non-smokers or light smokers (72%). Most patients were also diagnosed with adenocarcinoma (94.6%), whereas two patients were diagnosed with adenosquamous carcinomas, one with large cell neuroendocrine carcinoma and the other with sarcomatoid carcinoma. Seventeen patients (22.7%) had brain metastases and twenty-seven patients (36%) had accompanying pleural metastasis.

3.2. Genomic alterations and PD-L1 expression

Targeted DNA-based NGS was used to identify *RET* fusion subtypes. The *KIF5B-RET* subtype was identified for 73% (55/75) of patients, twelve patients (16%) had *CCDC6-RET* fusion and three patients (4%) had *NCOA4-RET* fusion. We identified several rare *RET* fusion partners, including *JMJD1C-RET*, *NRG3-RET*, *FXYD4-RET*, *CELF2-RET*, and *ARHGAP12*-RET (Fig. 1A). The most common concurrent mutations were *TP53* (17, 22.7%) and *PTEN* (3, 4%) (Fig. 2A). Two patients with *EGFR*-sensitive mutations acquired *RET* fusion after EGFR-TKI resistance. The PD-L1 expression assay was performed in twenty patients, of these five patients exhibited PD-L1 overexpression (≥50%), ten patients exhibited intermediate (1–49%) expression and five patients were PD-L1 negative (<1%) (Fig. 1B).

3.3. Clinical outcomes of RET inhibitor treatment

Twenty-one patients received either cabozantinib or selective RET inhibitors. Pralsetinib, the only approved selective RET inhibitor in China, was administered to eleven patients (14.7%) and ten patients (90.9%) received pralsetinib as second or later line therapy. The ORR was 54.5% and disease control rate (DCR) was 90.9% (Fig. 3A). Median PFS was not available on the date of data cutoff (3 Dec 2021). Four patients received another selective RET inhibitor, selpercatinib, in clinical trials, with an ORR of 50% and DCR of 100%. The PFS was 13.0, 10.0 and 11.7 months (Fig. 3C). Cabozantinib, the most common MKIs for *RET* fusion, was administered to six patients after failure of standard therapy. Only one patient had a partial response, ORR and DCR were 16.7% and 83.3%, respectively, median PFS was 3.1 months. Selective RET inhibitors displayed superior efficacy compared to cabozantinib for *RET* fusion-positive NSCLC (Fig. 3B).

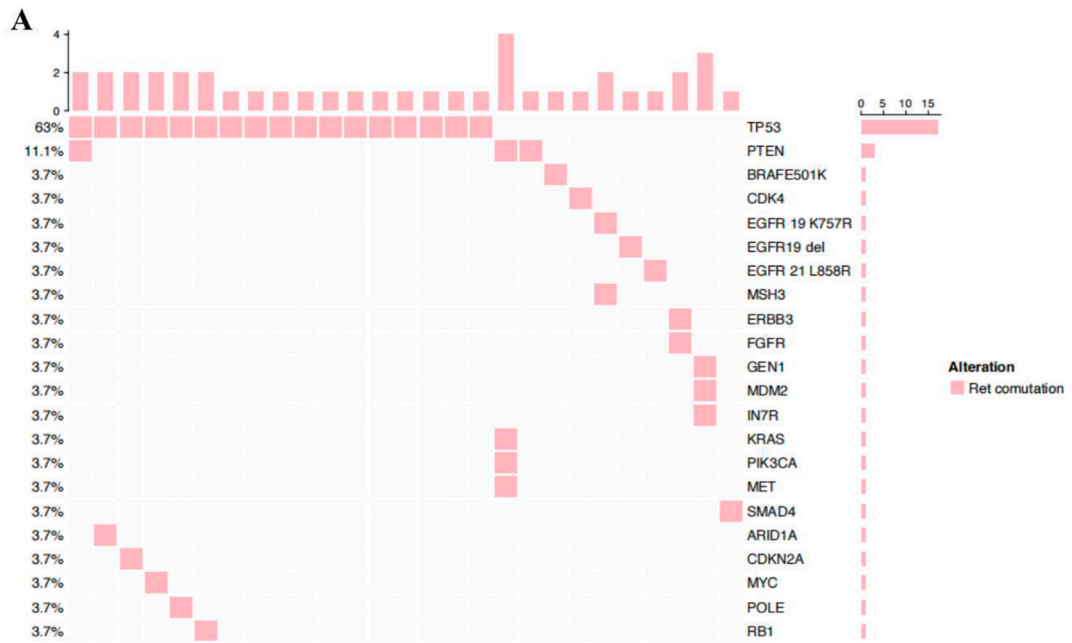

Fig. 2. Co-mutations in *RET* fusion NSCLC. Abbreviations: RET: rearranged during transfection; NSCLC: non-small cell lung cancer.

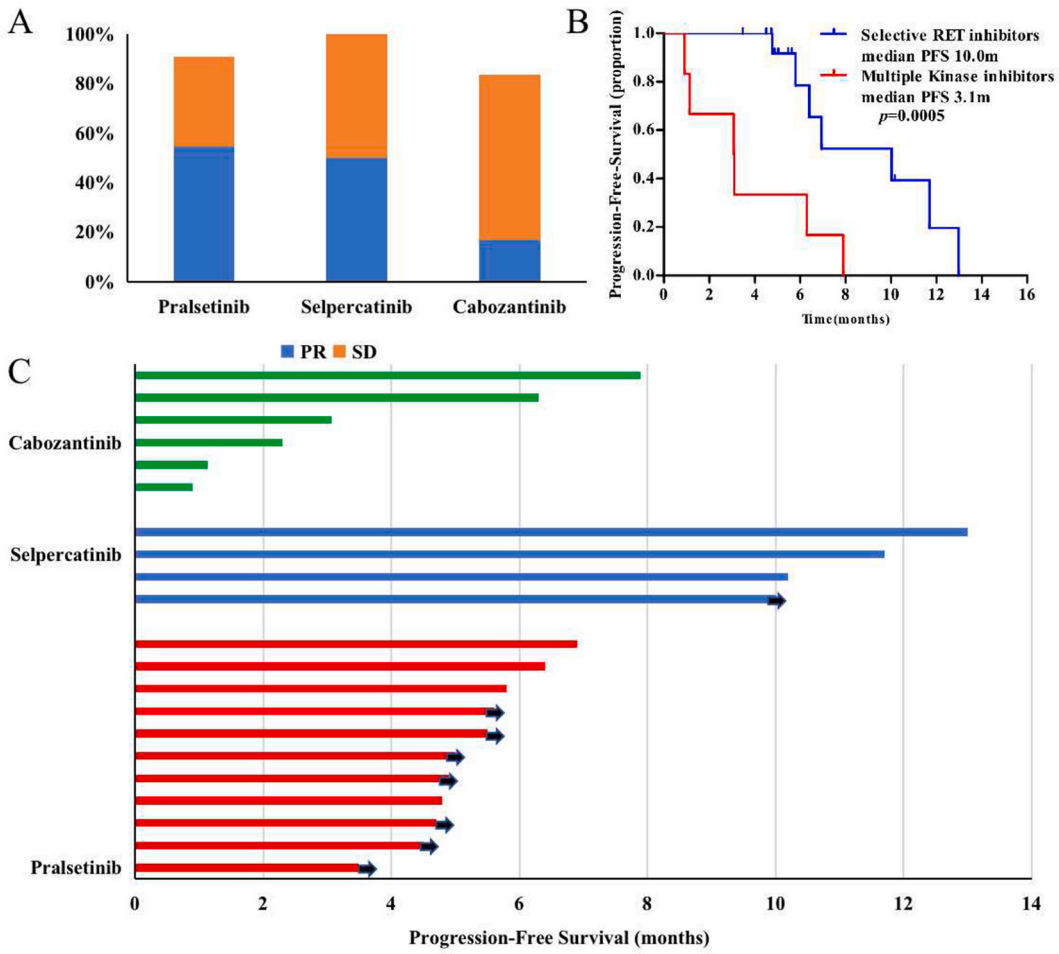

Fig. 3. Clinical efficacy of patients with advanced NSCLC received RET inhibitors. A: Clinical response types. B: Progression free survival by RET inhibitors. C: Swimmer plot of PFS across cabozantinib, selpercatinib and pralsetinib cohorts. Abbreviations: RET: rearranged during transfection; PFS - progression-free survival, PR - partial response, SD - stable disease.

3.4. Clinical outcomes of ICI treatment

Fifteen patients received chemoimmunotherapy, one patient received mono-immunotherapy. Four patients were treated with RET inhibitors after failure of immunotherapy. Patient characteristics and ICI responses are shown in Table 2. Seven patients received ICIs as the first-line therapy, including one pembrolizumab monotherapy and six chemoimmunotherapy. In previously untreated patients undergoing ICI treatment, we observed an ORR of 71.4% and a DCR of 100%. One patient (P 1) had objective response to mono-immunotherapy and one patient (P 4) had durable remission after first-line chemo-immunotherapy with PFS over 12 months. After failure of first line chemotherapy, the ORR to ICIs was lower, only one of nine (11%) patients achieved partial response (Table 3). Median PFS was 7.5 months (95% CI 4.5–10.5) and 4.7 (months (95% CI 1.1–8.3) for first- and subsequent-line treatments, respectively. Four patients had PD-L1 overexpression (>50%), one received pembrolizumab monotherapy, and the other three patients received pemetrexed, carboplatin, and pembrolizumab or camrelizumab. The ORR was 75% and the DCR was 100%.

Patient with KIF5B-RET fusion and PD-L1 overexpression sequentially responds to pembrolizumab and selpercatinib

A 63-year-old woman presented with cough and multiple lung masses. Bronchoscopic biopsy revealed lung adenocarcinoma. Tests for common driver mutations such as *EGFR, KRAS, ALK, ROS1*, *MET*, and *BRAF* were negative. Tumor tissues showed high levels of PD-L1 expression (TPS 90%). She was administrated pembrolizumab monotherapy as first line therapy and achieved a confirmed partial response. Five months later, clinical evaluation showed disease progression with an enlarged lung mass. A repeat biopsy of the lung mass showed poorly differentiated adenocarcinoma and PD-L1 overexpression (TPS 70%). We performed NGS with a 1021-gene panel and detected *KIF5B-RET* fusion. Owing to the unavailability of selective RET inhibitors in China between 2018 and 2020, she received five lines of therapy, including chemoimmunotherapy and anlotinib. She was subsequently treated with the MKI cabozantinib as the seventh-line treatment, which was discontinued a month after initiation because of disease progression in the liver. She took part in the selpercatinib study in China, and imaging indicated a partial response. Thirteen months after selpercatinib treatment, computed tomography showed pleural effusion and enlarged liver lesions. Pleural cytology revealed the presence of adenocarcinoma cells.

Table 2
Patient characteristics and immune checkpoint inhibitors response.

Case	Age/ Sex	Histology	Stage	PD-L1	RET **Fusion**	Immunotherapy	Treatment Lines	Before or after RET-TKI	Response	PFS (months)
P1	63/F	Ade	IV	90%	KIF5B-RET	Pembrolizumab	1	Before	PR	5.6
P2	66/M	Ade	IV	NA*	JMJD1C-RET	Pemetrexed + Camrelizumab	3	–	SD	7.9
P3	55/M	Ade	IV	20%	KIF5B-RET	Pemetrexed + Carboplatin + Bevacizumab + Pembrolizumab	2	–	SD	7.2
P4	54/F	Ade	IV	NA*	KIF5B-RET	Pemetrexed + Carboplatin + Camrelizumab	1	–	PR	12.6
P5	48/M	Ade	IV	5%	KIF5B-RET	Pemetrexed + Carboplatin + Pembrolizumab	3	Before	SD	6.6
P6	43/M	Ade	IV	0	FXYD4-RET	Nab-paclitaxe + Bevacizumab + Tislelizumab	3	–	PR	6.6
P7	65/M	Ade	IV	80%	KIF5B-RET	Pemetrexed + Carboplatin + Pembrolizumab	1	–	SD	7.5
P8	63/M	Ade	IV	1%	KIF5B-RET	Pemetrexed + Carboplatin + Bevacizumab + Camrelizumab	2	Before	PD	1.5
P9	54/M	Ade	IV	NA*	KIF5B-RET	Pemetrexed + Carboplatin + Tislelizumab	1	–	PR	6.1
P10	47/F	LCNC	IV	0	KIF5B-RET	Nab-paclitaxe + Durvalumab	4	Before	SD	3.5
P11	56/F	Ade	IV	NA*	KIF5B-RET	Paclitaxe + Sintilimab	2	–	SD	4.7
P12	49/M	Ade	IV	35%	KIF5B-RET	Docetaxe + Nedaplatin + Pembrolizumab	2	–	PD	0.8
P13	79/M	Ade	IV	NA*	KIF5B-RET	Pembrolizumab + Anlotinib	2	–	PD	1.3
P14	63/M	Ade	IV	NA*	CCDC6-RET	Pemetrexed + Carboplatin + Bevacizumab + Toripalimab	1	–	SD	9.4
P15	65/F	Ade	IV	95%	KIF5B-RET	Pemetrexed + Carboplatin + Pembrolizumab	1	–	PR	5.6
P16	49/F	Ade	IV	90%	KIF5B-RET	Pemetrexed + Carboplatin + Camrelizumab	1	–	PR	5.1

Note: *NA defined as PD-L1 expression unknown.

Table 3
Clinical response of immune checkpoint inhibitors.

	ORR	DCR	Median PFS (months)
First line (n = 7)	5 (71.4%)	7 (100%)	7.5
Subsequent line (n = 9)	1 (11%)	6 (66.7%)	4.7
PD-L1 positive (n = 8)	3 (37.5%)	6 (75%)	6.6
PD-L1 negative or unknown (n = 8)	3 (37.5%)	7 (87.5%)	6.1
PD-L1 high (≥50%) (n = 4)	3 (75%)	4 (100%)	5.6

Abbreviations: ORR: objective response rate. DCR: disease control rate. PFS: progression-free survival.

Molecular testing of the pleural effusion cell-free DNA (cfDNA) revealed *KIF5B-RET* fusion, *KRAS* p.A146V mutation, and *EGFR* amplification with a copy number of 2.1 (Fig. 4).

4. Discussion

Platinum-based chemotherapies are the standard care for treatment of naïve *RET* fusion-positive NSCLC in China. Selective RET inhibitors are recommended after failure of standard chemotherapy. The efficacy of ICIs in these subtype of patients remains uncertain. In this study, we found a relatively high proportion of PD-L1 expression in *RET* fusion-positive NSCLC. Efficacy associated with ICIs, especially for patients with high PD-L1 expression levels and treatment naive patients, were comparable to those reported for unselected populations. The selective RET inhibitors, selpercatinib and pralsetinib, displayed superior outcomes compared with the MKIs cabozantinib.

In this study, half of the *RET* fusion patients were female, non-smokers, and diagnosed with adenocarcinoma. Patients with *RET* fusion subtypes had clinical characteristics that were consistent with previous studies [2]. We identified *RET* fusion in one large-cell neuroendocrine carcinoma and one sarcomatoid carcinoma. To our knowledge, this is the first report of sarcomatoid carcinoma

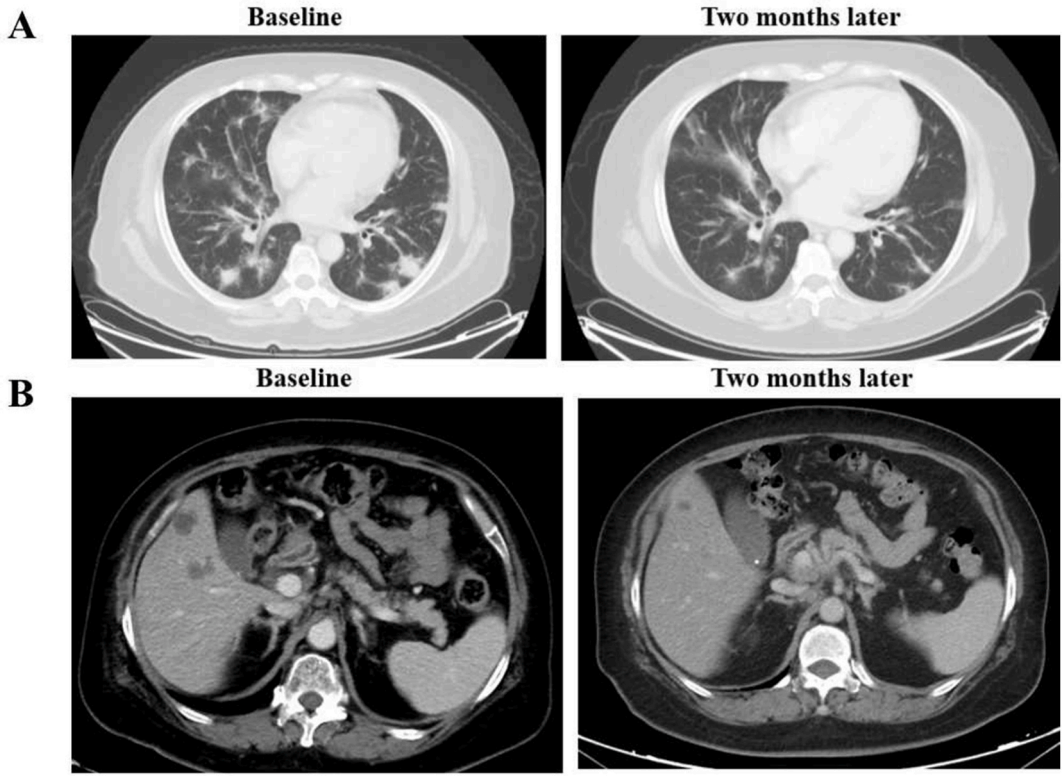

Fig. 4. Clinical response of pembrolizumab and selpercatinib for the case with *RET* fusion and PD-L1 over-expression. A: CT scan revealing the clinical response to pembrolizumab. B: CT scan revealing the clinical response to selpercatinib. Abbreviations: PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; CT: computed tomography.

accompanied by *RET* fusion. We found that 75% of *RET* fusion-positive lung cancers exhibited positive (>1%) PD-L1 expression. This is consistent with a previous report that *RET* fusion-positive NSCLC was associated with high PD-L1 expression [16]. In our study, *TP53* co-mutations occurred more frequently compared with other genes. Previous studies have shown that concurrent mutations in tumor suppression genes, such as *TP53* and *PTEN*, contribute to inferior outcomes for EGFR-TKI treatments when compared to the pure *EGFR* mutation subgroup [17]. Owing to the limited number of patients receiving selective RET inhibitors, we did not find influence of *TP53* co-mutation on the clinical outcomes. Further research is warranted to evaluate the impact of *TP53* co-mutation on selective RET inhibitors.

Before the approval of selective target agents, some patients with *RET* fusion-positive lung cancer received ICIs as the first-line therapy, either as monotherapy or in combination with chemotherapy. Previous retrospective studies reported a poor response to ICIs with a 6.3% ORR and median PFS of approximately 2.1–3.4 months [12,18]. Given the small sample size and that most patients had low PD-L1 expression, efficacy of ICI treatment in patients with *RET* fusion-positive cancer remains unclear. In this study, approximately 75% of patients exhibited positive PD-L1 expression. Four patients with PD-L1 overexpression (>50%) were administrated pembrolizumab or pembrolizumab plus pemetrexed and carboplatin as first-line treatment. Three patients obtained a partial response and one had stable disease. Lu et al. reported a satisfactory response to ICIs in two patients with *RET* fusion and high PD-L1 expression [19]. Marinello et al. reported that ICIs as monotherapy and combined with chemotherapy showed durable clinical response, with an ORR of 31% and 43%, and median PFS of 5.0 months and 9.4 months, respectively. Biomarker analysis showed relatively high PD-L1 expression in ICI responders [20]. In the randomized phase III trial LIBRETTO-431, Zhou et al. reported patients receiving platinum based chemotherapy with pembrolizumab had better PFS than those previously reported in Keynote189 trial [21]. These results suggested that ICIs, especially for patients with PD-L1 overexpression, combined with chemotherapy, may offer benefits for *RET* fusion-positive NSCLC. Our study contributes information on real-world outcomes of ICIs in patients with *RET* fusion-positive lung cancers.

As a member of tyrosine kinase receptor family, RET shares a similar kinase domain structure to other tyrosine kinase receptors [22]. Multi-kinase inhibitors such as cabozantinib, vandetanib, sunitinib, and alectinib have demonstrated activity against *RET* fusion-positive cancers [5,6,23]. The ORR (18%–37%) and median PFS (2.3 months) were lower compared to those in patients with other driver gene-positive cancers receiving targeted agents [24]. Selective RET inhibitors were then developed, and results from clinical trials such as ARROW (NCT03037385), LIBRETTO-001 (NCT03157128) and LIBRETTO-431(NCT04194944) demonstrated superior activity and tolerability [7,8,21]. Our real-world data also showed that selective RET inhibitors had favorable efficacy compared with cabozantinib for RET fusion NSCLC cancers.

Here, we report a case with *KIF5B-RET* fusion and PD-L1 overexpression that sequentially responded to pembrolizumab, chemo-immunotherapy, and later-line selpercatinib. Following resistance to selpercatinib, pleural effusion cfDNA testing revealed *KIF5B-RET* fusion, *KRAS* p.A146V mutation, and *EGFR* amplification. Currently, limited reports describe resistance mechanisms to selective RET inhibitors. Solomon et al. reported that three patients with *RET* fusion-positive NSCLC acquired RET G810 solvent-front mutations after selpercatinib resistance [25]. Lin et al. found three patients acquired *MET* amplification and one acquired *KRAS* amplification [26]. Preclinical studies showed that activation of the EGFR pathway mediated cancer cells resistance to RET inhibitors [27,28]. Mechanisms of resistance to selective RET inhibitors still need to be explored.

This study evaluated the real-world efficacy of ICIs and RET inhibitors in *RET* fusion-positive NSCLC, however, the study has several limitations. As this was a retrospective analysis, it was exposed to potential bias. The number of patients receiving selective RET inhibitors or ICIs was relatively small, despite it being one of the larger cohorts reported in China. Different combinations of chemotherapy and ICIs may also influence the efficacy of immunotherapy. Future analyses of ICIs, particularly in PD-L1 over-expression populations and use in combination with chemoimmunotherapy, are warranted.

5. Conclusions

This study observed that selective RET inhibitors had superior efficacy compared to cabozantinib. We also found a relatively high proportion of PD-L1 expression in *RET* fusion-positive NSCLC. Efficacy of ICIs, especially for PD-L overexpression and treatment naive patients, were comparable to those reported for unselected populations, warranting further investigation.

List of abbreviations: DCR, disease control rate. EGFR, epidermal growth factor receptor. ICIs, immune checkpoint inhibitors. MKIs, multi-kinase inhibitors. NGS, next generation sequencing. NSCLC, non-small-cell lung cancer. ORR, objective response rate. PD-L1, programmed death ligand 1. PFS, progression free survival. RET, Rearranged during transfection. TPS, tumor proportion score.

Declarations

Ethics statement

This study was reviewed and approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences, with the approval number NCCC2020C-499. All patients provided informed consent to participate in the study. All patients provided informed consent for the publication of their anonymised case details and images.

Consent for publication

Written informed consent for publication was obtained from all participants.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Rui Wan: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Weihua Li:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Zhijie Wang:** Writing – review & editing, Project administration. **Jia Zhong:** Writing – review & editing, Project administration. **Lin Lin:** Writing – review & editing, Project administration. **Jianchun Duan:** Writing – review & editing, Project administration. **Jie Wang:** Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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