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Review on Ret-Gene Fusion Positive Non-Small Cell Lung Cancer

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Abstract: RET (rearranged during transfection) gene fusion–positive non–small cell lung cancer (NSCLC) represents a distinct molecular subtype, occurring in approximately 1–2% of NSCLC cases, predominantly among younger, non-smoking patients with adenocarcinoma histology. RET fusions result in constitutive activation of RET tyrosine kinase signaling, driving tumorigenesis. Accurate detection through next-generation sequencing (NGS) or RNA-based assays is essential for guiding targeted therapy. The development of selective RET inhibitors, such as selpercatinib and pralsetinib, has revolutionized treatment, demonstrating high response rates, durable disease control, and favorable safety profiles compared with traditional chemotherapy or multikinase inhibitors. Despite these advances, acquired resistance and central nervous system progression remain significant challenges. RET fusion–positive NSCLC exemplifies the success of precision oncology, highlighting the importance of comprehensive molecular profiling and continued research into next-generation inhibitors and combination treatment strategies to further improve patient outcomes.

Keywords: RET gene fusion (NSCLC), Tyrosine kinase inhibitors, Next-generation sequencing, Chemotherapy

I. INTRODUCTION

The RET proto-oncogene makes a protein that acts as a receptor tyrosine kinase, which is important for the development of the nervous system, intestines, and kidneys. Under normal conditions, the RET protein has three main parts: An extracellular domain – the outer part that binds to specific signalling molecules (ligands). A transmembrane domain – a section that anchors the protein in the cell membrane. An intracellular domain – the inner part that has tyrosine kinase activity, meaning it can activate other proteins inside the cell by adding phosphate groups. For RET to work, it needs to interact with molecules called GDNF (glial cell line-derived neurotrophic factor) family ligands and their co-receptors (GFRα proteins). When these form a complex and bind to RET's outer domain, it triggers auto-phosphorylation (self-activation) of the inner kinase part. This activation turns on several cell signalling pathways that control growth, survival, and differentiation. Sometimes, mutations or rearrangements in the RET gene cause it to become overactive (gain-of-function). These abnormal changes are found in several types of cancers, such as thyroid cancer and non-small-cell lung cancer (NSCLC). In medullary thyroid cancer, RET usually has activating point mutations. In NSCLC and papillary thyroid carcinoma, RET often undergoes chromosomal rearrangements, which make the protein constantly active without needing a ligand. This overactive RET signaling drives uncontrolled cell growth and survival through major pathways like RAS–MAPK, PI3K–AKT, PKC, and JAK–STAT3.[1]

The most common treatment-related adverse events of grade 3 or higher included neutropenia, affecting 43 patients (18%), hypertension in 26 patients (11%), and anemia in 24 patients (10%) within the ARROW group (Griesinger et al., 2022). Additionally, pneumonitis, classified as grade three or higher, was observed in 2% of patients diagnosed with RET fusion-positive NSCLC (Gainor et al., 2021). Pneumocystis jirovecii pneumonia (PJP), an opportunistic fungal infection, is often seen in immunocompromised individuals, including those suffering from AIDS, cancer, and those who have undergone organ transplants (Thomas and Limper, 2004), with mortality rates surpassing 20% (Morris et al., 2004). Nevertheless, there are few case reports that document instances of PJP induced by pralsetinib. The implications of rechallenging with pralsetinib remain unclear for cancer patients who have ceased treatment due to

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toxicity associated with PJP. In this regard, we present a case involving NSCLC that developed grade 3 pneumonitis after receiving pralsetinib as a fourth-.line treatment. The patient showed an enhanced response upon rechallenging with pralsetinib, indicating a favorable safety profile following complete recovery from PJP [2]

A new treatment has been revealed for NSCLC. Numerous clinical trials have demonstrated promising results for multi-kinase inhibitors exhibiting anti-RET activity in NSCLC, including Vandetanib, Cabozantinib, and Lenvatinib. These early agents showed relatively modest clinical efficacy alongside a significant incidence of treatment-related toxicity. Currently, Pralsetinib and Selpercatinib, two recently approved selective RET inhibitors for the treatment of RET fusion-positive NSCLC, have displayed robust outcomes. Nevertheless, all patients who have undergone these treatments will ultimately develop resistance to the medications. The novel solvent-front mutations KIF5B-RET G810C/S/R may signify an on-target resistance mechanism to Pralsetinib and Selpercatinib. However, off-target resistance has been identified as a more prevalent mechanism of resistance to RET inhibitors. Potential off-target resistance gene alterations to RET inhibition include MET amplification, activating PIK3CA mutations or PTEN loss, EGFR amplification, ERBB2 amplification, KRAS gain or mutation, and BRAF V600E alteration. Numerous clinical experiences have already shown significant survival benefits for NSCLC patients treated with endothelial growth factor receptor (EGFR)-TKIs, particularly within Asian populations. Previous in vitro studies have indicated that EGFR signaling is associated with resistance to RET inhibitors in lung cancer cells, suggesting that a multi-targeted TKI with both anti-RET and anti-EGFR effects may enhance efficacy in lung cancer treatment. Furthermore, tumour growth, recurrence, and microenvironment are linked to angiogenesis mediated by the well-known therapeutic target, vascular endothelial growth factor receptor (VEGFR). Additionally, a study utilizing KIF5B-RET models has demonstrated that KIF5B-RET fusions recruit multiple kinases, including EGFR, and increase the overall level of VEGFR. This underscores the necessity for concurrent inhibition of RET, EGFR, and VEGFR in specific tumour types.[3]

Being relatively obscure until just over a century ago, with only 374 confirmed cases recorded globally as per Adler's report in 1912.1 Regrettably, the current global burden of lung cancer, which encompasses NSCLC (accounting for nearly 85%, as emphasized in this article) and small cell lung cancer (SCLC), has evolved into a critical societal, public health, and economic challenge, due to its alarming prevalence of approximately 2.5 million new cases and over 1.8 million fatalities in 2022, making it the leading cause of cancer in both genders and across all age groups.2 In China, the statistics are similarly striking, with 4,824,703 new cases and 2,574,176 deaths, respectively. Since 2006, thanks to significant advancements in screening and diagnostic methodologies, high-precision radiotherapy (RT), surgical interventions, and innovative targeted therapies and immunotherapies based on biomarkers 3 the incidence of NSCLC has been declining annually by 2.5% in males and 1% in females in certain countries with exceptionally high Human Development Index (HDI), alongside a reduction in mortality rates**.** However, the five-year survival rate for NSCLC remains below 20% in the majority of countries, showing minimal variation based on HDI.2 As a result, prioritizing investments in preventive strategies, such as addressing key cancer risk factors (e.g., smoking, obesity, and behavioral legacies leading to complex environmental exposures) and employing cutting-edge technological resources to thoroughly investigate the mechanisms of occurrence, progression, and metastasis of NSCLC is of utmost importance. This approach will enable the translation of these insights into highly effective, low-toxicity medications and precise treatment protocols, ultimately possessing the potential to save countless lives impacted by NSCLC worldwide. Although the initial financial outlay may seem overwhelming in the short term, the considerable net economic and social advantages for nations over the forthcoming decades should not be overlooked.5 Consequently, this review provides a comprehensive overview of the subject [4]

In cases of advanced or recurrent RET fusion gene-positive non-small cell lung cancer, selpercatinib has been authorized as a first-line therapy . Although hyponatremia was noted in the LIBRETTO-001 study, the underlying causes and clinical progression are still not well understood .We present a case of SIADH induced by selpercatinib, which showed improvement following the cessation of the drug and was safely reintroduced at a lower dosage.[5]

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The traditional screening techniques for these fusions are labour-intensive and necessitate samples that are both high in quality and quantity. In this context, we present an innovative and effective approach that combines the advantages of multiplexing PCR with the sensitivity of mass spectrometry [6]

In this review, we provide a summary of the effectiveness and safety of all available treatments for RET fusion-positive NSCLC, including those in patients with central nervous system (CNS) metastases. To gather pertinent published information, a pragmatic and structured literature search was conducted in Embase and MEDLINE from January 1, 2015, to March 12, 2021.[7]

The RET proto-oncogene (RET) encodes a transmembrane receptor tyrosine kinase, specifically known as the proto-oncogene tyrosine protein kinase receptor RET, which plays a crucial role in the physiological processes of embryonic development for both the nervous system and the kidneys1,2.RET fusions and mutations are responsible for oncogenic transformation, resulting in the abnormal activation of the RET receptor tyrosine kinase3.These RET fusions are present in 1–2% of non-small-cell lung cancers (NSCLCs), around 20% of papillary thyroid cancers, and less than 1% of various other solid tumours, such as ovarian, pancreatic, salivary, and colorectal cancers[8]

2. PATIONT INFORMATION

A total of 39 samples exhibiting RET fusions were gathered from Hunan Provincial tumour Hospital, Tianjin Cancer Institute, and the Tumour Hospital of the Chinese Academy of Medical Sciences between 2016 and 2018. The origin of the cells was determined through histological analysis in accordance with the 4th World Health Organization Classification Patient characteristics, including gender, age, and clinical stage, were documented. Cancer stages were assessed based on the 8th TNM staging system. Overall survival (OS) data were accessible for 21 samples, while progression-free survival data were available for 14 samples. The treatment regimens for each patient were extracted from their medical records. The research was carried out in compliance with the Declaration of Helsinki (as revised in 2013). This study received approval from the Research Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences (No. 18-118/1696), and informed consent was obtained from all participating patients

3. TARGETED DNA SEQANCING

The quality of gDNA was evaluated to ensure that the A260/A280 ratio falls within the range of 1.8 to 2.0. For patients with accessible DNA, targeted DNA sequencing was conducted. The DNA was analyzed using the Lung Plasma panel (Burning Rock Biotech), which encompasses 168 cancer-related genes. The concentration of the DNA samples was quantified using the Qubit dsDNA assay to confirm that the genomic DNA exceeded 40 ng. Fragments ranging from 200 to 400 bp were selected using beads (Agencourt AMPure XP kit; Beckman-Coulter, Brea, CA), followed by hybridization with the capture probe baits, hybrid selection utilizing magnetic beads, and PCR amplification. Subsequently, a bioanalyzer high-sensitivity DNA assay was employed to assess the quality and size range. The indexed samples that available were then sequenced on a Miseq (Illumina, San Diego, CA) using paired-end reads. [9]

Pearson's $\chi 2$ test was conducted in the statistical analyses to assess whether there was a correlation between CD133 and CTA expression with clinical-pathological parameters. Spearman's rank correlation was utilized to investigate any potential mutual relationship in the expression levels. For univariate survival analyses, the Kaplan-Meier method was employed, and the log-rank test was applied to identify statistical differences between life tables. All analyses were executed using the SPSS statistical package version 14.0 (SPSS Inc, Chicago, IL). A P value of less than 0.05 was considered statistically significant. All statistical tests were two-sided.[10]

Methods Data source This retrospective observational study employed the Flatiron-Foundation Medicine Climaco-Genomics database. The CGDB integrates Flatiron Health's longitudinal database, which contains electronic health record (EHR) data from over 265 cancer clinics (approximately 800 sites of care) and encompasses more than 2 million cancer patients in the United States, linked to extensive genomic profiling data sourced from Foundation Medicine, Inc. (FMI). The de-identified patient-level clinical data from the EHR comprises structured data (e.g., laboratory values, prescribed medications) as well as unstructured data gathered through technology-enabled chart abstraction from

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physicians' notes and other unstructured documents (e.g., detailed biomarkers). The de-identified patient-level genomic data from FMI includes specimen characteristics (e.g., tumour mutation burden, pathologic purity), alteration-level specifics (e.g., genomic position, reference and alternate alleles, mutant allele count, minor allele frequency), and therapeutic recommendations that were communicated to the clinician at the time of testing. Death dates are recorded as month and year to maintain confidentiality and are sourced from three channels: EHR; social security death index; and published obituary notices. All data are de-identified, and measures are implemented to prevent re-identification to safeguard patients' confidentiality. Institutional Review Board (IRB) approval with a waiver of informed consent (Copernicus Group IRB) was secured by Flatiron Health prior to the provision of these datasets and the execution of this study. Eligibility criteria Patients with metastatic NSCLC identified in the CGDB were eligible for this study if they were aged 18 years or older at the time of diagnosis and had received their initial systemic anti-cancer therapy within 180 days of metastatic diagnosis.[11]

We gathered sequencing data from 1,587patients whose tissue samples were assessed to confirm tissue adequacy (surface area ≥25 mm2, volume≥1 mm3, nucleated cellularity ≥80%, and tumour content ≥20%). DNA was extracted using the QIAamp DNA FFPE(Formalin-fixed and paraffin-embedded) Tissue Kit (Qiagen, California, USA) following the manufacturer's guidelines. A targeted NGS library was constructed based on a prior publication18. Nucleotide fragments were selected and hybridized with capture probe baits. Genomic DNAs were analyzed using a capture-based targeted sequencing panel, which is commercially available from Burning Rock Biotech (Guangzhou, China). Selected exons and introns of 8 out of 56 cancer-related genes were covered, encompassing 170 kb of the human genome. The median sequencing depth achieved was 1855×. Subsequently, a bioanalyzer high sensitivity DNA assay was employed to assess their quality and size range. The indexed samples were then sequenced using a Next-Siq 500 (Illumina, Inc., USA with paired-end reads.[12]

4. REVIEW

4.1 Biology and clinicopathological features of RET-positive NSCLC

RET rearrangements are found in approximately 1–2% of patients diagnosed with NSCLC, typically affecting younger individuals who are light or never smokers, and are characterized by adenocarcinoma histology. These rearrangements are linked to a significant incidence of brain metastases at the time of diagnosis.7–10 The fusions occur between the C-terminal region of RET, which encodes the intracellular kinase domain, and the N-terminal region of various gene partners. This results in the abnormal expression of chimeric fusion proteins that localize in the cytosol, leading to ligand-independent constitutive activation of RET and its downstream signalling pathways, thereby facilitating cancer cell proliferation and survival.11 Up to now, multiple fusion gene partners have been identified, with KIF5B being the most prevalent, accounting for 70–80% of cases, followed by CCDC6, while less frequently observed fusion partners include NCOA4, TRIM33, and CLIP1.12,13 RET fusions in tumours can be detected using fluorescence in situ hybridization (FISH) and next-generation techniques. Sequencing (NGS) is preferred, while reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) exhibit low sensitivity and considerable variability in specificity, thus they are not regarded as standard diagnostic tools.12 Nevertheless, FISH is linked to frequent false-positive outcomes concerning the detection of all RET rearrangements, including those that do not lead to a functional oncogenic fusion.14 As a result, FISH is not the most suitable method for multiplex screening aimed at identifying patients who may benefit from RET-selective TKIs.15 Up to now, taking into account the overall cost-effectiveness and the capability to detect multiple molecular alterations simultaneously, NGS is deemed the preferred method.16,17 In particular, DNA-based NGS has certain limitations when compared to RNA-based sequencing, such as the lack of intron coverage, where genomic breakpoints that generate fusion genes may occur, and the absence of transcription level information, which could potentially result in false-negative outcomes.17 Additionally, for patients with insufficient or inadequate tissue for genomic profiling, liquid biopsies present a feasible alternative to tissue genotyping.15 Indeed, circulating cell-free DNA testing utilizing NGS-based methods can identify RET genetic alterations with a high concordance to tissue testing, although the sensitivity for fusions detected by NGS is lower in

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plasma than in tissue.18 In pathology, RET-positive tumours are more often poorly differentiated in comparison to ALK-positive or EGFR mutated tumours and are associated with certain subtypes of adenocarcinoma, specifically solid, papillary, and lepidic patterns,12,19 as well as lymphangitic spread and psammoma bodies, indicating that the presence of these two features should raise suspicion for potential RET rearrangements.20 Furthermore, RET-rearranged tumours generally present as small peripheral lesions (<3 cm) but are characterized by early lymph node involvement (N2 disease) and a high rate of pleural dissemination and brain. Sequencing (NGS) is preferred, while reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) exhibit low sensitivity and considerable variability in specificity, thus they are not regarded as standard diagnostic tools.12 Nevertheless, FISH is linked to frequent false-positive outcomes concerning the detection of all RET rearrangements, including those that do not lead to a functional oncogenic fusion.14 As a result, FISH is not the most suitable method for multiplex screening aimed at identifying patients who may benefit from RET-selective TKIs.15 Up to now, taking into account the overall cost-effectiveness and the capability to detect multiple molecular alterations simultaneously, NGS is deemed the preferred method.16,17 In particular, DNA-based NGS has certain limitations when compared to RNA-based sequencing, such as the lack of intron coverage, where genomic breakpoints that generate fusion genes may occur, and the absence of transcription level information, which could potentially result in false-negative outcomes.17 Additionally, for patients with insufficient or inadequate tissue for genomic profiling, liquid biopsies present a feasible alternative to tissue genotyping.15 Indeed, circulating cell-free DNA testing utilizing NGS-based methods can identify RET genetic alterations with a high concordance to tissue testing, although the sensitivity for fusions detected by NGS is lower in plasma than in tissue.18 In pathology, RET-positive tumours are more often poorly differentiated in comparison to ALK-positive or EGFR mutated tumours and are associated with certain subtypes of adenocarcinoma, specifically solid, papillary, and lepidic patterns,12,19 as well as lymphangitic spread and psammoma bodies, indicating that the presence of these two features should raise suspicion for potential RET rearrangements.20 Furthermore, RET-rearranged tumours generally present as small peripheral lesions (<3 cm) but are characterized by early lymph node involvement (N2 disease) and a high rate of pleural dissemination and brain. Recommendations for NSCLC.28 Following radical surgical resection, adjuvant chemotherapy consisting of four cycles of platinum-based agents yields a 5-year survival advantage of 4–5% when compared to observation or placebo in cases of stage II–IIIA resectable tumours or when the primary tumour exceeds 4 cm in size, whereas observation remains the preferred option for earlier stage tumors.29,30 The function of TKIs in this context has yet to be established due to limited data and the absence of routine standard molecular testing in clinical practice. Nevertheless, numerous studies have been initiated to assess the impact of both EGFR-TKIs and ALK-TKIs in early-stage NSCLC. The phase III trial ADAURA demonstrated that adjuvant osimertinib, a third-generation EGFR-TKI, was linked to significantly improved disease-free survival compared to placebo in patients with resected stage IB–IIIA EGFR-positive NSCLC, regardless of whether chemotherapy was administered, although overall survival (OS) data remained immature. Likewise, several ongoing clinical trials are presently investigating the effectiveness of RET-TKIs in early-stage RET-positive NSCLC (Table 1). The NAUTIKA1 is a multicentre, multi-arm, phase II study evaluating neoadjuvant pralsetinib, a selective RET inhibitor, in patients with resectable stage II–III RET-positive NSCLC (NCT04302025). Patients exhibiting a pathological response will receive adjuvant therapy, which includes four cycles of chemotherapy followed by up to 2 years of pralsetinib. The LIBRETTO-432 is a double-blinded, randomized phase III study examining the efficacy of selpercatinib (another selective RET inhibitor) against placebo in terms of event-free survival (i.e., time to recurrence, progression, or death) in patients with stage IB–IIIA RET-positive NSCLC after definitive locoregional treatment (surgery or radiation therapy) (NCT04819100.[1]

5. ADVANCE DISEASE

5.1 Non-selective RET fusion-positive inhibitors

Vandetanib is an oral multi-target inhibitor exhibiting anti-angiogenic and anti-RET has approved vandetanib, which primarily acts to inhibit the RET tyrosine kinase signaling pathway, for the treatment of advanced medullary thyroid

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carcinoma. In vitro studies have shown that the growth of CCDC6-RET-positive LC-2 lung adenocarcinoma cells can be inhibited by vandetanib. Furthermore, the combination therapy of vandetanib and everolimus has the potential to alter efflux mediated by P-gp/Abcb1 and Bcrp1/Abcg2, enhance penetration across the blood-brain barrier, and extend the survival duration of patients with brain metastases. Additionally, it can inhibit the transplantation of CCDC6-RET-positive lung adenocarcinoma tumours into athymic mice and the carcinogenesis of KIF5B-RET transgenic mice in vivo According to the available Phase I and Phase II trials, vandetanib was well tolerated at a daily dosage of 300 mg. Lee et al. conducted a Phase II clinical trial involving 18 patients with RET fusion-positive metastatic or recurrent NSCLC, all of whom had previously undergone and responded to platinum-based doublet chemotherapy. These patients were enrolled between July 2013 and October 2015 and were administered vandetanib at a dose of 300 mg per day. The trial reported an objective response rate (ORR) of 18%, a median progression-free survival (mPFS) of 4.5 months, and a median overall survival (MOs) of 11.6 months. The most frequently observed grade three or higher treatment-related adverse events (TRAEs) included hypertension (89%), rash (72%), diarrhea (44%), acne (28%), and asymptomatic QT prolongation (11%). In May 2021, Yoh et al. published the final follow-up data from a Phase II clinical trial they conducted between April 2013 and May 2015, which included 19 previously treated RET fusion-positive NSCLC patients. These patients exhibited an ORR of 53% (95% CI: 31-74), an mPFS of 6.5 months, and an MOs of 13.5 months. The most common grade three or higher TRAEs reported were hypertension (84.2%), diarrhea (78.9%), acneiform rash (63.2%), asymptomatic QT prolongation (47.4%), and dry skin (42.1%). It is noteworthy that vandetanib has a limited objective remission rate, shows no significant advantages in terms of efficacy, and has a considerable incidence of grade three or higher TRAEs, which fundamentally restricts its clinical use. Cabozantinib (XL184) is a multichines inhibitor that targets RET, VEGFR-1/2/3, MET, ROS1, AXL, and other kinases. Cabozantinib has received approval in certain regions for the treatment of RET fusion-positive NSCLC, medullary thyroid cancer, and advanced renal cell carcinoma. Nakahara et al. conducted a Phase I study in which 43 NSCLC patients were treated with cabozantinib at a dosage of 60 mg per day; eight patients achieved varying degrees of remission, while 16 patients experienced stable disease. The adverse events reported included hypertension, proteinuria, and other related issues.

5.2 Selective RET fusion-positive inhibitors

Selpercatinib (LOXO-292) is a highly selective RET inhibitor that operates through ATP competition (58). It effectively suppresses RET fusions, such as KIF5B-RET and CCDC6-RET, along with mutations like V804L, V804M, and M918T (78). Following the findings from the Phase I/II Libretto-001 trial, selpercatinib received regular approval from the FDA for the treatment of adults with locally advanced or metastatic RET fusion-positive NSCLC (11). In addition to its notable inhibitory effects on RET, the drug has shown commendable target specificity, tolerance, and effectiveness in treating intracranial conditions (79). In September 2022, Drilon et al. (80) released the most recent results from their registrational LIBRETTO-001 phase I/II trial, which is a global multicentre clinical study. This trial involved 247 patients with advanced RET fusion-positive NSCLC who had previously undergone platinum-based chemotherapy, as well as 69 patients who had not received any prior treatment. The current patient count is more than double that reported in 2020 (81), enhancing the credibility of their reported drug effects. All participants were administered selpercatinib at a dosage of 160 mg twice daily. At the data cut-off point, the overall response rate (ORR) was determined to be 61% among 105 platinum-treated patients, with a median duration of response (mDOR) of 28.6 months and a median progression-free survival (mPFS) of 24.9 months. Comparable results were observed in the LIBRETTO-001 clinical trials conducted in Japan and China. The study from China (82) included 26 patients with RET.

In patients with fusion-positive NSCLC, 18 had previously undergone chemotherapy or immunotherapy, while 8 were treatment-naïve. The overall response rate (ORR) was 61.1% for those who had been treated before and 87.5% for treatment-naïve individuals, with median progression-free survival (mPFS) and median overall survival (MOs) not yet reached at the time of data cut-off. Among 38 patients in the Japanese study (83) who had prior chemotherapy or

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immunotherapy, the ORR was 55.3% (95% CI, 38.3-71.4). This suggests that the treatment of RET fusion-positive NSCLC with selpercatinib may not show significant differences across various populations. Interestingly, 106 patients with initial intracranial metastases achieved an ORR of 85% (95% CI, 65-96) and a mPFS (95% CI, 13.8-NR) of 19.4 months, which is quite promising for the survival of stage IV lung cancer patients. Furthermore, among the 22 responders with measurable CNS metastases, the median duration of response (mDOR) was 9.4 months (95% CI, 7.4-15.3). This indicates that selpercatinib exhibits favorable intracranial reactivity, which is significant for extending the survival of NSCLC patients with intracranial metastases. A similar heightened intracranial response to selpercatinib was observed in another study. Subbiah et al. reported the effectiveness of selpercatinib at a dose of 160 mg twice daily for one year in 80 patients with RET fusion-positive NSCLC and brain metastases. Among 22 patients with evaluable intracranial lesions, the intracranial ORR at the data cut-off was 82%, with 23% of patients achieving complete remission. Overall, 80 patients had an intracranial mPFS of 13.7 months, and the mDOR was not reached at the data cut-off. The favorable safety profile of selpercatinib was also highlighted in the trial conducted by Drilon et al. (80). Treatment-related adverse events (TRAEs) occurred in 44% of patients, with the most common grade three or higher TRAEs being hypertension (19.7%), increased ALT (11.4%), increased AST (8.8%), diarrhoea (5.0%), and prolonged electrocardiogram QT (4.8%). It is evident from these studies that selpercatinib demonstrates a high response rate, effective targeting, and a good safety profile. Libelling the phase I/II trial, Griesinger et al. provided an update on August 13, 2022, regarding their latest analysis (87). A total of 281 patients with RET fusion-positive NSCLC were included in the study, which took place from March 17, 2017, to November 6, 2020. These patients were administered a phase II dose of 400 mg of Pralsetinib once daily, with the primary endpoint being the overall response rate (ORR). The results were encouraging, showing an ORR of 72% in treatment-naïve patients and 59% in those who had previously undergone platinum-based chemotherapy. The median duration of response (mDOR) for chemotherapy patients was 22.3 months, while it was not reached for treatment-naïve patients. Notably, all treatment-naïve patients and 97% of those who had received platinum-based chemotherapy exhibited reductions in tumor volume following treatment, with respective progression-free survival rates of 13.0 months and 16.0 months. Furthermore, similar to Selpercatinib, Pralsetinib demonstrated significant intracranial efficacy, achieving an intracranial remission rate of 70% (95% CI 35-93) in patients with intracranial metastases post-treatment. The mDOR in this subgroup was recorded at 10.5 months (95% CI 5.5-12.6 months). Among the 281 patients, 7% (20/281) discontinued treatment due to treatment-related adverse events (TRAEs). In the cohort of 116 treatment-naïve patients, 08 (93%) experienced a TRAE, with the most frequently observed grade three or higher TRAEs being neutropenia (18%), hypertension (10%), elevated serum creatine phosphokinase (9%), and lymphopenia (9%). In the pre-treated population, the predominant grade three or higher TRAEs included neutropenia (22%), anemia (18%), and hypertension (13%). Based on the outcomes of these studies, pralsetinib is characterized by good tolerability and safety, a favorable ORR and median progression-free survival (mPFS), and a low incidence of side effects such as neutropenia and hypertension. Nevertheless, the occurrence of TRAEs associated with Pralsetinib was found to be higher compared to Selpercatinib. In terms of rational application, Pralsetinib continues to be a preferred treatment option for patients diagnosed with RET fusion-positive NSCLC. [13]

Following the identification of positive RET expression in the NSCLC samples, we examined the potential mechanisms that could underlie this expression. Initially, we conducted an analysis of gene mutations in the hot-point exons of RET-positive samples utilizing a Genomic DNA Purification Kit (Thermo Fisher Scientific, USA). However, we found no RET gene mutations in the hot-point exons 8, 10, 11, or 13–16 across the 16 RET-positive samples. To further investigate the specific mechanisms of RET expression in NSCLC, we assessed RET fusion and RET copy number variants in these 16 RET-positive samples. RT-PCR rearrangement testing revealed that only two samples of moderately and poorly differentiated lung adenocarcinomas exhibited RET rearrangement, both involving RET-KIF5B fusion partners. The IHC results indicated a strong positive (++). Subsequently, we examined RET gene copy number alterations in exons 4 and 8, as well as intron 13, in the remaining 14 samples. in the copy number of the RET gene.[14]

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6. CHEMOTHERAPY

Until the emergence of specific RET inhibitors, chemotherapy remained the primary treatment for RET fusion NSCLC. Some studies indicated that these patients were responsive to pemetrexed-based regimens. In the GLORY global study, 108 advanced NSCLC patients with RET fusion received first-line chemotherapy, resulting in a median PFS of 6.6 and 7.8 months, while the median OS was 23.6 and 24.8 months, respectively. In conclusion, chemotherapy could provide certain clinical benefits for RET fusion NSCLC. Prior to the clinical availability or applicability of targeted drugs, platinum-based regimens were one of the treatment options for patients with RET fusion NSCLC

7. COMBINEDTHERAPY

The combination of vandetanib and everolimus resulted in remission for all six patients with RET fusion-positive NSCLCs. Additionally, it demonstrated antitumor activity in refractory cases involving cabozantinib and brain metastasis. Furthermore, MET amplification was identified in four patients participating in the LIBRETTO-001 study, where the combination of selpercatinib and the MET/ALK/ROS1 inhibitor crizotinib also exhibited clinical activity and good tolerability. In conclusion, combined treatment approaches may offer clinical benefits to patients with RET fusion NSCLC; however, their safety requires further validation

7.1 Immune checkpoint inhibitors

The combination of vandetanib and everolimus resulted in remission for all six patients with RET fusion-positive NSCLCs. Additionally, it demonstrated antitumor activity in refractory identified in four patients participating in the LIBRETTO-001 study, where the combination of selpercatinib and the MET/ALK/ROS1 inhibitor crizotinib also exhibited clinical activity and good tolerability. In conclusion, combined treatment approaches may offer clinical benefits to patients with RET fusion NSCLC; however, their safety requires further validation [15]

The response model, which is based on spatial analysis, emphasizes the essential function of M1 and M2 macrophages as well as CD4 T cells in forecasting the response to PD-1-targeted immunotherapy. Uniform Manifold Approximation and Projection (UMAP) visualizations encompassing all 14 cell types (Fig. 4g), together with the expression dynamics of each marker identified in spatial proteomic data, reveal that M1 (CD68+) and M2 (CD163+) macrophages exhibit elevated PD-L1 expression in comparison to PanCK+Ki67+ proliferating tumor cells. In the Yale cohort, no progressors demonstrated a notably higher PD-L1 expression in both tumor cells and macrophages. Nevertheless, comparative analysis indicated that PD-L1 expression on macrophages, in contrast to that on tumor cells, was consistently linked to prolonged progression-free survival (PFS) (Extended Data Fig. 4a, b). To mitigate limitations arising from sample size, we amalgamated data from the Yale and UQ cohorts to bolster statistical power (Extended Data Fig. 4c, d). The combined analysis validated a significant relationship between macrophage PD-L1 expression and PFS, while the PD-L1 expression in tumor cells remained statistically insignificant. Importantly, PD-L1 expression on tumor cells was associated with clinical response in only one cohort; however, this association was not observed in the other cohort, highlighting inconsistency across datasets. Regression analysis further corroborated this pattern. PD-L1 expression exhibited a strong correlation with the average proportions of M1 or M2 macrophages or CD14+ myeloid cells ($P < 0.001$, Spearman's rank), but not with PanCK+ tumor cells ($P = 0.17$, Spearman's rank; Extended Data Fig. 4e–h). These results imply that the presence of PD-L1 on macrophages may serve as an indicator of a favorable response to **treatment.**[16]

7.2 Analysis of Immune Cell Infiltration and Correlation

We utilized ssGSEA to assess immune infiltration in NSCLC and to explore the potential immunomodulatory effects of ExoNSCLC-DEGs. Significant differences in immune cell infiltration were noted between NSCLC and normal tissues. In particular, the levels of infiltration for immune cell subsets, such as myeloid suppressor cells (MDSC), neutrophils, and regulatory T cells (Treg) in NSCLC, were significantly higher compared to normal tissues. Conversely, dendritic cells and natural killer (NK) cell subsets were markedly reduced, while activated B cells showed

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a significant increase in NSCLC tissues relative to normal tissues. Additionally, a correlation analysis between the expression of ExoNSCLC-DEGs and immune cell populations indicated an interaction between the two. Notably, S100A4 exhibited a broad positive correlation with various types of immunosuppressive cells, including MDSCs, macrophages, neutrophils, and regulatory T cells. This implies that S100A4 may play a pivotal role in promoting tumor immune evasion mechanisms.

8. EARLY PREDICTION OF NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer (NSCLC) continues to pose a significant health challenge globally, primarily due to the absence of effective early diagnostic biomarkers. Recently, exosome-related genes have surfaced as promising diagnostic markers owing to their involvement in tumor progression and immune regulation. This study aimed to identify exosome-related gene signatures as early predictive biomarkers for NSCLC and assess their diagnostic and therapeutic relevance. We integrated gene expression data from the GEO and TCGA databases. Core ExoNSCLC-DEGs were identified through three machine learning techniques to develop a diagnostic model for NSCLC, which was validated using ROC curves, calibration curves, and DCA curves. Furthermore, immune infiltration analysis, drug enrichment, molecular docking analysis, and regulatory network analysis were conducted to further investigate the potential mechanisms of action of ExoNSCLC-DEGs. qRT-PCR experiments confirmed the reliability of gene expression. We established a diagnostic model comprising six core ExoNSCLC-DEGs (including GPM6A, HYAL1, S100A4, ROBO4, LRRK2, and HBA1). The diagnostic model exhibited outstanding predictive performance in independent cohorts (AUC > 0.98). The calibration curve and DCA curve illustrated the clinical applicability of the model. Immune infiltration analysis indicated the potential immune effects of certain ExoNSCLC DEGs, such as S100A4 and LRRK2, which may be crucial in tumor immune evasion. Drug enrichment analysis forecasted potential therapeutic agents, particularly sunitinib targeting LRRK2. The regulatory network further pinpointed the key RNA-binding proteins and transcription factors that govern these biomarkers. qRT-PCR experiments validated the reliability of the expression of ExoNSCLC-DEGs in bioinformatics analysis. The diagnostic model based on the six ExoNSCLC-DEGs demonstrates robust diagnostic performance and clinical applicability. Comprehensive research on ExoNSCLC-DEGs offers new insights into the pathogenesis of NSCLC and suggests new avenues for future investigations.[17]

8.1 Protein isolation and western blot analysis

Dissected lung tissue was promptly transported on ice to our laboratories immediately following lung surgery and subsequently frozen at −80°C. Later, the frozen lung samples were lysed using RIPA Buffer (Thermo Fisher Scientific, Cat# 89900) along with an inhibitor cocktail (complete Mini EDTA-free, Roche Diagnostics, Cat# 11836170 001). The samples were then homogenized with SpeedMill PLUS (Analytic Jena) in Innu SPEED lysis Tubes P (Analytic Jena, Cat# 845-CS-1020250) and centrifuged at 3000 rpm for 5 minutes at 4°C. The supernatant was incubated on ice for 30 minutes and then subjected to another centrifugation at 2000g for 5 minutes at 4 °C. The final extraction was achieved through an additional centrifugation of the supernatant for 45 minutes at maximum speed at 4°C, and the protein concentration was measured using the Bradford Assay (Protein Assay Dye Reagent Concentrate, Bio Rad, Cat# 5000006). This was followed by protein denaturation at 95 °C for 5 minutes in a mixture of reducing loading buffer (4xLDS Sample Buffer, Thermo Fisher Scientific, Cat# NP0007) and DTT (1M, Thermo Fisher Scientific, Cat# P2325). A mini-PROTEAN TGX Stain-Free Gel (Bio-Rad, Cat# 4568086) was utilized with 20µg of proteins per well, which were run at 120V and 150mA for 1 hour. The proteins were subsequently transferred to a 0.2 µm nitrocellulose membrane (Trans-Blot Turbo Transfer Pack, Bio-Rad, Cat# 1704158) using a Western Blot Trans-Blot Turbo System (Bio-Rad). The transfer and protein loading were evaluated and documented using a ChemiDoc. Imaging System (Bio-Rad). After washing and blocking the membrane with 3% powdered milk (Carl Roth GmbH, Cat# T145.3) in Tween SDS buffer for 1 hour at room temperature, the membrane was incubated overnight at 4°C with the primary antibody against Blimp1, cat PA5-20310 (1:500) (Invitrogen) or GAPDH (Cell Signaling Cat 14C10) dissolved in blocking solution. Following this, the membrane was washed and incubated with the compatible secondary antibody, mouse anti

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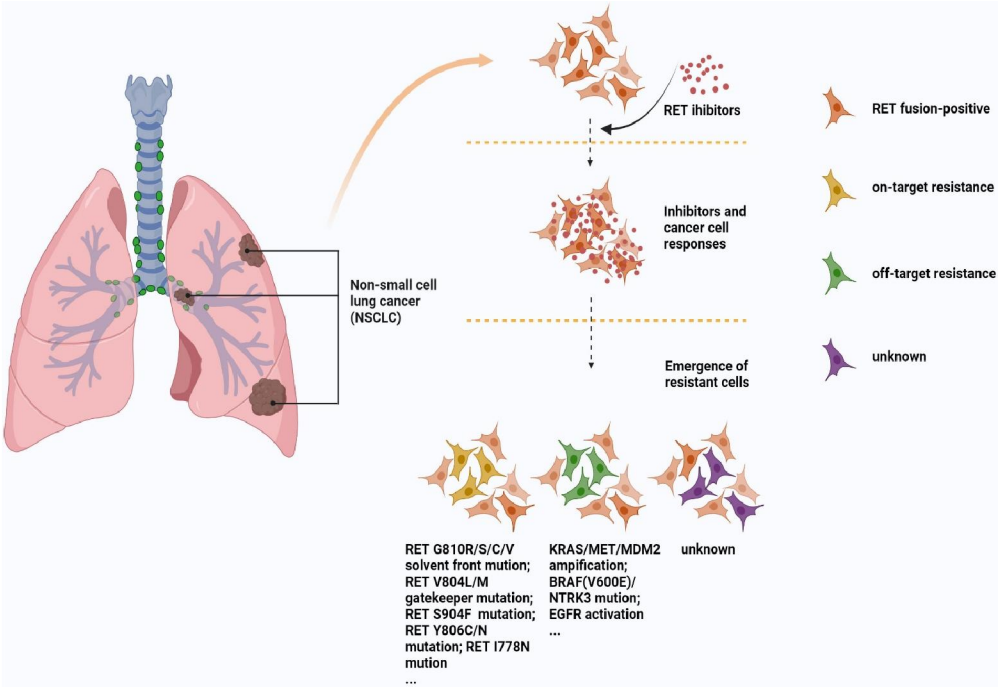
rabbit-IgG-HRP (sc-2357 Santa Cruz) (1:2000) for both Blimp1 and GAPDH in blocking buffer for 1 hour at room temperature.[18]



[Fig. no. 1 RET- GENE Fusion positive for non-small cell lung cancer] [19]

8.2 DIGNOSTIC TESTING FOR RET GENE FUSION TISSUE

RET fusions can be identified in tissue biopsies through various techniques, such as FISH, IHC, and reverse transcription PCR. However, these methods have limitations, including the examination of a restricted number of gene partners and the inability to discover novel gene fusion partners. Additionally, they may exhibit weak staining patterns and reactivity in protein-dependent assays. In contrast, next-generation sequencing (NGS) of DNA or RNA can analyse multiple genes at once, enhancing the assay's sensitivity to detect these rare occurrences. RNA sequencing offers a more thorough approach, as it not only identifies expressed fusion genes and distinguishes splicing isoforms but also quantifies fusion transcripts. Furthermore, RNAseq can detect both known and unknown expressed gene fusions, as it does not depend on sequencing intronic regions that may contain large repetitive sequences, which are known to hinder sequencing efficiency. Given the limited availability of tissue samples, employing a comprehensive genomic analysis may represent the most effective strategy for identifying oncogenic driver mutations, including RET rearrangements. Nevertheless, not all patients can undergo comprehensive genomic profiling, as up to 40% of tissue biopsies may be insufficient for molecular testing. Liquid biopsies are a well-established, FDA-approved molecular diagnostic tool that utilize circulating cell-free DNA (cfDNA) released from advanced-stage solid tumours. This cfDNA can be analyzed for tumor-specific alterations using hybrid-capture digital next-generation sequencing. Numerous studies have shown the effectiveness of liquid biopsy in identifying oncogenic driver mutations, leading to favorable clinical outcomes when patients receive targeted therapy. Another important application of liquid biopsy is the detection of acquired molecular mechanisms of resistance to targeted therapy, which may be overlooked if repeated tissue biopsies are not conducted during disease progression.[20]

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9. COMAN GENE FUSION

ALK is recognized as a fusion gene associated with anaplastic large-cell lymphoma, which functions as a transmembrane receptor tyrosine kinase and is part of the insulin receptor family (41). Approximately 3–7% of patients with non-small cell lung cancer (NSCLC) possess an ALK fusion, predominantly within the adenocarcinoma subtypes. These instances are mutually exclusive with KRAS and EGFR mutations (3). In 2007, Soda et al. (2) identified the echinoderm microtubule-associated protein 4 (EML4)-ALK fusion in a cohort of NSCLC patients. Furthermore, various forms of ALK fusion, aside from ALK-EML4, have been documented in lung cancer, including KIF5B and KLC1.

10. UNCOMAN GENE FUSION

NTRK fusion is found in various solid tumours, including frequent instances in certain rare tumours. It also represents a specific percentage of common tumours, such as lung, breast, thyroid, and colorectal cancers. The most prevalent types of NTRK gene fusion are ETV6-NTRK3 and TPM3-NTRK1 . The approval of medications targeting this fusion may offer new hope to patients with diverse cancers, and established guidelines for different cancers suggest that as long as tumours exhibit the NTRK gene fusion, suitable targeted therapies can be considered for administration, including larotrectinib and entrectinib. Larotrectinib is thefirst pan-TRK selective inhibitor undergoing clinical development. In a study that evaluated three phase I/II clinical trials, eligible participants consisted of NTRK fusion-positive patients with locally progressive or metastatic solid tumours.[21]

11. CASE PRESENTATION

In this case study, a 60-year-old patient diagnosed with stage IV lung adenocarcinoma and possessing a KIF5B-RET fusion gene received pralsetinib as the fourth-line treatment. Following this, the patient experienced fever and dyspnea 2.5 months later. However, there was no positive response to the empirical antibiotic therapy that was given. The computed tomography results revealed extensive ground-glass opacities along with multiple cystic lesions in both lungs, in addition to patchy consolidations in the lower right lung. The diagnosis of PJP was definitively established through bronchoalveolar lavage. The patient's condition was successfully managed with a combination of oral trimethoprim/sulfamethoxazole and intravenous caspofungin, along with clindamycin. The patient made a full recovery from PJP. Subsequently, he was rechallenged with pralsetinib, and as of the most recent follow-up, there has been no indication of progressive disease.[2] Upon evaluation, her temperature was recorded at 36.7°C, blood pressure at 144/76 mmHg, heart rate at 77 beats per minute, and the oxygen saturation was 97% while breathing ambient air. There were no signs of anemia or jaundice. Superficial lymph nodes were not palpable.

Breath sounds were diminished in the right lung. Point tenderness was noted on some vertebrae. Laboratory findings highlighted an elevated lactate dehydrogenase (LDH) level of 497 U per liter (reference range: 124–222) and an increased carcinoembryonic antigen (CEA) level of 248.8 ng per milliliter (reference value: <5).

12. FUTURE PERSPECTIVES

In light of the significant outcomes achieved through effective RET inhibition and the resulting resistance to RET-selective inhibitors, the advancement of next-generation RET-TKIs is critically important and is presently the focus of numerous ongoing clinical trials involving patients with advanced NSCLC harbouring RET fusions (NCT04161391, NCT03780517). Among these novel agents, TPX-0046 has shown activity against various RET fusions and mutations, including solvent front mutations, and has exhibited promising antitumor efficacy in patient-derived xenograft tumor models. Next-generation RET-TKIs should not only address resistance mutations but also enhance clinical efficacy and facilitate crossing the blood-brain barrier. Additionally, combining RET inhibitors with other targeted therapies (e.g., MET inhibitors) may provide a valuable therapeutic approach to counteract off-target resistance.

Moreover, the randomized phase III trial LIBRETTO-431 is currently assessing selpercatinib in comparison to platinum-pemetrexed with or without pembrolizumab in treatment-naive patients with locally advanced or metastatic

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RET-positive non-squamous NSCLC (NCT04194944).59 Lastly, the phase III trial Accele RET Lung, which compares pralsetinib to standard-of-care therapy as first-line treatment for RET-positive NSCLC, is currently underway (NCT04222972).[7]

Upon evaluation, her temperature was 36.7°C, blood pressure 144/76 mmHg, heart rate 77 beats per minute, and the oxygen saturation was 97% while breathing ambient air. There were no signs of anemia or jaundice. Superficial lymph nodes were not palpable. Breath sounds were diminished in the right lung. Point tenderness was noted on some vertebrae.[22]

II. CONCLUSION

RET gene fusion–positive non–small cell lung cancer represents a distinct molecular subtype of NSCLC characterized by oncogenic RET rearrangements that drive tumor growth. The identification of RET fusions through molecular testing is crucial, as it enables the use of highly effective targeted therapies. Selective RET inhibitors such as selpercatinib and pralsetinib have demonstrated significant and durable clinical benefits, with improved response rates and favorable safety profiles compared to conventional chemotherapy or multikinase inhibitors. Therefore, comprehensive genomic profiling should be standard practice for all patients with advanced NSCLC to ensure optimal, personalized treatment selection. Ongoing research aims to overcome resistance mechanisms and improve outcomes through next-generation RET inhibitors and combination strategies

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