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Review Article

RET Fusion-Positive Non-small Cell Lung Cancer: The Evolving Treatment Landscape

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Abstract

The objective of this narrative review is to summarize the efficacy and safety of available therapies for rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (NSCLC), including in patients with central nervous system (CNS) metastases. Background information is provided on *RET* rearrangements in NSCLC and the molecular testing options available as well as an overview of clinical guidelines for molecular testing, which recommend broad molecular testing, including for *RET* rearrangements. The efficacy and safety of potential treatments for *RET* fusion-positive NSCLC, including multikinase inhibitors, RET-selective inhibitors, pemetrexed-based therapy, and immunotherapies are reviewed from Phase I/II and `real-world' studies, alongside an overview of primary and secondary resistance mechanisms. The RET-selective inhibitors, selpercatinib and pralsetinib, are preferred first-line therapy options for patients with *RET* fusion-positive metastatic NSCLC and are recommended as subsequent therapy if RET inhibitors have not been used in the first-line setting.

Key words: *RET* fusion-positive NSCLC; treatment; precision medicine; *RET* rearrangement; oncogene-addiction.

Implications for Practice

This comprehensive review covers a range of topics in *RET* fusion-positive NSCLC that have direct relevance to cancer care. Clinically relevant background information on *RET* rearrangements is provided, along with an overview of molecular testing options available and clinical guidelines for molecular testing, noting that application of guideline-based molecular testing in practice is suboptimal. A key focus of the article is on the efficacy and safety of potential treatments for patients with *RET* fusion-positive NSCLC, including those with CNS metastases.

Introduction

Lung cancer remains the leading cause of death from cancer worldwide despite advances in the understanding of risk, biology and immunologic control, and the advent of newer treatment options.[1] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 84% of all lung cancer diagnoses.[2]

The identification of oncogenic drivers and the subsequent development of targeted therapies (TTs) has established biomarker-based treatment for metastatic NSCLC as standard of care (SOC). International guidelines[3-5] recommend that patients whose tumor harbors an actionable molecular aberration should receive the appropriate TT.

Rearranged during transfection (*RET*) rearrangements were first identified as oncogenic drivers in NSCLC in 2012.[6] The proportion of patients with NSCLC who have *RET* rearrangements (ie, fusion-positive disease) is approximately 1%-2%.[7-10] However, in clinical practice, not all patients with NSCLC are tested for *RET* rearrangements; therefore, the proportion of patients with *RET* fusion-positive NSCLC who are eligible for TT will be less than 1%-2%. Improvements can be made in precision medicine with increased biomarker testing and use of TTs, although equitable access varies among countries.[11]

In this review, we summarize the efficacy and safety of all available therapies for *RET* fusion-positive NSCLC, including in patients with central nervous system (CNS) metastases. To identify relevant published data, a pragmatic, structured literature search was carried out in Embase and MEDLINE from January 1, 2015, to March 12, 2021. Full details of the search strategy, study selection, and data extraction are available in the Supplementary Material.

RET Rearrangements and Molecular Testing

Although *RET* mutations and fusions have both been identified in several cancers,[12] only fusions are known to be involved in NSCLC development.[6,9] RET activation typically involves

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ligand binding, interactions with a co-receptor, and homodimerization, resulting in the formation of a multiprotein complex.[13] Most RET fusion proteins lack a transmembrane domain and are chimeric cytosolic proteins that exert their oncogenic influence via constitutive activation of RET kinase domain.[14] This enhances activity of various downstream signaling pathways including phosphatidylinositol-3-kinase/protein kinase B, RAS/RAF, and mitogen activated protein kinase,[13,14] which, in turn, increase cell proliferation, survival, migration, and differentiation (Figure 1).[13]

As noted, *RET* fusions occur in 1%-2% of patients with NSCLC,[7-10,15] and 46% of patients develop brain metastases over their lifetime.[16] *RET* rearrangements correlate with adenocarcinoma histologic subtype in patients with never-smoking status,[17] patients of a younger age (≤60 years),[10,18] and more advanced disease stage,[9] and potentially may confer higher chemosensitivity (particularly to pemetrexed-based regimens).[18,19]

At least 45 *RET* gene fusion partners have been identified in lung cancers, the most common being *KIF5B-RET* (70%-90%), followed by *CCDC6-RET* and *NCOA4-RET*.[9,14,20] Although the clinical implications of specific gene fusion partners are currently not well defined, there are data suggesting that the efficacy of RET-selective inhibitory drugs[21,22] and some multikinase inhibitors (MKIs; eg, vandetanib) may vary depending on the *RET* fusion partner (Section 3). A retrospective analysis in patients with *RET* fusion-positive NSCLC found that selective RET inhibitors were associated with improved survival outcomes versus untreated patients, and irrespective of treatment received, patients with *CCDC6-RET* fusions had better survival outcomes than those with *KIF5B* fusions.[21] Recent data with pralsetinib from the ARROW trial also indicated that patients with *CCDC6-RET*-driven disease may have a better prognosis than those with *KIF5B-RET* driven disease.[22]

Molecular testing techniques available to detect *RET* rearrangement include whole genome sequencing, next-generation sequencing (NGS), reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH) and immunohistochemistry (Table 1).[23,24] Of these, immunohistochemistry testing is the most convenient, but it has poor sensitivity (false positive up to 40%) and specificity (false negative up to 40%) in the detection of *RET* rearrangements[24] and is generally not used for biomarker testing in the workup for NSCLC.

RT-PCR has also been used in *RET* screening studies using predefined primers to detect *RET* fusions. The strength of RT-PCR lies in its rapid turn-around time and the ability to identify the specific *RET* fusion; however, it does not detect unknown fusion partners or variants or those not preselected for the test. Furthermore, poor preservation of RNA in the tumor sample can reduce test sensitivity.

Given the increasing number of potentially actionable driver alterations in NSCLC, there is a need for techniques enabling multiplex testing that is not limited to predefined primers. NGS allows for concurrent screening for gene fusions across thousands of genes or the whole genome without knowledge of the possible fusion partners. Multigene sequencing spares valuable tissue biopsies and can be used on both tumor and liquid samples. Typically, NGS diagnostic tests utilize standard NGS panels that can be customized, and these customized tests can be used to identify gene alterations that can be treated with TTs.[25] According to the European Society for Medical Oncology (ESMO) recommendations for detection of *RET* fusions in daily practice and clinical research,[24] RNA-based NGS is considered the first choice in *RET* detection based on better sensitivity, specificity, and ability to detect fusion partner and expression level of gene fusion (Table 1). This is why RNA-based NGS assays should be considered as first choice in the *RET* screening process. RNA NGS assays require high-quality RNA (ie, the fragile nature of RNA may impact the quality of the assay), whereas DNA NGS assays have more limited sensitivity for detection of fusion genes because they require proper optimization of the panel to include intronic regions.[24] Another testing approach is optimizing mutation and fusion detection in NSCLC by sequential DNA and RNA sequencing, which may be more efficient than parallel DNA and RNA NGS for certain subgroups (eg, smoking-associated NSCLC).[26] Interestingly, a recent retrospective study (RETING) in which patients with NSCLC were identified as *RET* fusion positive or negative as part of routine clinical care showed almost complete concordance between NGS and FISH results upon retesting.[27] *RET* rearrangements can also be detected using circulating tumor DNA (ctDNA).[28] The primary advantages of ctDNA testing are the ability to test for a broad panel of molecular alterations simultaneously, as well as the possibility of sparing the patient invasive procedures and re-collecting the sample easily if needed. The primary concern is the lower sensitivity, especially in patients with fewer extra-thoracic metastatic lesions or lower disease burden.[29]

Clinical Guidelines for Molecular Testing

After a patient has received a morphological diagnosis of NSCLC, the next consideration is therapy-predictive biomarker testing. National Comprehensive Cancer Network (NCCN) NSCLC Panel and ESMO guidelines recommend testing for a number of key predictive biomarkers after

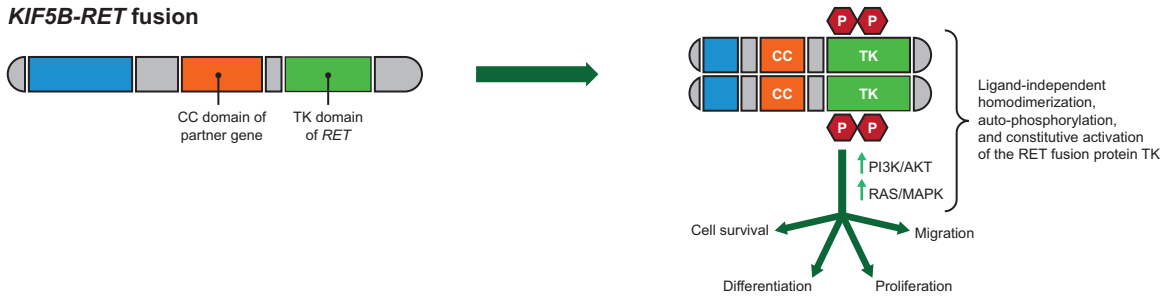

Figure 1. Schematic model of the mechanism of rearranged during transfection (RET) rearrangements (adapted from[13]). Intrachromosomal rearrangement (eg, *KIF5B-RET* fusion) results in ligand-independent homodimerization, auto-phosphorylation, and constitutive activation of the RET fusion protein tyrosine kinase, which leads to increased cell survival, proliferation, migration, and differentiation by activation of downstream pathways including PI3K/AKT and MAPK. Abbreviations: AKT, protein kinase B; MAPK, mitogen activated protein kinase; PI3K, phosphoinositide 3 kinases; RET, rearranged during transfection.

Table 1. Differential features of molecular testing techniques (adapted fromBelli et al.[24]).

Technique	Specificity	Sensitivity	Detection of fusion partner?	Other advantages or disadvantages
IHC	++	++	No	Convenient but low sensitivity and specificity
Break apart FISH	+++	+++	No[a]	Rapid technique that requires little tissue
RT-PCR	+++	++/+++	Yes (known only)	Does not detect unknown fusion partners or those not preselected
RNA-sequencing NGS	+++	+++	Yes	Expensive, requires high-quality RNA, may detect alterations of uncertain clinical significance and gene expression
DNA-sequencing NGS	++/+++	++	Yes	Use of circulating tumor DNA requires shorter turnaround time and is less invasive than tissue/tumor testing

[a]Yes if a specific fusion partner probe is used.
FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction; ++ indicates moderate; +++ indicates high.

patients have been diagnosed with metastatic NSCLC and ideally before initial treatment.[5,30] NCCN guidelines recommend broad molecular testing using a validated test(s) that assesses a minimum of the following potential genetic variants: *EGFR* mutations (category 1), *ALK* rearrangements (category 1), *BRAF* mutations (category 2A), *MET*ex14 skipping mutations (category 2A), neurotrophic tyrosine receptor kinase 1/2/3 gene fusions (category 2A), *RET* rearrangements (category 2A), Kirsten rat sarcoma (*KRAS*) mutations (category 2A), and *ROS1* rearrangements (category 2A).

The ESMO Translational Research and Precision Medicine Working Group launched a project to review the available methods for the detection of *RET* gene alterations, their potential applications, and strategies for their implementation. The recommended approach is that, for patients with NSCLC with available formalin-fixed paraffin-embedded specimens, NGS should be used to detect *RET* fusions; if these specimens are unavailable, FISH or RT-PCR is indicated depending on local availability, cost, and/or the amount of tumor cells available for analysis.[24]

Unfortunately, not all patients will have equal access to therapy-predictive biomarker testing as its availability varies widely between different geopolitical health systems.[5] For example, NGS testing is costly and requires specialized dedicated personnel and is therefore not available at all clinical sites for routine clinical care.[24,31] Consequently, application of guideline-based molecular testing appears to be inconsistent and suboptimal. Observational data from across Europe indicate considerable variability in uptake of biomarker testing for NSCLC, ranging from 65% to 85% (2011–2016) across Germany, Italy, and Spain for patients with advanced nonsquamous NSCLC, although the rate of molecular testing generally increases over time.[32] For example, testing for *EGFR* mutations increased from 71% to 81% during 2014-2017 across five European countries (France, Germany, Italy, Spain, and the UK). Real-world data from Germany found the testing rate for *RET* alterations in NSCLC in routine care was 26.9% for nonsquamous (n = 2921) and 4.5% for squamous (n = 796) histology.[33]

Potential Treatments for *RET* Fusion-Positive NSCLC

Until recently, platinum-based doublets (with or without immunotherapy) were the recommended systemic therapy for all patients newly diagnosed with stage IV NSCLC because of the lack of routine molecular testing at the time. With increased testing for *RET* alterations in clinical practice, the efficacy and safety of a number of potential treatments for *RET* fusion-positive NSCLC have been evaluated in phase I and II trials (Table 2) and in "real-world" (eg, retrospective or observational) studies. These include MKIs, *RET*-selective inhibitory drugs, pemetrexed-based chemotherapy, and immunotherapies.

Multikinase Inhibitors

Several multitarget agents with anti-RET activity have shown inhibition of RET signaling and proliferation of cells expressing *RET* rearrangements in preclinical models[6,34-36] and demonstrated efficacy in clinical trials in unselected patients with NSCLC.[37-40] In general, results of clinical trials in molecularly selected patients with *RET* fusion-positive NSCLC have shown modest efficacy or equivocal results with MKIs (Table 2).

Vandetanib, Cabozantinib, and Lenvatinib

Vandetanib selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), *RET,* and *EGFR* signaling.[34,41] Among 19 patients with *RET* fusion-positive NSCLC who were treated with vandetanib in the phase II LURET trial, 47% experienced an objective response, median progression-free survival (PFS) was 6.5 months, median overall survival (OS) was 13.5 months and OS at 12 months was 52.6%.[42] A post hoc analysis demonstrated that patients treated with vandetanib who harbored the *CCDC6-RET* fusion had a numerically longer PFS and OS than those with the *KIF5B-RET* fusion.[42] Broadly similar findings to those of the LURET study were reported in other phase I or II trials with vandetanib (with or without everolimus)[43,44] (Table 2). The most common grade ≥3 treatment-related adverse events (TRAEs) with vandetanib in the LURET trial were hypertension (68.4%), rash acneiform (15.8%), diarrhea (10.5%), and QT corrected interval prolonged (10.5%); 4 of 19 patients (21%) discontinued therapy because of adverse events (AEs)[42] (Table 2).

Cabozantinib has low nanomolar (ie, strong) activity against RET, in addition to its activity against MET, VEGFR-2, AXL, TIE2, and KIT.[45] In a phase II trial in patients with *RET* fusion-positive NSCLC,[46,47] objective response rate (ORR) was 28%, median PFS was 5.5 months, and median OS was

Table 2. Efficacy and safety summary of phase I and II trials in patients with *RET* fusion-positive NSCLC.

Study name	Study design	Patient population	Efficacy summary	Common grade 3 or worse TRAEs	Other safety data
Broad-spectrum tyrosine kinase inhibitors (MKIs)					
Vandetanib					
NCT01823068[43]	Phase II, multicenter, open-label trial	Metastatic or recurrent NSCLC with a *RET* rearrangement (n = 18)	ORR = 18%, Median PFS = 4.5 months, Median OS = 11.6 months	Hypertension (n = 3), QT prolongation (n = 2), and elevation of aminotransferases (n = 1)	
LURET[42]	Phase II, multicenter, open-label trial	Previously treated *RET*-altered advanced NSCLC (n = 19)	ORR = 47.4% (95% CI 24.4-71.1), Median PFS = 6.5 months (95% CI 3.9-9.3), Median OS = 13.5 months (95% CI 9.8-28.1)	Hypertension (68.4%), rash acneiform (15.8%), diarrhea (10.5%), and QT corrected interval prolonged (10.5%)	4 of 19 pts (21%) discontinued treatment due to AEs
NCT01582191[44]	Phase I trial (in combination with everolimus)	Stage IV NSCLC with an *RET* rearrangement (n = 13)	ORR = 54%, Median PFS = 4.4 months (95% CI 3.4, NR)	Diarrhea (21%), thrombocytopenia (16%), QTc prolongation (5%), and rash (5%)	
Cabozantinib					
NCT01639508[46]	Phase II single-arm trial	Advanced *RET*-altered NSCLC (n = 26) [n = 25 response-evaluable]	ORR = 28% (95% CI 12-49), Median PFS = 5.5 months (95% CI 3.8-8.4), Median OS = 9.9 months (95% CI 8.1-NR)	Asymptomatic lipase elevation (15%), increased ALT (8%), increased AST (8%), thrombocytopenia (8%), and hypophosphatemia (8%)	19 of 26 patients (73%) required a dose reduction due to TRAEs
Lenvatinib					
NCT01877083[54]	Phase II, multicenter, open-label trial	*RET* fusion-positive lung adenocarcinoma (n = 25)	ORR = 16% (95% CI 4.5-36.1), Median PFS = 7.3 months (95% CI 3.6-10.2), Median OS = NR	Hypertension (68%), nausea (60%), decreased appetite (52%), diarrhea (52%), and proteinuria (48%)	6 of 25 pts (24%) discontinued treatment due to TEAEs; 13 of 25 pts (52%) had serious AEs; fatal AEs occurred in 3 pts, 1 of which was considered a TRAE
Alectinib					
ALL-RET[20]	Phase I/II, single-arm, open-label, multi-institutional trial	Previously treated *RET*-altered NSCLC (n = 34)	ORR (RET inhibitor naïve, n = 25) = 4%, Median PFS = 3.4 months (95% CI 2.0-5.4), Median OS = 19.0 months (95% CI 5.4-NR)	In phase II (n = 28), the following grade ≥3 TRAEs were each reported in 1 pt (4%): pneumonitis, creatine phosphokinase increase, bilirubin increase, hyponatremia, and neutropenia	
RXDX-105[a]					
NCT01877811[55]	Phase I/Ib, multicenter, open-label, dose-escalation, and dose-expansion trial	*RET* fusion-positive NSCLC, TKI naïve (n = 31); *RET* fusion-positive lung cancer, prior TKI (n = 9)	ORR (TKI naïve) = 19% (95% CI 8-38), ORR (prior TKI) = 0% (95% CI 0-34)	In pts treated with any dose/any tumor type: fatigue (25%), diarrhea (24%), hypophosphatemia (18%), maculopapular rash (18%), non-maculopapular rash (17%), nausea (15%), elevated ALT (14%) or AST (13%), muscle spasms (13%), decreased appetite (11%), and vomiting (10%)	4 dose-limiting toxicities were reported: rash, fatigue, diarrhea, and hyperbilirubinemia
RET-selective inhibitory molecules					
BOS172738					
NCT03780517[66]	Phase I dose-escalation and dose-expansion phase trial	*RET*-altered advanced solid tumors (NSCLC and medullary thyroid cancers) [n = 67]	NSCLC ORR = 33%	Across both cancer types: creatine phosphokinase increase (54%), dyspnea (34%), facial edema, AST elevation, anemia (25% each), neutropenia, diarrhea (22% each), fatigue (21%), and constipation (20%)	

Table 2. Continued

Study name	Study design	Patient population	Efficacy summary	Common grade 3 or worse TRAEs	Other safety data
Selpercatinib					
LIBRETTO-001[58,59]	Phase I/II, open-label trial	Pts with *RET* fusion-positive advanced NSCLC had previously received at least platinum-based chemotherapy (n = 247) or were previously untreated (n = 69)	Pts who previously received at least platinum-based chemotherapy: ORR = 61% (95% CI 55-67), PFS = 24.9 months (95% CI 19.3-NR), 2-year OS = 69% (95% CI 62-75), Treatment-naive pts: ORR = 84% (95% CI 73-92), PFS = 22.0 months (95% CI 13.8-NR), 2-year OS = 69% (95% CI 55-80)	Safety population of 796 pts with any *RET*-altered cancer: hypertension (13%), increased ALT (9%), increased AST (6%)	One grade 5 TRAE reported; discontinuation due to TRAEs: 3% (25/796)
Pralsetinib					
ARROW[63,65]	Phase I/II, multi-cohort, open-label trial	Pts with *RET* fusion-positive NSCLC who had previously received at least platinum-based chemotherapy (n = 130) or were previously untreated (n = 107)	Pts with previous platinum-based chemotherapy: ORR = 63.1% (95% CI 54.2-71.4); PFS = 16.4 months (95% CI 11.4-22.3); OS = 44.3 months (95% CI 26.9-44.3), Treatment-naive pts: ORR = 77.6% (95% CI 68.5-85.1), PFS = 12.6 months (95% CI 9.2-16.6), OS = NR (95% CI 31.9, NR)	Neutropenia (20%), anemia (12%), and hypertension (12%)	Discontinuation due to TRAEs: 10% (safety population of 281 patients)

[a]The development of RXDX-105 has been discontinued.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; MKIs, multikinase inhibitors; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pt(s), patient(s); RET, rearranged during transfection; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event

9.9 months, although 19 of 26 patients (73%) required a dose reduction due to TRAEs (Table 2).

A retrospective global registry study (GLORY) of 165 patients with *RET* fusion-positive lung cancer across 29 centers showed that the majority of patients were non-smokers (63%), 98% of tumors were classified as adenocarcinoma, and *KIF5B* was the most common *RET* fusion partner (72%). ORRs with cabozantinib (n = 21), vandetanib (n = 11), and sunitinib (n = 10) were 37%, 18%, and 22%, respectively. Median PFS was 3.6, 2.9, and 2.2 months, and the median OS was 4.9, 10.2, and 6.8 months, respectively. In the same registry, among 108 patients treated with chemotherapy, the ORR was 52%, and PFS and OS were 6.6 and 23.6 months, respectively.[48] However, a retrospective study of 39 Chinese patients with NSCLC (9 evaluable) reported no objective response.[49]

Lenvatinib has activity against VEGFR1-3, fibroblast growth factor receptors 1-4, RET, and other targets.[50-53] A total of 25 patients with lung adenocarcinomas and *RET* alterations were treated with lenvatinib in a phase II open-label multicenter study in Japan.[54] ORR was 16%, and median PFS was 7.3 months. The 12-month OS rate was 40% and 67% for patients with *KIF5B-RET* or *CCDC6-RET* fusions, respectively, and median PFS was 3.6 and 9.1 months, respectively. Three fatal AEs were reported, including one considered to be treatment related. Discontinuation of lenvatinib was reported in 6 of 25 patients (24%) due to treatment-emergent AEs (Table 2).

Alectinib

The MKI alectinib showed limited activity in a phase I/II Japanese study in *RET* fusion-positive advanced NSCLC, which was terminated early because of low recruitment.[20] Among 25 RET inhibitor-naïve patients, ORR was 4%, with a median PFS and OS of 3.4 and 19.0 months, respectively (Table 2).

RXDX-105

An exploratory phase I/Ib trial examined the efficacy of the oral VEGFR-sparing MKI RXDX-105.[55] RXDX-105 is known to have inhibitory activity against wild-type RET, as well as select mutant proteins (eg, RETM918T), and chimeric oncoproteins generated by *RET* fusion (KIF5B-RET, CCDC6-RET, NCOA4-RET, and PRKAR1A-RET). Although objective response was reported in 6 of 31 patients (ORR 19%) with *RET* fusion-positive NSCLC, the exact ORR varied significantly according to gene fusion partner (0% with the *KIF5B* partner vs. 67% with non-*KIF5B* partners). The most frequently reported grade ≥3 TRAEs were fatigue, diarrhea, and hypophosphatemia (Table 2). The development of RXDX-105 has been discontinued.

RET-Selective Inhibitory Drugs

Novel highly selective molecules that inhibit RET are recent therapeutic discoveries that target fusion proteins and downstream signaling. Although, in general, these agents appear to have greater efficacy and fewer AEs than MKIs in patients with *RET*-altered NSCLC (Table 2), head-to-head comparative trials in the RET-altered NSCLC population are lacking. Nevertheless, the RET-selective inhibitors selpercatinib and pralsetinib are preferred first-line therapy options for patients with *RET* fusion-positive metastatic NSCLC and are

recommended as subsequent therapy if RET inhibitors have not been used in the first-line setting.[30]

Selpercatinib

Selpercatinib is a highly selective and potent RET inhibitor with CNS activity specifically designed to target activated RET signaling. Selpercatinib is approved in the US for metastatic *RET* fusion-positive NSCLC as well as *RET*-altered thyroid cancers.[56] In the EU, selpercatinib is approved for adults with advanced *RET* fusion-positive NSCLC not previously treated with a RET inhibitor, as well as *RET*-altered thyroid cancers.[57]

In the phase I/II clinical trial LIBRETTO-001,[58,59] selpercatinib was evaluated in adolescent and adult patients with any type of solid tumor harboring an activating *RET* alteration (ie, fusions or mutations). Among 247 patients with NSCLC who had previously received platinum-based chemotherapy (median 2 prior systemic lines), the ORR was 61% and median duration of response (DoR) was 28.6 months. After a median follow-up period of 24.7 months, this population achieved a median PFS of 24.9 months, a 2-year PFS rate of 51% and a 2-year OS rate of 69%.[59]

For the 69 treatment-naïve patients with NSCLC in LIBRETTO-001, the ORR was 84% and the 2-year OS rate was 69%.[59] At a median follow-up of 21.9 months, the median PFS was 22.0 months. Among 796 patients with any *RET*-altered cancer who received at least one dose of study medication, 3% discontinued treatment because of TRAEs, and one grade 5 TRAE (acute respiratory failure) was observed.[59] The most frequently reported grade ≥3 TRAEs were hypertension (13%), increased alanine aminotransferase (ALT) (9%), and increased aspartate aminotransferase (AST) (6%)[59] (Table 2). The most frequently reported AEs (≥25% of patients) were edema, diarrhea, fatigue, dry mouth, hypertension, increased ALT/AST, abdominal pain, constipation, rash, nausea, increased blood creatinine, and headache. The safety profile observed in patients with NSCLC was consistent with that of the full safety patient population.[59]

An off-target effect of selpercatinib is that it inhibits the VEGF signaling pathway, and therefore has the potential to adversely affect wound healing and increase the risk of hypertension and bleeding.[56]

Pralsetinib

Pralsetinib is a highly potent, oral, selective RET inhibitor that targets *RET* alterations, regardless of the tissue of origin. It is approved in the US for the treatment of *RET*-altered lung or thyroid cancers[60] and in the EU for *RET* fusion-positive NSCLC not previously treated with an RET inhibitor.[61]

The ARROW study[62-65] was a multicohort, open-label phase I/II study designed to determine the safety and efficacy of pralsetinib in *RET*-altered solid tumors. In the NSCLC cohort, for the 130 patients previously treated with a platinum-based regimen, the ORR was 63%.[65] Median DoR was 38.8 months, median PFS was 16.4 months, and OS was 44.3 months.

Among 107 treatment-naïve patients, ORR was 78%, median DoR was 13.4 months, median PFS was 12.6 months, and median OS was not reached.[65]

Among patients with *RET* fusion-positive NSCLC in the safety population (n = 281), the most frequently reported TRAEs were neutropenia (46%), increased AST (41%), anemia (38%), leukopenia (34%), increased ALT (30%), constipation (26%), hypertension and fatigue (both 25%), and there was one TRAE (pneumonia) leading to death.[63] The most frequently reported grade ≥3 TRAEs were neutropenia (20%), anemia (12%), and hypertension (12%)[63] (Table 2). At the latest data cutoff, discontinuation due to TRAEs was reported in 10% of patients, and the most common (≥10%) grade ≥3 AEs overall were anemia (23%), hypertension (18%), decreased neutrophil count (14%), pneumonia (13%), and neutropenia (11%).[65]

Similar to selpercatinib, an off-target effect of pralsetinib is inhibition of the VEGF signaling pathway, with the potential to adversely affect wound healing and increasing the risk of hypertension and bleeding.[60]

BOS172738

NCT03780517 is a phase I study of a potent and selective oral RET kinase inhibitor, BOS172738, consisting of a dose-escalation and dose-expansion phase for patients with *RET*-altered advanced solid tumors. Common grade ≥3 TRAEs included elevated creatine phosphokinase, dyspnea, and facial edema (Table 2). ORR was 33%, with a report of response in the CNS, indicating potential activity also in patients with CNS metastasis.[66]

Pemetrexed-Based Chemotherapy

Findings from several real-world studies indicate that *RET* rearranged lung cancers are sensitive to pemetrexed-based systemic therapy and that pemetrexed-based regimens appear to be the optimal choice of cytotoxic chemotherapy in patients with *RET* fusion-positive NSCLC (Table 3).[19,67-69] In a retrospective review of 104 patients, median PFS with pemetrexed-based treatment was significantly improved for patients with *RET* fusion-positive disease compared with *KRAS*-mutant lung cancers.[67] Furthermore, an ORR of 45% was reported,[67] which is greater than the previously reported ORR of 28% with cabozantinib.[70] PFS was also significantly improved with pemetrexed-based versus non-pemetrexed-based regimens as first- and second-line therapy,[19] and PFS results were also favorable for pemetrexed-based regimens compared with the MKI vandetanib or immune checkpoint inhibitors (ICIs).[68]

Immune Checkpoint Inhibitors

Although anti-programmed death-1/programmed death-ligand 1 (PD1/PD-L1)-directed ICIs are widely used to treat patients with cancer (including NSCLC), early trials with oncogene-driven advanced NSCLC demonstrated limited efficacy and a possible increased risk of toxicity.[71] Results of several real-world studies with ICIs in patients with *RET* fusion-positive NSCLC have also been disappointing.

RET-altered tumors, along with other oncogenic-driven NSCLC, tend to have both low PD-L1 expression and low tumor mutational burden. This suggests that these cancers could be defined as "biologically cold" and could partially explain the poor outcomes observed in patients with *RET* fusion-positive NSCLC treated with ICIs.[72-75] Moreover, RET has been validated as an inhibitor of major histocompatibility complex class I expression.[74] Retrospective studies found that patients with any *RET*-altered malignancy who received non-ICI therapy were at a decreased risk of disease progression compared with those who received ICIs.[76] In patients with *RET* fusion-positive NSCLC, in which those with PD-L1 expression >50% received first-line pembrolizumab and those

Table 3. Overview of real-world studies (retrospective analyses) with pemetrexed-based regimens in patients with *RET* fusion-positive NSCLC.

Study	Patient population	Results
Drilon et al[67]	104 patients with NSCLC with *RET* (n = 18) or other (n = 86) rearrangements	Median PFS with pemetrexed-based regimens in *RET* fusion-positive NSCLC (19 months) similar to *ALK*- (19 months) and *ROS1*-rearranged (23 months) disease, and significantly improved vs. *KRAS*-mutant disease (19 vs. 6 months; P < .001)
Lee et al[68]	59 Korean patients	Median PFS results were favorable for pemetrexed-based regimens (9.0 months [95% CI 6.9-11.2] vs. vandetanib (2.9 months [95% CI 2.0-3.8] and ICIs (2.1 months [95% CI 1.6-2.6]). Median OS results were also favorable for pemetrexed-based regimens: 24.1 months (95% CI 15.2-33.0) vs. 9.3 months (95% CI 0.3-18.3) and 12.4 months (95% CI 2.9-21.8)
Shen et al[19]	62 Chinese patients	Median PFS significantly improved with pemetrexed-based vs non-pemetrexed-based regimens as first-line (9.2 vs. 5.2 months; P < .01) and second-line (4.9 vs. 2.8 months; P < .05) treatment. Median OS (n = 38) was 35.2 vs. 22.6 months (P = .052)
Song et al[69]	11 Chinese patients	Median PFS of first-line pemetrexed-based regimens in patients whose disease recurred or became metastatic after surgery (n = 4) was 7.5 months

Abbreviations: CI, confidence interval; ICIs, immune checkpoint inhibitors; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RET, rearranged during transfection; ROS, reactive oxygen species.

with PD-L1 <50% received first-line chemotherapy, PFS was significantly shorter with ICI treatment (2.9 vs. 18.5 months; P < .001).[77] In the real-world IMMUNOTARGET study, median PFS was similar for patients with NSCLC with *RET* fusions treated with anti-PD1/PD-L1 ICI versus the overall cohort (2.1 months; 95% confidence interval [CI] 1.3-4.7 vs. 2.8 months; 95% CI 2.5-3.1), and the difference in OS was also not statistically significant.[72] Other retrospective analyses of patients with *RET*-altered lung cancers also showed poor median PFS with ICI therapy, even in patients with tumors that expressed a higher level of PD-L1,[73,78] and similar OS versus untreated patients.[21]

Brain Metastases in *RET*-Altered NSCLC

Data from registries and retrospective studies have demonstrated up to 25% of patients with RET-altered NSCLC have brain metastases at diagnosis, and approximately 50% of patients will develop brain metastases during their lifetime.[16,79]

Preclinical evidence indicated the potential for enhanced intracranial efficacy of selpercatinib and pralsetinib.[80] Subsequently, both have demonstrated promising intracranial efficacy in the LIBRETTO-001 and ARROW clinical studies, respectively.

Among 15 patients with measurable intracranial metastases at baseline receiving pralsetinib in the ARROW phase I/II study, 8 (53%) had an intracranial response, including 3 complete responses.[65] Median duration of intracranial response was 11.5 months at a median follow-up of 29.7 months.

In the LIBRETTO-001 trial, 106 patients had brain metastasis at baseline, and 26 had measurable disease.[59] Among patients with measurable disease, the intracranial ORR was 85% (27% with CR, 58% with partial response [PR]), with a CNS median DoR of 9.4 months at a median follow-up period of 25.8 months. No disease progression was identified. In all 106 patients, median CNS PFS was 19.4 months at a median duration of follow-up of 22.1 months. In 178 patients with no baseline CNS metastasis, the estimated probability of observing intracranial progression at 2 years was 0.7%.

The ongoing LIBRETTO-431 study[81] has been designed to determine whether selpercatinib can prevent or delay intracranial progression in patients with NSCLC who begin treatment without intracranial involvement. The ongoing AcceleRET Lung study with pralsetinib in patients with *RET* fusion-positive NSCLC will also evaluate time to intracranial progression.[82] In the retrospective SIREN study evaluating selpercatinib in *RET* fusion-positive NSCLC, ORR was 100% among eight patients with measurable brain metastases.[83] In a real-world study evaluating pralsetinib in *RET* fusion-positive NSCLC in Italy, patients with measurable brain metastases (n = 6) had an intracranial ORR of 83%, and intracranial disease control rate was 100%.[84]

Mechanisms of Resistance to RET Inhibition

Acquired resistance can develop with tyrosine kinase inhibitors (TKIs) through activation of alternative mechanisms bypassing the targeted kinase and via secondary on-target mutations that interfere with drug binding (Figure 2).[85,86] Multiple distinct mechanisms of resistance are often seen in the same patient, and sequential RET-directed treatment may require combination therapy with inhibitors targeting alternative MAPK effectors.[87]

Primary Resistance

MET activation was found to be a targetable mediator of resistance to RET-directed therapy in a retrospective study with selpercatinib. Four single-patient protocols were used to combine selpercatinib with the MET/ALK/ROS1 inhibitor crizotinib in patients with an unusually short benefit from selpercatinib, whereas the combination therapy resulted in extended patient responses. Notably, in three of the four cases, *MET* amplification was present prior to selpercatinib exposure, indicating an intrinsic tumor resistance.[88]

MET amplification was observed in 15% of 23 tumor and liquid biopsies from patients with advanced *RET* fusion-positive NSCLC treated with pralsetinib and selpercatinib.[89] Median PFS and duration of therapy in this cohort were 6.3 and 7.2 months, respectively, shorter than has been reported from the phase I/II trials of selpercatinib and pralsetinib, suggesting a bias in the study toward early progressors.

In a retrospective analysis of NGS data from 95 patients with *RET* fusion-positive NSCLC who were treated with a RET inhibitor, primary resistance (disease progression with 6 months) developed in 23% of patients, and *KRAS* and *SMARCA4* mutations were identified only in poor

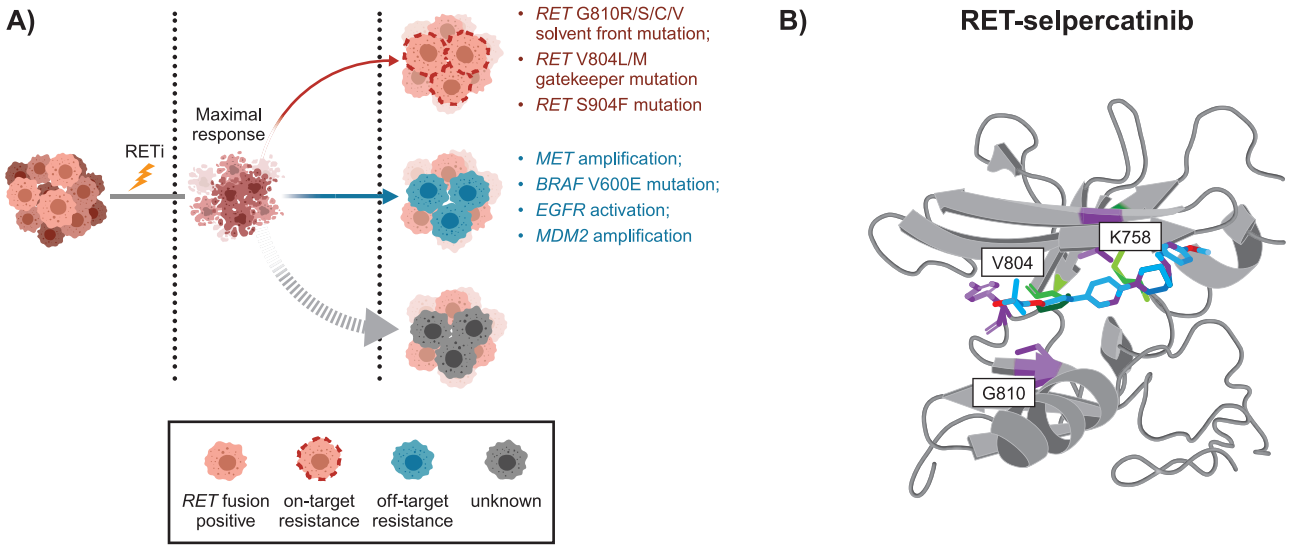

Figure 2. Mechanism of acquired resistance to RET TKIs in *RET* fusion-positive NSCLC (A) and simplified co-crystal structure of RET-selpercatinib complex (B) (adapted from Lu and Zhou, and Thein et al.[85,86]). In part B, V804 is a gatekeeper residue and K758 is a gatewall residue; magenta denotes residues where selpercatinib-resistant mutations have been identified. Abbreviations: CC, coiled coil; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RET, rearranged during transfection; RETi, RET inhibitor; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor.

responders, suggesting a role for these co-mutations in primary resistance.[90]

Secondary Resistance

For the overall drug class, TKIs either occupy both the front and the back clefts of the drug-binding pockets by passing through the gate that separates the front and back clefts or bind only the front cleft. A significant number of cases of mutations leading to TKI drug resistance can be traced back to those occurring at the "gatekeeper" residue in the hinge region of the kinase, directly preventing or weakening the interaction with the inhibitor molecule.[91] In contrast, for RET-selective inhibitory drugs, crystal structure studies of RET-kinase-selpercatinib and RET-kinase-pralsetinib complexes have shown that they both dock one end in the front cleft of the drug-binding pocket without inserting through the gate; this novel binding mode is responsible for their high-affinity binding and their ability to avoid disruption of the gatekeeper mutations. However, it also leaves them vulnerable to non-gatekeeper mutations, such as solvent front mutations (those that reside in the solvent front of the adenosine triphosphate-binding pocket in the catalytic region of the kinase domain).[91]

ctDNA and tissue from patients with *RET* fusion-positive NSCLC and *RET* mutation-positive medullary thyroid cancer who had subsequently developed disease progression after an initial response to selpercatinib was examined.[92] Solvent front mutations were identified at residue glycine (G)810 that limited the inhibitory activity of selpercatinib, pralsetinib, cabozantinib, and vandetanib because of the prevention of drug binding as evaluated in enzyme and cell-based assays. Although tissue was examined from only a small cohort of patients in this study, the approach utilizing a combination of preclinical and clinical studies is a novel one that could result in the acceleration of development of a next-generation selective RET TKI capable of inhibiting both solvent front and gatekeeper mutations.[92] Acquired *RET* mutations affecting the *RET* G810 residue in the kinase solvent front were also identified in a small proportion of tissue and/or plasma samples from patients with *RET* fusion-positive NSCLC following treatment with selpercatinib or pralsetinib.[89,93] Other *RET* mutations of potential relevance to the development of resistance to RET-selective inhibitory drugs include *RET* L730 and V804.[91,93]

MET amplification can also be an acquired/secondary mechanism of resistance to RET inhibitors.[88,89] *MET* amplification was identified in post-treatment tissue/plasma biopsies in patients with *RET* fusion-positive NSCLC resistant to treatment with selpercatinib or pralsetinib. Thus, resistance to selective RET inhibition may be driven by RET-independent mechanisms such as acquired *MET* amplification.[88,89] Secondary *RET* mutations, novel *RET* rearrangements and MET/MYC amplifications were also identified after RET inhibitor therapy in patients with *RET* fusion-positive NSCLC.[90]

Upfront combination treatments may be explored to prevent potentially resistant clones from emerging. To maximize the potential patient benefit, identifying the appropriate patients for each specific combination, determining when combination strategies should be implemented, and testing the potential of alternating different treatment regimens will all be critical to prevent or delay resistance.[86,87]

RET Fusions as a Mechanism of Resistance to Other Primary Oncogene Drivers

RET-selective inhibitory drugs may have a role in patients whose tumors become resistant to other primary oncogene drivers, such as *EGFR* mutations.[94] Twelve patients having advanced *EGFR*-mutated NSCLC with an acquired *RET* fusion detected from tissue or plasma following osimertinib therapy received selpercatinib in combination with osimertinib, across three selpercatinib compassionate access programs.[95] Among the evaluable patients, five had a response (50%), which included four confirmed PRs and one unconfirmed PR. For patients who experienced a response, the median DoR was 11 months (range 7.4 to >16.7). Thus, for patients with *EGFR*-mutant NSCLC with an acquired *RET*

fusion as a mechanism of EGFR inhibitor resistance, the addition of selpercatinib to osimertinib is feasible and potentially effective but remains investigational. This combination will be evaluated prospectively in the phase II ORCHARD study (NCT03944772).

Future Directions and Conclusions

The recent FDA approvals of selpercatinib and pralsetinib have led to expanded treatment options for patients with *RET* fusion-positive NSCLC. Current NCCN guidelines[30] indicate that *RET* rearrangements are considered "established biomarkers," reflecting the recently published clinical trial data for their corresponding TTs. Selpercatinib and pralsetinib are first-line therapy options for patients with *RET* fusion-positive metastatic NSCLC and are recommended as subsequent therapy if RET inhibitors have not been used as first-line therapy.

Next-generation RET inhibitors such as TPX-0046, which has demonstrated activity in drug-resistant and drug-naïve *RET*-driven preclinical cancer models, may also provide treatment options in the future, although further research is needed. Results of an ongoing phase I/II trial with this agent (NCT04161391) in patients with advanced solid tumors harboring *RET* fusions or mutations will be of interest. Other next-generation RET inhibitors, such as LOXO-260 and TAS0953/HM06,[96] have also demonstrated robust activity in preclinical models of *RET* alterations, suggesting the potential to extend durable disease control for patients with *RET*-altered cancers following the development of acquired resistance to RET-selective drugs. For example, TAS0953/HM06 has shown inhibitory effects against a range of mutations, including *RET* solvent front mutations.[96] An ongoing trial with LOXO-260 (NCT05225259) will evaluate the drug in patients with *RET*-altered tumors that did not or are no longer responsive to treatment with currently available RET inhibitors.

Novel combinations for overcoming drug resistance such as the addition of the MET inhibitor crizotinib to selpercatinib in patients with increased MET expression may be a useful strategy in the treatment of *RET* fusion-positive NSCLC, although patient numbers are limited.[88] In four selpercatinib-treated patients with *RET* fusion-positive NSCLC with *MET* amplification (identified in post-treatment biopsies), the addition of crizotinib to selpercatinib provided clinical benefits such as relief of bone pain and/or partial responses.[88] Cabozantinib or tivantinib (an MET inhibitor that has been evaluated in advanced solid tumors) may also be beneficial in this setting, although data are currently not available for these combinations.

Of interest will be findings from the ongoing phase III LIBRETTO-431 trial, which will compare the efficacy of selpercatinib versus SOC chemotherapy with or without pembrolizumab in untreated patients with locally advanced/metastatic *RET* fusion-positive non-squamous NSCLC.[81] In addition, AcceleRET Lung, an international, open-label, randomized, phase III study, will evaluate the efficacy and safety of pralsetinib versus SOC for first-line treatment of advanced/metastatic *RET* fusion-positive NSCLC (NCT04222972).[82,97]

TTs are also under evaluation in settings such as early disease and adjuvant treatment of NSCLC. The LIBRETTO-432 phase III trial in patients with *RET* fusion-positive NSCLC with early-stage disease (IB-IIIA) will evaluate the efficacy and safety of adjuvant selpercatinib versus placebo following definitive radiotherapy or surgery with a curative intent (NCT04819100).[98] The phase II NAUTIKA1 trial will evaluate multiple therapies in biomarker-selected patients with resectable stages IB-III NSCLC (NCT04302025), including pralsetinib neoadjuvant treatment in the *RET* fusion-positive cohort.

Despite the benefits of TT, lack of awareness and inconsistent application of guideline-based molecular testing is widespread across all regions of the world.[99] As more actionable targets are identified, there is a greater need for the use of multigene testing techniques to optimize sample analysis and reduce time before treatment commencement.

RET-selective inhibitory drugs, such as selpercatinib and pralsetinib, have demonstrated favorable efficacy and tolerability in patients with *RET*-altered cancers and have additionally shown promising efficacy in patients with brain metastases, which eventually develop in approximately half of patients with *RET* fusion-positive NSCLC. Selpercatinib and pralsetinib are preferred first-line therapy options for patients with *RET* fusion-positive metastatic NSCLC and are recommended as subsequent therapy if RET inhibitors have not been used in the first-line setting. Next-generation RET inhibitors are currently under development to overcome the solvent front *RET* mutations that emerge in some patients treated with selective RET inhibitors.

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Conflict of Interest

Silvia Novello reported consulting/advisory relationships (speakers bureau or advisor) with Eli Lilly, MSD, Roche, BMS, Takeda, Pfizer, AstraZeneca, and Boehringer Ingelheim. Raffaele Califano reported honoraria and consultancy fees from AstraZeneca, Boeringher Ingelheim, Lilly Oncology, Roche, Pfizer, MSD, Bristol Myers Squibb, Takeda, Bayer, Ipsen, Janssen, and Novartis, grants paid to Institution for conduct of clinical trials or contracted research from Roche, AstraZeneca, Pfizer, Clovis, Lilly Oncology, MSD, BMS, Abbvie, Takeda, and Novartis, stock ownership with The Christie Private Care; non-remunerated activities include Principal Investigator for trials with Roche, AstraZeneca, Pfizer, Clovis, Lilly Oncology, MSD, BMS, Abbvie, Takeda, and Novartis; other non-remunerated membership: ESMO and EORTC. Niels Reinmuth reported honoraria for educational lectures and advisory services from AstraZeneca, Boehringer Ingelheim, BMS, MSD, Pfizer, Roche, Lilly, Takeda, Merck, Sanofi, and Janssen. Antonella Tamma and **Tarun Puri** are employees of Eli Lilly and Company with stock options.

Author Contributions

Conception/design: A.T., T.P. Provision of study material: A.T., T.P. Collection and/or assembly of data: A.T., T.P. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval: All authors.

Data Availability

No new data were generated or analyzed in support of this research.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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