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REVIEW ARTICLE

Treatment of non–small cell lung cancer with *RET* rearrangements

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Abstract

Aberrant activation of the *RET* oncogene by mutations or gene fusions drives various malignancies, including 1%–2% of all non–small cell lung cancers (NSCLCs) that harbor *RET* gene fusions. Initial attempts to target *RET* fusion–positive NSCLC with poorly selective multikinase RET inhibitors were associated with significant toxicities and limited efficacy. Two highly potent and selective RET small-molecule inhibitors, selpercatinib and pralsetinib, were granted accelerated approval for advanced *RET* fusion–positive NSCLC by the US Food and Drug Administration, and have been shown to be highly effective both in treatment-naive and previously treated patients with NSCLC. Selpercatinib has shown superiority over chemotherapy in a phase 3 study (LIBRETTO-431) in previously untreated patients with *RET* fusion–positive NSCLC, which established its place as the standard of care in this patient population. This review discusses the biology and clinical characteristics of *RET*-rearranged NSCLC and summarizes the evolution of treatment strategies, current understanding of mechanisms of resistance, and development of new-generation agents to overcome resistance.

KEYWORDS
lung cancer, non–small cell lung cancer (NSCLC), pralsetinib, RET, *RET* fusion, *RET* NSCLC, *RET* rearrangements, selpercatinib

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality globally by accounting for 1.8 million deaths worldwide.[1] Non–small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, with adenocarcinoma being the most common histological subtype. Molecular characterization of NSCLC has identified targetable oncogenic alterations in more than half of all lung adenocarcinomas.[2,3] International guidelines recommend mandatory biomarker testing in patients with newly diagnosed NSCLC to guide treatment selection with drugs directed at molecular targets approved for routine use as well as broader testing that may be used to support early drug access or clinical trials.[4–6]

The rearranged during transfection (*RET*) gene may be aberrantly activated by mutations or gene fusions in approximately 2% of all cancers.[7] Although *RET*-activating mutations most frequently occur

in medullary thyroid carcinoma (MTC),[8] *RET* gene fusions are found in 5%–10% of papillary thyroid carcinoma (PTC) cases and 1%–2% of all NSCLCs.[9,10]

Early clinical trials using poorly selective multikinase inhibitors (MKIs) in *RET*-rearranged NSCLC yielded disappointing results, with low response rates (16%–32%) and a modest median progression-free survival (mPFS) of 2.2–7.3 months coupled with substantial toxicities.[11–15] The recent advent of potent and selective RET inhibitors, with enhanced efficacy and reduced toxicity, has transformed the treatment landscape for *RET*-rearranged NSCLC. In May 2020, the US Food and Drug Administration (FDA) granted accelerated approval of selpercatinib, a potent selective RET inhibitor, for adults with advanced *RET* fusion–positive NSCLC and *RET*-mutant thyroid cancers, which marked the first approval of a targeted therapy for *RET*-driven malignancies.[16] The timeline of key genomic discoveries and drug development in *RET*-rearranged NSCLC is summarized in Figure 1.

Despite the remarkable and often durable responses seen with selective RET inhibitors, the eventual emergence of drug resistance remains problematic. In this review, we summarize the current knowledge and progress in targeting *RET*-rearranged NSCLC, with an emphasis on current treatment strategies, and explore key challenges in addressing resistance to RET-targeted therapy.

BIOLOGY AND CLINICAL CHARACTERISTICS

Biology of RET

The *RET* proto-oncogene, located on chromosome 10q11.2, encodes a transmembrane glycoprotein receptor tyrosine kinase (RTK) that contains three components: a large extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain.[17–19] *RET* activation involves formation of a multimeric protein complex with ligands of the RET receptor, which results in autophosphorylation of several intracellular tyrosine residues.[20–22] This results in the activation of downstream signaling pathways, including the Ras/MAPK and PI3K/AKT pathways, that regulate cellular differentiation and proliferation.[17,19]

RET as an oncogene

RET signaling is essential for renal organogenesis and enteric neurogenesis.[23] Germline *RET* mutations are linked to Hirschsprung disease, a congenital disease characterized by failure of enteric nervous system development, and with multiple endocrine neoplasia 2 syndrome.[20,24]

RET can act as an oncogene in various malignancies when aberrantly activated,[18,20] predominantly via gain-of-function missense mutations in both the extracellular and cytoplasmic domains and chromosomal rearrangements that generate fusion genes containing the kinase domain of RET.[20,25]

In hereditary MTC, germline *RET* mutations have been reported in more than 90% of patients.[26] In contrast, somatic *RET* mutations are found in approximately 50% of patients with sporadic MTC.[27] *RET* mutations, particularly the M918T mutation, confer a poor prognosis in MTC.[27] *RET* rearrangements are found in PTCs (20%–70%), Spitz tumors (3%), approximately 1%–2% of NSCLCs, and rarely in other malignancies, including colorectal cancer and breast cancer.[25,28,29]

In NSCLC, oncogenic activation of *RET* occurs via chromosomal rearrangements, which result in the fusion of the 3′ portion of *RET*,

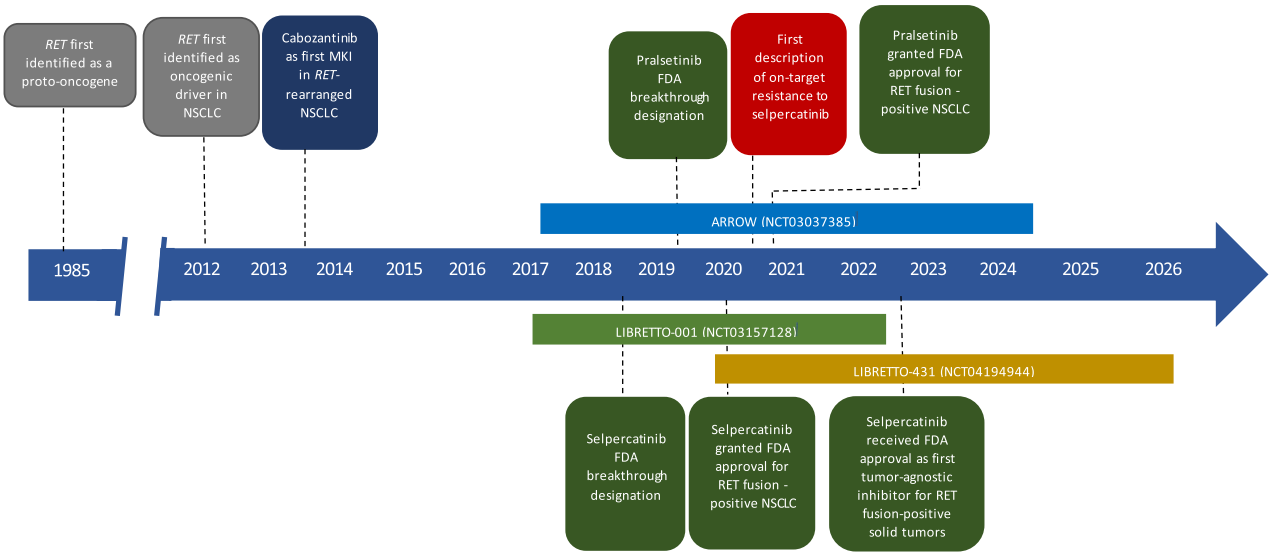

FIGURE 1 Timeline of genomic discoveries and key drug development in *RET*-rearranged NSCLC. *RET* was first identified as a proto-oncogene in 1985, and was first reported as an oncogenic driver in NSCLC in 2012. Since their identification, *RET* rearrangements have been investigated as potential therapeutic targets in several prospective clinical trials. Two selective RET inhibitors, selpercatinib and pralsetinib, were granted accelerated FDA approval for advanced *RET* fusion–positive NSCLC. FDA indicates US Food and Drug Administration; MKI, multikinase inhibitor; NSCLC, non–small cell lung cancer.

including the kinase domain on chromosome 10, with a 5′ upstream partner gene such as *KIF5B*.[10,30] *RET* fusion proteins demonstrate oncogenic properties via increased expression together with dimerization of the upstream partner gene, which leads to the aberrant activation of *RET* in cells.[31] The specific fusion partner confers distinct properties that may affect drug sensitivity, at least in preclinical models.[30]

Clinical and molecular characteristics in NSCLC

RET rearrangements are found in 1%–2% of all patients with NSCLC, and are typically enriched in adenocarcinoma histology.[7,9,32,33] The clinical characteristics of this distinct population include younger patients with minimal or no prior smoking history and more advanced disease at diagnosis.[9,32,34] Notably, approximately 20% of patients have central nervous system (CNS) metastases present at diagnosis,[34] with a lifetime cumulative prevalence of approximately 45%.[35]

The most frequent upstream fusion partner in *RET*-rearranged NSCLC is *KIF5B* (70%–90%), followed by *CCDC6* (10%–25%).[11,34] Other fusion partners identified include *NCOA4* (2%), *ARL9* (2%), *ERC1* (1%), and *KIAA1468* (1%).[11,34] In contrast, *CCDC6* is the most commonly identified fusion partner in *RET*-rearranged PTC.[33] *RET* rearrangements are typically mutually exclusive with other oncogenic driver alterations such as *EGFR* or *KRAS* mutations and *ALK* or *ROS1* rearrangements.[9] In NSCLC, *TP53* is the most commonly observed comutation (19%).[34] *RET*-rearranged NSCLCs typically have lower programmed death ligand 1 (PD-L1) expression and tumor mutation burden (TMB), with a median PD-L1 of 10%–26% compared with 45%–50% and a median TMB of 2.5 mutations per megabase as compared to 9.8 mutations per megabase in other NSCLC biopsies.[34,36–38]

MOLECULAR TESTING OF *RET*-REARRANGED NSCLC

The recommended diagnostic approach for *RET* fusion detection is the use of a multigene next-generation sequencing (NGS) panel to test for a range of actionable oncogenic alterations in NSCLC, preferably with RNA-based testing, which has high sensitivity and specificity to detect *RET* fusions.[4–6] If NGS is not available, fluorescence in situ hybridization (FISH) or reverse transcription–polymerase chain reaction–based assays are the preferred approaches.[4–6] Immunohistochemistry (IHC) as a standalone test has limited value in detecting *RET*-rearranged NSCLC.

European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network guidelines strongly recommend mandatory molecular testing, including testing for *RET* rearrangements, for newly diagnosed patients with nonsquamous histology and selected cases of squamous histology.[5,6] A summary of the various diagnostic methods used to detect *RET* alterations is found in Table 1 (modified from the ESMO Translational Research and Precision Medicine Working Group, a collaborative project to review the current methods and strategies to detect *RET* alterations[4]).

For patients with unavailable or insufficient tumor tissue, liquid biopsy should be considered. Limitations to this approach include lower sensitivity, particularly in patients with a lower burden of

TABLE 1 Summary of features of molecular testing techniques for *RET*-rearranged NSCLC.

Method	Sensitivity	Specificity	Detection of fusion partner	Strengths	Weaknesses
IHC	Low to moderate	Moderate	No	Convenient, short turnaround, low number of cells required, low cost	Low to moderate sensitivity and specificity, not recommended as a standalone test
FISH	High	High	No, unless a specific fusion partner probe is used	Rapid technique, minimal tissue required for testing	Not optimal for extensive and multiplex screening, labor intensive, requires good-quality tissue
RT-PCR	Moderate to high	High	Yes, but unable to detect novel partners	Lower cost and less tissue required than multiple single assays	Unable to detect an unknown fusion partner, requires good-quality tissue
DNA-seq NGS	Moderate to high	High	Yes	Able to identify somatic mutations with low-variant allele frequencies and interrogate multiple gene targets	Limited sensitivity for detection of fusion genes, particularly if a fusion partner has not been characterized
RNA-seq NGS	High	High	Yes	Preferred method of testing where available, able to detect novel gene fusion with complex rearrangements	Expensive, requires high-quality RNA

Note: Modified from the European Society for Medical Oncology Translational Research and Precision Medicine Working Group. RNA-based NGS is the preferred method of testing where available for *RET* rearrangements.

Abbreviations: DNA-seq NGS, DNA sequencing by next-generation sequencing; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NSCLC, non–small cell lung cancer; RNA-seq NGS, RNA sequencing by next-generation sequencing; RT-PCR, reverse transcription–polymerase chain reaction.

disease, although newer NGS-based techniques in development may overcome this limitation.[39,40]

TREATMENT

Chemotherapy

The efficacy of chemotherapy in patients with *RET*-rearranged NSCLC has been described in several small retrospective series and in the control arm of the LIBRETTO-431 study (discussed below).[41–44] A retrospective series of 18 patients with *RET*-rearranged lung adenocarcinoma, treated with pemetrexed-based chemotherapy, had an mPFS of 19 months and an overall response rate (ORR) of 45%.[42] In the Global, Multicenter *RET* Registry (GLORY), 84 patients with advanced disease received platinum-based chemotherapy in the first-line setting. Of the 65 evaluable patients, 51% (33 of 65) achieved a complete or partial response, with an mPFS of 7.8 months and median overall survival (mOS) of 24.8 months (in the 70 patients with survival data).[11]

Immunotherapy

Data from retrospective studies indicated limited or no response to single-agent programmed cell death 1 (PD-1) inhibitor therapy. The IMMUNOTARGET registry included 16 patients with *RET*-rearranged NSCLC who received immunotherapy.[36] Only one patient achieved a complete or partial response, with an mPFS of 2.1 months.[36] In addition, a retrospective series from the Memorial Sloan Kettering Cancer Center demonstrated a 0% response rate among 13 evaluable patients, including patients with a PD-L1 expression of >1% (three patients with a PD-L1 expression of >10%).[45] Outcomes with combination chemotherapy and immunotherapy were reported in the LIBRETTO-431 study (discussed below).

Nonselective RET inhibitors

MKIs have substantial activity against other kinases in addition to RET, including, but not limited to, VEGFR2, MET, KIT, BRAF, and EGFR.[46] The nonselectivity for RET and potent inhibition of non-RET targets limit the efficacy of MKIs in *RET*-rearranged NSCLC. Several MKIs, such as cabozantinib, vandetanib, lenvatinib, and RXDX-105 (development discontinued), demonstrated modest clinical activity against *RET*-rearranged NSCLC, with an ORR of 16%–47%, mPFS between 2.2 and 7.3 months, and mOS of 4.9–11.6 months (summarized in Table 2).[11–15,47] Concurrent inhibition of non-RET targets confers the most significant toxicities seen with MKIs. Commonly observed grade 3 or 4 adverse events (AEs) related to VEGFR2 are hypertension (17%–68%) and proteinuria (16%), and those related to EGFR inhibition are associated with diarrhea (5%–52%) and rash (7%).[11–15,47] The use of MKIs frequently led to dose reductions (24%–73%) and permanent drug discontinuations (8%–24%).[11–15,47]

TARGETING RET WITH SELECTIVE RET INHIBITORS

Novel highly selective molecules that inhibit RET have been developed to overcome the limitations of MKIs. The key attributes of selective RET inhibitors include increased potency, the potential to inhibit diverse *RET* resistance mutations, improved CNS penetrance, and greater selectivity for RET kinase compared to VEGFR2 or other kinases, which lead to fewer treatment-related toxicities.[41,48–51] In addition, selective RET inhibitors have demonstrated activity on a

TABLE 2 Summary of key nonselective RET inhibitor trials in *RET* fusion–positive NSCLC.

Agent	Study	Study design	Patient population, No.	ORR, No. (%)	mPFS, months	mOS, months	Safety and toxicities (%)	Reference
Cabozantinib	NCT01639508	Phase 2, single arm	Advanced *RET*-altered NSCLC, 26 (25 evaluable)	7 of 25 (28)	5.5	9.9	≥G3 increased ALT (8), increased AST (8), thrombocytopenia (8)	Drilon 2016[12]
Vandetanib	NCT01823068	Phase 2, multicenter, open label	Metastatic *RET*-rearranged NSCLC, 17	3 of 17 (18)	4.5	11.6	≥G3 hypertension (17), QT prolongation (12), elevation of transaminases (6)	Lee 2017[13]
	LURET	Phase 2, multicenter, open label	Previously treated *RET*-altered advanced NSCLC, 19	9 of 19 (47)	4.7	11.1	≥G3 hypertension (68), rash (16), diarrhea (10), QT prolongation (10)	Yoh 2021[14]
Lenvatinib	NCT01877083	Phase 2, multicenter, open label	*RET* fusion–positive lung adenocarcinoma, 25	4 of 25 (16)	7.3	NE	≥G3 hypertension (68), nausea (60), diarrhea (52)	Hida 2019[15]

Abbreviations: AST, aspartate aminotransferase; G3, grade 3 toxicities per Common Terminology Criteria for Adverse Events; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NSCLC, non–small cell lung cancer; ORR, objective response rate.

wide spectrum of *RET* alterations, including *KIF5B–RET*, *CCDC6–RET*, M918T, C634W, and gatekeeper mutations V804L and V804M.[25]

Two of these selective small-molecule inhibitors, selpercatinib (LOXO-292) and pralsetinib (BLU-667), have progressed rapidly through clinical trials and entered clinical practice (summarized in Table 3). On the basis of the results of the phase 1 clinical trials conducted with selpercatinib and pralsetinib, both agents were granted breakthrough therapy designation by the FDA for advanced *RET* fusion–positive NSCLC post–platinum chemotherapy (September 2018 for selpercatinib on the basis of the LIBRETTO-001 trial; September 2020 for pralsetinib on the basis of the ARROW trial).[16,56] In May 2020, the FDA granted accelerated approval to selpercatinib for adults with advanced *RET* fusion–positive NSCLC and *RET*-mutant thyroid cancers,[16] and in September 2022, selpercatinib received FDA approval as the first tumor-agnostic inhibitor for *RET*-fusion solid tumors.[57]

Selpercatinib

Mechanism of action

Selpercatinib (LOXO-292) is a novel, highly selective oral RET kinase inhibitor that inhibits wild-type RET and multiple mutated *RET* isoforms and, to a degree, spares non-RET kinases such as VEGFR and FGFR.[50] It was designed to have favorable pharmacokinetic properties, including high oral bioavailability, CNS penetrance, predictable exposure, and a low potential for drug interactions.[16,50,52]

Preclinical models

In preclinical models, selpercatinib demonstrated potent activity against *RET*-fusion and *RET*-mutant cell lines but caused 20- to 1700-fold less growth inhibition in 83 cell lines against non-RET kinases.[50] Selpercatinib was 60- to 1300-fold more effective in inhibiting *KIF5B–RET* as compared to MKIs, as well as demonstrating antitumor activity against models harboring the V804M acquired resistance gatekeeper mutation,[50] a known acquired resistance mutation against which MKIs are postulated to be ineffective.

Clinical activity in first-line and later line settings

The efficacy of selpercatinib was first evaluated in LIBRETTO-001,[49,52] a phase 1/2, single-arm, multicenter, open-label, multicohort study that included patients with advanced solid tumors with *RET* fusion or mutation. The study included 247 patients with advanced NSCLC who had received prior platinum-based chemotherapy (median, two lines of therapy; 34% received prior MKIs) and 69 treatment-naive patients, all received selpercatinib.[49,52] In the 247 patients who had previously received platinum-based chemotherapy, the ORR was 61% (151 of 247).[49] The median duration of

TABLE 3 Summary of key selective RET inhibitor trials in *RET* fusion–positive NSCLC.

Agent	Study	Study design	Patient population, No.	ORR, No. (%)	mPFS, months	Intracranial ORR, No. (%)	OS, %	Safety and toxicities (%)	Reference
Selpercatinib	LIBRETTO-001	Phase 1/2, multicohort, open label, single arm	Metastatic *RET* fusion–positive NSCLC (prior platinum-based chemo, 247; treatment naive, 69)	Prior chemo, 151 of 247 (61); treatment naive, 58 of 69 (84)	Prior chemo, 24.9; treatment naive, 22.0	14 of 17 (82)	Prior chemo, 3 year, 58.5; treatment naive, 3 year, 57.1	≥G3 ALT increase (9), AST increase (6), hypertension (9), prolonged QT (2)	Drilon 2023[49]; Drilon 2020[52]; Subbiah 2021[53]
	LIBRETTO-431	Randomized, phase 3; randomized 2:1 to selpercatinib or platinum-based chemo with or without pembrolizumab (SOC)	Unresectable stage IIIB, IIIC, or IV *RET* fusion–positive NSCLC (212 in ITT population; 129 on selpercatinib and 83 on SOC)	Selpercatinib, 109 of 129 (84); SOC 54 of 83 (65)	Selpercatinib, 24.8; SOC, 11.2	Selpercatinib, 14 of 17 (82); SOC, 7 of 12 (58)	NR	≥G3 ALT increase (22), AST increase (13), hypertension (20), QT prolongation (9), thrombocytopenia (3)	Zhou 2023
Pralsetinib	ARROW	Phase 1/2, multicohort, open label, single arm	Advanced *RET*-altered NSCLC (prior platinum-based chemo, 136; treatment naive, 75)	Prior chemo, 80 of 136 (59); treatment naive, 54 of 75 (72)	Prior chemo, 16.5; treatment naive, 13.0	5 of 9 (56)	Prior chemo, 44.3; treatment naive, NR	≥G3 neutropenia (22), anemia (18), hypertension (13)	Gainor 2021[54]; Griesinger 2022[55]

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; chemo, chemotherapy; G3, grade 3 toxicities per Common Terminology Criteria for Adverse Events; ITT, intention-to-treat; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; SOC, standard of care.

response (mDoR) and mPFS were 28.6 and 24.9 months, respectively.[49] At a median follow-up of 24.7 months, 38% of patients were alive and progression free, and the estimated proportion of patients alive at 2 years was 69%.[49] Selpercatinib induced rapid and durable responses, with a median time to response of 1.9 months and the longest response ongoing at 43.3 months.[49]

In the 69 patients in the treatment-naive subgroup, the ORR was 84% (58 of 69).[49] The mDoR and mPFS were 20.3 and 22.0 months, respectively.[49] At a median follow-up of 21.9 months, the estimated proportion of patients alive and progression free at 2 years was 42%.[49] The median time to response was 1.8 months, with the longest response to selpercatinib ongoing at 39.3 months. Responses were observed regardless of the specific *RET* fusion partner.[49]

LIBRETTO-431, a randomized phase 3 study, evaluated the efficacy of selpercatinib in the first-line setting in comparison to the current standard-of-care (SOC) platinum-based chemotherapy with or without pembrolizumab control.[41] From March 2020 through August 2022, 256 patients were randomized to receive either selpercatinib (n = 158) or control (n = 98).[41] The intention-to-treat pembrolizumab population included 212 patients (129 patients received selpercatinib; 83 patients received SOC).[41]

In the preplanned interim efficacy analysis in the intention-to-treat pembrolizumab population, mPFS was 24.8 months with selpercatinib and 11.2 months with chemotherapy with or without pembrolizumab (hazard ratio [HR], 0.46).[41] In the preplanned subgroup analyses, PFS was longer with selpercatinib across all subgroups, including those based on PD-L1 expression, Eastern Cooperative Oncology Group performance status, and intracranial disease at baseline.[41] The ORR was higher in the selpercatinib group (84%) versus control (65%).[41] Responses with selpercatinib were durable with an mDoR of 24.2 months, as compared to 11.5 months with control.[41] Similar results were observed in the overall intention-to-treat population (which represented all patients enrolled), with an mPFS of 24.8 months with selpercatinib and 11.2 months with control (HR, 0.48).[41] OS data are immature. However, with 21 months of median follow-up, more than 78% of patients in each group were still alive, with approximately 60% of patients in the control group crossing over to receive selpercatinib.[41]

CNS activity

In LIBRETTO-001, 80 patients had brain metastases at baseline.[53] The intracranial ORR (iORR) was 82% (18 of 22), including 23% complete responses (five of 22).[53] The median CNS DoR was 10.1 months.[49] The intracranial mPFS was 13.7 months in the full NSCLC population.[53]

In LIBRETTO-431, 42 patients had confirmed brain metastases at baseline, 29 of whom had measurable disease (17 in the selpercatinib group; 12 in the control group).[41] The iORR was 82% (14 of 17) in the selpercatinib group and 58% (seven of 12) in the control group.[41] There was a 35% (six of 17) complete intracranial response in the selpercatinib group and 17% (two of 12) in the control group.[41] At 12 months, 76% of patients had an ongoing intracranial response with selpercatinib, compared to 63% in the control group.[41] Data on the median duration of intracranial response were immature.

Safety and toxicities

The safety of selpercatinib was characterized in the LIBRETTO-001 study (796 patients in the full safety population from the registrational data set) together with the LIBRETTO-431 study (256 patients).[41,49] The most common grade >3 treatment-emergent adverse events (TEAEs) observed with selpercatinib were hypertension (20.0%), alanine transaminase (ALT) increase (11%–22%), aspartate aminotransferase increase (9%–13.0%), diarrhea (1%–5%), and QT prolongation (5%–9.0%).[41,49] Artifactual elevations of creatinine, mostly grade 1–2, were reported in 15%–25% of patients.[41,49,58] In LIBRETTO-431, 10% (16 of 158) of patients in the selpercatinib group and 2% (two of 98) of patients in the control group discontinued treatment because of AEs.[41] Additional toxicities, notably chylous effusions, had been reported with selective RET inhibitors, most commonly observed in selpercatinib (7%), in a retrospective study.[59]

Pralsetinib

Pralsetinib (BLU-667) is a highly selective oral RET inhibitor that potently targets oncogenic *RET* fusions and mutations, including V804M acquired gatekeeper mutations.[54,60] Similar to selpercatinib, pralsetinib has a low affinity for off-target kinases, with a more favorable toxicity profile compared to MKIs. In preclinical models, pralsetinib was 88-fold more selective for RET than VEGFR2, a common target for MKIs.[60]

The ARROW study[54,55] is a phase 1/2, single-arm, multicenter, multicohort, open-label study to determine the safety and efficacy of pralsetinib in *RET*-altered solid tumors. In the updated analysis of the NSCLC cohort,[55] 136 patients with previous platinum-based chemotherapy received pralsetinib. ORR, mPFS, and mDoR were 59% (80 of 136), 16.5 months, and 22.3 months, respectively.[55] Among the 75 untreated patients, ORR, mPFS, and mDoR were 72% (54 of 75), 13.0 months, and not reached after a median follow-up of 7.4 months, respectively. mOS was not reached.[55]

The most common treatment-related serious AEs were pneumonitis (5%) and pneumonia (4%–6%).[55] The most common grade >3 TRAEs were neutropenia (22%), anemia (18%), and hypertension (13%).[55] In patients with *RET* fusion–positive NSCLC, 7% (20 of 281) discontinued pralsetinib because of AEs. There was one fatal event related to pralsetinib in the treatment-naive group from pneumonia.[55]

AcceleRET-Lung (NCT04222972), a phase 3 study of first-line pralsetinib versus platinum chemotherapy ± pembrolizumab in patients with advanced *RET* fusion–positive NSCLC, is ongoing.

MECHANISMS OF RESISTANCE

Selective RET inhibitors induce significant and durable tumor responses in *RET*-rearranged NSCLC, with an mDoR of 17.5 months with selpercatinib[52] and 11.0 months with pralsetinib.[55] However, the eventual emergence of drug resistance remains a challenge in patients treated with targeted therapies, and the understanding of the molecular mechanisms that contribute to resistance is essential to developing strategies that improve outcomes in these patients. Key studies evaluating the mechanisms of resistance to selective RET inhibitors are summarized in Table 4.

The *RET* V804M gatekeeper mutation[50] and *RET* S904F[68] were reported to mediate resistance after MKIs with selpercatinib and pralsetinib, which demonstrated preclinical and clinical activity against both mutations. The *RET* G810 solvent-front mutation was first described as an acquired, "on-target" resistance to selpercatinib in a study analyzing tissue and/or plasma of patients with *RET* fusion–positive NSCLC and *RET*-mutant MTC treated with selpercatinib, which provided early insight into selective RET inhibitor resistance.[61]

A subsequent study analyzing tissue and/or plasma from 18 patients with *RET* fusion–positive NSCLC who had previously received a selective RET inhibitor identified acquired *MET* amplification in three resistant cases (15%), acquired *RET* mutations affecting the *RET* G810 residue in the kinase solvent front in two cases (10%), and acquired *KRAS* amplification in one case (5%).[62] In a separate study of 79 patients who had developed resistance on selpercatinib for *RET* fusion–positive NSCLC, four patients were found to have *MET* amplification as a mechanism of resistance (one was evident before therapy with selpercatinib) with response to a combination strategy with selpercatinib and crizotinib.[64]

Rosen et al. analyzed 72 postprogression tumor biopsies and plasma specimens from patients treated with selpercatinib in LIBRETTO-001.[64] Two patients with primary resistance to selpercatinib had low allele frequencies of *KRAS* G12D and *KRAS* G12V mutations identified on plasma sequencing but not detected on tissue, which suggested intertumoral heterogeneity.[66] An identifiable acquired mechanism of resistance was identified in 11 of 18 patients (61%) who progressed on selpercatinib. In three cases, on-target resistance with emergence of secondary *RET* mutations such as *RET* G810C, *RET* G810S, and *RET* Y806C were identified.[66] MAPK-activating alterations, a key bypass mechanism, were identified in seven patients who acquired *KRAS*, *NRAS*, and *MET* or *FGFR1* amplifications.[66]

Resistance mechanisms were analyzed in 36 baseline plasma samples in the ARROW study with pralsetinib.[63] Acquired *RET* resistance mutations in the kinase domain such as *RET* G810C, *RET* L730V, *RET* G810S plus *RET* L730V, and *RET* G810C plus *RET* T729 L730delinsL were observed in 11% of patients, and potential off-target mechanisms of resistance including *MET* amplification and *BRAF* V600E were observed in a further 11% of patients.[63]

Shen et al. identified *RET* L730V/I mutations as being strongly resistant to pralsetinib but not to selpercatinib in xenograft tumors in mice.[69] *NTRK3* fusion and small cell transformation had also been reported as mechanisms of resistance to selective RET inhibitors.[65,67] Notably, the mechanism of resistance remains unidentified in up to 39%–90% of patients.[63,66,70]

FUTURE DIRECTIONS

Novel RET inhibitors

To address the observed acquired resistance to first-generation selective RET inhibitors, several next-generation RET inhibitors,

TABLE 4 Summary of key studies evaluating mechanisms of resistance to selective RET inhibitors.

RET inhibitor	Tissue and/or plasma samples, No.	Tumor type	Resistance mechanism	Reference
Selpercatinib	2 tissue, 9 plasma	NSCLC, MTC	*RET* G810C/S/R	Solomon 2020[61]
Selpercatinib	2 plasma	NSCLC, MTC	*RET* G810, Y806C/N	Subbiah 2021[50]
Selpercatinib or pralsetinib	23 tissue and plasma	NSCLC	*RET* G810, *MET* amplification, *KRAS* amplification	Lin 2020[62]
Pralsetinib	48 plasma	NSCLC	*RET* G810, L730, *MET* amplification, *BRAF* V600E	Gainor 2022[63]
Selpercatinib	4 tissue	NSCLC	*MET* amplification	Rosen 2021[64]
Selpercatinib	1 tissue	NSCLC	*NTRK3* fusion	Subbiah 2021[65]
Selpercatinib	18 tissue and plasma	NSCLC, MTC, others	*RET* G810C/S, Y806C, *KRAS*, *NRAS*, *BRAF*, *MET* amplification, *FGFR1* amplification	Rosen 2022[66]
Pralsetinib	1 tissue	NSCLC	Small cell transformation	Gazeu 2023[67]

Abbreviations: MTC, medullary thyroid cancer; NSCLC, non–small cell lung cancer.

including TPX0046 (NCT04161391), BOS172738 (NCT03780517), TAS0953/HM06 (NCT04683250), and LOXO-260 (NCT05241834), are being evaluated in ongoing phase 1/2 trials for *RET*-rearranged solid tumors (a list of next-generation selective RET inhibitors in development is summarized in Table 5). Preclinical models have demonstrated activity for some of these compounds against both solvent-front and gatekeeper mutations, including the G810 solvent-front mutations described above.[71–73]

Early-stage disease

The benefits of tyrosine kinase inhibitors have been recognized in the adjuvant space in the context of both *EGFR*-mutant and *ALK*-positive NSCLC.[74,75] Of interest will be the findings from LIBRETTO-432,[76] a global, randomized, phase 3 trial evaluating the efficacy and safety of adjuvant selpercatinib versus placebo in stage 1B–IIIA *RET* fusion–positive NSCLC after definitive surgery or radiation (NCT04819100). There are currently no similarly designed adjuvant studies with pralsetinib.

The benefit of the neoadjuvant approach is currently under evaluation in LIBRETTO-001 cohort 7 (NCT03157128), a single-arm cohort examining the efficacy and safety of neoadjuvant selpercatinib in patients with resectable stage IB–IIIA *RET* fusion–positive NSCLC.

In conclusion, selective RET inhibitors, such as selpercatinib and pralsetinib, have demonstrated unprecedented efficacy with durable responses and manageable safety profiles in patients with *RET* fusion–positive NSCLC. Selpercatinib has established its place as the preferred first-line option for these patients on the basis of results from the LIBRETTO-431 phase 3 trial, which underscores the importance of molecular testing to identify *RET* rearrangements in newly diagnosed NSCLC. However, acquired therapy resistance via various mechanisms limits treatment efficacy and remains challenging to overcome. The development of next-generation selective RET inhibitors aimed at circumventing critical mechanisms of resistance and the use of selective RET inhibitors in early-stage disease

TABLE 5 Summary of next-generation selective RET TKIs in development.

Agent	ClinicalTrials.gov identifier	Patient population, No.	Phase/design	Status	Last update
TPX0046 (RET/SRC inhibitor)	NCT04161391	Advanced solid tumors harboring *RET* fusions or mutations, 41	Phase 1/2, FIH	Terminated (adverse change in risk/benefit)	June 18, 2023
BOS172738	NCT03780517	Advanced solid tumors with *RET* gene alterations including NSCLC and MTC, 117	Phase 1	Completed recruitment	October 30, 2023
TAS0953/HM06	NCT04683250	Advanced solid tumors with *RET* gene abnormalities, 202	Phase 1/2	Recruiting in US and Japan	March 3, 2023
LOXO-260	NCT05241834	Advanced *RET* fusion–positive solid tumors, MTC, and other tumors with *RET* activation refractory to selective RET inhibitors, 110	Phase 1	Active, not recruiting	March 27, 2024
SY-5007	NCT05278364	Advanced solid tumors, including *RET* fusion–positive NSCLC or *RET*-mutated NSCLC or other *RET*-altered advanced solid tumors, 184	Phase 1/2, FIH	Recruiting in China	December 4, 2023
EP0031	NCT05443126	Advanced *RET*-altered malignancies, 265	Phase 1/2	Recruiting in US and Europe	April 19, 2024
APS03118	NCT05653869	Unresectable locally advanced or metastatic solid tumors harboring *RET* mutations or fusions, 35	Phase 1, FIH	Recruiting in China	June 15, 2023
TY-1091	NCT05675605	Advanced *RET*-altered NSCLC, MTC, and other *RET*-altered solid tumors that have progressed after standard therapy, 248	Phase 1/2, FIH	Recruiting in China	January 30, 2024
HEC169096	NCT05451602	Advanced solid tumors, including *RET* fusion–positive NSCLC, MTC, and other tumors with *RET* activation, 456	Phase 1/2	Recruiting in China	October 27, 2022
HS-10365	NCT06147570	Treatment-naive locally advanced or metastatic *RET* fusion–positive NSCLC, 62	Phase 2	Recruiting in China	November 27, 2023
HS269	NCT05058352	Advanced solid tumors that fail or where no standard treatment is available, 36	Phase 1, FIH	Recruiting in China	September 27, 2021
KL590586	NCT05265091	Advanced solid tumors carrying *RET*-fusion or -mutant genes, 414	Phase 1/2	Recruiting in China	October 13, 2022
HA121-28	NCT05117658	*RET* fusion–positive NSCLC after at least one line of therapy, 83	Phase 2	Recruiting in China	August 4, 2022

Abbreviations: FIH, first in human; MTC, medullary thyroid cancer; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

will likely result in further improvements in outcomes for patients with *RET* fusion–positive NSCLC.

AUTHOR CONTRIBUTIONS

Hui Jing Hoe: Conceptualization, methodology, data curation, writing–review and editing, writing–original draft, and resources. **Benjamin J. Solomon**: Conceptualization, methodology, data curation, writing–review and editing, writing–original draft, supervision, and resources.

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CONFLICT OF INTEREST STATEMENT

Benjamin J. Solomon has served on advisory boards for or received honoraria from Eli Lilly, Roche/Genentech, Pfizer, AstraZeneca, Amgen, Novartis, Loxo Oncology, Bristol-Myers Squibb, Merck Sharpe & Dohme, Janssen, Takeda, and GlaxoSmithKline. The other author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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