Review Article on Looking for Chimeras in NSCLC: Widen Therapeutic Options Targeting Oncogenic Fusions

Decade in review: a new era for RET-rearranged lung cancers

Noura J. Choudhury[1], Alexander Drilon[1,2]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Weill Cornell Medical College, New York, NY, USA

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Correspondence to: Alexander Drilon, MD. Memorial Sloan Kettering Cancer Center, 545 E73rd St., 22nd FL, New York, NY 10021, USA.
Email: drilona@mskcc.org.

Abstract: Targeted therapy has become the standard of care for non-small cell lung cancers with a range of targetable alterations, including *ALK* and *ROS1* kinase fusions. *RET* fusions drive the oncogenesis of 1–2% of NSCLCs and represent a substantial global burden of disease. Although these fusions were first identified more than thirty years ago, targeted therapy for RET fusion-positive lung cancers was only explored in the last decade. Whereas repurposed multikinase inhibitors were initially tested, selective inhibitors RET inhibitors have dramatically improved outcomes for patients whose tumors harbor these alterations. In 2020, the US Food and Drug Administration approved selpercatinib, a selective RET inhibitor, for adults with lung and thyroid cancers with RET rearrangements or mutations, making it the first targeted therapy to be approved for RET-altered cancers. While resistance to selective RET inhibition has been described, next-generation RET inhibitors are already being explored for patients who progress on prior RET kinase inhibitors.

Keywords: RET-fusion; non-small cell lung cancer (NSCLC); targeted therapies; multikinase inhibitors; LOXO-292; BLU-667

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Introduction

RET alterations are estimated to occur in approximately 2% of all human cancers (1). The oncogenic potential of *RET* was first identified in 1985 after the discovery that transfection with human lymphoma DNA could transform NIH 3T3 fibroblasts (2). *RET* fusions were later identified in papillary thyroid cancer in the 1980s, followed by the discovery of germline *RET* mutations as the causative genetic link in multiple endocrine neoplasia type 2 (MEN2) syndromes. In all, *RET* alterations are found in 5–10% of papillary thyroid cases (3) and the majority of medullary thyroid cancer (MTC) cases (4).

The *RET* proto-oncogene on chromosome 10q11.2 encodes for a transmembrane glycoprotein receptor tyrosine kinase whose ligands belong to the glial-derived neurotrophic factor (GDNF) family. In normal cellular functioning, *RET* signaling is essential for the development and maintenance of the kidneys (5) and enteric nervous system (6). Loss-of-function *RET* mutations can result in hereditary Hirschsprung disease (7) and some forms of congenital malformations of the kidneys and urinary tract (8). RET activation occurs when its GDNF ligands bind to cell membrane-bound GDNF family receptor (GFR) co-receptors, which induces RET homodimerization and auto-phosphorylation within the RET intracellular tyrosine kinase domains (9). This activates downstream signaling pathways involved in normal cellular differentiation and proliferation, such as the RAS, MAPK, PI3K and JAK-STAT pathways (10-12).

In non-small cell lung cancer (NSCLC), oncogenic activation of RET occurs by chromosomal rearrangement, which fuses the 3' coding region for the *RET* kinase domain on chromosome 10 with a 5' upstream partner gene containing one of several possible domains, such as a coiled-coil or LIS1 homology (13-15). This fusion induces ligand-

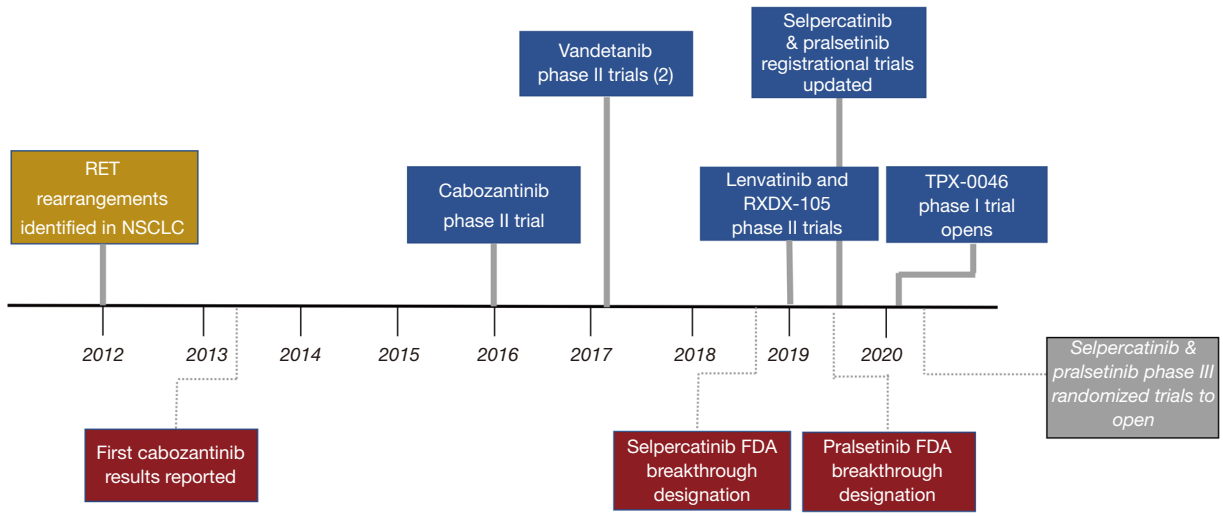

Figure 1 Timeline of advances in *RET*-rearranged NSCLC. Since its first identification in NSCLC in 2012, RET rearrangements have been investigated as a potential target in multiple phase II trials of targeted therapies in the last decade. NSCLC, non-small cell lung cancer.

independent dimerization, constitutive RET activation, and oncogenesis. Intrachromosomal rearrangements are most frequently seen, with partner genes such as *KIF5B*, *CCDC6*, and *NCOA4* also originating from chromosome 10, although interchromosomal partners have also been identified (16). The specific fusion partner and breakpoints locations in *RET* or upstream partners impact the properties of the formed oncoprotein, such as its subcellular location. Fusion partners also confer distinctive properties such as higher levels of activated RET oncoprotein (13) and formation of multikinase signaling hubs (17), both of which are seen with *KIF5B-RET* and are postulated to impact the fusion protein's drug sensitivity.

In contrast, in other cancer types, namely thyroid cancer but also breast and colorectal cancer (1), the primary mechanism of aberrant *RET* activation is point mutation. Mutations in the cysteine-rich extracellular domain, for example, define the hereditary syndrome MEN2A. MEN2A is characterized by the development of MTC and pheochromocytomas in the majority of patients, as well as hyperparathyroidism in a select subset (18). The hereditary syndrome MEN2B, which results in pheochromocytomas and MTC as well as a characteristic marfanoid habitus, is defined by point mutations in the intracellular kinase domain, with the most common alteration being RET^{M918T} (19).

RET fusions were not identified in NSCLC until 2012 (*Figure 1*), when four independent groups from the United States, Japan, and Korea reported *RET* fusions in 1–2% of lung cancer cases examined (13-15,20). Patients with *RET* fusions tend to be young, never smokers, and more frequently had adenocarcinomas over other histological types (21), characteristics that have since been further validated (22). Of note, these fusions are also seen, although less frequently, in older patients, those with a substantial smoking history, and non-adenocarcinoma histologies. Molecular profiling should thus be unbiased in relation to clinical or pathologic features. Soon after its identification in NCSLC, RET became a target for molecularly-targeted therapies, the first of which were existing multikinase inhibitors (MKIs).

Multikinase inhibitors

Until recently, there were no approved therapies specifically for *RET* fusion-positive NSCLCs. Several MKIs have been shown to have modest clinical activity against RET fusions in phase II clinical trials, leading to their use being supported by National Comprehensive Center Network guidelines as category 2A recommendations (23). As their name implies, MKIs target RET as well as kinases including VEGFR2, MET, KIT, BRAF or EGFR (24), depending on the particular agent in question; this contributes both to their off-target effects and decreased effectiveness against RET due to pharmacokinetic limitations.

Cabozantinib was the first MKI studied in *RET*-rearranged lung cancer in a prospective clinical trial. The clinical response of the first three patients in this single-arm phase II trial were reported in 2013 (25), with the

Table 1 Prospective clinical trials of multikinase inhibitors (MKIs) in *RET*-rearranged non-small cell lung cancer

Drug	First author & year	Clinical trial phase/number of patients	ORR	Median PFS (mo)	Median OS (mo)
Cabozantinib	Drilon, 2016	II, n=26 (25 evaluable)	7/25 (28%)	5.5	9.9
	Nokikhara, 2019	I, n=2 RET patients	1/2 (50%)	NE	NE
Sorafenib	Horiike, 2016	II, n=3	0/3 (0%)	NE	NE
Vandetanib	Lee, 2017	II, n=17	3/17 (18%)	4.5	11.6
	Yoh, 2017	II, n=19	9/19 (47%)	4.7	11.1
Lenvatinib	Hida, 2019	II, n=25	4/25 (16%)	7.3	NE
RXDX-105	Drilon, 2019	I, n=31	6/31(19%)	NE	NE

The clinical activity of several MKIs has been tested in small prospective clinical trials. ORR, objective response rate; mo, months; PFS, progression-free survival; OS, overall survival; NE, not evaluable or not reached in published report. RXDX-105 has since been discontinued by the manufacturer.

full results of 26 patients published in 2016 (26). Enrolled patients had metastatic or unresectable NSCLC with a *RET* fusion, 20 of whom had received at least one prior line of chemotherapy. Of the 25 patients analyzed, seven (28%) demonstrated a partial response (PR) with an additional nine (36%) achieving stable disease (SD). There were no complete responses (CR). The median progression-free survival (PFS) was 5.5 months with an overall survival (OS) of 9.9 months.

Vandetanib, lenvatinib, sorafenib and RXDX-105 have also been studied in prospective clinical trials (*Table 1*). Of these, a Japanese trial of 18 patients treated with vandetanib reported the highest objective response rate (ORR) of 53% (27), with a median PFS of 6.5 months and an OS of 13.5 months (28). Other phase II trials of sorafenib (3 patients), lenvatinib (25 patients), and vandetanib (19 patients) reported ORRs ranging from 0 to 18% and median PFS ranging from 4.7 to 7.3 months (29-32). Of note, of the MKIs, RXDX-105 is the only one that relatively spares VEGFR2, a characteristic which was hypothesized to allow tolerable dose up-titration to more clinically active plasma concentration levels. In a phase I/IB trial, however, the ORR was similar to those reported for other MKIs (ORR =19% or 6/31 patients) (33). RXDX-105 was discontinued later in 2019.

Retrospective series of MKIs have reported similar response rates. The GLORY database included 169 patients with *RET*-rearranged NSCLC, with 53 patients receiving at least one MKI (22). Cabozantinib, which 21 patients received, had the highest ORR of 37%, followed by vandetanib (18%) and sunitinib (22%). Responses were also seen with lenvatinib and nintedanib. No responses were seen with sorafenib, alectinib, ponatinib and regorafenib, although the number of patients who received each agent were in the single digits. The median OS for patients in the registry was 6.8 months, which highlighted the need for a more active RET inhibitor beyond standard MKIs. The results of the interventions in GLORY, as well as three other retrospective series of alectinib (34,35) and vandetanib (36), are summarized in *Table 2*.

MKI limitations

The response to MKIs in *RET*-rearranged NSCLC was notably disappointing compared to other targeted therapies in lung cancer. For context, the ORRs for osimertinib, alectinib, and entrectinib for untreated *EGFR*, *ALK*, and *ROS1*-altered NSCLC are 80% (37), 83% (38), and 77% (39), respectively. The relatively modest response and limited overall durability for MKIs in *RET*-fusion positive NSCLCs is likely due to several factors, the most important of which are non-selectivity for RET, potent inhibition of non-RET targets such as VEGFR2 (which contributes to dose-limiting toxicity and drug discontinuation), and intrinsic and acquired resistance.

Off-target kinase inhibition by MKIs contributes to the comparative lack of efficacy in *RET*-rearranged disease by several mechanisms. First, the concurrent inhibition of non-RET targets mediates some of the most significant toxicities seen with MKIs. VEGFR2 inhibition can cause hypertension, hand-foot syndrome, and proteinuria (40), while EGFR inhibition can contribute to acneiform rash and diarrhea (41). Cabozantinib, vandetanib and lenvatinib all more potently inhibit VEGFR2 than RET (42,43). These treatment-related toxicities lead to dose reductions

Table 2 Retrospective studies of multikinase inhibitors (MKIs) in *RET*-rearranged non-small cell lung cancer (NSCLC)

Drug	First author & year	Number of patients	ORR	Median PFS (mo)	Median OS (mo)
Cabozantinib	Gautschi, 2017	19	7/19 (37%)	3.6	4.9
Vandetanib	Gautschi, 2017	11	2/11 (18%)	2.9	10.2
	Platt, 2015	3	0/3 (0%)	NE	NE
Lenvatinib	Gautschi, 2017	2	1/2 (50%)	NE	NE
Sorafenib	Gautschi, 2017	2	0/2 (0%)	NE	NE
Sunitinib	Gautschi, 2017	9	2/9 (22%)	2.2	6.8
Alectinib	Lin, 2016	4	1/4 (25%)	NE	NE
	Gautschi, 2017	2	0/2 (0%)	NE	NE
	Ribeiro, 2020	4	0/4 (0%)	NE	NE
Ponatinib	Gautschi, 2017	2	0/2 (0%)	NE	NE
Regorafenib	Gautschi, 2017	1	0/1 (50%)	NE	NE
Nintedanib	Gautschi, 2017	2	1/2 (50%)	NE	NE

The majority of these results come from the GLORY international registrational database of *RET*-rearranged NSCLC. ORR, objective response rate; mo, months; PFS, progression-free survival; OS, overall survival; NE, not evaluable.

Table 3 Tolerability of RET inhibitors

Drug	Dose-reduction rate	Drug-discontinuation rate
Cabozantinib	19/26 (73%)	2/26 (8%)
Vandetanib	4/17 (23%)	NA
	10/19 (53%)	4/19 (21%)
Lenvatinib	16/25 (64%)	5/25 (20%)
Sorafenib	1/3 (33%)	NA
Selpercatinib	NA	9/531 (1.7%)
Pralsetinib	NA	8/120 (7%)

Multikinase inhibitors (MKIs) used against *RET*-rearranged NSCLC are limited by off-target toxicity, most notably VEGFR2 kinase inhibition. The above table highlights the dose-reduction rates and the drug-discontinuation rates of several MKIs compared to the RET-selective inhibitors, selpercatinib (LOXO-292) and pralsetinib (BLU-667). NA, not applicable or not provided in the original studies.

and consequently, potentially decreased on-target inhibition of RET (26). Drug reduction rates for MKIs range from 23% to 73%, and are summarized in *Table 3*. Second, the lack of selectivity for RET makes it difficult for these agents to more meaningfully inhibit RET in patients due to relatively reduced potency *in vivo* and limited plasma exposures. While the latter issue is not a universal problem among MKIs in driver-positive lung cancers (e.g., crizotinib is active against ALK/ROS1 fusions), this has been a substantial limitation for drugging RET fusions.

MKI resistance

There are known mechanisms of both intrinsic and acquired resistance with MKI therapy that may contribute to limited therapeutic response. Several acquired resistance mutations have been identified, although some have only been discovered in cell lines during *in vitro* treatment with MKIs and are hypothesized, but not proven, to propagate resistance in humans during treatment. These include RET^{I788N} (44), solvent-front mutation RET^{G810A} (45), and gatekeeper mutation RET^{V804L} (45,46). In contrast, both gatekeeper mutation RET^{V804M} (47) and RET^{S904F} (48), a mutation in the activation loop of the RET kinase domain, were discovered in patient samples (plasma and tissue, respectively) after progression on vandetanib. An alternative mechanism of resistance to RET inhibition derived from preclinical models includes activation of the mitogen-activated protein kinase (MAPK) pathway (44), possibly by acquisition of *NRAS* mutations (49). Finally, certain fusion partners are thought to potentially mediate intrinsic resistance to certain MKIs (50). For example, both RXDX-105 and vandetanib have diminished activity against tumors

with *KIF5B-RET* fusions (27,33), suggesting that this particular fusion may be less susceptible to non-selective RET inhibition.

Combination strategies have been utilized in attempts to overcome innate or acquired resistance postulated with MKI monotherapy. The strategy of combining vandetanib with the mammalian target of rapamycin (mTOR) inhibitor everolimus was tested in the clinic after preclinical data suggested that mTOR inhibition may both improve blood-brain barrier penetration and overcome resistance mediated by AKT amplification (51). Of 13 *RET*-rearranged patients, 7 had a PR (ORR =54%), including all three patients with brain metastases (52). However, 17/19 patients (89%) required dose reduction after the first cycle due to toxicity, indicating that tolerability may limit combination strategies.

Chemotherapy

In the GLORY registry, 84 patients with advanced disease received platinum-based chemotherapy as first-line treatment. Complete or partial responses were seen in 33 of 65 evaluable patients (51%), with a median PFS of 7.8 months and median OS of 24.8 months in 70 patients with survival data (22). A retrospective series of 18 patients with lung adenocarcinoma also demonstrated an ORR of 45% with median PFS of 19 months in patients treated with pemetrexed-based regimens, which was similar to contemporaneous responses to pemetrexed-based therapy in *ROS1*- and *ALK*-rearranged lung cancers (53). Anecdotal success of long-term (>2 years) treatment with single-agent pemetrexed has also been reported (54). In summary, chemotherapy represents a viable treatment option for patients with RET-rearranged NSCLC during their treatment course, and pemetrexed-based chemotherapy should be considered when possible.

Immunotherapy

Responses to immunotherapy in RET-rearranged lung cancer have not been characterized prospectively but are thought to be poor, based on available data from retrospective studies. The IMMUNOTARGET registry included 16 patients with *RET* fusions who were treated with immune checkpoint blockade as a second or higher line of therapy. A 6% response rate to immune checkpoint blockade was observed, with a median PFS of 2.1 months (55). Similar immunotherapy response rates were observed for patients with ALK and ROS1 driver alterations. A second retrospective series from Memorial Sloan Kettering (MSK) described a 0% response rate among 16 patients with RET-rearranged NSCLC treated with immunotherapy, even among patients with PD-L1 expression ≥1%, including one with PD-L1 expression >50% (56). Notably, the majority of evaluated cases in the MSK series (21/26 or 80.7%) had <50% PD-L1 expression, indicating RET-rearranged tumors may be less immunologically active. In contrast, a separate retrospective series included 9 *RET*-rearranged NSCLC patients treated with single-agent immunotherapy in the second or third-line setting. Of 8 evaluable patients, 3 (37%) achieved a PR, 2 (25%) achieved SD, and 3 (37%) had PD (57). Data in large, prospective cohorts is thus necessary to draw more definitive conclusions on the activity of single-agent immunotherapy. Notably, outcomes with combination chemotherapy and immunotherapy have not been described to date and represent a highly relevant data set to examine.

Selective RET inhibitors

The modest activity of MKIs against RET both demonstrated a clear need for more selective therapies and highlighted the ideal characteristics needed for such agents to be effective. Selpercatinib, formerly known as LOXO-292, and pralsetinib, formerly known as BLU-667, are two such agents whose early clinical results were reported in 2017–2018 and subsequently updated in 2019. Both are notable for potent *in vitro* and *in vivo* selective activity against both wild-type and mutated RET with significantly diminished affinity for VEGFR2 and other kinases, a crucial feature for resolving dose-limiting toxicity. From early clinical results, both agents were granted Breakthrough Therapy designation by the US Federal Drug Administration (FDA) for advanced NSCLC with RET fusions after progression on platinum chemotherapy, in September 2018 for selpercatinib and May 2019 for pralsetinib. In May 2020, selpercatinib was approved by the FDA for adults with advanced lung and thyroid cancers with RET fusions or mutations, making it the first targeted therapy approved for RET-driven cancers.

Selpercatinib is a highly selective, ATP-competitive small molecular RET inhibitor with preliminary in-human results reported in 2017. In preclinical models, selpercatinib demonstrated both >100-fold higher potency against RET compared to non-RET kinase targets and uniform

activity in *RET*-altered xenograft models, independent of kinase fusion partner (58). In particular, the compound demonstrated promising *in vivo* activity against RET^{V804M}, a known acquired resistance mutation against which MKIs are postulated to be ineffective (59).

The results of LIBRETTO-001, the phase 1/2 dose escalation/expansion trial of selpercatinib in advanced solid tumors with *RET*-fusion positive alteration, were first reported at the Annual Meeting of the American Society for Clinical Oncology (ASCO) in 2018. In 2019 at the World Conference of Lung Cancer (WCLC), the results of the first 105 patients with NSCLC who had received prior platinum chemotherapy were updated. In contrast to MKIs, the overall ORR was 68%, with 66% achieving PR and only 2% of patients demonstrating PD as their best response (60). The responses did not vary by prior treatment received (chemotherapy, immune checkpoint blockade or MKIs) or by fusion partner. Recognizing that follow up was yet to mature, the median PFS was 18.4 months, with a median 7.5 months of follow-up. The majority of treatment-related toxicities were grades 1 or 2, and included fatigue, diarrhea, constipation, dry mouth, nausea, and dyspnea, highlighting the tolerability of the compound when off-target inhibition is minimized. There were two treatment-related AEs that were grade 3 or higher, which were tumor lysis syndrome and increased ALT.

Preclinical and early clinical results of pralsetinib were published in 2018, and similarly highlighted the drug's selectivity against RET. In enzymatic assays, pralsetinib inhibited wild-type and mutated RET with sub-nanomolar potency and was 90-fold more selective for RET than VEGFR2 (61). The first results of the global ARROW study, a registrational trial that included both a dose escalation and dose expansion phase in multiple solid tumors, were released at ASCO in 2019. Of 57 evaluable patients, the ORR was 56%, all of which were PRs. Six patients remained on treatment for more than six months (62). The ORR for patients previously treated with chemotherapy was also high at 60% (18/30) and comparable to the results of selpercatinib. The responses seen were independent of prior therapy received and *RET* fusion partner. Pralsetinib was similarly well-tolerated, with the majority of treatment-related toxicities being grade 1 and reversible, which included constipation, neutropenia, AST elevation, hypertension, diarrhea, and dry mouth. 28% of patients had grade 2 or higher treatment-related toxicity events.

Intracranial disease

In addition to the comparatively higher response rates and tolerability of both RET-selective compounds, the improvement in intracranial response is particularly noteworthy. About 45% of patients with *RET* alterations in NSCLC develop brain metastases during the lifetime of treatment, demonstrating a crucial need for therapies with adequate CNS penetration (63). The CNS response rate with MKIs has been poor. In a retrospective series of 11 patients with CNS metastases treated with MKIs, only two had an intracranial response (63). In contrast, of the 11 patients with CNS metastases in LIBRETTO-001, two (18%) achieved intracranial CR, eight (73%) PR, and one SD (9%). In addition, a case report from MSK in 2019 described complete resolution of leptomeningeal disease with initiation of selpercatinib, in addition to partial response of CNS parenchymal lesions (64). Similarly, in the ARROW study, seven of nine patients with measurable brain metastases achieved shrinkage of CNS disease and no patients developed new brain metastases while on treatment.

Selective inhibitor resistance

As expected, acquired resistance eventually emerges even with highly selective RET inhibitors. A case series published in January 2020 described $RET^{G810R/S/C}$ mutations in the RET solvent front detected in circulating tumor DNA in two patients just prior to progression on selpercatinib (65). The authors used structural modeling to elucidate that the mutations sterically hinder binding of selpercatinib, thus resulting in loss of activity. A possible solution to resistance mediated by RET solvent-front mutations is already in the clinic. TPX-0046 is a novel RET/SRC inhibitor that in enzymatic assays demonstrated high potency against RET^{G810R}, with a mean IC_{50} of 17 nM, compared to IC_{50} >500 nM with pralsetinib or selpercatinib (16). Therefore, TPX-0046 may be able to overcome solvent-front mutation-mediated resistance after treatment with selpercatinib or pralsetinib. A phase I clinical trial testing TPX-0046 in multiple solid tumors, including NSCLC, has recently opened (NCT04161391).

Future directions and conclusions

From the initial identification of RET rearrangements

in NSCLC in 2012 to the present, investigation into therapeutic options has rapidly grown. While treatment with repurposed MKIs held modest promise initially, the substantial increase in activity and favorable safety profile of the RET-selective agents selpercatinib and pralsetinib have made MKIs significantly less desirable first-line RET TKI options. The future of first-line RET TKI therapy for NSCLC with *RET* fusions clearly lies in selective RET inhibition, which seems to have overcome the major deficiencies seen with MKIs.

In early 2020, a randomized phase III trial of selpercatinib compared to platinum-pemetrexed with or without pembrolizumab in treatment-naïve *RET* fusion positive NSCLC is expected to open (NCT04194944). In addition, a phase III open-label trial of pralsetinib in first-line treatment of RET fusion positive NSCLC compared to platinum chemotherapy-based regimen is also planned for early 2020 (NCT04222972). With these trials, in addition to expanded recruitment of the existing phase II trials for both drugs, it is likely that not only one, but two drugs will likely soon be approved in a variety of regulatory environments for use in NSCLC with *RET* alterations. The beginning of the new decade, therefore, is likely the beginning of an unprecedented era for patients whose cancers harbor *RET* alterations.

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