ORIGINAL ARTICLE

# A Phase II Study of the Multikinase Inhibitor Ponatinib in Patients With Advanced, *RET*-Rearranged NSCLC

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## ABSTRACT

**Introduction:** *RET* rearrangements define a distinct molecular subset of NSCLC. The multikinase inhibitor ponatinib reveals potent activity in preclinical models of *RET*-rearranged NSCLC.

**Methods:** In this single-arm, multicenter, phase II trial, we evaluated the clinical activity of ponatinib in patients with advanced, previously treated, *RET*-rearranged NSCLC (NCT01813734). *RET* rearrangements were identified through fluorescence in situ hybridization or next-generation sequencing. Ponatinib was administered at a dose of 30 mg once daily. Patients without a documented objective response were eligible to dose-escalate ponatinib to 45 mg daily. The primary end point was objective response rate.

**Results:** Between August 2014 and December 2017, nine patients were enrolled. The median age was 58 years (range 49–73 y). Eight patients (89%) had a history of brain metastases. The median number of previous lines of therapy was three (range 1–5). Of the nine evaluated patients, five (55%) experienced tumor shrinkage from baseline, but no confirmed responses were observed (objective response rate 0%). The disease control rate was 55%. With a median follow-up of 9.33 months, the median progression-free survival and overall survival were 3.80 months (95% CI: 1.83–5.30) and 17.47 months (95% CI: 6.57–19.20), respectively. The most common treatment-related adverse events were rash (n = 5; 56%), constipation (n = 4; 44%), and diarrhea (n = 4; 44%). No treatment-related thromboembolic or cardiac events were observed. The study was stopped prematurely owing to slow accrual and lack of clinical activity.

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**Conclusions:** Ponatinib has limited clinical activity in patients with *RET*-rearranged NSCLC. Continued development of more potent and selective RET inhibitors is needed.



*Keywords:* RET fusion; ponatinib; multikinase inhibitor; non–small cell lung cancer

## Introduction

Targeted therapies have dramatically reshaped the therapeutic landscape of NSCLC. Molecular genotyping to assess for genetic alterations in key oncogenic drivers (e.g., *EGFR*, *ALK*, and *ROS1*) is now routine, and more than 10 small-molecule tyrosine kinase inhibitors (TKIs) have gained regulatory approvals for the treatment of oncogene-driven NSCLC to date.[1] In patients with well-established therapeutic targets, such as *EGFR* mutations or *ALK* rearrangements, TKIs have produced marked improvements in response rates, progression-free survival (PFS), and toxicity profiles compared with standard cytotoxic chemotherapies.[2-5] With the success of this approach, efforts are ongoing to identify additional molecular targets in NSCLC.

Genetic alterations in the *RET* gene are implicated in the molecular pathogenesis of various malignancies, including NSCLC.[6] Chromosomal rearrangements involving *RET* were first identified in NSCLC in 2012.[7-10] *RET* rearrangements lead to the formation of oncogenic fusion proteins that result in constitutive downstream signaling and oncogenic transformation. It has since been recognized that *RET* rearrangements are found in approximately 1% to 2% of patients with NSCLC and define a distinct molecular subset of the disease.[11] In treatment-naive patients, *RET* rearrangements are largely exclusive of genetic alterations in other oncogenic drivers, such as *EGFR*, *ALK*, and *ROS1*. Nonetheless, patients with *RET*-rearranged NSCLC share many clinical and pathologic characteristics with these oncogenic subtypes, including enrichment among never-smokers and underlying adenocarcinoma histology.[12]

Early preclinical studies using multikinase inhibitors (MKIs) with anti-RET activity (e.g., vandetanib, sunitinib) provided initial proof of principle that *RET* rearrangements are sensitive to RET inhibition.[8-10] Subsequently, several single-arm studies explored the clinical activity of MKIs in *RET*-rearranged (*RET*-positive) NSCLC. For example, in a phase II study of cabozantinib, objective responses were observed in 28% of patients with *RET*-positive NSCLC.[13,14] Similarly, the MKIs vandetanib and lenvatinib produced objective response rates (ORRs) of 16% to 47% and median PFS of 4.5 to 7.3 months.[15-17] Although these studies provided early evidence that *RET* rearrangements are actionable drivers in NSCLC, the clinical activity of these MKIs was modest, and dosing was frequently limited by off-target toxicities. Thus, there is a need for improved RET-directed inhibitors.

Ponatinib is an oral MKI that was initially designed and approved for the treatment of chronic myelogenous leukemia.[18] In addition to targeting BCR-ABL, ponatinib is a potent inhibitor of RET. In Ba/F3 models expressing *RET* fusions, ponatinib revealed low nanomolar activity ($IC_{50}$ viabilities 6–21 nM) and was more potent than other MKIs, including cabozantinib, vandetanib, and lenvatinib.[19] Ponatinib also revealed significant antitumor activity in a patient-derived xenograft model expressing a *KIF5B-RET* fusion. On the basis of these encouraging preclinical findings, we sought to investigate the clinical activity of ponatinib in *RET*-positive NSCLC.

## Materials and Methods

### Study Design and Participants

This study was an investigator-initiated, multicenter, open-label, phase II clinical trial examining the efficacy and safety of ponatinib in patients with *RET*-rearranged NSCLC. Eligible patients had histologically or cytologically confirmed advanced, *RET*-rearranged NSCLC that had progressed on at least one previous line of therapy. Patients were required to have measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[20] Other eligibility criteria included age 18 years or older; Eastern Cooperative Group performance status 0 to 2; and adequate hematologic, renal, and hepatic functions. Patients with brain metastases were eligible if they had been adequately treated or were asymptomatic.

Molecular testing for *RET* rearrangements was performed locally at each site in Clinical Laboratory Improvement Amendments–certified laboratories. Methods of acceptable molecular testing included RET fluorescence in situ hybridization (FISH) or targeted next-generation sequencing (NGS) analysis. RET FISH was considered positive if more than 15% of cells revealed split signals.

In earlier clinical trials evaluating ponatinib, arterial thrombotic events were reported.[21,22] Therefore, patients with any history of arterial thrombotic disease, including previous myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease, were excluded. Patients with a history of venous thromboembolism

within 6 months of study entry were also excluded. The protocol was approved by the institutional review board at each site, and all patients provided written informed consent before participation.

### Study Procedures

Ponatinib was administered orally at a dose of 30 mg once daily in continuous 28-day cycles. Of note, as this was among the first studies of ponatinib in a population of patients with NSCLC, our starting dose of ponatinib was lower than the U.S. Food and Drug Administration (FDA)-approved dose of 45 mg once daily.[23] This was intended to reduce the risk of thrombotic events. In addition, mandatory thromboprophylaxis was required for all study participants. This included aspirin (81 or 325 mg daily) and statin therapy (e.g., atorvastatin 10 mg daily).

Treatment with ponatinib was continued until there was evidence of progressive disease, death, or unacceptable toxicity. Continuation of ponatinib beyond RECIST-defined progression was allowed for ongoing clinical benefit as determined by the treating investigator. Dose escalation of ponatinib to 45 mg daily was permitted in patients who did not experience an objective response within two to four cycles of therapy or in participants who experienced an objective response on ponatinib but subsequently relapsed. Dose escalation was not permitted if a patient experienced a vascular adverse event of any grade or if the patient experienced any treatment-related adverse event of grade 3 or higher.

Computed tomography of the chest, abdomen, and pelvis was performed at baseline and every 8 weeks thereafter. After 10 cycles, repeat response assessments were performed every 12 weeks. Brain imaging, either magnetic resonance imaging or a contrast-enhanced computed tomography, was required at study entry. Follow-up brain imaging was not required unless patients were found to have underlying brain metastases. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.0.

### Outcomes

The primary end point of the study was ORR according to RECIST version 1.1. The secondary end points included disease control rate (defined as the rate of complete response, partial response, and stable disease), PFS, overall survival (OS) rate at 1 year, and safety. PFS was measured from the date of ponatinib initiation until radiographic progression or death. OS was measured from the date of ponatinib initiation. Patients still alive at the time of data cutoff were censored at the time of the last follow-up.

### Statistical Considerations

The null and alternative hypotheses for the ORR were set at 10% and 30%, respectively. The null hypothesis of 10% was based on the historical response rates to second-line chemotherapy among patients progressing on platinum-doublet chemotherapy.[24] We initially planned to enroll a total of 20 patients with *RET*-rearranged NSCLC, which would have a one-sided type I error of 13% and a power of 89%. However, owing to slow accrual and limited clinical activity, the decision was made to stop the study prematurely in December 2017.

PFS and OS rates were estimated using the Kaplan-Meier method. Statistical analysis was performed using SAS version 9.4 (SAS Institute). This study is registered with ClinicalTrials.gov (number NCT01813734).

## Results

### Study Population

Between August 2014 and June 2017, nine patients with advanced, *RET*-rearranged NSCLC were enrolled and received at least one dose of ponatinib. Baseline clinical and pathologic characteristics are summarized in Table 1. The median age at the time of study entry was 58 years (range 49–73 y). Five participants (56%) were women. All patients had adenocarcinoma histology, and most patients (67%) were never-smokers. More importantly, eight patients (89%) had a previous history of brain metastases before study entry.

*RET* fusions were identified using FISH in three patients (33%) and targeted NGS in six patients (66%). In patients with *RET* fusions detected through NGS, *RET* fusion partners included *KIF5B* (n = 3; 50%), *TRIM33* (n = 1; 16%), and unknown/not reported (n = 2; 33%). In general, the patients had been heavily pretreated. The median number of previous lines of therapy was three (range 1–5). Three patients (33%) had earlier received MKIs with RET activity (cabozantinib [n = 1], sunitinib [n = 1], and RXDX-105 [n = 1]). Of the three patients who had been treated with RET MKIs before study entry, one patient had previously achieved a confirmed partial response to cabozantinib. However, the patient had discontinued cabozantinib owing to disease progression after approximately 5 months. This patient received ponatinib without intervening therapy. The second patient, previously treated with an MKI, had received sunitinib for approximately 4 months but had failed to achieve an objective response. This patient went on to receive four intervening lines of therapy before study entry. The third patient, previously treated with an MKI, had received approximately 2 weeks of RXDX-105 but had come off the study owing to Stevens-Johnson syndrome. None of the patients above had received selective

**Table 1.** Baseline Patient Characteristics

| Characteristics | N = 9 |
|---|---|
| Age, y | |
| Median | 58 |
| Range | 49-73 |
| Sex, n (%) | |
| Male | 4 (44) |
| Female | 5 (56) |
| Race, n (%) | |
| White | 7 (78) |
| Asian | 0 (0) |
| Other | 2 (22) |
| Histology, n (%) | |
| Adenocarcinoma | 9 (100) |
| ECOG performance status, n (%) | |
| 0 | 6 (67) |
| 1 | 3 (33) |
| Smoking status, n (%) | |
| Never | 6 (67) |
| Light (≤10 pack-y) | 2 (22) |
| Heavy (>10 pack-y) | 1 (11) |
| Brain metastases, n (%) | |
| Present | 8 (89) |
| Absent | 1 (11) |
| *RET* testing, n (%) | |
| FISH | 3 (33) |
| Next-generation sequencing | 6 (66) |
| Previous RET MKIs, n (%) | |
| Yes | 3 (33) |
| No | 6 (66) |
| Previous lines of therapy, n (%) | |
| Median | 3 |
| Range | 1-5 |

ECOG, Eastern Cooperative Group; FISH, fluorescence in situ hybridization; MKI, multikinase inhibitor.

RET inhibitors (e.g., pralsetinib, selpercatinib) before study entry.

### *Efficacy*

Among the nine patients with *RET*-positive NSCLC who were treated with ponatinib, no confirmed objective responses were observed (ORR 0%; Fig. 1). Tumor shrinkage was seen in five patients, including two patients with a decrease in tumor size greater than or equal to 30%. In one instance, the patient was observed to have a 41% decrease in tumor size at the time of first imaging assessment (Fig. 2*A–D*), but confirmatory imaging revealed disease progression at the next response assessment. A second patient was observed to have 48% tumor shrinkage from baseline, but the first imaging assessment revealed a new brain metastasis consistent with progressive disease. More importantly, the patient continued ponatinib beyond progression and remained on therapy for nearly 2 years before discontinuation for further central nervous system (CNS) progression. Of note, this patient had previously received RXDX-105.

In total, five patients (56%) had the best response of stable disease, three patients (33%) had progressive disease, and one patient (11%) clinically deteriorated and died before repeat disease assessment. Thus, the disease control rate with ponatinib in *RET*-positive NSCLC was 56%. Among the three patients previously treated with RET MKIs, one had primary progression on first imaging assessment and a second was taken off the study before completion of cycle two owing to clinical progression. The third patient, detailed above, remained on ponatinib for nearly 2 years despite a best response of progressive disease in the setting of new CNS involvement.

Median follow-up time was 9.33 months. The median PFS was 3.80 months (95% CI: 1.83–5.30; Fig. 3). At the time of data cutoff, six patients (67%) had died. Median OS was 17.47 months (95% CI: 6.57–19.20). The OS rate at 1 year was 56%.

### *Safety and Toxicity*

All nine patients were evaluated for toxicity. The most common treatment-related adverse events were rash (n = 5; 56%), constipation (n = 4; 44%), diarrhea (n = 4; 44%), abdominal pain (n = 2; 22%), nausea (n = 2; 22%), and dry skin (n = 2; 22%) (Table 2). The only grade 3 or higher treatment-related adverse event observed was grade 3 dry skin in one patient. No treatment-related thromboembolic or cardiac events were observed and no treatment-related deaths occurred.

Of the nine patients treated with ponatinib, five patients (56%) required dose interruption for treatment-related adverse events. Two patients (22%) ultimately required a dose reduction of ponatinib from 30 mg to 15 mg once daily. One patient had ponatinib dose escalated to 45 mg once daily at the time of disease progression as permitted by the study protocol. The patient completed one cycle of therapy without new adverse events but ultimately discontinued therapy to pursue additional therapeutic options.

## Discussion

*RET* rearrangements have recently emerged as important new oncogenic drivers in NSCLC; however, there are no approved RET inhibitors to date.[6,12] In this study, we evaluated the clinical activity of the MKI ponatinib in patients with *RET*-rearranged NSCLC. Despite encouraging preclinical data in *RET*-rearranged models,[19] we observed limited clinical activity of ponatinib in *RET*-positive NSCLC.

Several factors may have contributed to the lack of clinical activity of ponatinib in this trial. First, the dose of ponatinib may have been suboptimal. The FDA-approved dose of ponatinib is 45 mg once daily[23];

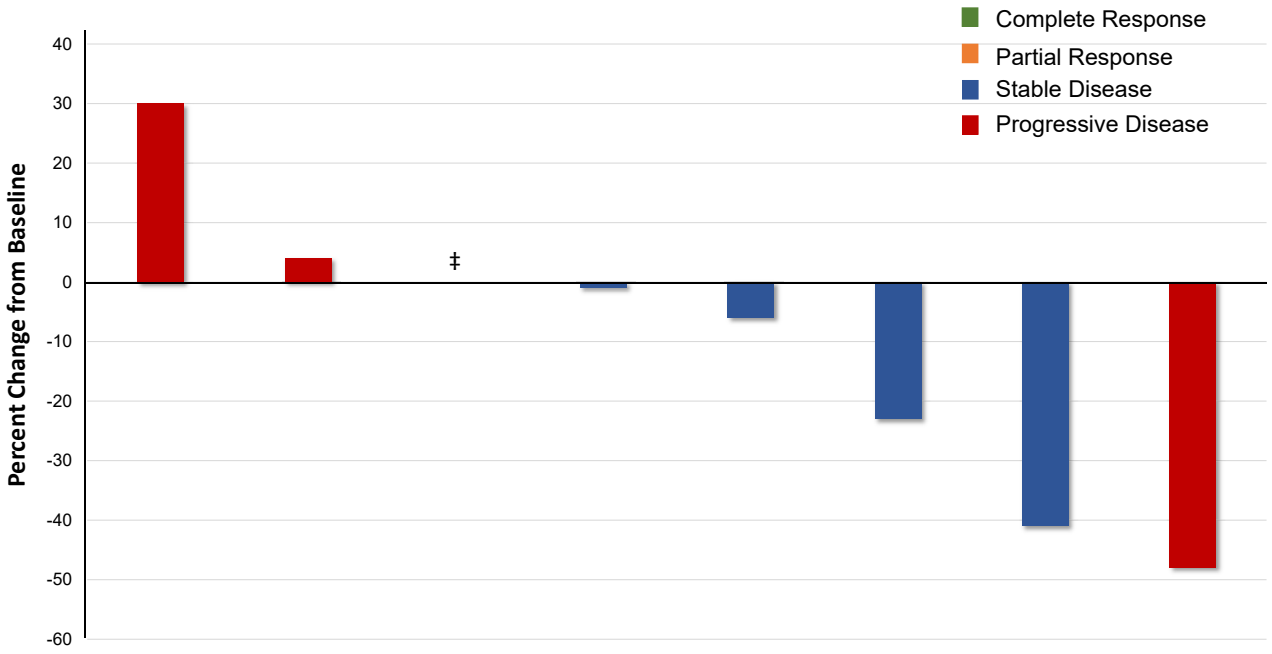


**Figure 1.** Best objective responses according to Response Evaluation Criteria in Solid Tumors v1.1. The bars represent the best percentage change in target tumor burden from baseline. One patient (‡) had a best percentage change of 0%. One patient died before the repeat response assessment and is, therefore, not depicted.

however, patients in this study received a starting dose of 30 mg once daily. The rationale for this starting dose was to try to mitigate the risks of arterial and venous occlusive events associated with ponatinib, especially as this was one of the first trials of this agent in a patient population with lung cancer. Nonetheless, the low starting dose, along with ponatinib's off-target effects and need for dose interruptions (56%) and dose reductions (22%) in this trial, may have led to inadequate target inhibition of RET. A second key factor that may have impacted our results is the makeup of our study patient population. The patients had generally been heavily pretreated with a median of three previous lines of therapy. Moreover, in contrast to previous series and trials of *RET*-rearranged NSCLC, our cohort was heavily enriched with patients with brain metastases, which is historically a poor prognosis indicator.[25] Indeed, nearly 90% of patients in our study population had brain metastases. Data on the CNS penetration of ponatinib is limited, but preclinical studies suggest that ponatinib has limited activity in intracranial orthotopic models and undergoes transporter-mediated drug efflux from the brain.[26,27] Consistent with these findings, we observed that the one patient in our study with the greatest tumor shrinkage from baseline (−48%) was ultimately characterized as having progressive disease owing to the appearance of new brain metastasis on the first disease reassessment. Thus, the high frequency of baseline brain metastasis in this study, together with the limited CNS penetration of ponatinib, may have also contributed to the low response rates observed.

Beyond inadequate target inhibition and poor CNS penetration, a third factor that may have influenced our study results is that several patients had been previously treated with anti-RET MKIs before study entry. Currently, insights into the molecular mechanisms of resistance to RET MKIs are limited, though *RET* resistance mutations have been rarely described.[28,29] In this study, three patients (33%) had been MKI-pretreated, and all experienced primary progression. Repeat molecular analysis of their tumors before study entry was not available in any case. Nonetheless, it is possible that this previous exposure to RET inhibitors may have reduced the activity of ponatinib in these patients.

Overall, this study adds to a growing literature that MKIs have limited activity in patients with *RET*-rearranged NSCLC. In prospective trials of cabozantinib, vandetanib, lenvatinib, and RXDX-105, objective responses were reported in 15% to 47% of patients with *RET*-positive NSCLC, but the median PFS in each study was under 8 months.[14-17,30] Likewise, in a global registry series, the median PFS among patients with *RET* fusions who were treated with MKIs outside of a clinical trial was only 2.3 months.[31] Thus, RET MKIs are significantly less active in *RET*-rearranged NSCLC compared with the impressive clinical activity of genotype-specific TKIs in

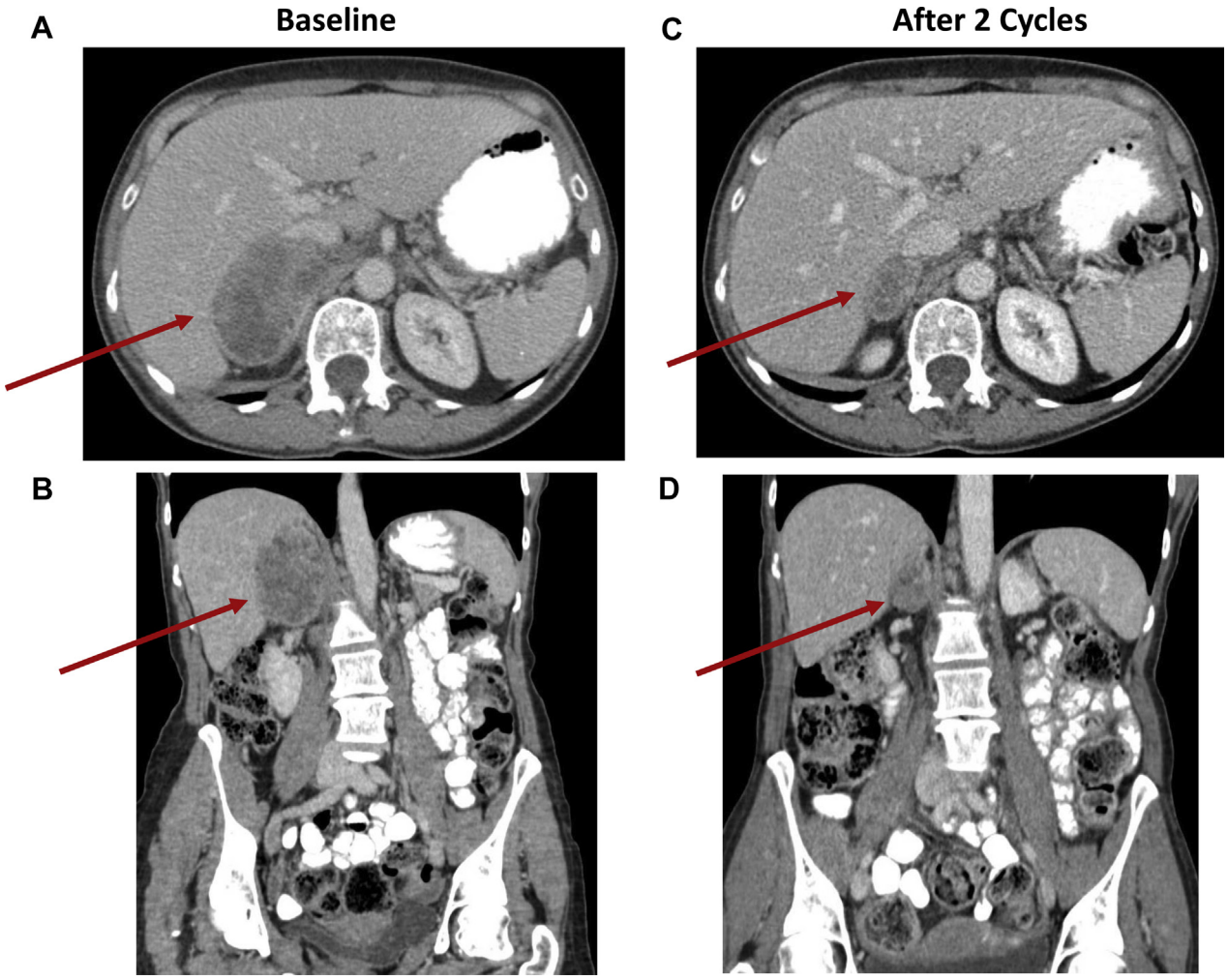


**Figure 2.** *(A, B)* Baseline axial and coronal computed tomography images from a patient with *RET*-positive NSCLC before study entry. A large right adrenal metastasis is highlighted by red arrows. *(C, D)* Repeat axial and coronal computed tomography images after two cycles of ponatinib reveal a marked interval reduction in the size of the right adrenal metastasis.

patients with alterations in other targetable oncogenic drivers, such as *EGFR*, *ALK*, and *ROS1*. Collectively, this underscores the need for clinical development of more potent and selective RET inhibitors.

A significant limitation of this study is the small sample size. This largely reflects the changing therapeutic landscape for *RET*-rearranged NSCLC, which led to the premature closure of this study. Recently, two highly potent and selective RET inhibitors, pralsetinib (formerly BLU-667) and selpercatinib (formerly LOXO-292), have entered clinical testing. In preclinical models, each agent has revealed low nanomolar activity against various *RET* alterations and increased potency compared with representative MKIs (e.g., cabozantinib).[32,33] Importantly, these agents also generally spare inhibition of VEGFR2, a key distinction from the MKIs. In

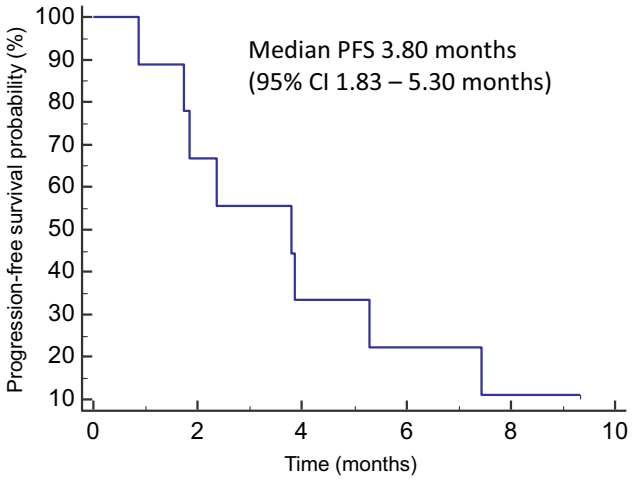


**Figure 3.** Progression-free survival on ponatinib (N = 9).

**Table 2.** Treatment-Related Adverse Events

| Adverse Events, n (%) | Any Grade | Grade 3/4 |
|---|---|---|
| Rash | 5 (55) | 0 |
| Constipation | 4 (44) | 0 |
| Diarrhea | 4 (44) | 0 |
| Abdominal pain | 2 (22) | 0 |
| Dry skin | 2 (22) | 1 (11) |
| Nausea | 2 (22) | 0 |
| Fatigue | 1 (11) | 0 |
| Myalgia | 1 (11) | 0 |
| Anemia | 1 (11) | 0 |
| Bloating | 1 (11) | 0 |
| Epistaxis | 1 (11) | 0 |
| Facial flushing | 1 (11) | 0 |
| Headache | 1 (11) | 0 |
| Hypophosphatemia | 1 (11) | 0 |
| Alopecia | 1 (11) | 0 |
| Alkaline phosphatase elevation | 1 (11) | 0 |

an ongoing phase I/II study of pralsetinib (ARROW; NCT03037385), objective responses were seen in 58% of patients with *RET*-rearranged NSCLC (N = 48), including responses in 71% of treatment-naive patients (N = 7).[34] Similarly, in phase I/II study of selpercatinib (LIBRETTO-001; NCT02157128), objective responses were observed in 68% of patients with *RET*-rearranged NSCLC (N = 105), and the median PFS was 18.4 months.[35] More importantly, both pralsetinib and selpercatinib have revealed antitumor activity in patients with *RET*-rearrangements previously treated with MKIs and in patients with CNS metastases.[34,36] On the basis of this promising activity, both agents have received breakthrough therapy designation by the FDA.

In summary, despite encouraging preclinical activity in *RET*-rearranged models, we found that ponatinib had limited clinical activity in patients with advanced, *RET*-positive NSCLC in this phase II study. More broadly, this and other studies of MKIs in *RET*-rearranged NSCLC highlight the challenges of drug repurposing strategies, especially when the repurposed agents are unable to completely inhibit the target or have significant off-target toxicities. Moving forward, attention should be placed on the continued development of more potent and selective RET inhibitors for *RET*-rearranged NSCLC.

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