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A phase 2 study of lenvatinib in patients with *RET* fusion-positive lung adenocarcinoma☆

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ABSTRACT

Objectives: Despite improved outcomes associated with immunotherapies for non-small cell lung cancer (NSCLC), many patients do not respond to treatment. Therefore, there is still an unmet need for molecularly targeted therapies in this patient population. Fusions of the *RET* oncogene have been identified as driver alterations in patients with NSCLC. Lenvatinib is a multityrosine kinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, RET, and other targets. This study evaluated the safety and efficacy of lenvatinib in patients with *RET* fusion-positive lung adenocarcinoma.

Materials and methods: In this phase 2, multicenter, open-label study (NCT01877083), patients with *RET*-positive lung adenocarcinoma received oral lenvatinib 24 mg/day. The primary end point was objective response rate (ORR) by investigator review per Response Evaluation Criteria In Solid Tumors v1.1 criteria. The secondary end points included safety and tolerability, progression-free survival (PFS), and overall survival (OS).

Results: Of 536 patients who screened for study inclusion and exclusion, 25 patients with *RET* translocations (*KIF5B-RET* [n = 13] and *CCDC6-RET* [n = 12]) were identified and received lenvatinib. The overall ORR was 16% (95% CI: 4.5%–36.1%). At data cutoff (February 3, 2016), the median PFS was 7.3 months (95% CI: 3.6–10.2) and the median OS was not reached. Duration of response was not estimable at the time of data cutoff. All patients experienced a treatment-emergent adverse event (TEAE); 23 (92%) patients experienced a TEAE of ≥ grade 3, and 6 (24%) patients discontinued lenvatinib due to a TEAE. The most common TEAEs were hypertension (68%), nausea (60%), decreased appetite (52%), diarrhea (52%), and proteinuria (48%).

Conclusions: Lenvatinib demonstrated activity in patients with *RET* fusion-positive lung adenocarcinomas; although the response rate was relatively low, the median PFS supports the activity of lenvatinib in these patients.

1. Introduction

Lung cancer is responsible for an estimated 1.7 million deaths worldwide per year, and identifying additional therapeutic options represents an area of unmet need [1,2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases with adenocarcinoma representing 36%–60% of cases [3–5].

Historically, 5-year survival rates for stage IV NSCLC have ranged from 1% to 9.6% [6,7]. However, the more recent advent of immunotherapies in health care has resulted in improved 3-year and 5-year overall survival (OS) rates for patients with advanced NSCLC. For example, patients treated with nivolumab had an estimated 5-year OS rate of 16% [8], and patients receiving atezolizumab or pembrolizumab had 3-year OS rates that ranged from 19% to 26% [9,10].

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The development of molecularly targeted agents provides opportunities to improve outcomes in patients with advanced NSCLC who harbor specific genetic abnormalities [11]. Fusions in the rearranged during transfection (*RET*) proto-oncogene have been reported in 1%–2% of patients with NSCLC [12–14]. In NSCLC, these gene rearrangements result in the expression of oncogenic fusion proteins retaining the kinase domain but leading to downstream ligand-dependent growth and proliferation. In 2012, four transcript variants of *KIF5B-RET* gene fusions were first identified in patients with NSCLC [12,14]. When *KIF5B-RET* was introduced to an IL-3-dependent hematopoietic cell line, the cells were transformed and were no longer IL-3-dependent. These cell lines were sensitive to multikinase inhibitors with anti-RET activity [14]. Since then, 15 *RET* fusions have been reported in NSCLC [15]. Additional *RET* fusion partners identified in NSCLC include *WAC* [16], *CCDC6*, *NCOA4* [17], *FRMD4A* [18], and *TRIM33* [19], with the two most frequent being *KIF5B-RET* and *CCDC6-RET* [20]. Typically, these genetic alterations are identified in younger nonsmoking patients with adenocarcinoma. Treatment of *RET*-fusion-driven NSCLC is currently focused on multikinase inhibitors with known anti-RET activity.

Lenvatinib is a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)1–3, fibroblast growth factor receptors (FGFR)1–4, platelet-derived growth factor receptor alpha (PDGFRα), RET, and KIT [21–24]. Lenvatinib is approved as a monotherapy for the treatment of patients with radioiodine-refractory differentiated thyroid cancer and unresectable hepatocellular carcinoma, and is approved in combination with everolimus for advanced renal cell carcinoma following 1 prior antiangiogenic therapy [25]. Lenvatinib was granted accelerated approval in combination with pembrolizumab for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high or mismatch repair deficient, who have disease progression following prior systemic therapy, and are not candidates for curative surgery or radiation [25]. This study evaluates the efficacy and safety of lenvatinib in patients with *RET* fusion-positive lung adenocarcinoma.

2. Materials and methods

2.1. Patients

Patients who were 18 years or older were eligible if they had cytologically or histologically confirmed *RET* fusion-positive lung adenocarcinoma. Key eligibility criteria included patients who had received ≤ 3 previous systemic therapies for adenocarcinoma of the lung (and patients with > 3 previous systemic therapies could be enrolled on a case-by-case basis), measurable disease per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and life expectancy ≥ 12 weeks. Additional inclusion criteria included blood pressure ≤150/90 mmHg and adequate bone marrow, hepatic, and renal function. Key exclusion criteria comprised any anticancer therapy within 21 days or other investigational therapy within 28 days of the study drug treatment, untreated or clinically unstable brain or meningeal metastases, significant cardiovascular impairment, gastrointestinal malabsorption, major surgery within the past 3 weeks, active infection requiring treatment, or proteinuria (urine protein ≥ 1 g/24 h). Patients with bleeding or thrombotic disorders were excluded from the study, as well as those using anticoagulants such as warfarin or similar agents requiring therapeutic international normalized ratio monitoring. Patients being treated with low molecular weight heparin could be included. Patients with any other active malignancy within the previous 2 years were excluded, except for adenocarcinoma of the lung, definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix. All patients provided written informed consent.

2.2. Study design and treatment

This phase 2, multicenter, open-label study assessed the safety and efficacy of lenvatinib in patients with *KIF5B-RET*-positive lung adenocarcinoma and other *RET* translocations (ClinicalTrials.gov identifier NCT01877083). The study was conducted at 14 study sites in 4 countries (United States, Japan, Singapore, and Taiwan) from April 2013 to February 2016.

Tumor samples from potentially eligible patients with unknown *RET* status were sent to a local or central laboratory for testing by next-generation sequencing (NGS). If available, tumor samples from patients whose tumors had been previously determined by an approved assay (ie, fluorescence in situ hybridization/reverse transcription-polymerase chain reaction) to have *KIF5B-RET*-positive or other *RET* translocations were sent to a central laboratory for confirmation by NGS. Patients with confirmed *RET*-positive lung adenocarcinoma received oral lenvatinib 24 mg once daily in 28-day cycles. Patients received study treatment until progressive disease (PD), unacceptable toxicity, or withdrawal of consent. The primary data cutoff point (February 3, 2016) was reached after either completion of 6 cycles of treatment or discontinuation of the treatment for all enrolled patients had occurred. Patients could continue to receive study treatment in 28-day cycles in the extension phase of the trial until PD, development of unacceptable toxicity, or withdrawal of consent. Patients were followed every 8 weeks for survival until death or withdrawal of consent. Patients on study treatment for ≥ 48 weeks, who discontinued without PD, continued follow up with tumor assessments every 8 to 12 weeks until PD or the initiation of another anticancer therapy. A limited data update was performed as of December 28, 2017, which reported the patient disposition and exposure to study drug for the 5 patients who remained on treatment after the original data cutoff date.

The study protocol was approved by the relevant institutional review boards/independent ethics committees of the participating study sites. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

2.3. Clinical assessments

The primary end point was the objective response rate (ORR), defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) as their best overall response. Tumor assessments were based on investigator assessment of radiologic response according to RECIST v1.1. Secondary end points included progression-free survival (PFS), OS, and pharmacokinetics. Exploratory end points included disease control rate (DCR; defined as CR + PR + stable disease [SD; duration ≥ 7 weeks]), clinical benefit rate (CBR; defined as CR + PR + durable SD [≥ 23 weeks]), time to response (TTR), duration of response (DOR), and patient-reported health-utility scores. PR or CR were confirmed ≥ 4 weeks after initial response.

2.4. Pharmacokinetics

Blood samples were collected predose, 0.5–4 h, and 6–10 h postdose on cycle 1 day 1; predose, 0.5–4 h, and 6–10 h postdose on cycle 1 day 15; predose and 2–12 h postdose on cycle 2 day 1; and predose on cycle 3 day 1. Plasma concentrations of lenvatinib were determined by liquid chromatography/tandem mass spectrometry.

2.5. Statistical analysis

Given the rarity of *RET* fusion-positive lung adenocarcinomas, no formal sample size determination was performed. The full analysis set was used for efficacy assessments and included all patients who received ≥ 1 dose of lenvatinib. ORR was presented with corresponding 2-sided, exact binomial 95% confidence intervals (CIs) calculated using the Clopper-Pearson method. Time-to-event outcomes were estimated

using the Kaplan-Meier method. For patients with a confirmed CR or PR, the DOR and TTR were estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS version 9.2.

3. Results

3.1. Patient disposition and demographics

Overall, 536 patients were screened to identify eligible patients with *RET* fusion-positive lung adenocarcinoma. Of these, a total of 25 patients were eligible to receive treatment: 13 patients with *KIF5B-RET* and 12 patients with *CCDC6-RET*. At the time of primary data cutoff (February 3, 2016), treatment was ongoing for 5 (20%) patients, whereas 20 (80%) patients had discontinued treatment (See **Table, Supplemental Data 1A**, for patient disposition). Updated cumulative disposition data are reported as of December 28, 2017, once the remaining 5 patients had discontinued treatment (See **Table, Supplemental Data 1B**). Patient baseline characteristics are summarized in Table 1. The median age was 63 years, the majority of patients were female (72%), never smokers (56%), and had an ECOG performance status of 0 (60%). Of the 25 patients in the study, 36% had 3 or more prior therapies, 56% had 1–2 lines of prior therapy, and 2 (8%) patients were treatment-naïve.

3.2. Efficacy

The primary end point of ORR was 16.0% (95% CI: 4.5–36.1); all were partial responses (Table 2). ORRs were similar between patients with *KIF5B-RET* and *CCDC6-RET* fusion variants (15.4% and 16.7%, respectively). However, differences were noted between patients with the *KIF5B-RET* fusion variant versus the *CCDC6-RET* fusion variant in both DCR (61.5% vs 91.7%, respectively) and CBR (30.8% vs 66.7%, respectively; Table 2). The ORR for the subset of patients (n = 7) who received other RET-targeted therapy prior to study entry was 14.3%. The ORR for patients who did not receive RET-targeted therapy (n = 18) prior to study entry was 16.7%. The majority of patients in this study experienced a reduction in tumor volume (Fig. 1**)**.

The median PFS was 7.3 months (95% CI: 3.6–10.2) (Table 2 and Fig. 2A). The median PFS was numerically longer for patients with *CCDC6-RET* fusion variants versus the *KIF5B-RET* fusion variant (9.1 months vs 3.6 months, respectively). The median DOR was not estimable, as only one patient with an objective response had progressive disease at the data cutoff date. However, the DOR for the 4 patients who had a PR ranged from 1.8 to 10.2 months at the time of censoring. At the time of data cutoff, the median OS was not yet reached (Fig. 2B); however, the 12-month survival rate was 40% for patients with *KIF5B-RET* and 67% for patients with *CCDC6-RET* fusions.

Table 1
Patient demographics and baseline characteristics.

Parameter	*KIF5B-RET* (n = 13)	*CCDC6-RET* (n = 12)	Total (N = 25)
Median age, years (range)	61.0 (34, 75)	65.5 (38, 78)	63.0 (34, 78)
Sex, n (%)			
Male	2 (15.4)	5 (41.7)	7 (28.0)
Female	11 (84.6)	7 (58.3)	18 (72.0)
Race, n (%)			
White	4 (30.8)	4 (33.3)	8 (32.0)
Asian	9 (69.2)	8 (66.7)	17 (68.0)
ECOG performance status, n (%)			
0	9 (69.2)	6 (50.0)	15 (60.0)
1	4 (30.8)	6 (50.0)	10 (40.0)
Smoking history, n (%)			
Never smoked	8 (61.5)	6 (50.0)	14 (56.0)
Current smoker	0 (0)	1 (8.3)	1 (4.0)
Former smoker	3 (23.1)	4 (33.3)	7 (28.0)
Unknown	2 (15.4)	1 (8.3)	3 (12)
Number of prior anticancer therapies, n (%)			
0	1 (7.7)	1 (8.3)	2 (8.0)
1	7 (53.8)	1 (8.3)	8 (32.0)
2	2 (15.4)	4 (33.3)	6 (24.0)
3	2 (15.4)	4 (33.3)	6 (24.0)
≥ 4	1 (7.7)	2 (16.7)	3 (12.0)
RET-targeted therapy,[a] n (%)			
Cabozantinib	0 (0)	3 (25.0)	3 (12.0)
Vandetanib	2 (15.4)	3 (25.0)	5 (20.0)
VEGF-targeted therapy,[a] n (%)			
Bevacizumab	6 (46.2)	4 (33.3)	10 (40.0)
BIBF 1120	0 (0)	1 (8.3)	1 (4.0)
Cabozantinib	0 (0)	3 (25.0)	3 (12.0)
Sorafenib	0 (0)	1 (8.3)	1 (4.0)
Vandetanib	2 (15.4)	3 (25.0)	5 (20.0)

ECOG, Eastern Cooperative Oncology Group; VEGF, vascular endothelial growth factor.

[a] One patient had received prior therapy with both cabozantinib and vandetanib.

3.3. Pharmacokinetics

Predose and postdose plasma concentrations of lenvatinib were assessed for all patients (N = 25) (see the **Figure, Supplemental Data 2**, for a graphic on plasma concentration of lenvatinib over time). The time of dose administration proximal to collection of lenvatinib pharmacokinetic samples was not recorded for a large percentage of samples; therefore, the planned population pharmacokinetic modeling analysis could not be performed for this study.

3.4. Safety

For the primary data cutoff period (ie, February 3, 2016), exposure to study drug is summarized in the **Table, Supplemental Data 3A**. Overall, the median number of cycles was 6 (range: 1–30), the median duration of exposure was 16 weeks (range: 2.0–117.1), and the median dose intensity was 122.9 mg/week (range: 58.8–194.5). Of note, patients with *KIF5B-RET* generally had fewer cycles of treatment and lower exposure to lenvatinib compared with patients with *CCDC6-RET* fusions. Updated data on patient exposure were collected at the end of the study (data cutoff: December 28, 2017) and are presented in **Table, Supplemental Data 3B**. Overall, the median number of cycles remained unchanged (ie, 6 cycles), while the median duration of exposure increased to 20.6 weeks (range: 2.0–205.9).

All treated patients experienced at least 1 treatment-emergent adverse event (TEAE) (Table 3). The most common any-grade TEAEs were hypertension (68%), nausea (60%), decreased appetite (52%), diarrhea (52%), proteinuria (48%), vomiting (44%), and headache (40%) (Table 4). Grade ≥ 3 TEAEs occurred in 92% (23/25) of patients (Table 3). The most common grade ≥ 3 TEAEs were hypertension (56%), hyponatremia (20%), proteinuria (16%), pneumonia (16%), and nausea (12%) (Table 4). Serious adverse events (AEs) were reported in 13 patients (52%), and fatal AEs occurred in 3 patients (12%) (Table 3). Of these, 2 deaths were considered unrelated to lenvatinib therapy (cardiac failure and dyspnea secondary to PD), whereas the third death was considered treatment related (pneumonia). Overall, 19 (76%) patients required treatment interruption, 16 (64%) patients required dose reduction, and 6 (24%) patients discontinued treatment, due to TEAEs (Table 3).

4. Discussion

In this phase 2 study, lenvatinib demonstrated antitumor activity and a manageable safety profile in patients with *RET* fusion-positive lung adenocarcinoma. The ORR was 16% and the median PFS was 7.3 months. Most patients (64%) had received 2 or fewer prior anticancer regimens. In contrast, in a study of lenvatinib in patients who had nonsquamous NSCLC (not screened for the presence of *RET* fusions) and failed ≥ 2 prior systemic anticancer regimens, the ORR was 10% and

Table 2
Efficacy results.

Parameter	*KIF5B-RET* (n = 13)	*CCDC6-RET* (n = 12)	Total (N = 25)
Best overall response, n (%)			
Complete response	0 (0)	0 (0)	0 (0)
Partial response	2 (15.4)	2 (16.7)	4 (16.0)
Stable disease	6 (46.2)	9 (75.0)	15 (60.0)
Progressive disease	3 (23.1)	0 (0)	3 (12.0)
Not evaluable[a]	1 (7.7)	1 (8.3)	2 (8.0)
Unknown[b]	1 (7.7)	0 (0)	1 (4.0)
Objective response rate,[c] n (%)	2 (15.4)	2 (16.7)	4 (16.0)
(95% CI)	(1.9–45.4)	(2.1–48.4)	(4.5–36.1)
Disease control rate,[d] n (%)	8 (61.5)	11 (91.7)	19 (76.0)
(95% CI)	(31.6–86.1)	(61.5–99.8)	(54.9–90.6)
Clinical benefit rate,[e] n (%)	4 (30.8)	8 (66.7)	12 (48.0)
(95% CI)	(9.1–61.4)	(34.9–90.1)	(27.8–68.7)
Median PFS, months (95% CI)	3.6 (1.0–NE)	9.1 (2.3–10.2)	7.3 (3.6–10.2)
PFS rate, % (95% CI)[f]			
3 months	59.3 (27.5–81.0)	90.0 (47.3–98.5)	73.9 (50.6–87.5)
6 months	29.7 (5.1–60.9)	80.0 (40.9–94.6)	56.3 (31.9–75.0)
12 months	29.7 (5.1–60.9)	0 (NE–NE)	15.6 (1.0–47.4)
Median OS, months (95% CI)	11.4 (4.2–NE)	NE (4.3–NE)	NE (5.8–NE)
OS rate, % (95% CI)[f]			
3 months	84.6 (51.2–95.9)	91.7 (53.9–98.8)	88.0 (67.3–96.0)
6 months	60.6 (29.4–81.4)	75.0 (40.8–91.2)	67.8 (45.7–82.4)
12 months	40.4 (8.3–71.9)	66.7 (33.7–86.0)	54.5 (29.4–74.0)
24 months	40.4 (8.3–71.9)	NE (NE–NE)	54.5 (29.4–74.0)

CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.
[a] Applied to 2 patients whose best response of SD was < 7 weeks' duration at the time of data cutoff.
[b] Applied to 1 patient who had no tumor assessment data available.
[c] Objective response rate is defined as the percentage of patients who achieved a complete or partial response.
[d] Disease control rate is defined as the percentage of patients who achieved a complete response or partial response, plus those who had stable disease for at least 7 weeks.
[e] Clinical benefit rate is defined as the percentage of patients who achieved a complete response or partial response, plus those who had durable stable disease for at least 23 weeks.
[f] Point estimates are based on the Kaplan-Meier method and 95% CIs are based on the Greenwood formula.

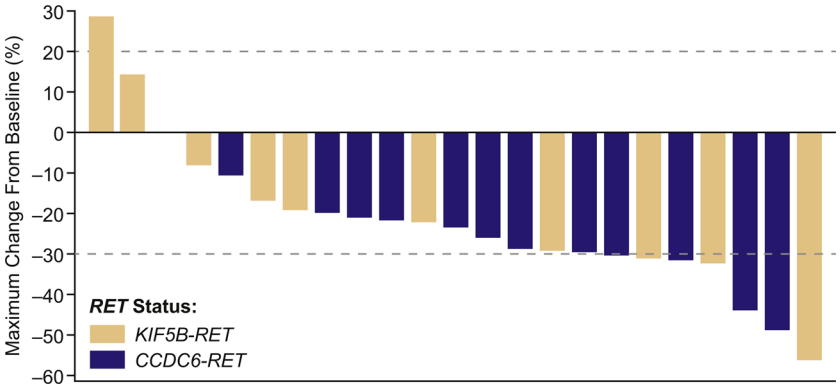

Fig. 1. Waterfall plot of maximum percent change in summed diameter of target lesions from baseline to nadir, full analysis set.
Four patients had confirmed PRs. The remainder of the responses were unconfirmed (SD or NE).
Two patients are not included because they did not have results from postbaseline evaluations.
NE, not evaluable; PR, partial response; SD, stable disease.

the median PFS was 5.2 months [26]. Prior clinical trials, with other RET-targeted tyrosine kinase inhibitors in NSCLC, showed a median PFS that ranged from 4.7 to 5.5 months [27,28] compared with the median PFS of 7.3 months observed in this study.

The targeting of *RET* fusion-positive cancers with multikinase inhibitors can be problematic because high doses are required to achieve optimal RET inhibition levels, which may cause toxicity relating to other targets. Thus, recent therapeutic targeting of these cancers has shifted to RET-specific inhibition. Recently, RET-specific inhibitors BLU-667 and LOXO-292 have been investigated and preliminary clinical data suggest that they may be effective anticancer agents in patients with NSCLC and other cancers harboring *RET* translocations [29–32]. Subbiah et al reported anticancer activity in 2 patients with *KIF5B-RET* fusions where both patients showed a PR after 16 weeks of treatment with BLU-667 at doses of 200–300 mg/d [29]. In the ARROW study, BLU-667 demonstrated potent antitumor activity and was well tolerated in patients with *RET* fusion-positive NSCLC [32]. Of the 79 patients enrolled, 44 had *KIF5B-RET* and 16 had *CCDC6-RET* fusions. The ORR was 56% (95% CI, 42–69; 32 PR, 9 PR pending confirmation, 20 SD, 5 PD) (NCT03037385) [32]. Additionally, in a phase 1 study of 26 patients with *RET* fusion-positive NSCLC treated with the RET-targeted inhibitor LOXO-292, the ORR was 65% (17/26) (NCT03157128) [30].

One possible explanation for the low response rate observed in this study may be that at the clinically appropriate and tolerable dose used in this trial, the RET inhibitory activity of lenvatinib was low. Another explanation may be that the *RET* fusion variants examined in this study do not drive the development of lung adenocarcinoma for some patients in this study population. This hypothesis is supported by our observation that efficacy outcomes differed between patients with different *RET* fusions. Notably, in this study, patients with *CCDC6-RET* fusions had longer PFS versus those with *KIF5B-RET* fusions (9.1 months vs 3.6

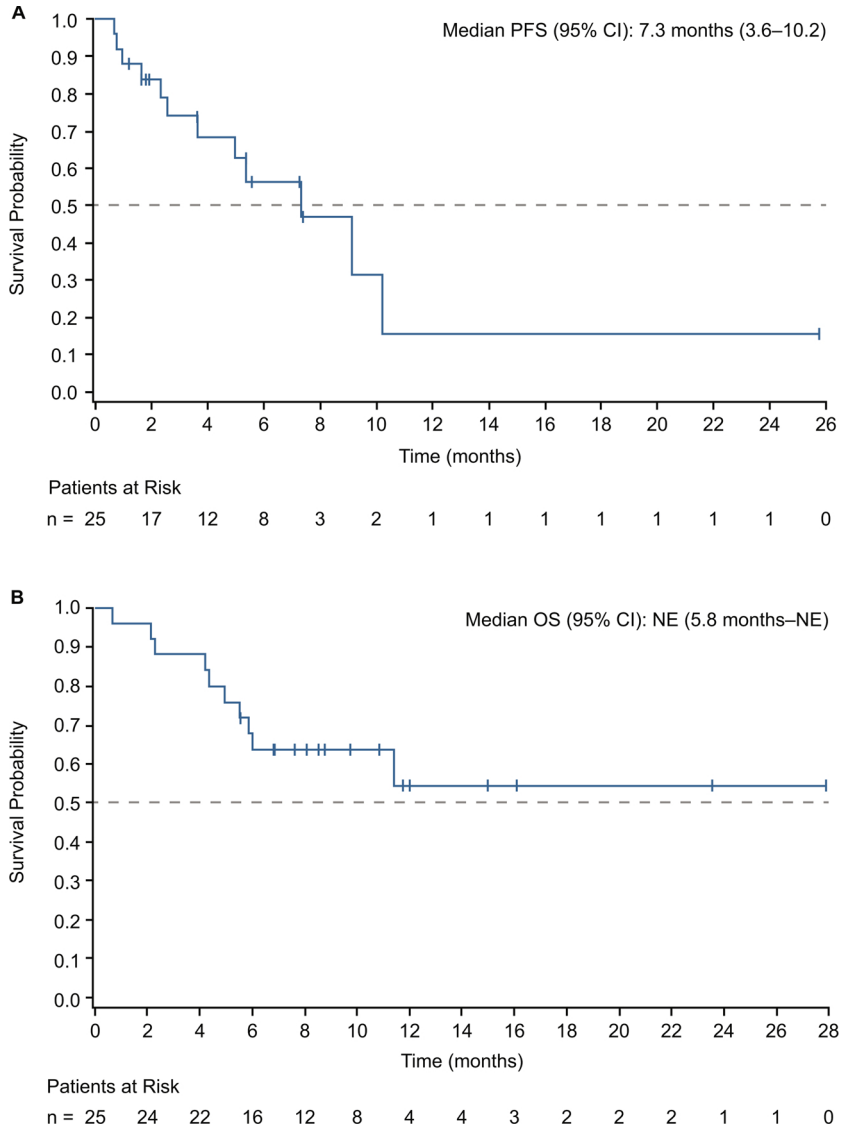

Fig. 2. (A) Kaplan-Meier estimate of PFS, investigator assessment; (B) Kaplan-Meier estimate of OS, full analysis set.
CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

Table 3
Summary of treatment-emergent adverse events, safety analysis set.

Parameter, n (%)	*KIF5B-RET* (n = 13)	*CCDC6-RET* (n = 12)	Total (N = 25)
TEAEs	13 (100.0)	12 (100.0)	25 (100.0)
Grade ≥ 3 TEAEs	12 (92.3)	11 (91.7)	23 (92.0)
Serious adverse events	6 (46.2)	7 (58.3)	13 (52.0)
Deaths	1 (7.7)	2 (16.7)	3 (12.0)
TEAEs leading to drug interruption	10 (76.9)	9 (75.0)	19 (76.0)
TEAEs leading to dose reduction	6 (46.2)	10 (83.3)	16 (64.0)
TEAEs leading to drug discontinuation	3 (23.1)	3 (25.0)	6 (24.0)

TEAE, treatment-emergent adverse event.

months, respectively). A similar result was observed in a phase 2 study of patients with NSCLC treated with vandetanib in which the reported PFS was numerically longer for patients with *CCDC6-RET* (n = 6) compared to *KIF5B-RET* fusions (n = 10) (8.3 months vs 2.9 months, respectively) [28]. It is also possible that the *RET*-fusion partner has prognostic value, although further study is needed to determine if this is the case.

An alternative explanation for the observed difference in PFS between the two *RET* fusion variants is that the inhibitory activity of lenvatinib may differ depending on the fusion partner. However, in vitro assays have demonstrated that lenvatinib inhibits the auto-phosphorylation of both *KIF5B-RET* and *CCDC6-RET* [23]. Moreover, the two *RET* gene fusions were similarly sensitive to lenvatinib in cellular assays at concentrations in the 30–100 nM range [23]. These observations, however, may be obscured when treating patients because the *KIF5B-RET* fusion is thought to result in higher levels of RET expression than other fusions [33]. As such, increased levels of inhibitor would be necessary to treat patients with *KIF5B-RET* fusions. It is important to note, however, that the patient numbers for each *RET* variant type in this study were low; therefore, further studies would be needed to confirm the most appropriate study population for any future evaluation of lenvatinib in NSCLC.

The safety profile of lenvatinib in patients with NSCLC was generally consistent with previous lenvatinib monotherapy studies [26,34,35], and no new safety signals were observed. As expected, the most common AEs with lenvatinib treatment included hypertension, nausea, diarrhea, and proteinuria, which are known class effects of VEGFR-targeted agents [36,37]. Although all patients experienced an AE, only 6 (24%) patients had an AE that led to study discontinuation, and most of the toxicities could be effectively managed with the

Table 4
Treatment-emergent adverse events that occurred in at least 10% of patients.

	KIF5B-RET (n = 13)		*CCDC6-RET* (n = 12)		Total (N = 25)	
Preferred term, n (%)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hypertension	9 (69)	8 (62)	8 (67)	6 (50)	17 (68)	14 (56)
Nausea	7 (54)	1 (8)	8 (67)	2 (17)	15 (60)	3 (12)
Decreased appetite	9 (69)	0 (0)	4 (33)	0 (0)	13 (52)	0 (0)
Diarrhea	4 (31)	0 (0)	9 (75)	2 (17)	13 (52)	2 (8)
Proteinuria	6 (46)	3 (23)	6 (50)	1 (8)	12 (48)	4 (16)
Vomiting	5 (39)	1 (8)	6 (50)	1 (8)	11 (44)	2 (8)
Headache	3 (23)	0 (0)	7 (58)	0 (0)	10 (40)	0 (0)
Fatigue	2 (15)	0 (0)	7 (58)	2 (17)	9 (36)	2 (8)
Decreased platelet count	5 (39)	1 (8)	2 (17)	0 (0)	7 (28)	1 (4)
Increased aspartate aminotransferase level	2 (15)	0 (0)	4 (33)	0 (0)	6 (24)	0 (0)
Constipation	2 (15)	0 (0)	4 (33)	0 (0)	6 (24)	0 (0)
Cough	3 (23)	0 (0)	3 (25)	0 (0)	6 (24)	0 (0)
Hyponatremia	2 (15)	2 (15)	4 (33)	3 (25)	6 (24)	5 (20)
Increased alanine aminotransferase level	2 (15)	0 (0)	3 (25)	0 (0)	5 (20)	0 (0)
Arthralgia	2 (15)	1 (8)	3 (25)	0 (0)	5 (20)	1 (4)
Dyspnea	2 (15)	0 (0)	3 (25)	1 (8)	5 (20)	1 (4)
Peripheral edema	4 (31)	0 (0)	1 (8)	0 (0)	5 (20)	0 (0)
Decreased weight	0 (0)	0 (0)	5 (42)	0 (0)	5 (20)	0 (0)
Dehydration	2 (15)	0 (0)	2 (17)	0 (0)	4 (16)	0 (0)
Dry mouth	1 (8)	0 (0)	3 (25)	0 (0)	4 (16)	0 (0)
Dry skin	1 (8)	0 (0)	3 (25)	0 (0)	4 (16)	0 (0)
Hypoalbuminemia	2 (15)	0 (0)	2 (17)	0 (0)	4 (16)	0 (0)
Pneumonia	1 (8)	1 (8)	3 (25)	3 (25)	4 (16)	4 (16)
Abdominal pain	0 (0)	0 (0)	3 (25)	0 (0)	3 (12)	0 (0)
Alopecia	0 (0)	0 (0)	3 (25)	0 (0)	3 (12)	0 (0)
Increased blood creatinine level	1 (8)	0 (0)	2 (17)	0 (0)	3 (12)	0 (0)
Dysphonia	1 (8)	0 (0)	2 (17)	0 (0)	3 (12)	0 (0)
Hypothyroidism	0 (0)	0 (0)	3 (25)	0 (0)	3 (12)	0 (0)
Musculoskeletal pain	2 (15)	0 (0)	1 (8)	0 (0)	3 (12)	0 (0)
Myalgia	3 (23)	0 (0)	0 (0)	0 (0)	3 (12)	0 (0)
Decreased neutrophil count	2 (15)	0 (0)	1 (8)	0 (0)	3 (12)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	2 (15)	0 (0)	1 (8)	0 (0)	3 (12)	0 (0)
Pyrexia	3 (23)	0 (0)	0 (0)	0 (0)	3 (12)	0 (0)
Rash	1 (8)	0 (0)	2 (17)	0 (0)	3 (12)	0 (0)

Adverse event terms are sorted in descending order of frequency in the "Total" column and then alphabetically.
Patients with 2 or more adverse events in the same preferred term were counted only once for that preferred term.

prepared dose-toxicity management plan.

Although we did not have proximal dose-administration data to perform a population pharmacokinetic analysis, we did observe that data from lenvatinib plasma concentration assessments versus nominal sample collection times were similar to those seen in previous studies [38]. Another potential limitation of this study is that no independent centralized review of tumor assessments was performed, as tumor response was assessed based on the investigator's assessment of the imaging scans using RECIST v1.1. Other limitations of this study are typical of phase 2 studies and include the small and nonrandomized patient population, as well as potential variations between local-laboratory-based *RET* testing and those of central-laboratory testing.

In conclusion, lenvatinib treatment resulted in antitumor activity and manageable tolerability in patients with *RET* fusion-positive lung adenocarcinomas, with no new safety signals detected. However, since the sample size was small and this study was preliminary in nature, no definitive conclusions can be drawn with regard to the activity of lenvatinib in the *KIF5B-RET* and *CCDC6-RET* patient subpopulations. Further study of lenvatinib treatment in this patient population is warranted.

Role of the sponsor

Sponsors participated in the design and conduct of the study, data collection, data management, data analysis, data interpretation, manuscript review, manuscript approval, and decision to submit for publication. Sponsors also funded the professional medical writer, who provided medical writing assistance.

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Appendix A. Supplementary data

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