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A Phase 2 Single Arm Trial of Cabozantinib in Patients with Advanced *RET*-Rearranged Lung Cancers

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SUMMARY

Background—*RET* rearrangements are found in 1–2% of non-small cell lung cancers. Cabozantinib is a multikinase RET inhibitor that produced a 10% response rate in unselected patients with lung cancers. To evaluate the activity of cabozantinib in patients with *RET*-rearranged lung cancers, we conducted a prospective phase 2 trial in this molecular subgroup.

Methods—We enrolled patients in this open-label, Simon two-stage, phase 2 trial if they met the following criteria: metastatic or unresectable lung cancer harboring a *RET* rearrangement, Karnofsky performance status of >70%, and measurable disease. Cabozantinib was administered at 60 mg daily. The primary objective was to determine the overall response rate (RECIST v1·1).

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Declaration of interest

AD has received honoraria from Exelixis. The other authors declared no conflicts of interests.

Author contributions

AD designed the trial in cooperation with representatives of Exelixis. D, MA, MV, AP, MG, GR, CR, and MK were involved in the treatment of patients and data collection. NR, LW, MA, ML, JM, RS, and RSS were involved in molecular and pathologic analysis of study samples. AD and AN had access to the raw data. AN performed statistical analyses. AD wrote the first draft of the manuscript. All authors were involved in editing and writing the final draft of this manuscript. All authors agreed to submit this article for publication. AD had full access to all the data in the study and had final responsibility for the decision to submit for publication.

This analysis was performed in an intent to treat fashion in patients who received at least one dose of cabozantinib and underwent imaging performed at baseline and at least one protocol-specified follow up time point. The secondary objectives were to determine progression-free survival, overall survival, and toxicity. The accrual of *RET*-rearranged lung cancer patients to this protocol has been completed. This study was registered with ClinicalTrials.gov, number NCT01639508.

Findings—Twenty six patients with *RET*-rearranged lung adenocarcinomas were treated with cabozantinib. *KIF5B-RET* was the predominant fusion type identified in 16 (62%) patients. The study met its primary endpoint with confirmed partial responses observed in seven of 25 response-evaluable patients (overall response rate 28% [95% CI 12–49%]). The most common grade 3 treatment-related adverse events were asymptomatic lipase elevation in four patients (15%), increased alanine aminotransferase in two patients (8%), increased aspartate aminotransferase in two patients (8%), thrombocytopenia in two patients (8%), and hypophosphatemia in two patients (8%). No drug-related deaths were observed. Nineteen patients (73%) required dose reduction due to drug-related adverse events.

Interpretation—The observed activity of cabozantinib in patients with *RET*-rearranged lung cancers defines *RET* rearrangements as actionable drivers in patients with lung cancers. An improved understanding of tumor biology and novel therapeutic approaches will be required to improve outcomes with RET-directed targeted therapy.

INTRODUCTION

Targeted therapy has reshaped the care of many patients with lung cancers. Similar to sensitizing *EGFR*, *BRAF*, and *MET* mutations, recurrent gene rearrangements have emerged as actionable drivers in patients with *ALK*- and *ROS1*-rearranged lung cancers. In these individuals, dramatic improvements in response and progression-free survival compared to chemotherapy have been achieved with tyrosine kinase inhibition.[1, 2]

RET rearrangements are drivers of lung cancer oncogenesis.[3] As with other recurrent gene rearrangements, the downstream *RET* gene maintains an intact tyrosine kinase domain, and is fused to a variety of upstream partners.[4] While *KIF5B-RET* is the most common, multiple other fusion genes such as *CCDC6-RET*, *NCOA4-RET*, and *TRIM33-RET* have been reported.[5] *RET* fusions are activating in vitro and in vivo.[6] Upstream gene partners provide dimerization domains that result in ligand-independent signaling. Increased growth pathway activity downstream of the chimeric oncoprotein drives tumor cell proliferation and survival. The use of RET inhibitors results in the inhibition of downstream signaling and tumor growth.[6–8]

RET fusions are genomic alterations that can be routinely identified in the clinic.[9] These are found in 1–2% of unselected lung cancers and tend to be mutually exclusive with other lung cancer drivers.[3] Patients with *RET*-rearranged lung cancers are commonly never smokers or have a minimal history of prior tobacco exposure.[10] From a pathologic perspective, *RET* fusions are identified largely in lung adenocarcinomas of the solid subtype or with signet ring cells.[11] *RET* rearrangements can be identified by a number of tests including reverse transcriptase polymerase chain reaction (RT-PCR), fluorescence in situ hybridization

(FISH), anchored multiplex polymerase chain reaction-based RNA sequencing, and broad, hybrid capture-based next-generation sequencing of DNA.[12]

Cabozantinib is a multikinase inhibitor with low nanomolar (IC50 5·2 nM) activity against RET, in addition to its activity against ROS1, MET, VEGFR2, AXL, TIE2, and KIT.[13] The use of cabozantinib results in the inhibition of lung cancer models harboring *RET* rearrangements. Shortly after publication of the first reports of the identification of *RET* rearrangements in tumors from patients with lung cancers in late 2011[14] and early 2012,[3, 15, 16] we launched this phase 2 trial of cabozantinib for patients with *RET*-rearranged lung cancers. To our knowledge, this was the first prospective trial to test a RET inhibitor in a molecularly-enriched cohort of patients whose tumors harbored *RET* fusions.[5]

METHODS

Study design and patients

This was an open-label, Simon two-stage[17] phase 2 trial conducted at a single center in the USA. We included patients if they were 18 years of age or greater with metastatic or unresectable pathologically-confirmed lung cancers that harbored a *RET* rearrangement. Central pathologic confirmation was performed. Other eligibility criteria included a Karnofsky Performance Status of greater than 70%, adequate hematologic, renal, and hepatic function, and measurable disease by the Response Criteria Evaluation in Solid Tumors (RECIST) version 1·1.[18] We included patients with treated or asymptomatic brain metastases. There were no restrictions on the number or type of prior systemic therapies except for cabozantinib.

Due to the potential antiangiogenic effects of cabozantinib mediated by its concomitant anti-VEGFR2 activity, patients were excluded if they had a history of significant bleeding, cavitating pulmonary lesions, tumors invading the tracheobronchial tree or major blood vessels, or a gastrointestinal disorder associated with a high risk of perforation or fistula formation. We excluded individuals receiving low molecular weight heparin, clopidogrel, or warfarin at therapeutic doses (appendix, p 1–2). This study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by an institutional review board and all patients provided written informed consent prior to participation.

Tumor samples underwent either fluorescence in situ hybridization (FISH) or broad, hybrid capture-based next-generation sequencing in a Clinical Improvements Amendments (CLIA) laboratory to detect *RET* rearrangement. A dual-color break-apart FISH test was performed using institutional probes. Next-generation sequencing of tumor DNA was performed using one of two assays: MSK-IMPACT (Integrated Mutational Profiling of Actionable Cancer Targets) or FoundationOne (appendix, p 2).

Procedures

Cabozantinib was administered in tablet form at a starting dose of 60 mg orally once daily, the U.S. Food and Drug Administration (FDA)-approved dose for the treatment of patients with advanced renal cell carcinoma. Of note, plasma exposures (area under the plasma

concentration-time curve) of the tablet formulation used in this study are comparable to the capsule formulation of cabozantinib that is administered at the FDA-approved dose of 140 mg daily for the treatment of patients with metastatic medullary thyroid carcinoma. Cabozantinib was administered in 28-day cycles. Treatment was continued until there was evidence of progression of disease or unacceptable toxicity. For patients who developed progression of disease according to RECIST v1·1,[18] continued treatment with cabozantinib was permitted if the investigator felt that clinical benefit was maintained. Dose interruption and reduction followed a prescribed algorithm. A maximum of two dose reductions were allowed to 40 mg daily and 20 mg daily, respectively (appendix, p 3).

Computed tomography of the chest, abdomen, and pelvis was performed at baseline, 4 weeks after cabozantinib initiation, and every 8 weeks after the first response assessment scan (i.e. scans were performed at weeks 4, 12, 20, and so forth, appendix, p 2). Imaging of the brain was not required by the protocol. Treatment-related adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4·0. Any patient who received one or more doses cabozantinib was included in the toxicity evaluations.

Outcomes

The primary objective was to determine the overall response rate, defined as the proportion of patients with a confirmed complete response or partial response according to RECIST version 1·1. Secondary outcomes were progression-free survival, overall survival, and safety. Progression-free survival was measured from the date of initiation of cabozantinib until radiologic progression by RECIST version 1·1 or death. Patients alive and progression-free at the time of the last data cutoff were censored at the time of the last follow-up. Overall survival was measured from the date of initiation of cabozantinib treatment until death. Patients alive at the time of the last data cutoff were censored at the time of the last follow-up. Patients were deemed evaluable for an analysis of the activity of cabozantinib if they received at least one dose of study drug, and computed tomography imaging was performed at baseline and at least one protocol-specified follow up time point. One patient who did not meet these criteria was replaced, as is described later.

Statistical analysis

We used a Simon two-stage[17] minimax design to test the null hypothesis of a 10% overall response rate, the historical response rate to chemotherapy in an unselected population who have previously received a platinum doublet, against the desired alternative of 30% overall response rate. This had a one-sided type I error of 10% and a power of 90%. In the first stage of this design, 16 patients were accrued. If no responses or one response was observed, the study was to be terminated and declared negative. If at least two responses were observed, an additional nine patients were accrued to the second stage. The study was deemed to have met its primary endpoint if confirmed responses were observed in five or more patients out of a total of 25 response-evaluable patients. Patients were deemed not assessable if they did not receive any cabozantinib or did not undergo any post-baseline protocol-defined computed tomography scan. Safety analyses were based on the intention to treat population that received at least one dose of cabozantinib. The objective response rate was calculated

along with an exact 95% confidence interval. The progression-free survival, overall survival, duration of treatment, and duration of response were evaluated by the Kaplan-Meier method. The progression-free survival and overall survival were compared between subgroups by log-rank tests. The toxicity rates were calculated along with exact 95% confidence intervals. All statistical analyses were conducted in R 3.2.2. While this trial has completed the accrual of patients with *RET*-rearranged lung cancers, it is ongoing as several patients remain on active treatment. This trial is registered with ClinicalTrials.gov, number NCT01639508.

Role of the funding source

Exelixis provided funding for study drug and research-related tests and assessments on this protocol. The authors were supported in part by funding from the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748 that did not directly fund study costs. The authors wrote this article without any external funding or editorial support. AD designed the trial in cooperation with representatives of Exelixis. Exelixis was not involved in the collection, analysis, or interpretation of the data.

RESULTS

Between July 13, 2012 and April 30, 2016, 26 patients were enrolled. Data are presented up to June 7, 2016. Patient baseline characteristics are shown in table 1. Comprehensive molecular profiling, including next-generation sequencing in 19 cases, did not reveal concurrent activating alterations involving known targets of cabozantinib including ROS1, MET, and AXL. The most common *RET* fusion identified was *KIF5B-RET* in 16 patients (62%). Thirteen patients (50%) received one prior line of chemotherapy. No patients received a RET tyrosine kinase inhibitor prior to therapy with cabozantinib. The median follow-up time was 8·9 months (interquartile range 4.1–18.8). Twenty five of the 26 enrolled patients were evaluable for an analysis of the activity of cabozantinib. The remaining patient did not undergo repeat protocol imaging and was replaced as prespecified. This patient remains included in the toxicity analysis.

Of the 25 evaluable patients, while no complete responses were observed, this trial met its primary endpoint with confirmed partial responses were observed in seven patients (figure 1A). No patient had disease progression as their best overall response. The overall response rate was 28% (n=7, 95% CI 12–49%). Response to therapy was observed early. Of the seven patients with a confirmed partial response, disease shrinkage of 30% or greater was noted at the first response assessment in five patients (71%). The median duration of response was 7·0 months (95% CI 3·7–38·9). Response by fusion type were as follows: confirmed responses were observed in three of 15 patients (20%) with *KIF5B-RET*, and two of six patients (33%) with unknown upstream partners (FISH positive). Responses were observed in patients whose tumors harbored *TRIM33-RET* or *CLIP1-RET*, and no responses were observed in patients whose tumors harbored *CCDC6-RET* or *ERC1-RET* (figure 1B).

The duration of cabozantinib therapy is shown in figure 2. The median duration of treatment was 4·7 months (interquartile range 3·1–8·4). Twelve patients (48%) were treated with cabozantinib beyond six months, including four patients (16%) who were treated with cabozantinib beyond one year. At the time of analysis, four patients (16%) remained on

cabozantinib, including one patient on treatment more than three years after drug was first administered. Three patients were treated with cabozantinib beyond radiologic disease progression due to ongoing clinical benefit. Of these three patients, one had asymptomatic progression in the central nervous system with the development of new brain metastases that were radiated, and two had asymptomatic extracranial radiologic progression.

At the time of the data cutoff 19 patients (76%) either had disease progression or died (figure 3a). The median progression-free survival was 5·5 months (95% CI 3·8 to 8·4). There were 16 death events. The median overall survival was 9·9 months (95% CI 8·1-not reached, figure 3b). Post-hoc exploratory analyses of the activity of cabozantinib by prior lines of therapy, previous bevacizumab exposure, and fusion type, and the activity of cabozantinib in patients with brain metastases are included in the appendix (appendix 3–7, 9). These analyses were not prespecified by the protocol.

Twenty six patients treated were evaluable for toxicity. Treatment-related adverse events were predominantly grade 1 or grade 2 (table 2) and one or more drug-related toxicities of any grade were observed in 25 patients (overall toxicity rate of 96·2%, 95% CI 80·4–99·9%). The most common treatment-related adverse events of any grade were increased alanine aminotransferase, increased aspartate aminotransferase, hypothyroidism, diarrhea, palmar plantar erythrodysesthesia, and skin hypopigmentation. The most common grade 3 treatment-related adverse events were lipase elevation in four patients (15%), increased alanine aminotransferase in two patients (8%), increased alanine aminotransferase in two patients (8%), decreased platelet count in two patients (8%), and hypophosphatemia in two patients (8%). Patients in whom these toxicities were observed were asymptomatic and these adverse events resolved to grade 1 or better with dose modification. No grade 4 or grade 5 treatment-related events were observed. While no drug-related deaths were observed, 16 patients died during the course of follow up on this study. The reasons for these deaths included disease progression in 14 patients, and acute respiratory failure in two patients, one immediately following a thoracentesis, and one from suspected disease-related pulmonary embolism.

Nineteen patients (73%) required a cabozantinib dose reduction due to intolerable grade 2 or grade 3 drug-related toxicities. The most common reasons for dose reduction included palmar plantar erythrodysesthesia in seven patients (37%), fatigue in three patients (16%), and diarrhea in two patients (11%). Other reasons for dose reduction included transaminitis, thrombocytopenia, proteinuria, nausea, oral mucositis, and hypertension. One dose reduction to 40 mg daily was required in 19 patients (58%), and two dose reductions to 20 mg daily were required in four patients (15%). For the majority of patients who required a dose reduction, their dose was first reduced within the first two cycles as is shown in the appendix (appendix, p 8). Two patients (8%) discontinued cabozantinib due to drug-related toxicity, specifically retroperitoneal hemorrhage in one patient (4%), and thrombocytopenia in one patient (4%).

DISCUSSION

We demonstrate that the multikinase RET inhibitor cabozantinib is active in patients with advanced *RET*-rearranged lung cancers. The overall response rate of 28% with cabozantinib is comparable to the activity of single-agent BRAF tyrosine kinase inhibitor therapy (response rate of 33% with dabrafenib) in patients with advanced *BRAF* V600E-mutant lung cancers[19] and exceeds that of single-agent ERBB2 (HER2) tyrosine kinase inhibitor therapy in *ERBB2* exon 20-mutant lung cancers (response rate of 12% with dacomitinib).[20] Furthermore, it exceeds the activity of single-agent immune checkpoint inhibition (response rate of 20% with nivolumab)[21] and single-agent chemotherapy (response rate of 9% with pemetrexed and 8% with docetaxel) after progression on initial platinum doublet therapy in unselected patients with advanced non-small cell lung cancers.[22] Responses on this trial were brisk and durable, with two patients remaining on therapy past two and a half years.

While clinically meaningful benefit was observed with cabozantinib, its activity was lower than that observed with ALK- and ROS1-directed tyrosine kinase inhibitor therapy (response rates of 57% and 72%) in patients with *ALK*- and *ROS1*-rearranged lung cancers, respectively.[2,23] It was also lower than the response rates achieved with EGFR tyrosine kinase inhibitor therapy in treatment-naïve patients with *EGFR*-mutant lung cancers.[24] The median PFS and the median OS of cabozantinib in *RET*-rearranged lung cancers were likewise lower than that observed for single-agent tyrosine kinase inhibitor therapy in *EGFR*-mutant, and *ALK*- and *ROS1*-rearranged lung cancers.[2, 23, 24] A number of factors might account for these discrepancies.

First, dose reductions were required in the majority of patients due to drug-related toxicities, as has been observed in studies of cabozantinib in other solid tumors. Cabozantinib is a multikinase inhibitor that is much more effective at inhibiting VEGFR2 (IC50 0·04 nM) than RET (IC50 5·20 nM) and its other targets including ROS1 and MET.[13] Dose-limiting palmar-plantar erythrodysesthesia, gastrointestinal toxicities, and other events were likely mediated by inhibition of VEGFR2 and other kinases. While the average peak concentrations of cabozantinib at the reduced doses of 40 mg and 20 mg daily exceed the cellular IC50 required to inhibit RET,[25] this nevertheless raises the possibility of decreased on-target inhibition of RET at the deliverable doses. Moving forward, it would not be unreasonable to explore alternative dosing regimens that both minimize drug-related toxicities and potentially maximize target inhibition of cabozantinib and other multikinase inhibitors with activity against RET.

Second, multikinase inhibition may not be the most effective strategy for inhibiting *RET* fusions. RET inhibitors that are currently in clinical development for *RET*-rearranged lung cancers, including vandetanib, lenvatinib, sunitinib, and ponatinib, are multikinase inhibitors that, similar to cabozantinib, may be limited in their ability to inhibit RET relative to their other kinase targets.[26] Alectinib, a multikinase inhibitor with activity against RET,[7] may represent an agent that could be dosed to more effectively target RET due to its favorable safety profile in comparison to other RET inhibitors, however, highly RET-specific tyrosine kinase inhibitors are already in preclinical development. These RET-specific inhibitors are likely to achieve much more effective inhibition of the RET kinase in comparison to

currently available RET-directed therapies. In addition, these newer drugs are likely to have a wider therapeutic window in patients, and thus may be more tolerable and amenable to chronic administration at full doses. On the other hand, the possibility that the concurrent inhibition of angiogenesis by multikinase RET inhibitors is responsible, in part, for the activity of these drugs cannot be fully discounted.

Third, the biology of *RET*-rearranged lung cancers may dictate the need for combination therapy. As mentioned previously, similar to cabozantinib, an overall response rate of 33% can be achieved with the use of single-agent BRAF inhibition (dabrafenib) in *BRAF* V600E-mutant lung cancers. This response rate almost doubles to 63% with the use of combined BRAF and MEK inhibition (dabrafenib and trametinib) in comparable patients.[27] Similarly, *RET*-rearranged lung cancers may rely on bypass pathways that are not addressed by the variety of RET inhibitors that are currently available. Lung cancers with *RET* fusions may also harbor additional genomic alterations that blunt the response to targeted therapy. While at least one trial is currently exploring combinatorial therapy for patients with *RET*-rearranged lung cancers,[28] the potential for increased toxicity with dual tyrosine kinase inhibitor therapy must be kept in mind. In this respect, RET-specific tyrosine kinase inhibitors or monoclonal antibody therapy with a potentially more favorable toxicity profile in comparison to tyrosine kinase inhibitor therapy may ultimately serve as better candidates for combination treatments.

This trial has limitations. Due to tissue constraints, not all tumors underwent broad hybrid capture-based next-generation sequencing on this study. Given the hypothesis that upstream gene partners may affect response to RET inhibition, future trials would benefit from comprehensive molecular profiling that elucidates both the upstream gene partner and identifies concurrent genomic alterations that may affect response. In addition, this single-center study may not represent the breadth of patients with *RET*-rearranged lung cancers. Fortunately, early data from other series[29–31] have confirmed that multikinase RET inhibitors are active in patients with *RET*-rearranged lung cancers. Lastly, confirmation of the results of our phase 2 trial in a larger group of patients will likely be required in order to obtain regulatory approval considering the response rate achieved in this series.[32]

In conclusion, this phase 2 trial met its primary endpoint. The RET inhibitor cabozantinib can produce rapid and durable responses in patients with *RET*-rearranged lung cancers. Dose reductions, likely related to "off-target" toxicities due to concomitant VEGFR2 inhibition, are frequently required. We look forward to the final results from ongoing trials of other multi-kinase RET inhibitors. Furthermore, we anticipate the transition to RET-specific tyrosine kinase inhibitors in the clinic shortly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014; 371(23):2167–77. [PubMed: 25470694]
2. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non–small-cell lung cancer. N Engl J Med. 2014; 371(21):1963–71. [PubMed: 25264305]
3. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med. 2012; 18(3):382–4. [PubMed: 22327622]
4. Suehara Y, Arcila M, Wang L, et al. Identification of KIF5B-RET and GOPC-ROS1 fusions in lung adenocarcinomas through a comprehensive mRNA-based screen for tyrosine kinase fusions. Clin Cancer Res. 2012; 18(24):6599–608. [PubMed: 23052255]
5. Drilon A, Wang L, Hasanovic A, et al. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov. 2013; 3(6):630–5. [PubMed: 23533264]
6. Saito M, Ishigame T, Tsuta K, Kumamoto K, Imai T, Kohno T. A mouse model of KIF5B-RET fusion-dependent lung tumorigenesis. Carcinogenesis. 2014; 35(11):2452–6. [PubMed: 25064355]
7. Kodama T, Tsukaguchi T, Satoh Y, et al. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. Mol Cancer Ther. 2014; 13(12):2910–8. [PubMed: 25349307]
8. Verbeek HH, Alves MM, de Groot JW, et al. The effects of four different tyrosine kinase inhibitors on medullary and papillary thyroid cancer cells. J Clin Endocrinol Metab. 2011; 96(6):E991–5. [PubMed: 21470995]
9. Michels S, Scheel AH, Scheffler M, et al. Clinicopathological Characteristics of RET Rearranged Lung Cancer in European Patients. J Thorac Oncol. 2016; 11(1):122–7. [PubMed: 26762747]
10. Wang R, Hu H, Pan Y, et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol. 2012; 30(35):4352–9. [PubMed: 23150706]
11. Lee SE, Lee B, Hong M, et al. Comprehensive analysis of RET and ROS1 rearrangement in lung adenocarcinoma. Mod Pathol. 2015; 28(4):468–79. [PubMed: 25234288]
12. Drilon A, Wang L, Arcila ME, et al. Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches. Clin Cancer Res. 2015; 21(16):3631–9. [PubMed: 25567908]
13. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011; 10(12):2298–308. [PubMed: 21926191]
14. Ju YS, Lee WC, Shin JY, et al. A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res. 2012; 22(3):436–45. [PubMed: 22194472]
15. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med. 2012; 18(3):375–7. [PubMed: 22327624]
16. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med. 2012; 18(3):378–81. [PubMed: 22327623]
17. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials. 1989; 10(1):1–10. [PubMed: 2702835]
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1. 1). Eur J Cancer. 2009; 45(2):228–47. [PubMed: 19097774]
19. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016; 17(5):642–50. [PubMed: 27080216]
20. Kris MG, Camidge DR, Giaccone G, et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol. 2015; 26(7):1421–7. [PubMed: 25899785]

21. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373(17):1627–39. [PubMed: 26412456]
22. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004; 22(9):1589–97. [PubMed: 15117980]
23. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non small-cell lung cancer. N Engl J Med. 2010; 363(18):1693–703. [PubMed: 20979469]
24. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361(10):947–57. [PubMed: 19692680]
25. Nguyen L, Benrimoh N, Xie Y, Offman E, Lacy S. Pharmacokinetics of cabozantinib tablet and capsule formulations in healthy adults. Anticancer Drugs. 2016; 27(7):669–78. [PubMed: 27139820]
26. Mologni L, Redaelli S, Morandi A, Plaza-Menacho I, Gambacorti-Passerini C. Ponatinib is a potent inhibitor of wild-type and drug-resistant gatekeeper mutant RET kinase. Mol Cell Endorinol. 2013; 377(1–2):1–6.
27. Planchard D, Besse B, Groen HJ, et al. Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. 2016; 17(5):642–50. [PubMed: 27080216]
28. Subbiah V, Berry J, Roxas M, et al. Systemic and CNS activity of the RET inhibitor vandetanib combined with the mTOR inhibitor everolimus in KIF5B-RET re-arranged non-small cell lung cancer with brain metastases. Lung Cancer. 2015; 89(1):76–9. [PubMed: 25982012]
29. Lee S-H, Lee J-K, Ahn M-J, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement. J Clin Oncol. 2016; 34:2016. (suppl; abstr 9013).
30. Seto T, Yoh K, Satouchi M, et al. A phase II open-label single-arm study of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC): Luret study. J Clin Oncol. 2016; 34:2016. (suppl; abstr 9012).
31. Gautschi O, Wolf J, Milia J, et al. Targeting RET in patients with RET-rearranged lung cancers: Results from a global registry. J Clin Oncol. 2016; 34:2016. (suppl; abstr 9014).
32. Oxnard GR, Wilcox KH, Gonen M, Polotsky M, Hirsch BR, Schwartz LH. Response Rate as a Regulatory End Point in Single-Arm Studies of Advanced Solid Tumors. JAMA oncology. 2016; 2(6):772–9. [PubMed: 26914340]

PANEL: RESEARCH IN CONTEXT

Evidence before this study

The search terms "*RET* rearrangement" and "non-small cell lung cancer" were used to search PubMed for articles published between 2000 and 2016. *RET* is a proto-oncogene. Activation by mutation and rearrangement drive oncogenesis in thyroid and lung cancers. The first reports of *RET* rearrangements in lung cancers were published in late 2011 and early 2012. The most common gene rearrangement in *RET*-rearranged lung cancers is *KIF5B-RET. RET* rearrangements were found predominantly in lung adenocarcinomas from patients with minimal to no prior tobacco exposure. Multikinase inhibitors were tested in *RET*-rearranged models in vitro and in vivo and resulted in decreased cell viability and inhibition of tumor growth. Prior to this publication, case reports of clinical responses to the multikinase inhibitors cabozantinib and vandetanib described durable benefit with the use of these drugs.

Added value of this study

This study demonstrated in a prospective fashion that cabozantinib is active in patients with advanced *RET*-rearranged lung cancers with an overall response rate of 28%, a median progression-free survival of 6 months, and a median overall survival of 10 months. Responses were brisk and durable. Dose reductions were frequent due to drug-related adverse events.

Implications of all the available evidence

Launched in 2012 shortly after the first reports of *RET* fusions in lung cancer, this protocol represented the first prospective clinical trial initiated to establish the activity of a RET inhibitor for patients with *RET*-rearranged lung cancers. The activity observed was comparable to the activity of single-agent tyrosine kinase inhibition in other molecular cohorts of patients with lung cancers (dabrafenib in BRAF *V600E*-mutant lung cancers). It also exceeded the response rate of cabozantinib in unselected patients, and single-agent chemotherapies used in the second line setting for the treatment of non-small cell lung cancers.

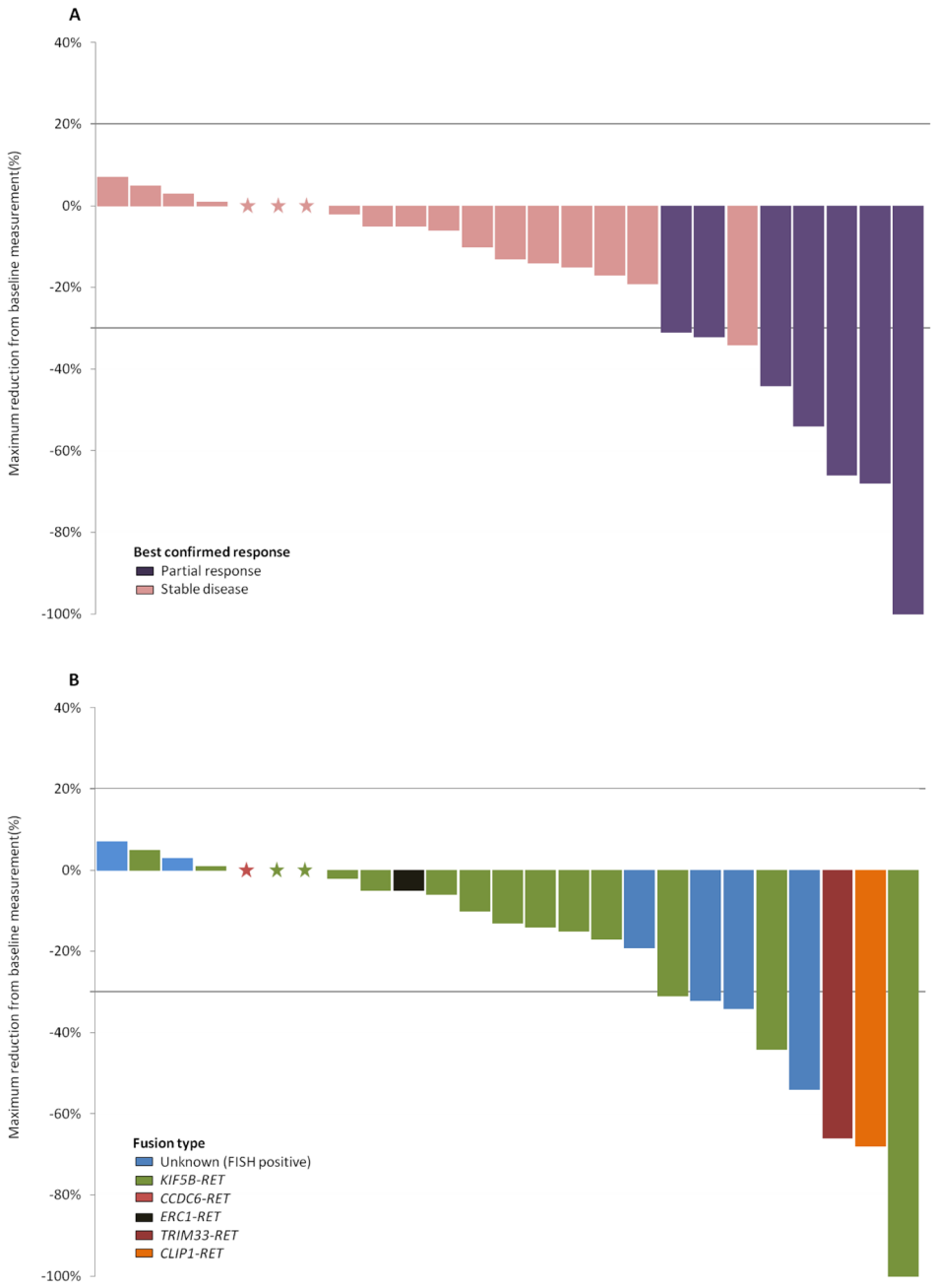

Figure 1. Tumour response

The waterfall plot of maximal reduction in the size of indicator lesions in response to cabozantinib in 25 patients with evaluable disease is depicted by type of response (A) and by fusion type (B). Stars represent patients whose maximum reduction of disease burden was 0%.

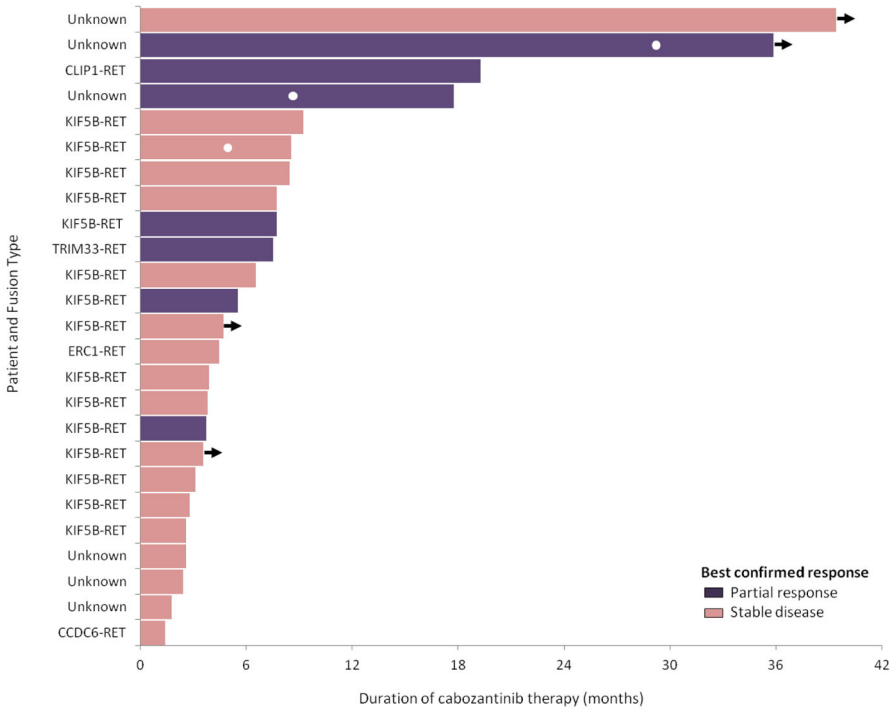

Figure 2. Duration of therapy

Duration of cabozantinib therapy is shown for 25 evaluable patients. Each bar represents the period of time from the first dose to the last dose of cabozantinib. Arrows denote ongoing treatment at the time of data cutoff. White circles denote the development of radiographic progression by RECIST v1.1 in patients who were treated past progression for ongoing clinical benefit.

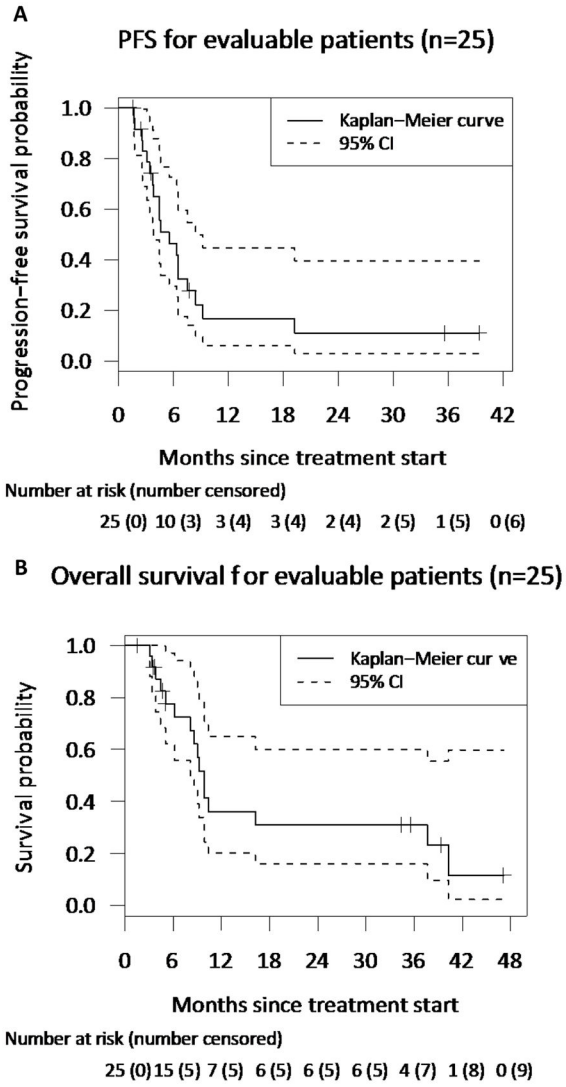

Figure 3. Kaplan-Meier curves of progression-free survival and overall survival

Both curves include 25 evaluable patients who were treated with cabozantinib. Dotted lines represent 95% CI.

Table 1

Baseline Characteristics

Patients with *RET*-rearranged lung cancers who received cabozantinib (n=26)	
Age	**median 59 (interquartile range 54–67)**
Sex	
Male	11 (42%)
Female	15 (58%)
Race	
Caucasian	19 (73%)
Asian	6 (21%)
African American	1 (6%)
Karnofsky performance status	
100%	0
90%	7 (27%)
80%	19 (73%)
Cigarette smoking history	
Never smoker	17 (65%)
>0–15 pack years	8 (31%)
>15 pack years	1 (4%)
Prior chemotherapy regimens	
0	6 (23%)
1	13 (50%)
≥2	7 (27%)
Adenocarcinoma	26 (100%)
Fusion type	
KIF5B-RET	16 (62%)
CCDC6-RET	1 (4%)
TRIM33-RET	1 (4%)
CLIP1-RET	1 (4%)
ERC1-RET	1 (4%)
Unknown (FISH-positive)	6 (22%)
Brain metastases at baseline	
Not present	16 (62%)
Present, treated	5 (19%)
Present, untreated and asymptomatic	5 (19%)

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Table 2

Treatment-related toxicities of cabozantinib are summarized. Grade 1 and 2 adverse events observed in 10% or more of patients are listed while any grade 3, 4, or 5 event observed in any patient regardless of frequency is included.

Treatment-Related Adverse Event	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	25 (96%)	21 (81%)	2 (8%)	2 (8%)	0	0
Aspartate aminotransferase increased	19 (73%)	16 (62%)	1 (4%)	2 (8%)	0	0
Hypothyroidism	18 (69%)	4 (15%)	14 (54%)	0	0	0
Diarrhea	16 (62%)	12 (46%)	4 (15%)	0	0	0
Palmar plantar erythrodysesthesia	15 (58%)	9 (31%)	6 (23%)	1 (4%)	0	0
Skin hypopigmentation	13 (50%)	0	13 (50%)	0	0	0
Platelet count decreased	13 (50%)	8(31%)	3 (12%)	2 (8%)	0	0
Fatigue	12 (46%)	4 (15%)	7 (27%)	1 (4%)	0	0
Oral mucositis	12 (46%)	11 (42%)	0	1 (4%)	0	0
Lipase increased	9 (35%)	3 (12%)	2 (8%)	4 (15%)	0	0
Nausea	8 (31%)	5 (19%)	3 (12%)	0	0	0
Dysgeusia	9 (31%)	6 (23%)	2 (8%)	0	0	0
Serum amylase increased	7 (27%)	5 (19%)	2 (8%)	0	0	0
Hypomagnesemia	7 (27%)	6 (23%)	1 (4%)	0	0	0
Vomiting	6 (23%)	6 (23%)	0	0	0	0
Weight loss	6 (23%)	5 (19%)	1 (4%)	0	0	0
Hypophosphatemia	5 (19%)	0	3 (12%)	2 (8%)	0	0
Constipation	5 (19%)	5 (19%)	0	0	0	0
Anorexia	5 (19%)	1 (4%)	4 (15%)	0	0	0
Hypertension	5 (19%)	0	4 (15%)	1 (4%)	0	0
Blood bilirubin increased	5 (19%)	3 (12%)	2 (8%)	0	0	0
Dry skin	5 (19%)	5 (19%)	0	0	0	0
Hoarseness	4 (15%)	2 (8%)	2 (8%)	0	0	0
Anemia	3 (12%)	2 (8%)	1 (4%)	0	0	0
Alopecia	3 (12%)	3 (12%)	0	0	0	0
Alkaline phosphatase increased	3 (12%)	2 (8%)	1 (4%)	0	0	0

Treatment-Related Adverse Event	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Retroperitoneal hemorrhage	1 (4%)	0	0	1 (4%)	0	0
Hypertension	1 (4%)	0	0	1 (4%)	0	0