Original Study

Results of a Phase II Placebo-controlled Randomized Discontinuation Trial of Cabozantinib in Patients with Non–small-cell Lung Carcinoma

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Abstract

Cabozantinib is an inhibitor of receptor tyrosine kinases, including MET, vascular endothelial growth factor receptors, AXL, RET, and ROS1. We assessed cabozantinib in 60 patients with non–small-cell lung carcinoma enrolled in a phase II randomized discontinuation trial. Tumor regression was observed in most patients, including patients with KRAS and epidermal growth factor receptor mutations. The safety profile was consistent with that reported for cabozantinib in other solid tumors.

Introduction: Cabozantinib, an orally bioavailable tyrosine kinase inhibitor with activity against MET, vascular endothelial growth factor receptor 2, AXL, ROS1, and RET was assessed in patients with non–small-cell lung carcinoma (NSCLC) as part of a phase II randomized discontinuation trial with cohorts from 9 tumor types. **Patients and Methods:** Patients received cabozantinib 100 mg/day during a 12-week open-label lead-in stage. Those with stable disease per Response Evaluation Criteria in Solid Tumors version 1.0 at week 12 were randomized to cabozantinib or placebo. Primary endpoints were objective response rate (ORR) at week 12 and progression-free survival (PFS) after randomization. **Results:** Sixty patients with NSCLC who had received a median of 2 prior lines of therapy were enrolled. ORR at week 12 was 10%; 6 patients had a confirmed partial response, and no patients had a complete response. Overall disease-control rate (ORR + stable disease) at week 12 was 38%. Tumor regression was observed in 30 (64%) of 47 patients with post-baseline radiographic tumor assessments, including 3 or 4 patients with KRAS or epidermal growth factor receptor mutations, respectively. Median PFS after randomization was 2.4 months for both the cabozantinib and placebo arms. Median PFS from first dose for the entire cohort was 4.2 months. The most common grade 3/4 adverse events were fatigue (13%), palmar-plantar erythrodysesthesia (10%), diarrhea (7%), hypertension (7%), and asthenia (5%); 1 treatment-related grade 5 adverse event (hemorrhage) was reported during the lead-in stage. **Conclusion:** Cabozantinib exhibited clinical activity based on ORR and regression of tumor lesions in pretreated patients with NSCLC, including in patients with KRAS mutations.

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Introduction

Non–small-cell lung carcinoma (NSCLC), which includes adenocarcinoma and squamous cell carcinoma, accounts for ~80% of all lung cancer cases and is the leading cause of cancer-related deaths in the United States.[1] Mutations in KRAS and epidermal growth factor receptor (EGFR) are common oncogenic drivers for NSCLC, whereas other less frequent drivers include mutations, rearrangements and gene fusions involving ALK, BRAF, RET, or ROS1.[2-4] Tyrosine kinase inhibitors (TKIs) targeting EGFR, ALK, BRAF, and ROS1 have improved disease management; nonetheless, patients typically acquire resistance against these targeted therapies in 6 to 12 months.[4-8]

MET activation has been implicated in the development of EGFR TKI resistance in NSCLC.[9,10] In preclinical models of the disease, EGFR TKI resistance was mitigated via combined inhibition of EGFR and MET,[9] whereas in a phase II study with EGFR TKI-resistant patients, capmatinib, a MET TKI, in combination with gefitinib, showed an overall disease control rate of 80% (NCT01610336).[11] Furthermore, in a vascular endothelial growth factor receptor (VEGFR) inhibitor-resistant human NSCLC xenograft model, treatment with a MET inhibitor resensitized the tumors to anti-VEGFR therapy.[12]

Like MET, activation of AXL has also been shown to be associated with resistance to EGFR-targeted therapy in lung cancer; AXL and its ligand GAS 6 were shown to be overexpressed in NSCLC tumors with acquired resistance to erlotinib, both in xenograft models and in patients.[13] Transient overexpression of wild-type AXL in NSCLC cells induced resistance to erlotinib that was reversed via pharmacologic inhibition of AXL activity.[13] AXL was also shown to be a marker for epithelial to mesenchymal transition, a cellular process associated with therapeutic resistance in NSCLC.[14] In other preclinical models, dual inhibition of AXL and MET resensitized NSCLC tumors previously made resistant to EGFR TKIs by the overexpression of AXL.[15] In addition, an AXL-specific antibody-drug conjugate induced complete tumor regression in a xenograft model of NSCLC.[16]

Apart from MET and AXL, the co-occurrence of RET rearrangement with activated EGFR mutations has also been reported in patients with EGFR-mutated tumors that progressed on either first- or second-generation EGFR TKI therapy. This finding indicates that RET rearrangement may serve as a potential resistance mechanism to EGFR TKI in EGFR-mutated NSCLC.[17]

Cabozantinib is a small-molecule inhibitor of tyrosine kinases including MET, VEGFRs, AXL, RET, and ROS1.[18,19] It is approved for treatment of progressive metastatic medullary thyroid carcinoma and advanced renal cell carcinoma (RCC).[20-22] Several early-stage clinical studies demonstrated the activity of cabozantinib in specific cohorts of NSCLC. In a cohort of patients with RET-rearranged metastatic or unresectable NSCLC in a phase II single-arm trial, cabozantinib showed an overall response of 28%,[23] and a patient with metastatic NSCLC harboring a ROS1 mutation (D2033N) and resistant to crizotinib experienced a 92% reduction in disease burden at 12 weeks of cabozantinib treatment.[24] Another patient harboring MET exon 14 deletions achieved complete remission of metastatic disease following 4 weeks of cabozantinib treatment.[25] In another study, cabozantinib treatment resulted in a complete intracranial response in a patient with NSCLC with MET exon 14 deletions.[26] Further, in a phase II trial, cabozantinib or cabozantinib + erlotinib improved progression-free survival (PFS) over erlotinib alone in patients with EGFR wild-type NSCLC.[27]

In this report, we describe the efficacy and safety of cabozantinib as a single agent in a cohort of previously treated patients with NSCLC who were not prospectively selected based on mutational status of any known driver oncogenes. This cohort derives from a phase II randomized discontinuation trial (RDT) that evaluated the activity of cabozantinib in 9 different tumor types, including NSCLC.

Patients and Methods

Patients

Patients were enrolled between September 2, 2009 and May 30, 2013. For the NSCLC cohort, eligible patients had pathologically and radiologically confirmed NSCLC regardless of histologic subtype (including squamous cell carcinoma) with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Patients were required to have evidence of progression on computed tomography, magnetic resonance imaging, or bone scan at screening. The study also required an Eastern Cooperative Oncology Group performance status 0 or 1, adequate hematologic and end-organ function, and no more than 3 prior systemic anticancer treatment regimens. Patients with known brain metastases, radiation therapy within 2 weeks before the first dose of the study treatment, or clinically significant intercurrent illness were excluded. Other exclusion criteria included prior exposure to cabozantinib and uncontrolled hypertension (sustained blood pressure readings of >140 mmHg systolic, or >100 mmHg diastolic, not controlled with anti-hypertensive medication). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and informed consent documents were approved by the institutional review boards of the participating institutions, and informed consent was obtained from all patients.

Study Design

The primary objective of this trial was to evaluate the efficacy of cabozantinib in multiple solid tumors, including NSCLC. The study was designed as an RDT (see Supplemental Figure 1 in the online version)[28,29]; the primary endpoint of the lead-in stage was objective response rate (ORR) at week 12, and the primary endpoint of the randomized phase was PFS. At week 12, patients with evidence of response by RECIST criteria (≥30% decrease in the sum of measurable lesions) remained on open-label cabozantinib, and patients with progression (≥20% increase in measurable disease or new lesions) discontinued treatment. Patients who did not satisfy the criteria for response or progression were denoted to have stable disease (SD) and were randomized (1:1) to either placebo or cabozantinib in a double-blinded fashion. An interactive voice response system was utilized for randomization. Patients, investigators, and sponsor personnel were masked to treatment assignments. All randomized patients were followed until progression, at which point treatment assignment was unblinded. Patients who were receiving cabozantinib discontinued, and patients who

were receiving placebo were offered to restart cabozantinib. Patients who restarted cabozantinib after first progression on placebo were followed until subsequent progression.

Study Drug Administration

Patients received cabozantinib at a daily oral dose of 100 mg (freebase weight) during the 12-week open-label lead-in stage. Dosing with cabozantinib was delayed or reduced if clinically significant toxicities developed, as previously described.[30] Treatment could be reduced at the discretion of the investigator; the recommended initial dose reduction was to 60 mg daily, and the lowest permitted dose was 19.7 mg. Interruption of dosing for >3 weeks required withdrawal from treatment.

Study Assessments

Patients were assessed for safety every 3 weeks, and tumors were assessed by radiographic imaging (computed tomography and/or magnetic resonance imaging) every 6 weeks throughout the study. The PFS analysis was conducted based on investigator-assessed response by RECIST version 1.0. Other clinical assessments included medical and cancer history, physical examination, vital signs and body weight, electrocardiography, Eastern Cooperative Oncology Group performance status, laboratory analyses (serum chemistry, hematology, coagulation, and urinalysis), concomitant medications, adverse events (AEs), and information on subsequent anticancer treatment. Assessments for exploratory endpoints included determination of EGFR and KRAS mutational status in available archival tumor tissue. Detection of MET, AXL and RET was not performed owing to unavailability of regulatory consent from some of the recruiting sites.

Study Oversight

A study oversight committee monitored efficacy during the lead-in stage. An independent data monitoring committee monitored safety in the blinded randomized stage.

Statistical Considerations

The study employed an adaptive design with an assumed stable disease rate of 35% at week 12 to estimate the total target enrollment per cohort from the number of patients planned for randomization in each cohort. The target enrollment of 200 patients per tumor-type cohort was chosen to achieve the goal of 70 randomized patients and 52 events post-randomization. This design had an 80% power in each cohort to detect a hazard ratio of 0.5 for PFS post-randomization. The study employed an adaptive design: enrollment into a cohort could be halted if an insufficient number of patients had disease stabilization owing to high rates of either objective response or progression during the lead-in stage.

The Kaplan-Meier method was employed to estimate medians for the primary analysis of PFS from the date of randomization, and the log-rank test was used for inference testing. For an analysis of overall PFS from the date of first dose including the lead-in stage, the estimation method as described by Ratain et al[28] was utilized. All treated patients contributed to the PFS estimate through the first 12 weeks. After week 12, PFS was estimated as a weighted average of those continuing open-label treatment and those randomized to cabozantinib. The weights corresponded to the fraction of patients continuing open-label treatment at week 12 and the proportion of patients randomized at week 12 (including placebo). This study is registered with ClinicalTrials.gov (NCT00940225).

Table 1 Baseline Demographic and Clinical Characteristics of Patients (N = 60)

Characteristic	Entire Treated Population (N = 60)	
	No. Patients	%
Age, y		
Median	66	
Range	36-87	
Gender		
Male	33	55
Female	27	45
Race		
Asian	2	3
Non-Asian	58	97
ECOG performance status		
0	19	32
1	41	68
Histologic subtype		
Squamous cell	17	28
Adenocarcinoma	34	57
Large cell carcinoma	4	7
Other[a]	5	8
Bone metastases	15	25
Never smokers	13	22
EGFR status		
Mutation detected	6	10
No mutation detected	24	40
Unknown	30	50
KRAS status		
Mutation detected	5	8
No mutation detected	21	35
Unknown	34	57
Prior lines of therapy		
0	2	3
1	10	17
2	18	30
≥3	30	50
Prior anti-VEGF pathway therapy	20	33
Prior anti-EGFR therapy	3	5

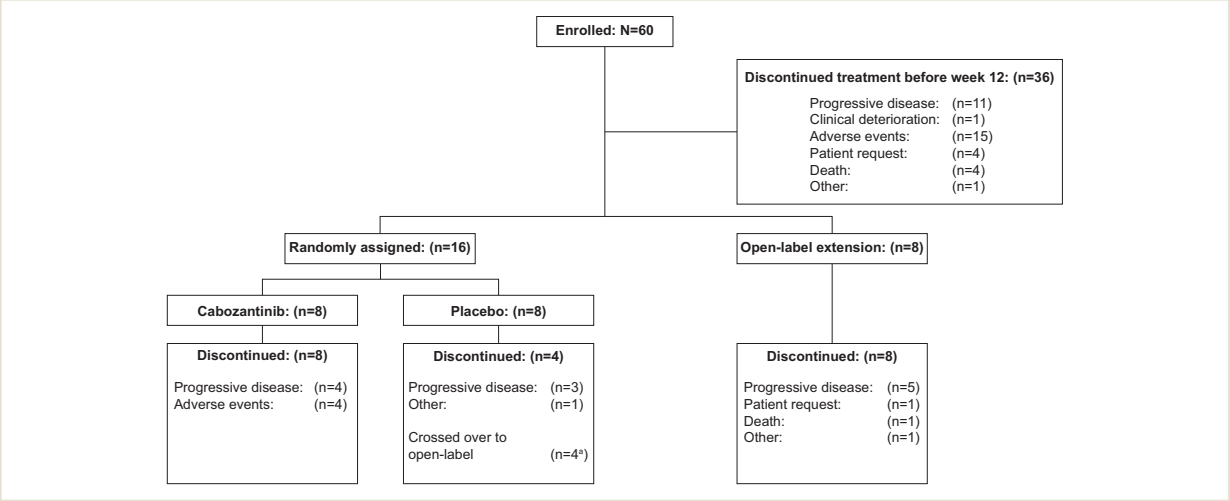
Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor.
[a]Neuroendocrine differentiation, poorly differentiated malignant neoplasm, or sarcomatoid.

Results

Patient Characteristics and Disposition

Based on high response rates in other cohorts of the study during the lead-in phase, enrollment into the randomization stage was halted by the study oversight committee before the planned sample size was achieved in any of the tumor cohorts, including NSCLC.

Figure 1 Disposition of Enrolled Patients With Non–Small-Cell Lung Carcinoma. [a]Four Patients Crossed Over to the Cabozantinib Open-Label, and Eventually All Discontinued Treatment: 3 Patients Discontinued Owing to Adverse Events, and 1 Discontinued Owing to the Investigator's Decision Independent of Any Adverse Event



Sixty patients with NSCLC were enrolled in the United States, Belgium, and Taiwan. Baseline demographic and clinical characteristics are summarized in Table 1. Twenty patients received prior treatment with an anti-VEGF pathway therapy, and 3 patients received prior anti-EGFR therapy. EGFR mutations and KRAS mutations were detected in 6 of 30 and 5 of 26 patients, respectively, whose tissue samples were available for evaluation. Of the 60 patients enrolled in the 12-week lead-in stage, 36 patients discontinued study treatment, which included 12 patients with progressive disease and 15 patients with AEs. At week 12, 8 patients who responded (including 6 that had confirmed partial responses [PRs]) continued open-label cabozantinib. Sixteen patients were randomized 1:1 to either cabozantinib or placebo. Four patients in the placebo arm crossed over to the open-label cabozantinib arm following disease progression. The treatment status for all 60 patients is summarized in Figure 1.

Response Rate in the 12-week Lead-in Stage

The ORR at week 12 was 10% (95% confidence interval [CI], 4%-20%); 6 patients had a confirmed PR and none of the patients had a complete response (CR) (Table 2). The disease control rate (CR + PR + SD) at week 12 was 38% (Table 2). In addition, 30 (64%) of 47 patients with ≥1 post-baseline tumor assessment had at least 1 assessment demonstrating a reduction of measurable disease. This included tumor reductions in 3 patients with KRAS and 4 patients with EGFR mutations. A summary of best change in measurable disease for these patients is shown in a waterfall plot (Figure 2).

Progression-Free Survival and Overall Survival

The primary endpoint of the randomized stage was PFS after week 12 for patients who had SD at week 12 and were randomized to either receive placebo or continue cabozantinib. There was no statistical difference in PFS for cabozantinib versus placebo. Median PFS post-randomization was 2.4 months (95% CI, 1.35-2.89 months) for cabozantinib and 2.4 months (95% CI, 1.38-2.66 months) for placebo (Figure 3A). However, the protocol-defined target enrollment was not achieved, and therefore the study was not statistically powered to evaluate this endpoint. The estimated median overall PFS for the entire treatment period from the start of the study including all 60 treated patients was 4.2 months (95%, CI 1.41-5.39 months) (Figure 3B). The median overall survival for all patients from first dose of cabozantinib was 7.7 months (95% CI, 5.1-9.6 months).

Exploratory Analyses of the Effects of Cabozantinib on Hemoglobin

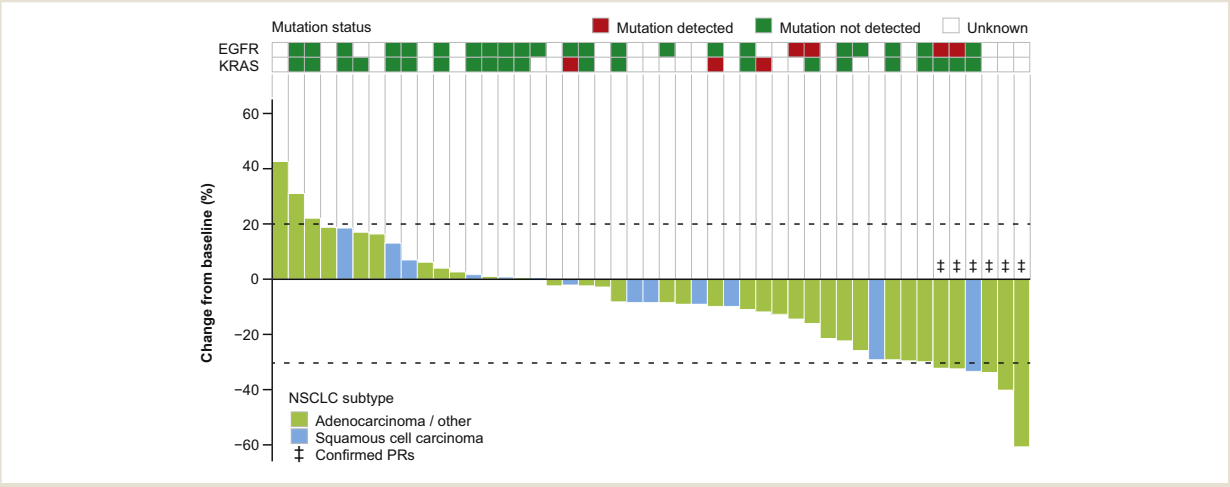
Previous studies have shown that treatment with antiangiogenic agents, including cabozantinib, can lead to an increase in

Table 2 Summary of Week 12 Response in Patients With NSCLC by RECIST 1.0 (N = 60)

Parameter	No. Patients	%
Best overall response during the 12-week lead-in stage		
Confirmed complete response	0	0
Confirmed partial response[a]	6	10
Stable disease	29	48
Progressive disease	12	20
Unable to evaluate	1	2
Missing	12	20
Disease stabilization rate at week 12[b]	23	38

Abbreviations: NSCLC = Non–small cell lung carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors.
[a]All responses were confirmed within 18 weeks.
[b]Disease stabilization rate is defined as confirmed partial response or stable disease at week 12.

Figure 2 Best Change From Baseline in Investigator-Assessed Measurements of Soft-Tissue Lesions Using Response Evaluation Criteria in Solid Tumors (Version 1.0) was Determined for Patients Who had Baseline and at Least 1 Post-Baseline Radiographic Tumor Assessment (n = 47). Reported Molecular Status is Based on Sponsor Analysis and Investigator Reporting



Abbreviations: EGFR = epidermal growth factor receptor; NSCLC = non–small-cell lung carcinoma; PR = partial response.

hemoglobin levels.[30-33] In the current study, cabozantinib treatment during the lead-in stage was associated with an increase in hemoglobin levels. The median increase in hemoglobin level from baseline was 10.6% at week 2, 8.8% at week 4, 7.7% at week 6, 7.6% at week 8, 7.7% at week 10, and 1.2% at week 12. The maximum increase in hemoglobin levels in 9 (15%) patients of 60 who had baseline values <11 g/dL was a median of 1.2 g/dL (range, 0.7-3.0 g/dL), with increases occurring as early as 2 weeks after initiation of cabozantinib.

Safety

The median duration of exposure was 61.5 days, and the median average daily dose was 67.8 mg. Twenty-four patients (40%) underwent dose reductions owing to AEs. During the 12-week lead-in stage, the lowest dose received was 100 mg by 58% of patients, 60 mg by 28% of patients, 50 mg by 2% patients, and 39.4 mg by 12% patients. Any one patient may have undergone multiple dose reductions. In the lead-in stage, 15 (25%) patients discontinued study treatment because of an AE, and 20 patients discontinued study treatment owing to AEs over the entire period of the study.

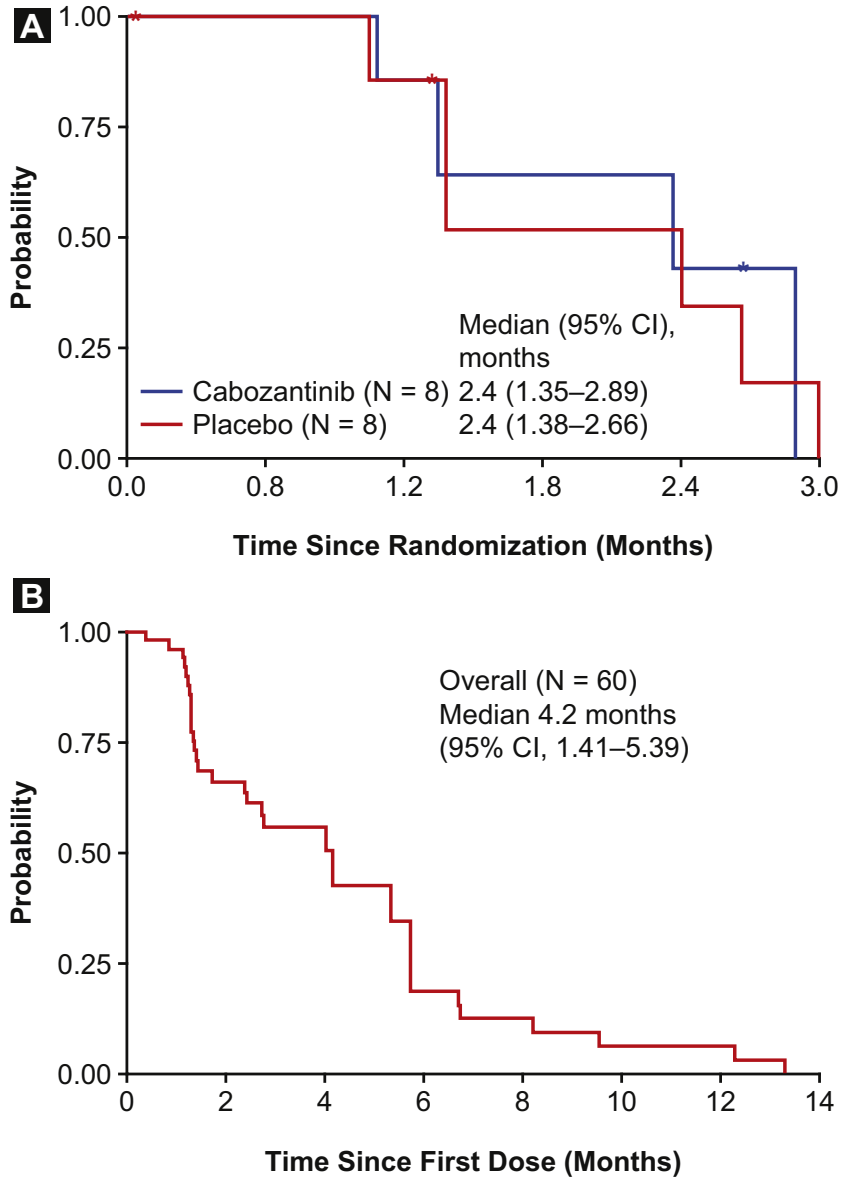
AEs reported during the lead-in stage of the study irrespective of relationship to study treatment are summarized in Table 3. Fifty-nine (98%) patients had at least 1 AE. The most common ≥ grade 3 events were fatigue (13%), palmar-plantar erythrodysesthesia (10%), diarrhea (7%), hypertension (7%), and asthenia (5%). The most common serious AEs were pneumonia (7%) and dehydration (5%). One treatment-related grade 5 AE of hemorrhage was reported during the lead-in stage. In a retrospective review, the baseline tumor assessment of this patient showed a tumor mass infiltrating the pulmonary artery, which would have been an eligibility violation had it been identified during screening.

Discussion

In this trial, a cohort of 60 patients with advanced NSCLC treated with a starting dose of 100 mg/day of cabozantinib had an ORR of 10% during the first 12 weeks of treatment and an overall median PFS of 4.2 months. PFS in the randomized portion of the study was 2.4 months for both cabozantinib and the placebo arms; however, the sample size was small owing to closure of enrollment, and the study was underpowered to evaluate this endpoint. This precludes any statistical interpretation of the data; however, it is in keeping with the goal of RDT trial design to assess preliminary clinical activity of drugs with minimum exposure to placebo.[34]

This NSCLC study population had received a median number of 2 prior lines of systemic therapy. The results indicate that cabozantinib has single-agent antitumor activity in patients with pretreated NSCLC, including both adenocarcinoma and squamous cell carcinoma. The overall median PFS of 4.2 months is notable, given that reported for erlotinib (2.2 months vs. 1.8 months with placebo) after the failure of first- or second-line chemotherapy in patients with NSCLC.[35] An enhanced efficacy of cabozantinib over erlotinib has been shown in another study, in which cabozantinib alone or in combination with erlotinib improved PFS compared with erlotinib alone (4.3 and 4.7 months vs. 1.8 months, respectively) in previously-treated patients with EGFR wild-type NSCLC.[27] In a trial of pemetrexed versus docetaxel in pretreated patients with NSCLC, the median PFS was only 2.9 months for each arm.[36] Antitumor activity of cabozantinib in heavily pretreated patients with NSCLC may reflect antiangiogenic effects (ie, targeting MET, VEGFR, and AXL in the stroma), direct effects on the cancer cells (ie, targeting RET, MET, ROS1, and/or AXL in the cancer cells), or a combination of these mechanisms. Based on observations in this study, there is a possibility that cabozantinib could be active in patients with NSCLC irrespective of their tumor mutational status.

Figure 3 Progression-Free Survival From Time of Randomization for Patients Assigned to Cabozantinib and Placebo (A) and for All Patients From the Time of First Cabozantinib Dose During the Lead-In Stage (B)



Abbreviation: CI = confidence interval.

The notion that cabozantinib may be active in patients harboring KRAS mutations is important, as effective targeted therapy options are limited in these patients.[4,37]

Cabozantinib has been shown to increase the hemoglobin levels in patients with prostate cancer and ovarian cancer.[30,33] Here, we report that cabozantinib was found to increase hemoglobin levels in patients with NSCLC as well. In this NSCLC cohort, 15% of patients had hemoglobin levels <11 g/dL. The proportion of patients with baseline hemoglobin levels <11 g/dL in other tumor cohorts of this study ranged from 20% to 32%, and the maximum increase in hemoglobin was generally observed within 2 to 4 weeks (unpublished data). The apparent pharmacodynamic increase in hemoglobin levels following cabozantinib treatment is in alignment with a recent meta-analysis that identified increased hemoglobin as a possible consequence of VEGF inhibitors in advanced RCC and suggested it to be a surrogate biomarker for the efficacy of VEGF pathway inhibition.[31] Thus, the activity we observed for cabozantinib in patients with EGFR or KRAS mutations in their tumors (ie, those without unique oncogenic drivers directly targeted by cabozantinib), may reflect potential susceptibility of EGFR- or KRAS-mutant tumors to a potent antiangiogenic agent.

Table 3 Most Frequently Reported Adverse Events During Lead-in Stage Regardless of Causality

Adverse Event[a]	All Grades (N = 60)		Grade ≥ 3[b] (N = 60)	
	No.	%	No.	%
Fatigue	35	58	8	13
Diarrhea	35	58	4	7
Decreased appetite	31	52	2	3
Nausea	21	35	1	2
Constipation	18	30	0	0
Dysphonia	18	30	0	0
Vomiting	18	30	1	2
Hypertension	15	25	4	7
Dysgeusia	15	25	0	0
Palmar-plantar erythrodysesthesia	12	20	6	10
Decreased weight	15	25	0	0
Asthenia	15	25	3	5

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.
[a]CTCAE v. 3.0 grading.
[b]One related grade 5 AE was reported during the lead-in stage: baseline tumor assessment showed a tumor mass infiltrating the pulmonary artery.

The median duration of exposure of cabozantinib was 62 days, and the median average daily dose was 67.8 mg during the lead-in, continued open-label, and randomized stages. Twenty-four (40%) patients underwent dose reductions during the lead-in stage, with a median time to first dose reduction of 37 days. Fifteen patients in the lead-in stage and 4 patients in the randomized stage discontinued treatment owing to AEs (Figure 1). Ninety-three percent of patients enrolled had grade 4 NSCLC at diagnosis, which may have contributed to discontinuations owing to AEs. Moreover, this was a heavily pretreated population, with 30% and 50% of patients having 2 and ≥3 prior lines of systemic therapies, which may also have contributed to the discontinuation rate. The AEs that were most common in the NSCLC cohort (eg, diarrhea, fatigue, decreased appetite, and nausea) were mainly mild to moderate in severity. The most frequent grade ≥3 AEs in this study were fatigue (13%), palmar-plantar erythrodysesthesia (10%), diarrhea (7%), hypertension (7%), and asthenia (5%). AEs in this study were consistent with those observed in the other cohorts of this phase II RDT and other studies involving patients with NSCLC in clinical trials of oral TKIs or anti-VEGF inhibitors.[27,30] To maximize clinical benefit, future investigators should be proactive in management of common toxicities associated with cabozantinib as these may otherwise lead to treatment discontinuation. Previous studies with other agents targeting the VEGF pathway have raised caution about the risk of hemorrhagic and cardiac events in patients.[27] The reported fatal pulmonary hemorrhage in this study is likely explained by the retrospectively detected infiltrating tumor mass of the pulmonary artery, which would have excluded this patient by study protocol requirements had it been identified at screening.

In the context of immunotherapy, cabozantinib in combination with atezolizumab is being evaluated in a phase Ib trial in patients with a variety of solid tumors, including 3 cohorts of patients with NSCLC (NCT03170960). Moreover, a randomized phase II trial (NCT03468985) will evaluate whether combination therapy of nivolumab and cabozantinib, or of nivolumab, ipilimumab, and cabozantinib versus nivolumab alone, extends PFS for previously treated patients with NSCLC. Additional evaluation of the combination of cabozantinib with immune checkpoint inhibitors is planned in NSCLC.

Conclusion

Cabozantinib exhibited clinical activity based on ORR in pretreated patients with NSCLC.

Clinical Practice Points

- Cabozantinib is a small-molecule inhibitor of receptor tyrosine kinases, including MET, VEGFRs, AXL, RET, and ROS1.
- Cabozantinib is approved in the United States and Europe for use in patients with progressive, metastatic medullary thyroid cancer and advanced RCC. Cabozantinib has demonstrated clinical efficacy in hepatocellular carcinoma as well as activity in a number of other solid tumors including NSCLC.
- MET, AXL, and RET have been implemented in the development of resistance to EGFR inhibitors in patients with NSCLC.
- This study demonstrated the activity, safety, and tolerability of cabozantinib in previously treated patients with NSCLC. Owing to closure of enrollment, the study was underpowered to evaluate PFS in the randomized portion of the study.
- Tumor regression was observed in the majority of patients, including patients with KRAS and EGFR mutations.
- The safety profile was consistent with that reported for cabozantinib in other solid tumors.
- These results support further study of cabozantinib in NSCLC as a single agent in molecularly-selected patients or in combination with checkpoint inhibitors.

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Disclosure

Dr Aftab is an employee and stockholder of Exelixis, Inc, and has patents related to cabozantinib. Dr Ramies is an employee of Exelixis, Inc. Dr Hellerstedt, Dr Gordon, Dr Kluger, Dr Vogelzang, and Dr Yasenchak declare no conflict of interest relating to the submitted work. Dr Lara reports support from Exelixis, Inc during the conduct of the study.

Supplemental Data

Supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.10.006.

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Supplemental Data

Supplemental Figure 1 Study Design