Phase 1 Study of Cabozantinib in Japanese Patients With Expansion Cohorts in Non–Small-Cell Lung Cancer

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Abstract

Cabozantinib was evaluated in 43 Japanese patients with advanced solid tumors. The maximum tolerated dose of cabozantinib capsules was determined to be 60 mg daily, and the recommended phase 2 dose of cabozantinib tablets was determined to be 60 mg daily. Cabozantinib had a manageable safety profile and antitumor activity in non–small-cell lung cancer.

Background: Cabozantinib inhibits tyrosine kinases including MET, AXL, VEGFR2, RET, KIT, and ROS1 and has demonstrated antitumor activity in multiple tumor types. The primary objective of this phase 1 study (NCT01553656) was to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of cabozantinib in Japanese patients. **Patients and Methods:** Patients with advanced solid tumors were enrolled at 2 sites in Japan. After determining the MTD and RP2D, an expansion in non–small-cell lung cancer (NSCLC) consisting of 3 molecularly defined cohorts (*EGFR* mutation; *KRAS* mutation; *ALK, RET,* or *ROS1* fusion) was initiated. The study was registered with ClinicalTrials.gov (NCT01553656). **Results:** Forty-three Japanese patients were enrolled (dose escalation, n = 23; NSCLC expansion, n = 20). The MTD of cabozantinib capsules was 60 mg daily, and the RP2D of cabozantinib tablets was 60 mg daily. Dose-limiting toxicities were hypertension, proteinuria, and venous embolism. Safety and pharmacokinetics in Japanese patients were consistent with those in non-Japanese patients. Common adverse events included palmar–plantar erythrodysesthesia, hypertension, and diarrhea. Reduction in tumor lesion size was observed in multiple tumor types in the dose-escalation cohorts, with partial responses observed in 4 of 9 patients with NSCLC (*EGFR* mutation, n = 1; *ALK* fusion, n = 2; and *RET* fusion, n = 1). In the NSCLC expansion, 4 patients with *EGFR*-mutant NSCLC had partial responses; the remaining 16 (*EGFR* mutation, n = 11; *KRAS* mutation, n = 2; *ALK* fusion, n = 1; and *RET* fusion, n = 2) had stable disease as best response. **Conclusion:** Cabozantinib had a manageable safety profile in Japanese patients with solid tumors. Responses were observed in diverse molecular subtypes of NSCLC.

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Keywords: Maximum tolerated dose, Recommended phase 2 dose, Safety, Solid tumors, TKI

Introduction

Cabozantinib inhibits oncogenic tyrosine kinases including MET, AXL, VEGFR2, RET, KIT, and ROS1.[1,2] VEGFR2 and MET promote tumor angiogenesis under hypoxic conditions.[3,4] Further, MET amplification is a mechanism of acquired resistance to EGFR or VEGFR inhibition.[4-10] Cabozantinib has shown

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evidence of antitumor activity in a variety of solid tumors, including renal-cell carcinoma (RCC),[11] medullary thyroid cancer (MTC),[12] hepatocellular carcinoma,[13] differentiated thyroid cancer,[14] urothelial carcinoma,[15] neuroendocrine tumors,[16] and non–small-cell lung cancer (NSCLC).[1,17-20] In NSCLC, antitumor activity has been observed in patients with wild-type *EGFR* and in molecular subtypes with *RET*[17] or *ROS1* fusions,[21] which occur in approximately 1% to 2% of NSCLC adenocarcinomas.[22,23]

Cabozantinib is available in capsule and tablet formulations, which are not bioequivalent.[24] The capsule formulation was developed first and is approved for the treatment of progressive metastatic MTC in the United States and progressive, unresectable locally advanced or metastatic MTC in Europe.[12] The tablet formulation is approved for the treatment of advanced RCC in the United States and for advanced RCC after prior VEGF-targeted therapy in Europe.[11,25,26]

In this phase 1 dose-escalation study, safety, tolerability, and pharmacokinetics (PK) of cabozantinib were evaluated in Japanese patients with advanced solid tumors. The primary objectives of the study were to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of cabozantinib capsules and tablets. Following dose escalation, an expansion cohort with molecularly defined subtypes of NSCLC was evaluated at the RP2D to further evaluate efficacy and safety in these patients.

Patients and Methods

Patients

Patients with advanced or metastatic solid tumors for whom standard of care was deemed ineffective or inappropriate were eligible provided they were $\geq$ 20 years of age; had an Eastern Cooperative Oncology Group performance status $\leq$ 2; and had adequate hematologic, hepatic, and renal function and no significant comorbidities. Prior anticancer therapies were allowed. Patients enrolled in the NSCLC expansion were required to have pathologically or cytologically confirmed NSCLC (stage IIIb or IV), measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0,[27] and documentation of one of the following: an *EGFR* mutation (and previous treatment with an EGFR inhibitor); a *KRAS* mutation; or a gene fusion of *RET*, *ROS1*, or *ALK* (and previous treatment with an ALK inhibitor).

Study Design and Treatment

The primary objective was to establish the MTD and/or RP2D of capsule and tablet formulations of once daily cabozantinib in Japanese patients with advanced solid tumors. The tablet was developed after the capsule and introduced into the study by a protocol amendment. Secondary objectives included assessments of safety, tolerability, plasma PK, and preliminary antitumor activity.

The study consisted of a dose-escalation and an expansion phase. The dose-escalation phase used a standard 3+3 study design with a dose-limiting toxicity (DLT) evaluation period (first dose through day 29) and a treatment extension period. A DLT was a cabozantinib-related adverse event (AE) during the evaluation period that required a dose reduction; resulted in failure to take $\geq$ 75% of planned cabozantinib; or was a grade 3 or 4 neutropenia, thrombocytopenia, or amylase or lipase elevation that met specified criteria. AEs considered DLTs are described in more detail in the Supplemental Methods in the online version. The MTD was defined as the highest dose at which $\leq$ 1 of 6 patients (or $<$ 33% if $\geq$ 9 patients were accrued at a dose level) experienced a DLT. The MTD could also be defined based on the totality of the safety data, even if the strict definition of DLTs had not been reached. The RP2D was to be at or below the MTD based on safety data from the DLT evaluation period and treatment extension period. Based on tumor responses in patients with NSCLC in the dose-escalation phase, 3 molecularly defined NSCLC expansion cohorts (*EGFR* mutation; *KRAS* mutation; or an *ALK*, *RET*, or *ROS* fusion) were added at the RP2D of the tablet formulation. To manage AEs, dose could be reduced by one dose level (from 80 mg to 60 mg, from 60 mg to 40 mg, and from 40 mg to 20 mg), or by more than one dose level if agreed upon with the sponsor. Patients could continue treatment until unacceptable toxicity or disease progression.

Assessments

Safety assessments included physical exams, laboratory evaluations, and electrocardiograms. AEs were assessed and graded by investigators according to the National Cancer Institute Common Terminology Criteria for AEs version 3.[28] During the DLT evaluation period, all patients were hospitalized to facilitate frequent safety assessments on days 1, 2, 5, 8, 15, 19, 20, and 29. For patients who continued in the treatment extension period, safety was assessed every 2 weeks for a period of 8 weeks and at least every 4 weeks thereafter in the outpatient setting. For patients in the NSCLC expansion, safety was assessed on days 1, 2, 19, 20, and 29; then every 2 weeks for a period of 8 weeks; and at least every 4 weeks thereafter. A follow-up visit occurred 30 days after discontinuation of cabozantinib.

Computed tomography or magnetic resonance imaging scans were taken at screening, day 29, and every 8 weeks thereafter. Tumor response was assessed using RECIST version 1.0.[27] Blood samples used for single-dose and steady-state PK were collected on day 1 and at steady state (day 19).

Data Analysis

Safety and efficacy analyses were conducted in all patients who received $\geq$ 1 dose of cabozantinib. Objective response rate (ORR) was defined by the percentage of patients who had a best overall response of complete or partial response (confirmed $\geq$ 4 weeks after initial response) at any time during the study. Duration of exposure was the time from first cabozantinib dose to the decision to discontinue study treatment. Time on treatment was the time from first cabozantinib dose to last cabozantinib dose. Statistical analyses were conducted by SAS 9.4 software (SAS Institute, Cary, NC). Data were summarized by cohorts.

PK analyses were conducted in all patients with evaluable PK concentrations who did not have any protocol deviations that might affect cabozantinib concentrations. Plasma samples were analyzed for cabozantinib using a validated liquid chromatography and mass spectrometry method. Data were summarized using Phoenix WinNonlin 6.3 (Certara; Pharsight, Princeton, NJ) and Microsoft Excel 2010 (Microsoft, Redmond, WA).

Table 1 Demographics and Baseline Characteristics

Characteristic	Dose-Escalation Cohorts (N = 23)	NSCLC Expansion Cohorts (N = 20)
Age (years), median (range)	58 (32-72)	65 (46-77)
Sex		
Male	16 (70)	7 (35)
Female	7 (30)	13 (65)
Smoking		
Never	7 (30)	14 (70)
Former	16 (70)	6 (30)
Current	0	0
Diagnosis		
NSCLC[a]	9 (39)	20 (100)
EGFR mutation		15 (75)
KRAS mutation		2 (10)
ALK fusion		1 (5)
RET fusion		2 (10)
Gastrointestinal stromal tumor	4 (17)	
Rectal cancer	3 (13)	
Pancreatic cancer[b]	2 (9)	
Other[c]	5 (22)	
Disease Characteristics		
Measurable disease	22 (96)	20 (100)
Metastatic disease	22 (96)	20 (100)
ECOG PS		
0	12 (52)	10 (50)
1	11 (48)	10 (50)
Prior radiotherapy	6 (26)	7 (35)
No. of Prior Systemic Therapy Regimens		
1-2	6 (26)	0
≥ 3	17 (74)	20 (100)
Prior Systemic Treatments		
Chemotherapy	18 (78)	20 (100)
Bevacizumab	3 (13)	10 (50)
Nivolumab		1 (5)
Tyrosine kinase inhibitors	12 (52)	19 (95)
Crizotinib	0	1 (5)[d]
Erlotinib	3 (13)[e]	10 (50)
Gefitinib	3 (13)[e]	13 (65)
Imatinib	4 (17)[f]	0
Sunitinib	4 (17)[f]	0
Vandetinib	0	1 (20)[g]

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non–small-cell lung cancer.
[a]NSCLC mutational status was not required in dose-escalation phase. Per investigator communication, 2 patients had *ALK* fusions, 1 patient had *EGFR* mutation, and 1 patient had *RET* fusion.
[b]Pancreatic ductal carcinoma.
[c]One patient each with thymic cancer, medullary thyroid cancer, leiomyosarcoma, carcinoid, or duodenal cancer.
[d]This patient had *ALK* fusion.
[e]Only for patients with NSCLC.
[f]All 4 patients with gastrointestinal stromal tumor received prior imatinib and sunitinib therapy.
[g]This patient had *RET* fusion.

Results

Patient Characteristics and Disposition

A total of 43 patients with advanced solid tumors were enrolled at 2 sites in Japan from March 28, 2011, to June 9, 2014. All patients received ≥ 1 dose of study treatment and were evaluated for safety and efficacy. Twenty-three patients were enrolled in dose-escalation cohorts for the capsule (n = 14) and tablet (n = 9) formulations of cabozantinib. Tumor types were NSCLC (n = 9; adenocarcinoma),

Table 2 All-Causality AEs Occurring in ≥ 30% of Patients

AE	Dose-Escalation Cohorts (N = 23)		NSCLC Expansion Cohorts (N = 20)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
PPE	23 (100)	2 (9)	16 (80)	3 (15)
Hypertension	20 (87)	3 (13)	13 (65)	6 (30)
Diarrhea	18 (78)	0	12 (60)	1 (5)
Decreased appetite	11 (48)	1 (4)	11 (55)	1 (5)
Hypothyroidism	1 (4)	0	10 (50)	0
Stomatitis	11 (48)	1 (4)	9 (45)	0
Decreased weight	13 (57)	2 (9)	8 (40)	0
Nausea	5 (22)	0	8 (40)	1 (5)
Dysgeusia	11 (48)	0	7 (35)	0
Constipation	7 (30)	0	6 (30)	0
Fatigue	2 (9)	0	6 (30)	0
Rash	11 (48)	0	4 (20)	1 (5)
Malaise	11 (48)	0	3 (15)	0
Dysphonia	12 (52)	0	2 (10)	0
Headache	7 (30)	0	1 (5)	0
Dry skin	8 (35)	0	0	0

Data are presented as n (%). AEs occurring at ≥ 30% in either NSCLC expansion or dose-escalation cohorts are listed and sorted by decreasing incidence in NSCLC expansion cohort. Laboratory abnormalities reports as AEs are not included. One grade 5 AE of respiratory failure was reported for a patient in the NSCLC expansion cohort. No related grade 5 AEs were reported during the study.
Abbreviations: AE = adverse event; NSCLC = non–small-cell lung cancer; PPE = palmar–plantar erythrodysesthesia.

gastrointestinal stromal tumors (GISTs; n = 4), rectal cancer (n = 3), pancreatic cancer (n = 2), and other (n = 5). All patients in the dose-escalation cohorts had metastatic disease, and all but 1 had measurable disease at baseline (Table 1). Prior therapies included chemotherapy (78%), tyrosine kinase inhibitors (TKIs; 52%), and bevacizumab (13%).

Twenty patients were enrolled in 3 NSCLC expansion cohorts defined by molecular subtypes of *EGFR* mutation (n = 15), *KRAS* mutation (n = 2), or gene fusions (*ALK* fusion, n = 1; *RET* fusion, n = 2) (Table 1). All 20 patients had metastatic disease at baseline. Prior therapies included chemotherapy (100%), TKIs (95%), and bevacizumab (50%).

All patients discontinued cabozantinib (Supplemental Table 1 in the online version). The study was closed when the primary study objectives were reached, and 3 patients still on treatment were discontinued. The most frequent reason for treatment discontinuation was disease progression (dose-escalation cohorts, 18/23 patients [78%]; NSCLC expansion cohorts, 14/20 patients [70%]).

Determination of the MTD and RP2D

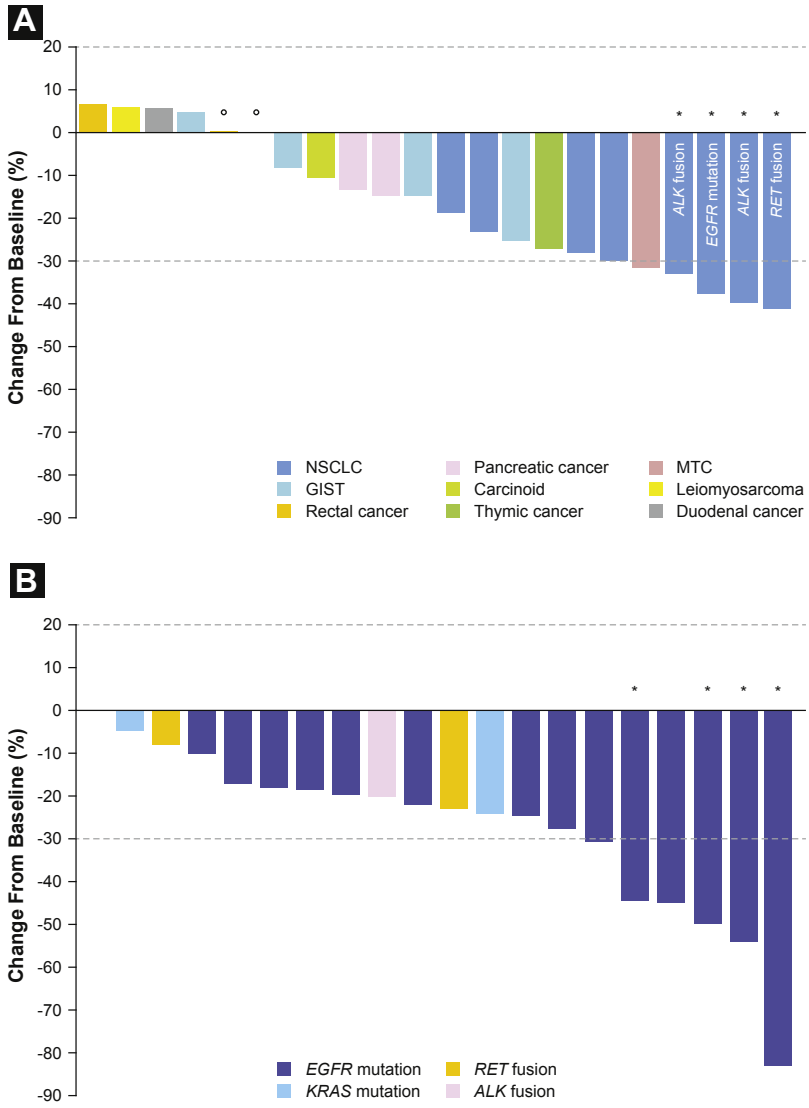
The following dose levels were evaluated: 40 mg capsule (n = 3), 60 mg capsule (n = 6), 80 mg capsule (n = 5), 40 mg tablet (n = 3), and 60 mg tablet (n = 6) (Supplemental Table 2 in the online version). No DLTs were observed in the first 3 patients enrolled in the 60 mg capsule cohort, and 3 patients were subsequently enrolled in the 80 mg capsule cohort, with none experiencing DLTs. However, the 80 mg capsule cohort was not fully expanded based on preliminary PK data from the initial 3 patients enrolled, which suggested a higher exposure in Japanese patients than observed in other studies of non-Japanese patients. Only 2 subsequent patients were enrolled in the 80 mg capsule cohort, and they

Table 3 Tumor Response Assessed by Investigator

Response	Dose-Escalation Cohorts						NSCLC Expansion Cohorts (N = 20)[a]
	Capsule			Tablet			
	40 mg (N = 3)	60 mg (N = 6)	80 mg (N = 5)	40 mg (N = 3)	60 mg (N = 6)	Total (N = 23)	
Objective response rate[b]	2 (67)	1 (17)	1 (20)	0	0	4 (17)	4 (20)
Partial response	2 (67)	1 (17)	1 (20)	0	0	4 (17)	4 (20)
Stable disease	1 (33)	4 (67)	4 (80)	3 (100)	6 (100)	18 (78)	16 (80)
Progressive disease	0	1 (17)	0	0	0	1 (4)	0

Data are presented as n (%).
Abbreviation: NSCLC = non–small-cell lung cancer.
[a]Received 60 mg tablets.
[b]Percentage of patients with overall response of confirmed complete response or partial response per Response Evaluation Criteria in Solid Tumors version 1.0. All responses were partial responses.

Figure 1 Best Tumor Target Lesion Regression for (A) Dose-Escalation Cohorts (N = 22) and (B) NSCLC Expansion Cohorts (N = 20). *Confirmed Partial Responses; 4 Patients in Dose-Escalation Cohorts (All With NSCLC) and 4 Patients in NSCLC Expansion Cohorts had Confirmed Partial Responses. °Best Percentage Change of 0.54 and 0 Was Observed for 2 Patients With Renal Cancer. One Patient in Dose-Escalation Cohort With NSCLC had Nonmeasurable Disease



Abbreviations: GIST = gastrointestinal stromal tumor; MTC = medullary thyroid cancer; NSCLC = non–small-cell lung cancer.

were dose-reduced to 60 mg before completion of the DLT evaluation period. One of these patients in the 80 mg capsule cohort experienced a DLT of grade 3 hypertension. Based on these data, 80 mg was deemed not tolerable. Three additional patients were subsequently enrolled in the 60 mg capsule cohort, with 1 patient experiencing a DLT of grade 3 hypertension. Because 1 out of 6 patients experienced a DLT in the 60 mg cohort, 60 mg was declared the MTD of the capsule.

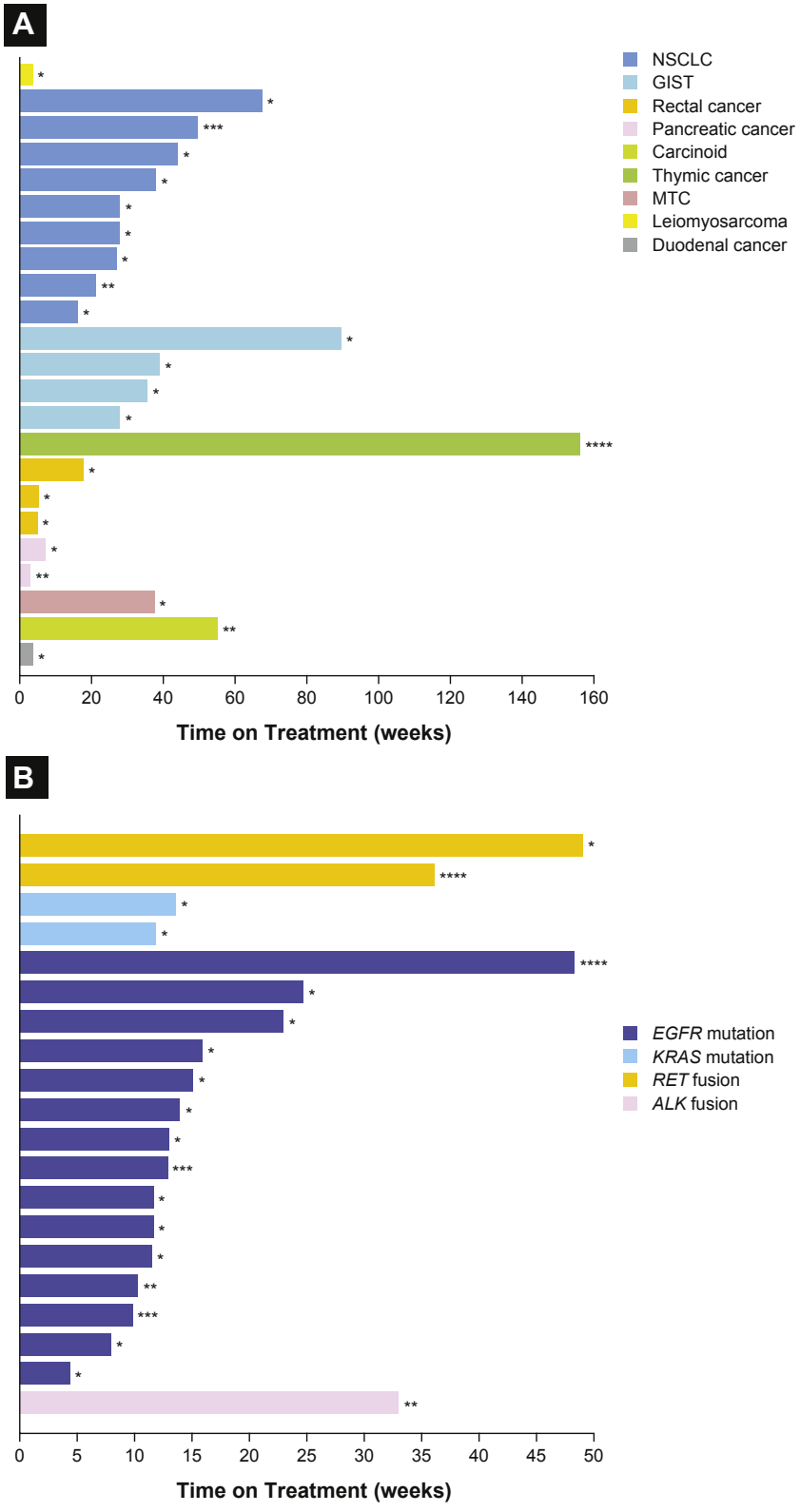
In the 60 mg tablet cohort, 1 of 6 patients enrolled experienced DLTs of grade 2 proteinuria and grade 3 venous embolism. Based on evaluation of the capsule, the decision was made not to exceed a 60 mg tablet dose, and 60 mg was designated the tablet RP2D.

Safety and Tolerability

Dose-escalation Cohorts. The median duration of exposure was 28.4 weeks (range, 4-156 weeks) for patients in the dose-escalation cohorts. Dose reductions due to AEs were experienced by 83% of patients in the 60 mg capsule cohort, 0 patients in the 40 mg capsule cohort, 67% of patients in the 60 mg tablet cohort, and 0 patients in the 40 mg tablet cohort. The most common AEs leading to dose reduction among all patients were palmar–plantar erythrodysesthesia (PPE; 22%) and decreased appetite (9%). The rate of discontinuation due to an AE was 13%.

All patients experienced an AE of any grade regardless of causality, with 70% experiencing ≥ grade 3 AEs. AEs experienced by ≥ 50% of

Figure 2 Time Receiving Treatment for (A) Dose-Escalation Cohorts (N = 23) and (B) NSCLC Expansion Cohorts (N = 20). Reasons for Discontinuation Are: *Progressive Disease, **Adverse Event, ***Investigator Decision, and ****Sponsor Decision



Abbreviations: GIST = gastrointestinal stromal tumor; MTC = medullary thyroid cancer; NSCLC = non–small-cell lung cancer.

patients in the dose-escalation cohorts (excluding AEs based on laboratory abnormalities) were PPE (100%), hypertension (87%), diarrhea (78%), decreased weight (57%), and dysphonia (52%) (Table 2). The most common grade 3 or higher AEs were hypertension (13%), PPE (9%), and decreased weight (9%). Laboratory abnormalities reported as AEs in ≥ 30% of patients are summarized in Supplemental Table 3 in the online version. AEs of increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) were each experienced by > 95% of patients in the dose-escalation cohorts (all grade 1 or 2). The most common grade 3 or higher AEs based on laboratory abnormalities were increased γ-glutamyl transferase (17%) and lymphopenia (13%).

Six patients (26%) experienced 9 serious AEs consisting of anemia, bile duct stone, dyspnea, venous embolism, hematemesis, intestinal obstruction, melena, pleural effusion, and proteinuria. No grade 5 AEs were reported.

NSCLC Expansion Cohorts

Median duration of exposure was 16.3 weeks (range, 8-51 weeks) for patients in the NSCLC expansion cohorts. Dose reductions were implemented for 85% of patients, and the median daily dose was 31.5 mg (range, 18-59 mg). The median time to first dose reduction was 7.3 weeks (range, 1.6-15.4 weeks). The most common AEs leading to dose reductions were PPE (25%) and increased AST (20%). The rate of discontinuation due to an AE was 10%.

All patients experienced an AE of any grade regardless of causality, with 90% experiencing grade 3 or higher AEs. AEs experienced in ≥ 50% of patients (excluding AEs based on laboratory abnormalities) consisted of PPE (80%), hypertension (65%), diarrhea (60%), decreased appetite (55%), and hypothyroidism (50%) (Table 2). The most common grade 3 or higher AEs were hypertension (30%) and PPE (15%). Laboratory abnormalities reported as AEs in ≥ 30% of patients are summarized in Supplemental Table 3 in the online version. More than 90% of patients experienced increased ALT or increased AST of any grade. The most common grade 3 or higher AEs based on laboratory abnormalities were neutropenia (25%) and increased ALT (15%).

Seven patients (35%) experienced 19 serious AEs, including dyspnea (n = 2), decreased performance status (n = 2), and pleural effusion (n = 2). One patient had a grade 5 treatment-related AE of respiratory failure within 30 days of the last dose of cabozantinib. No other grade 5 AEs were reported during the study.

Pharmacokinetics

Evaluable PK data were available for all 43 patients treated with cabozantinib (Supplemental Table 4 in the online version). Over the capsule dose range (40 mg, 60 mg, 80 mg), mean steady-state plasma exposures (AUC_{0-last}) increased slightly less than dose proportionally (ratio of 1:1.2:1.8 vs. dose ratio of 1:1.5:2). Over the tablet dose range (40 mg and 60 mg), mean steady-state plasma exposures increased slightly more than dose proportionally (ratio of 1:1.8 vs. dose ratio of 1:1.5). Mean steady-state plasma exposure was 31% higher for the 60 mg tablet cohort versus the 60 mg capsule cohort, but was within the range of the inter-patient variability (% coefficient of variation values of 33.3% and 35.6%, respectively). Compared with values on day 1, steady-state plasma exposures were 5.3- and 5.7-fold higher for the 60 mg capsule and tablet groups, respectively.

Efficacy

Dose-escalation Cohorts. ORR in the dose-escalation cohorts was 17% (4/23; 90% confidence interval, 6-36) (Table 3). Four patients (17%) had partial responses, and 18 patients (78%) had stable disease as best response. The 4 patients with partial responses were enrolled across all dose levels in the capsule cohorts, and all had NSCLC (per investigator communication: 1 with *EGFR* mutation, 2 with *ALK* fusions, and 1 with *RET* fusion). Duration of response ranged from 12.4 to 63.9 weeks. Reduction in target lesion size was observed in all dosing cohorts and with both formulations (Figure 1A). Three of the 4 patients with GISTs had a reduction in tumor target lesions.

Time on treatment for all patients in the dose-escalation cohorts ranged from 3.1 to 156.1 weeks (Figure 2A).

NSCLC Expansion Cohorts. ORR in the NSCLC expansion cohorts was 20% (90% confidence interval, 7-40). Four patients (20%) had partial responses, and 16 (80%) had stable disease as a best response (Table 3). All patients with partial responses had *EGFR*-mutant NSCLC. Duration of response ranged from 13.0 to 20.3 weeks for the 3 patients who experienced disease progression. Reduction in tumor lesion size was observed in all 3 NSCLC expansion cohorts (Figure 1B).

Time on treatment for all patients in the NSCLC expansion cohort ranged from 4.4 to 49.0 weeks (Figure 2B).

Discussion

This was a phase 1 dose-finding study of cabozantinib in Japanese patients with advanced solid tumors. Both capsule and tablet formulations were assessed. DLTs consisted of hypertension (grade 3; n = 2), proteinuria (grade 2), and venous embolism (grade 3). In Japanese patients, the MTD of cabozantinib capsules is 60 mg once daily, and the RP2D of cabozantinib tablets is 60 mg once daily. Regression in tumor target lesions was observed in multiple tumor types, irrespective of dose level or formulation.

The overall safety profile of cabozantinib in Japanese patients was consistent with the previously reported safety profile in non-Japanese patients.[11,12] The most frequently reported AEs during the study (PPE, hypertension, diarrhea, decreased weight, decreased appetite, dysphonia, and hypothyroidism) have been reported in other cabozantinib studies and are also commonly reported with VEGFR inhibitors and other TKIs.[29,30] Serious AEs were also consistent with the known safety profile of cabozantinib or sequelae of the tumor types in the study. Dose reductions were frequently employed to manage AEs, and discontinuations due to AEs were low.

Some AEs were reported at a higher frequency in this study than in studies in non-Japanese patients, including AEs of laboratory abnormalities and hypertension. More than 90% of all patients experienced increased AST or ALT; the majority were grade 1 or 2. A higher incidence of some AEs has been reported for other TKIs in Japanese patients relative to non-Japanese patients.[31] The observed incidence of some AEs may be confounded because of the small size of this study and the very frequent safety evaluations in an inpatient setting during the DLT evaluation period.

Steady-state plasma exposures were determined for both cabozantinib formulations. Steady-state plasma exposures of cabozantinib 60 mg tablets in Japanese patients were approximately 30% higher than those determined in other studies of non-Japanese patients with solid tumors (unpublished data). A 30% difference is within the range of inter-patient variability, suggesting that the difference is not clinically relevant. Differences between the steady-state plasma exposures observed for the 60 mg capsule and tablet formulations were also within the range of inter-patient variability.

Partial responses were observed in 4 of 9 patients with NSCLC. Regression in tumor target lesions was also observed in patients with GISTs, pancreatic cancer, MTC, carcinoid, and thymic cancer. Three of the 4 patients with GISTs had a reduction in tumor target lesions, with 1 patient on treatment for 20.6 months; all had received prior imatinib and sunitinib therapy. Cabozantinib inhibits KIT,[2] the most common oncogenic driver in GISTs,[32] providing a rationale for the observed activity.

Selection of the molecular cohorts in the NSCLC expansion was based in part on the molecular alterations of the 4 patients with partial responses in the dose-escalation cohorts (1 patient with *EGFR* mutation, 2 patients with *ALK* fusion, and 1 patient with *RET* fusion) and also on the mechanism of action of cabozantinib, which inhibits the receptor tyrosine kinases RET, ROS1, MET, and VEGFR2.[1,2] Partial responses were observed in 4 of 20 patients in the NSCLC expansion; all 4 patients had *EGFR*-mutant NSCLC. Patients with NSCLC can develop resistance to EGFR inhibition because of secondary mutations in *EGFR* or upregulation of the MET pathway through MET amplification or HGF overexpression,[5-9] which provides a rationale for the activity of cabozantinib, a potent MET inhibitor. The remaining 16 patients had stable disease as best response (11 with *EGFR* mutations, 2 with *KRAS* mutations, 1 with an *ALK* fusion, and 2 with a *RET* fusion), with a reduction in tumor size observed in all but 1 patient. Inhibition of VEGFR2 may also contribute to the observed activity of cabozantinib given that other agents that target the VEGF pathway have shown efficacy in NSCLC.[33] Cabozantinib also inhibits AXL, which is overexpressed in some NSCLCs and has been implicated in resistance to EGFR inhibition.[34-36]

The results in NSCLC presented here are consistent with results for cabozantinib in other clinical trials conducted in non-Japanese patients. A phase 2 study of 125 patients with *EGFR* wild-type NSCLC who had progressed after prior therapy showed that cabozantinib treatment alone and in combination with erlotinib significantly improved progression-free survival when compared with erlotinib alone. Oncogenic drivers for these patients were not identified; however, approximately 10% had known *KRAS* mutations.[19] In a phase 2, single-arm trial of patients with *RET* fusion−positive NSCLC, an ORR of 28% (7 of 25 patients) was reported with cabozantinib treatment.[21] Cabozantinib has also shown antitumor activity in other molecular subtypes of NSCLC, including in 1 patient with *ROS1* fusion with acquired crizotinib resistance[17] and in patients with mutations in the MET exon 14 splice sites that upregulate the MET pathway.[20]

Conclusion

Cabozantinib treatment had a manageable safety profile and antitumor activity in this phase 1 study of Japanese patients with solid tumors. Dose reductions were frequently implemented to manage AEs. In Japanese patients, the MTD of cabozantinib capsules is 60 mg once daily, and the RP2D of cabozantinib tablets is 60 mg once daily. Safety and PK profiles in Japanese patients were consistent with those in non-Japanese patients. Responses were observed in diverse molecular subtypes of NSCLC, adding to the clinical evidence of efficacy for cabozantinib in NSCLC. Further studies in NSCLC are warranted.

Clinical Practice Points

- Cabozantinib inhibits oncogenic tyrosine kinases including MET, AXL, VEGFR2, RET, KIT, and ROS1.
- Cabozantinib is approved to treat advanced stages of MTC and RCC in the United States and Europe.
- Cabozantinib has shown clinical efficacy in other solid tumors including hepatocellular carcinoma, differentiated thyroid cancer, urothelial carcinoma, neuroendocrine tumors, and NSCLC.
- Cabozantinib is available in capsule and tablet formulations, which are not bioequivalent.
- This study identified the MTD of cabozantinib capsules and the RP2D of cabozantinib tablets in Japanese patients.
- Safety and PK were consistent with that seen in previous studies of non-Japanese patients.
- Responses were seen in diverse molecular subtypes of NSCLC including patients with *EGFR* mutations, *ALK* fusions, and *RET* fusions.
- Dose levels for cabozantinib were established for Japanese patients, facilitating further clinical development in this patient population.
- Clinical activity in diverse molecular subtypes of NSCLC supports further evaluation of cabozantinib in these tumor types.

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Disclosure

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Supplemental Data

Supplemental methods and tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.12.018.

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Appendix

Supplemental Methods

Dose-limiting toxicity (DLT) was defined as any of the following cabozantinib-related adverse events (AEs) occurring during the DLT evaluation period:

- Any cabozantinib-related AE that required a dose reduction.
- Any cabozantinib-related AE that resulted in an inability to take $\geq$ 75% of the planned study treatment in the 29-day dose-escalation phase.
- Grade 3 thrombocytopenia with clinically significant bleeding or any grade 4 thrombocytopenia.
- Grade 3 neutropenia of $\geq$ 5 days' duration or any grade 4 neutropenia.
- Grade 3 or 4 neutropenia of any duration with a temperature of $>$ 38.5°C.
- Grade 4 amylase/lipase elevation of $>$ 4 days duration or grade 3 or worse amylase/lipase elevation associated with findings of pancreatitis, or pancreatic disorder considered to be life-threatening or resulting in chronic damage to the pancreas.

Supplemental Table 1 Patient Disposition

Reason for Discontinuation	Dose Escalation (N = 23)	NSCLC Expansion (N = 20)
Adverse event	3 (13)	2 (10)
Disease progression	18 (78)	14 (70)
Subject request	0	2 (10)
Investigator decision	1 (4)	0
Sponsor decision[a]	1 (4)	2 (10)

Data are presented as n (%).
Abbreviation: NSCLC = non–small-cell lung cancer.
[a]When the primary study objectives were reached, the study was closed, and patients remaining on study treatment discontinued therapy.

Supplemental Table 2 DLTs in the Dose-Escalation Phase

Cohort	N	No. of Patients With DLTs	Specific DLTs (CTCAE Grade)
Capsule			
40 mg	3	0	0
60 mg	6	1	Hypertension (grade 3)
80 mg	5	1	Hypertension (grade 3)
Tablet			
40 mg	3	0	—
60 mg	6	1	Proteinuria (grade 2), embolism venous (grade 3)

Adverse events were assessed and graded by investigators according to CTCAE version 3.
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity.

Supplementary Table 3 Laboratory Abnormalities Reported as AEs Occurring in ≥ 30% of Patients

	Dose-Escalation Cohorts (N = 23)		NSCLC Expansion Cohorts (N = 20)	
AE	Any Grade AE	Grade 3 or Higher AE	Any Grade AE	Grade 3 or Higher AE
ALT increased	22 (96)	0	18 (90)	3 (15)
AST increased	22 (96)	0	18 (90)	1 (5)
Proteinuria	12 (52)[a]	0	13 (65)	1 (5)
Neutropenia	10 (43)	2 (9)	11 (55)	5 (25)
ALP increased	11 (48)	1 (4)	10 (50)	0
TSH increased	19 (83)	0	9 (45)	0
GGT increased	10 (43)	4 (17)	9 (45)	2 (10)
Platelet count decreased	6 (26)	0	9 (45)	0
Hypoalbuminemia	10 (43)	1 (4)	9 (45)	0
Hypocalcemia	10 (43)	0	9 (45)	0
Hypophosphatemia	5 (27)	2 (9)	8 (40)	3 (15)
WBC count decreased	0	0	8 (40)	1 (5)
Hemoglobin decreased	6 (26)	0	7 (35)	0
Thrombocytopenia	9 (39)	0	7 (35)	1 (5)
Hyponatremia	3 (13)	2 (9)	7 (35)	2 (10)
Lipase increased	11 (48)	2 (9)	6 (30)	2 (10)
LDH increased	16 (70)	0	6 (30)	0
Leukopenia	14 (61)	0	6 (30)	0
Lymphopenia	8 (35)	3 (13)	4 (20)	2 (10)
Blood urine present	10 (43)	0	1 (5)	0
Hyperglycemia	7 (30)	0	1 (5)	0
Hypoproteinemia	8 (35)	0	0	0

Data are presented as n (%). AEs regardless of causality that occurred in ≥ 30% of patients in either NSCLC expansion or dose-escalation cohorts are summarized by decreasing incidence in NSCLC expansion cohorts.
Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transferase; LDH = lactate dehydrogenase; NSCLC = non–small-cell lung cancer; TSH = thyroid stimulating hormone; WBC = white blood cell.
[a]Reported as protein urine present in the dose-escalation cohorts.

Supplemental Table 4 Summary of Single-Dose and Steady-State Pharmacokinetics

Dose Level	No. of Patients	C_{max} (ng/mL), Mean (SD)		$AUC_{0\text{-last}}$ (Hour × ng/mL), Mean (SD)	
		Single Dose	Steady State	Single Dose	Steady State
Capsule					
40 mg	3	201.7 (28.7)	1506.6 (359.2)	3944.4 (420.1)	23668.7 (4839.6)
60 mg	6	439.7 (183.8)	1776.7 (708.0)	5703.4 (992.9)	28615.8 (10178.9)
80 mg	5	324.6 (101.7)	2923.3 (1305.0)	5938.4 (2335.0)	41396.7 (17143.4)
Tablet					
40 mg	3	252 (20.9)	1394.7 (513.9)	4199.4 (740.6)	20529.1 (5274.6)
60 mg	26	489.7 (191.9)	2056.6 (588.1)	7225.7 (1895.4)	37512.8 (12497.7)

Single-dose pharmacokinetic measurements are from study day 1 and steady-state measurements from day 19.
Abbreviations: $AUC_{0\text{-last}}$ = area under plasma concentration-time curve from time 0 to time of last observable value or dosing interval (approximately 24 hours); C_{max} = observed maximum plasma concentration; SD = standard deviation.