FDA Approval Summary: Cabozantinib for Differentiated Thyroid Cancer

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ABSTRACT

On September 17, 2021, the FDA approved cabozantinib (Cabometyx; Exelixis, Inc.) for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine (RAI)-refractory or ineligible. This is the first approval for patients with RAI-refractory locally advanced or metastatic DTC who have progressed following prior therapy and the first approval in pediatric patients with DTC. The approval was based on data from COSMIC-311 (Study XL184-311, NCT03690388), an international, randomized, double-blind trial in which patients with locally advanced or metastatic RAI-refractory DTC that progressed during or following treatment with at least one VEGFR-targeting tyrosine kinase inhibitor were treated with either cabozantinib 60 mg orally once daily ($N = 170$) or placebo with best supportive care ($N = 88$). The primary efficacy outcome measures were progression-free survival (PFS) and overall response rate (ORR) by blinded independent central review per RECIST 1.1. The median PFS was 11.0 months [95% confidence interval (CI), 7.4–13.8] in the cabozantinib arm compared with 1.9 months (95% CI, 1.9–3.7) in the control arm, with an HR of 0.22 (95% CI, 0.15–0.31). The endpoint of ORR was not met. No new safety signals were identified with the exception of hypocalcemia, which was added as a warning in the product labeling.

Introduction

Thyroid cancer is the most common endocrine malignancy, with approximately 15 new cases per 100,000 persons per year (1). Differentiated thyroid cancer (DTC) accounts for 90% of thyroid carcinomas and is comprised of three subtypes: papillary, follicular, and Hürthle cell carcinomas (2). DTC is 2.5 times more common in women and the median age of diagnosis is 51 years (1). The incidence of DTC has risen over the last several decades, likely due to increased screening; however, mortality remains stable at 0.5 per 100,000 persons per year (3).

First-line treatment of DTC includes surgery (thyroidectomy or lobectomy) and radioactive iodine (RAI), followed by lifelong levothyroxine replacement. While prognosis for patients with DTC is generally good, with 5-year overall survival (OS) of 98%, about 10% of patients have local tumor invasion or distant metastases at diagnosis and up to 30% recur after initial treatment (4). Risk factors for recurrence include male sex, extrathyroid invasion, and older age at diagnosis (5, 6). Patients who are RAI-refractory with metastatic disease have a worse prognosis with median OS of 2.5 to 3.5 years (7).

At the time of recurrence, patients with DTC may undergo re-resection, external beam radiotherapy, or systemic therapy (8, 9). Both lenvatinib and sorafenib are FDA approved for the treatment of adult patients with locally recurrent or metastatic, progressive, DTC that is refractory to RAI based on improvement in PFS compared with placebo (10, 11). Currently, there is no consensus or approved therapy for the treatment of disease after progression on a VEGFR tyrosine kinase inhibitor (TKI; ref. 12). There are no approved therapies for pediatric patients with DTC.

In addition to targeting VEGF and RET (rearranged during transfection) receptors like other approved TKIs, cabozantinib has additional targets, such as MET (hepatocyte growth factor) and AXL (tyrosine protein kinase receptor UFO), that may enhance efficacy by overcoming resistance mechanisms (13). There is clinical evidence that patients who discontinue a first-line TKI may derive clinical benefit from a second-line TKI (14, 15).

Cabozantinib (Cabometyx) was previously approved in a tablet formulation for the treatment of patients with advanced renal cell carcinoma (RCC), as a first-line treatment of advanced RCC in combination with nivolumab, and hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Cabozantinib (Cometriq) is also approved in a capsule formulation for progressive, metastatic medullary thyroid cancer; capsule and tablet formulations are not bioequivalent or interchangeable. The FDA approval summary of the marketing application for cabozantinib for DTC is provided below.

Regulatory History

Cabozantinib was granted Orphan Drug Designation for the treatment of patients with thyroid cancer on November 29, 2010 and received Breakthrough Therapy Designation on February 19, 2021. The supplemental NDA (sNDA) was submitted on June 4, 2021, and voluntarily utilized the Assessment Aid to facilitate FDA's review (16). The application was reviewed under the Summary Review program

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which relies on qualified data summaries from the applicant to support approval of a supplemental application, with targeted independent verification of the data analyses.

Mechanism of Action

Cabozantinib is an orally bioavailable multi-targeted kinase inhibitor with activity against MET and VEGFR-1, -2, and -3, as well as other receptors including AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes, such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment (17). No new nonclinical pharmacology/toxicology data were submitted in this sNDA.

Clinical Pharmacology

The population pharmacokinetic modeling included data from one phase I and six phase III clinical studies (with the exception of COSMIC-311), using the cabozantinib tablet formulation up to a dose of 60 mg in a total of 1,745 subjects. These data suggested that at the approved recommended dosage of 60 mg orally once daily, the observed cabozantinib pharamcokinetics in patients with DTC was consistent with those previously observed in patients with RCC and HCC; and that the predicted exposure in pediatric patients 12 years and older with BSA of 1.2 m^2 and higher would be comparable with that of adult patients.

In a phase I study in pediatric patients (NCT01709435) conducted by NCI-CTEP, a dosage of 40 mg/m^2 orally once daily showed antitumor activity in pediatric patients and the safety profile appeared to be consistent with that observed in adults. At this dosage, the mean (SD) steady state $AUC_{0-24\,h}$ was consistent with that of adult patients administered the approved recommended dosage of 60 mg orally once daily.

On the basis of results from this study along with the population pharmacokinetic analyses, a BSA-tiered dosing regimen was approved: 60 mg orally once daily in adult and pediatric patients 12 years of age and older with a BSA of 1.2 m^2 and higher, and 40 mg orally once daily for pediatric patients 12 years of age and older with a BSA less than 1.2 m^2.

Clinical Trials

The FDA approval of cabozantinib was based on the results of COSMIC-311 (NCT03690388), an international, randomized (2:1), double-blind, placebo-controlled trial for patients ages 16 and older with locally advanced or metastatic histologically or cytologically confirmed DTC who previously received or were ineligible for RAI and had progressed after another VEGFR TKI (either lenvatinib or sorafenib). Patients were randomized to receive cabozantinib 60 mg orally once daily or placebo with best supportive care until disease progression or unacceptable toxicity. Randomization was stratified by prior receipt of lenvatinib and age group (older or younger than 65 years). Patients randomized to placebo could cross-over at the time of blinded independent central review (BICR)-determined radiographic progression.

The multiple primary efficacy outcome measures of COSMIC-311 were PFS in the intent-to-treat population and ORR in the first 100 randomized patients, as assessed by BICR per RECIST 1.1. Tumor assessments were conducted every 8 weeks for the first 12 months on study, then every 12 weeks. The multiplicity issue resulting from analysis of two primary endpoints was addressed by applying a modified Bonferroni procedure (dividing the alpha between the multiple primary endpoints). For PFS, hypothesis testing between the two treatment arms was performed using the stratified log-rank test with a two-sided, 0.04 level of significance. For ORR, hypothesis testing between the two treatment arms was performed using Fisher exact test at the two-sided, 0.01 level of significance. OS was a descriptive outcome measure with no prespecified formal testing plan.

Demographics, disease characteristics, and prior treatment

The primary analysis of PFS included 187 randomized patients ($N = 125$ in the cabozantinib arm and $N = 62$ in the control arm). Because of the limited information fraction of 38% (74 events) at the prespecified interim analysis date, FDA requested a more mature PFS analysis prior to filing the application. An updated analysis of PFS was performed and included 258 randomized patients ($N = 170$ in the cabozantinib arm and $N = 88$ in the control arm); the information fraction was 68% (131 events). The demographic and baseline disease characteristics were generally balanced between the two arms. The median age was 65 years (range, 31–85 years), 53% were female, 70% were White, 19% were Asian, 2% were Black, 2% were American Indian or Alaska Native. Baseline Eastern Cooperative Oncology Group performance status was 0 (46%) or 1 (54%) and 93% of patients had metastatic disease. The demographic characteristics generally reflect the known profile of patients with RAI-refractory DTC in the United States, with the exceptions that this population was slightly older with a higher male predominance and there were more Asian patients and fewer Black patients than would be expected (18).

Prior therapies included RAI in 98% (5 patients were deemed ineligible due to iodine allergy or intact thyroid gland), radiotherapy in 51%, and all patients received at least one prior TKI (63% received lenvatinib, 60% received sorafenib, and 24% received both). Other systemic anticancer agents included cisplatin, doxorubicin, bleomycin, everolimus, ipilimumab, nintedanib, pazopanib, selumetinib, trametinib, and vandetanib (no more than 11 patients received each therapy). No patients were reported to have received a prior *RET* inhibitor, *NTRK* inhibitor, or pembrolizumab. The median time from progression on the most recent prior nonradiation systemic anticancer regimen to randomization was 1.4 months (range, 0.4–76 months) in the cabozantinib arm compared with 1.7 months (range, 0.5–76 months) in the control arm.

Efficacy results

A statistically significant improvement in PFS was observed in the cabozantinib arm over the control arm (**Table 1**; **Fig. 1**). The median PFS was 11.0 months [95% confidence interval (CI), 7.4–13.8] in the cabozantinib arm compared with 1.9 months (95% CI, 1.9–3.7) in the control arm, with a HR of 0.22 (95% CI, 0.15–0.31). The observed results were consistent in the stratification subgroups (prior lenvatinib vs. no prior lenvatinib and age ≤65 years vs. >65 years).

No statistically significant improvement was observed in ORR based on the prespecified primary analysis in the first 100 randomized patients. At the updated analysis, the ORR in the first 100 randomized patients was 18% (95% CI, 10%–29%) in the cabozantinib arm versus 0% (95% CI, 0%–11%) in the control arm. A HR of 0.76 (95% CI, 0.45–1.31) was observed for OS; however, as mentioned earlier, OS is considered a descriptive endpoint only.

Safety results

The safety profile of cabozantinib is generally consistent with prior clinical studies. The safety review focused on the 187 patients treated with cabozantinib in COSMIC-311, supported by pooled data from prior studies (Studies XL184-309, XL184-308, and A031203) of the

Table 1. Summary of efficacy results per BICR in COSMIC-311.

	Primary analysis		Updated analysis[a]	
	CABOMETYX (*n* = 125)	**Placebo (*n* = 62)**	**CABOMETYX (*n* = 170)**	**Placebo (*n* = 88)**
Progression-free survival				
Number of events, (%)	31 (25)	43 (69)	62 (36)	69 (78)
Median PFS in months (95% CI)	NR (5.7–NE)	1.9 (1.8–3.6)	11.0 (7.4–13.8)	1.9 (1.9–3.7)
HR (95% CI)[b]	0.22 (0.14–0.35)		0.22 (0.15–0.31)	
P[c]	<0.0001			
Overall response rate				
Overall response, % (95% CI)[d,e]	15% (7%–26%)	0% (0%–11%)	18% (10%–29%)	0% (0%–11%)
P[f]	0.0281			

Abbreviations: CI, confidence interval, NE, not evaluable; NR, not reached.
[a]No formal statistical testing was conducted at the time of the updated analysis.
[b]Estimated using the Cox proportional hazards model.
[c]Log-rank test stratified by receipt of prior lenvatinib (yes vs. no) and age (≤65 years vs. >65 years).
[d]All responses were partial responses.
[e]The analysis population overall response rate was the first 100 randomized patients (67 in the CABOMETYX arm and 33 in the placebo arm).
[f]Fisher exact test compared with an alpha boundary of 0.01.
Source: CABOMETYX (cabozantinib) package insert (ref. 17).

tablet formulation of cabozantinib (Cabometyx) for a total of 1,001 patients. In COSMIC-311, the most common (≥25%) treatment-emergent adverse events (TEAE) due to any cause in the cabozantinib arm were diarrhea, palmar-plantar erythrodysesthesia (PPE), fatigue, hypertension, and stomatitis. TEAEs that were more common in COSMIC-311 and had a ≥5% difference compared with prior pooled studies of cabozantinib were hypocalcemia and proteinuria. Hypocalcemia was considered serious and significant enough to warrant adding to the Warnings and Precautions section of the product labeling.

Serious adverse reactions occurred in 34% of patients who received cabozantinib, compared with 29% of patients who received placebo with supportive care. Serious adverse reactions in ≥2% of patients included diarrhea, pleural effusion, pulmonary embolism, and dyspnea. Fatal adverse reactions occurred in 1.6% of patients in the cabozantinib arm, including arterial hemorrhage (0.8%), and pulmonary embolism (0.8%). Fatalities in the control arm were primarily secondary to underlying disease, with the exception of 1 patient each with cardiac arrest, stroke, sepsis, and COVID-19 infection. Five percent (5%) of patients permanently discontinued cabozantinib due

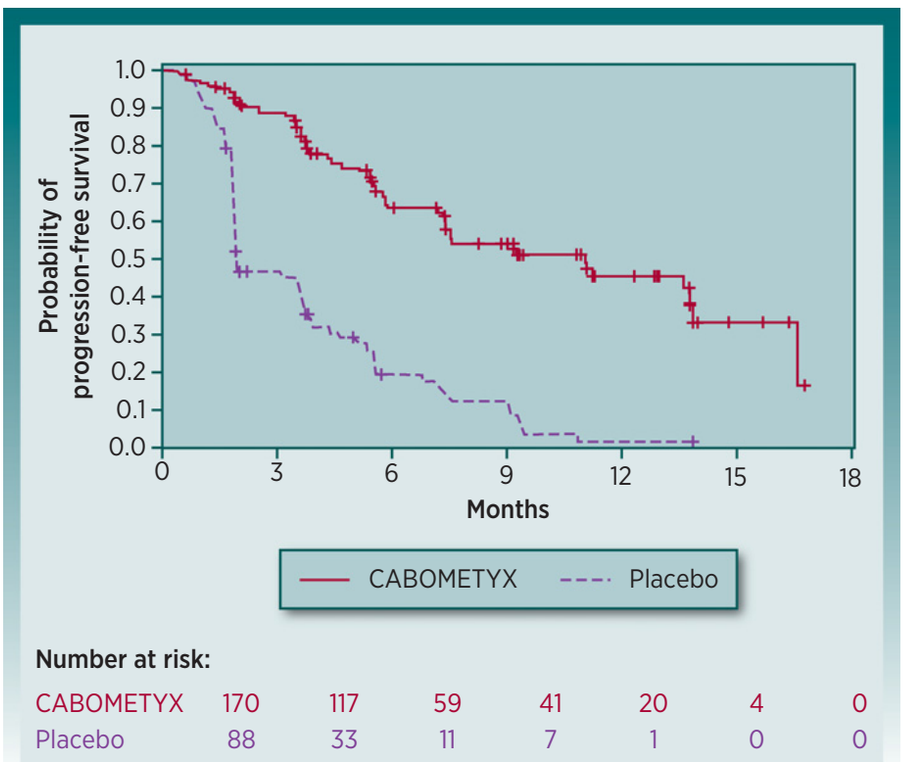

Figure 1.
Kaplan–Meier curve of PFS in COSMIC-311 (updated analysis, *N* = 258). Source: CABOMETYX (cabozantinib) package insert (ref. 17).

to an adverse reaction. Dosage interruptions and dose reductions due to an adverse reaction occurred in 72% and 56% of patients, respectively, primarily due to PPE, diarrhea, proteinuria, decreased appetite, fatigue, dyspnea, and hypertension.

Regulatory Insights

Review issues for this application included the generalizability of the patients in COSMIC-311 to the U.S. population, the appropriateness of the control arm, the impact of early censoring and dose reductions on the efficacy results, and the addition of hypocalcemia as a warning in the product label.

COSMIC-311 was an international multi-regional study that enrolled patients at 89 sites in 25 countries. FDA considered the generalizability of the results to the U.S. population because only 8% of patients were enrolled in the U.S. Notably, available therapies, including sorafenib and lenvatinib, are generally similar in all regions involved in COSMIC-311 and all patients in the study were required to have received either sorafenib or lenvatinib prior to enrollment. In a subgroup analysis, the observed improvement in PFS was consistent by region (North America, Europe, Asia, and the rest of the world).

FDA considered the appropriateness of placebo with best supportive care as the control arm in COSMIC-311. There is no consensus or approved therapy for the treatment of disease after progression on lenvatinib or sorafenib, supporting the choice of comparator to placebo with best supportive care. Additional factors that support the use of a placebo with best supportive care design include 2:1 randomization that favored the treatment arm, as well as a cross-over design where 60% of patients in the control arm who discontinued blinded study treatment due to progressive disease transitioned to the open-label study upon BICR confirmation of progressive disease. No therapy has demonstrated benefit after prior

Table 2. FDA benefit–risk analysis.

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• Thyroid cancer is the most common endocrine malignancy; DTC accounts for 90% of cases (1). • The incidence of DTC has risen over the last several decades, likely due to increased screening; mortality remains stable at 0.5 per 100,000 persons per year (3). • Median OS in patients with RAI-refractory metastatic DTC is 2.5 to 3.5 years (7).	DTC that is RAI-refractory and has progressed following prior VEGFR-targeted therapy is a serious and life-threatening condition.
Current treatment options	• There are no approved therapies for RAI-refractory DTC that has progressed following prior systemic therapy. • Lenvatinib (approved 2015) and sorafenib (approved 2013) are approved for patients with locally recurrent, advanced, or metastatic DTC refractory to or not amenable to RAI therapy. Lenvatinib is the preferred treatment option over sorafenib (12). • Cytotoxic chemotherapy has shown minimal efficacy in this setting. Resection of distant metastases and/or radiation can also be considered if feasible. • Other molecularly targeted therapies can be considered if clinical trials are not available or appropriate. Disease monitoring may be appropriate in asymptomatic patients with indolent disease (12).	No therapy has demonstrated benefit after prior treatment with lenvatinib or sorafenib in randomized studies. There is no consensus or approved therapy for the treatment of disease after progression on lenvatinib or sorafenib, supporting the choice of comparator to placebo with best supportive care in the trial supporting this sNDA.
Benefit	• Study XL184-311 (COSMIC-311), an international, multicenter, randomized trial of cabozantinib vs. placebo with best supportive care, is the primary study supporting this sNDA. • A total of 258 patients with locally advanced or metastatic DTC who had received or were ineligible for RAI and had progressed after lenvatinib and/or sorafenib were enrolled, with 170 in the cabozantinib arm and 88 in the control arm. • The median PFS was 11.0 months (96% CI: 7.4–13.8) in the cabozantinib arm ($N = 170$) compared with 1.9 months (96% CI: 1.9–3.7) in the control arm ($N = 88$), with an HR of 0.22 (95% CI: 0.15–0.31). • The difference in ORR between the two treatment arms was not statistically significant; at the updated analysis, the ORR in the first 100 randomized patients was 18% (95% CI: 10–29) in the cabozantinib arm compared with 0% (95% CI: 0–10) in the control arm.	The submitted evidence meets the statutory evidentiary standard for approval, with an improvement in PFS corresponding to an HR of 0.22 favoring cabozantinib over placebo with best supportive care. PFS has supported approvals of other targeted therapies in patients with DTC. The magnitude of improvement in PFS observed in COSMIC-311 is statistically significant and clinically meaningful.
Risk and risk management	• The primary safety population supporting this sNDA included patients randomly assigned to the cabozantinib arm of COSMIC-311. • The most common (≥25%) TEAEs in the cabozantinib arm were diarrhea, PPE, hypertension, and fatigue. • The most common (≥5%) grade 3 or 4 lab abnormalities were increased LDH, decreased corrected calcium, and decreased lymphocytes. • Serious adverse events occurred in 34% of patients in the cabozantinib arm. • There were two deaths (1.6%) due to an adverse event in the cabozantinib arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%). • Dose interruptions occurred in 69% of patients in the cabozantinib arm, dose reductions occurred in 57%, and permanent discontinuation occurred in 5%. • TEAEs that were more common in Study XL184-311 and had a ≥5% difference compared with prior pooled studies of cabozantinib were hypocalcemia and proteinuria.	A safety issue considered serious and significant enough to warrant adding to the Warnings and Precautions section of the USPI was hypocalcemia. Although cabozantinib can cause serious toxicities, these safety concerns are adequately addressed by information in the product labeling. The risk mitigation strategies included in the label are considered sufficient, and a REMS was not considered necessary for the safe use of cabozantinib.

Source: U.S. Food and Drug Administration. sNDA Multi-disciplinary Review and Evaluation (NDA 208692) and Approval Package: CABOMETYX (cabozantinib) (19).

treatment with lenvatinib or sorafenib in randomized studies. Given the magnitude of improvement, PFS was considered an acceptable endpoint for this application. In addition, an inference based on OS may have been influenced by the high degree of cross-over. While OS was considered a descriptive endpoint, there did not appear to be a detriment to survival in the treatment arm.

FDA also considered the impact of early censoring on the efficacy results. Nine percent (9%) of patients in each arm did not have a postbaseline tumor assessment. Given that the percentage of patients affected in each arm was similar, any bias due to early censoring, is expected to be minimal as it was evenly distributed across study arms. FDA also considered whether the rate of dose reductions influenced the efficacy results. Fifty-six percent (56%) of patients in the cabozantinib arm required a dose reduction due to an adverse event. Overall, exposure–response analyses indicated there was no relationship between exposure and efficacy (PFS). In an exploratory analysis, patients with dose reductions appeared to have improved PFS compared with those without dose reductions; however, this analysis is confounded by early discontinuation of study treatment in patients who progressed early and thus did not have time to experience dose reduction due to an adverse event.

Finally, FDA considered the risk of hypocalcemia significant enough to add it as a warning in product labeling. Events are modifiable with appropriate monitoring and supplementation. All-grade TEAEs of hypocalcemia occurred in 23% of patients in the cabozantinib arm of COSMIC-311 (including 7% of patients with grade 3 or four events), compared with 2% in the control arm and 6% overall in the pooled studies of cabozantinib. While hypocalcemia is a known complication of thyroidectomy, 95% of patients had normal corrected calcium values at baseline. Nine percent (9%) of patients with normal or grade 1 decreased corrected calcium at baseline worsened to grade 3 or 4 during study treatment. Seven patients (5.6%) required dose modifications for TEAEs of hypocalcemia; the duration of interruption ranged from 3 to 84 days; 3 patients had dose reductions and all events resolved. Hypocalcemia is included as a warning for other TKIs, including lenvatinib.

Conclusion

This approval of cabozantinib represents a new treatment option and addresses an unmet medical need for patients with refractory DTC (**Table 2**). This is the first approval for patients with RAI-refractory locally advanced or metastatic DTC who have progressed following prior therapy and the first approval in pediatric patients with DTC. The benefit:risk profile for this indication is favorable, with the results of COSMIC-311 providing substantial evidence of effectiveness of cabozantinib for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are RAI-refractory or ineligible. The magnitude of the observed treatment effect on PFS is statistically robust and clinically meaningful.

Authors' Disclosures

No disclosures were reported.

Disclaimer

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