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September 21, 2021
Submission to National Comprehensive Cancer Network Panel: Thyroid Cancer

Clinical Evidence in Support of Cabozantinib Tablets for Differentiated Thyroid Cancer

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On behalf of Exelixis, we respectfully request the National Comprehensive Cancer Network® (NCCN) Guidelines Panel for Thyroid Cancer review the following data as it considers potential changes to the guidelines related specifically to the management of patients with differentiated thyroid cancer (DTC) including papillary, follicular, and Hürthle cell carcinoma with progressive and/or symptomatic disease.

Specific Changes:
The current version of the NCCN Thyroid Carcinoma Guidelines includes cabozantinib as a Category 2A recommendation for patients with DTC including papillary, follicular, and Hürthle cell carcinoma with progressive and/or symptomatic disease if clinical trials are not available or appropriate. Exelixis requests consideration of a *Category 1, Preferred Regimen* recommendation for cabozantinib tablets in these patients who progress after prior VEGFR-targeted therapy. This recommendation would apply to patients with locally recurrent, advanced, and/or metastatic disease not amenable to radioiodine (RAI) therapy *(footnote hh on page Pap-9, footnote ee on page Foll-8, and footnote ff on page Hürt-8, in the Guidelines).*

FDA Clearance:
CABOMETYX® (cabozantinib tablets) is approved by the US Food and Drug Administration (FDA) as a treatment for:[1]

- Patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy (April 2016)
- Patients with advanced RCC (December 2017)
- Patients with hepatocellular carcinoma who have been previously treated with sorafenib (January 2019)
- Patients with advanced RCC, as a first-line treatment in combination with nivolumab (January 2021)
- Adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine (RAI)-refractory or ineligible (September 2021)

Rationale:
CABOMETYX is now FDA-approved in adult and pediatric patients ≥12 years old with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are RAI-refractory or ineligible.[1] Enclosed for your review are the COSMIC-311 publication and supplement as well as the current CABOMETYX package insert.

Clinical Evidence:

COSMIC-311 Trial
Study Design
COSMIC-311 is a Phase 3 randomized, double-blind study (NCT03690388) that evaluated the efficacy and safety of CABOMETYX vs. placebo in patients with RAI-refractory DTC who had progressed during

or after prior VEGFR-targeted therapy.[1] A total of 187 patients were enrolled and randomized 2:1 to receive CABOMETYX tablets (n=125) 60 mg orally daily or placebo (n=62) orally daily. Patients were stratified by prior lenvatinib (yes/no) and age (≤65 vs. >65 years old); those who received placebo were able to crossover to CABOMETYX treatment at the time of Blinded Independent Radiology Committee (BIRC)-confirmed progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Treatment was given until progression or unacceptable toxicity.[1] Tumor assessments were performed every 8 weeks for 12 months, and then every 12 weeks thereafter per RECIST v.1.1. Key eligibility criteria included patients ≥16 years old who had locally advanced or metastatic DTC that was RAI-refractory or ineligible, radiographic progression during or after treatment with up to 2 prior VEGFR TKIs (prior TKI must have included either lenvatinib or sorafenib), Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, adequate organ function, and serum thyroid stimulating hormone (TSH) <0.5 mIU/L. Key exclusion criteria included previous treatment with selective BRAF inhibitors, presence of untreated brain metastases, and uncontrolled, significant intercurrent illness.[4]

The multiple primary efficacy outcome measures were PFS in the ITT population, and overall response rate (ORR) in the first 100 randomized patients at 6 months, as assessed by BIRC per RECIST 1.1.[1] Tumor assessments were conducted every 8 weeks. Overall survival was a descriptive outcome measure and safety was also assessed. [4] The primary analysis of PFS included 187 randomized patients. An updated analysis of PFS was performed and included 258 randomized patients.[1]

Baseline Characteristics

The primary and updated analyses included 187 and 258 randomized patients, respectively. Baseline characteristics for the 258 randomized patients were as follows: median age was 65 years (range 31 to 85 years), 53% were female, 70% were White, 19% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.[1] Baseline ECOG performance status was 0 (46%) or 1 (54%) and 93% of patients had metastatic disease.

Efficacy

The trial demonstrated a statistically significant improvement in PFS (p<0.0001). The overall response rate was higher with CABOMETYX; however, the p-value of 0.0281 did not meet the prespecified significance level. At the time of interim analysis, median OS was not reached in either treatment arm (HR=0.54 [95% CI: 0.27-1.11]).[2] In the updated analysis, median OS for cabozantinib was 19.4 months [95% CI:(15.9-19.4)] vs. not estimable (NE), (NE-NE) for placebo [HR=0.76 (95% CI: 0.45-1.31)].[4]

Table 1 shows PFS and ORR, both by BIRC, for the primary and updated analyses.[1]

Table 1. COSMIC-311 Efficacy Results

	Primary Analysis		Updated Analysis[1]	
	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)
Hazard Ratio (95% CI)[2]	0.22 (0.14-0.35)		0.22 (0.15-0.31)	
p-value[3]	< 0.0001			
Overall Response Rate (95% CI)				
Overall Response, % (95% CI) [4, 5]	15% (7%-26%)	0% (0.0%-11%)	18% (10%-29%)	0% (0.0%-11%)
p-value[6]	0.0281			

[1] No formal statistical testing was conducted at the time of the updated analysis

	Primary Analysis		Updated Analysis[1]	
	CABOMETYX (n=125)	Placebo (n=62)	CABOMETYX (n=170)	Placebo (n=88)

[2] Estimated using the Cox proportional-hazard model
[3] Log-rank test stratified by receipt of prior lenvatinib (yes vs no) and age (≤65 years vs >65 years)
[4] All responses were partial responses
[5] The analysis population overall response rate was the first 100 randomized patients (67 in the CABOMETYX arm, and 33 in the placebo arm)
[6] Fisher's exact test compared to an alpha boundary of 0.01
Abbreviations: CI=confidence interval; NR=not reached; NE=not evaluable

Safety

The safety population in COSMIC-311 consisted of 125 patients treated with CABOMETYX and 62 patients treated with placebo.[1] At the time of primary efficacy analysis the median duration of treatment was 4.4 months (range: 0.0-15.7) in the CABOMETYX arm and 2.3 months (range: 0.3-11.6) for patients receiving placebo.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPE, fatigue, and hypertension, and stomatitis.[1] Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included diarrhea, pleural effusion, pulmonary embolism and dyspnea. Fatal adverse reactions occurred in 1.6% of patients in the CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%).

The median average daily dose was 42.0 mg for CABOMETYX.[1] The dose was reduced in 56% of patients receiving CABOMETYX; 22% of patients required a second dose reduction. The most frequent adverse reactions (≥5%) leading to dose reduction of CABOMETYX were PPE, diarrhea, fatigue, proteinuria, and decreased appetite. Dose interruptions occurred in 72% of patients receiving CABOMETYX. Adverse reactions requiring dosage interruption in ≥5% of patients were PPE, diarrhea, dyspnea, hypertension, decreased appetite and proteinuria. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 5% of patients.

Table 2 provides a summary of adverse reactions reported in ≥5% of CABOMETYX-treated patients, and Table 3 provides a summary of laboratory abnormalities reported in ≥10% of CABOMETYX-treated patients from the primary analysis in COSMIC-311.[1]

Table 2. COSMIC-311 Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients[1]

Adverse Reaction	CABOMETYX (n=125)		Placebo (n=62)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	% of Patients			
Gastrointestinal				
Diarrhea	51	7	3	0
Nausea	24	3	2	0
Vomiting	14	1	8	0
Stomatitis[3]	26	5	3	0
Dry mouth	10	1	2	0
General				
Fatigue[4]	42	10	23	0
Metabolism and Nutrition				
Decreased appetite	23	3	16	0
Skin and Subcutaneous Tissue				

Adverse Reaction	CABOMETYX (n=125)		Placebo (n=62)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
Palmar-planter erythrodysesthesia	46	10	0	0
Vascular				
Hypertension[5]	30	10	5	3
Investigations				
Weight decreased	18	1	5	0
Nervous System				
Dysgeusia	10	0	0	0
Headache	10	2	2	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	10	0	2	0
Pulmonary embolism	5	2	0	0
Renal and Urinary				
Proteinuria	15	1	3	0

[1] Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)
[2] NCI CTCAE Version 5.0
[3] Includes the following terms: mucosal inflammation, stomatitis
[4] Includes the following terms: fatigue, asthenia
[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

Table 3. COSMIC-311 Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients[1]

Laboratory Abnormality	CABOMETYX (n=125)		Placebo (n=62)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	% of Patients			
Chemistry				
LDH increased[2]	90	10	32	3
AST increased	77	1	18	0
ALT increased	66	2	11	0
Hypocalcemia	36	9	10	2
ALP increased	34	0	15	0
GGT increased	26	2	21	2
Hypomagnesemia	25	2	5	0
Hypoalbuminemia	19	1	7	0
Hypokalemia	18	1	3	0
Hyponatremia	15	0	10	2
Hyperbilirubinemia	12	0	5	0
Hematology				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0

[1] Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)
[2] Sponsor-defined grades for LDH were as follows: Grade 1 (>ULN to ≤2 × ULN), Grade 2 (>2 × ULN to ≤3 × ULN), Grade 3 (>3 × ULN).
Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; LDH=blood lactate dehydrogenase.

Updated Analysis

Efficacy results from the updated analysis are included in the CABOMETYX Prescribing Information and in Table 1 above.[1] Safety information for patients included in the updated analysis, while not provided in the Prescribing Information, were recently presented at the virtual 2021 European Society for Medical Oncology Congress, along with a subgroup analysis of PFS by BIRC according to prior sorafenib and/or lenvatinib use.

Safety

The safety population in the updated analysis consisted of 170 patients treated with cabozantinib and 88 patients treated with placebo.[4] A total of 67% of patients in the cabozantinib arm had a dose reduction due to an AE and 8.8% of patients discontinued treatment due to AEs (unrelated to DTC). The most common treatment-emergent AEs of any Grade reported in ≥25% of patients included diarrhea (62%), hand-foot skin reaction (47%), hypertension (32%), decreased appetite (31%), fatigue (29%), nausea (28%), increased alanine aminotransferase (25%), increased aspartate aminotransferase (25%), and hypocalcemia (25%).

Subgroup Analysis

A subgroup analysis of PFS by BIRC according to prior sorafenib and/or lenvatinib use was conducted. Cabozantinib improved PFS vs. placebo irrespective of prior exposure as shown in Table 4 below.[4]

Table 4. Progression-Free Survival by BIRC in Prior Therapy Subgroups[4]

Median 95% CI, months	**Cabozantinib**	**Placebo**
Prior Sorafenib/No Lenvatinib	**(n=63)**	**(n=33)**
	16.6 (11.0-NE)	3.2 (1.9-5.5)
	HR=0.13 (95% CI: 0.06-0.26)	
Prior Lenvatinib/No Sorafenib	**(n=68)**	**(n=34)**
	5.8 (5.1-9.3)	1.9 (1.7-3.7)
	HR=0.28 (95% CI: 0.16–0.48)	
Prior Lenvatinib and Sorafenib	**(n=39)**	**(n=21)**
	7.6 (3.8-13.8)	1.9 (1.8-3.8)
	HR=0.27 (95% CI: 0.13-0.54)	

Abbreviations: BIRC=blinded independent radiology committee; CI=confidence interval; HR=hazard ratio; NE=not estimable.

Should you have any questions, please contact us via email or phone using the contact information provided at the top of this letter.

References:

1. CABOMETYX®(cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. September 2021.
2. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(8):1126-1138.
3. Supplement to Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol.2021;S1470-2045(21)00332-6.
4. Capdevila J, Robinson B, Sherman SI, et al. Cabozantinib vs. placebo in patients with radioiodine-refractory differentiated thyroid cancer who have progressed after prior VEGFR-targeted therapy: updated results from the Phase 3 COSMIC-311 trial. Presented at the Virtual ESMO 2021 Congress; Sept 16-21.

Enclosures:

1. CABOMETYX® (cabozantinib tablets) Prescribing Information
2. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(8):1126-1138.
3. Supplement to Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol.2021;S1470-2045(21)00332-6.