NOW APPROVED[1]

Exelixis, Inc., is pleased to announce an important update regarding the treatment of differentiated thyroid cancer (DTC). CABOMETYX® (cabozantinib) is now FDA approved 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 radioactive iodine-refractory or ineligible.[1]

Meaningful results led to early unblinding in the COSMIC-311 trial.[2] COSMIC-311 was a phase 3, multicenter, randomized (2:1), double-blind, placebo-controlled trial in 258 RAI-R patients with DTC who had progressed after prior systemic treatment. Patients were treated until progression, and eligible placebo patients were allowed to cross over to receive open-label CABOMETYX after BIRC-confirmed progressive disease per RECIST 1.1. The multiple primary efficacy outcome measures were progression-free survival (PFS) in the ITT population (n=187), and overall response rate (ORR) in the first 100 randomized patients. This new approval is supported by clinical data from the COSMIC-311 trial, which showed that CABOMETYX delivered a significant benefit in the primary PFS analysis vs placebo (HR=0.22; $P<0.0001$).[1,3]

For more information, see enclosed additional details from the COSMIC-311 trial.

BIRC=blinded independent review committee; CI=confidence interval; FDA=US Food and Drug Administration; HR=hazard ratio; ITT=intent to treat; RAI-R=radioactive iodine-refractory; RECIST=Response Evaluation Criteria in Solid Tumors; VEGFR=vascular endothelial growth factor receptor.

INDICATION

CABOMETYX is indicated 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-refractory or ineligible.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Please see additional Important Safety Information throughout and full Prescribing Information.

CABOMETYX®
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

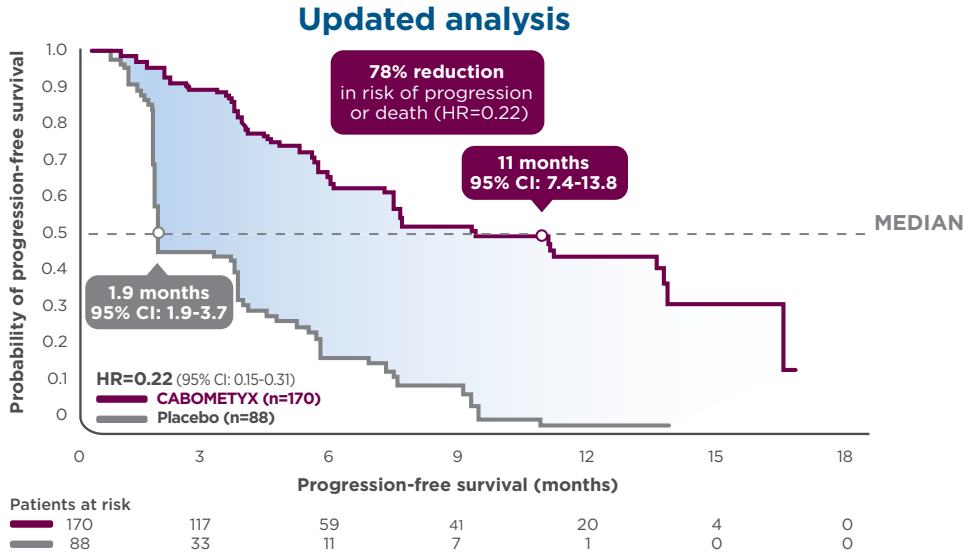
EXELIXIS®

CABOMETYX delivered a significant benefit in the primary PFS analysis[1]

78% reduction in risk of progression or death in both primary and updated analyses

- **Median PFS was not reached** in the primary analysis (n=125, 95% CI: 5.7-NE) vs PFS of 1.9 months with placebo (n=62, 95% CI: 1.8-3.6); HR=0.22, *P*<0.0001

Early and sustained separation demonstrated at updated analysis—with a median PFS of 11 months



No formal statistical testing was conducted at the time of the updated analysis.

NE=not estimable.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

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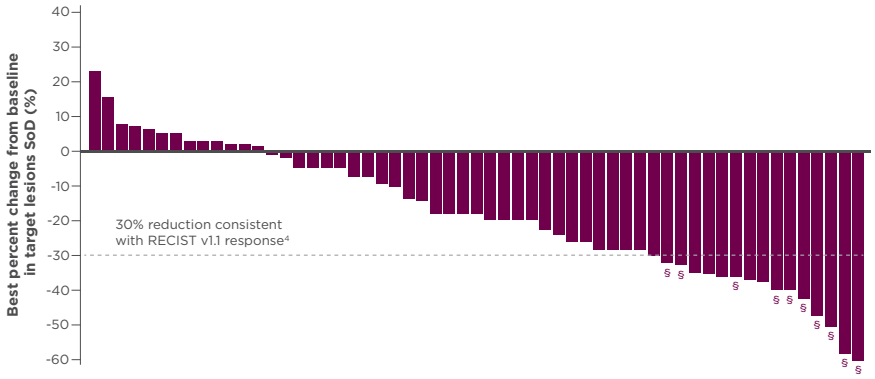
Tumor response observed at the OITT analysis[1,3]

- In the COSMIC-311 trial, the overall response rate (ORR) did not reach a prespecified endpoint for statistical significance (critical *P* value=0.01). Data below cover tumor response information collected, inclusive of ORR

	CABOMETYX	Placebo
ORR, % (95% CI)*	15 (7-26)	0 (0.0-11)
Stable disease, % (n/N)†	69 (46/67)	42 (14/33)
Disease control rate, % (n/N)‡	84 (56/67)	42 (14/33)

*P=0.0281.[1]
†Stable disease is defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD.[4]
‡Disease control rate is defined as the percentage of patients with a complete response, partial response, or stable disease, as measured by RECIST 1.[3]

76% of patients experienced tumor shrinkage with CABOMETYX at the OITT analysis[3,4]



Each vertical line represents 1 patient. The plot represents the best percentage change in tumor size from baseline in the evaluable patient population, as determined by the investigators, per RECIST 1.1.[3]

- Among patients with baseline and postbaseline target lesion assessment, 44 (76%) of 58 patients with ≥1 postbaseline target lesion assessment in the CABOMETYX arm had a reduction in target lesions compared with 9 (29%) of 31 patients in the placebo arm[3]

‡Data from OITT analysis of evaluable patients.[3]

§Confirmed partial response.[3]

OITT=objective response rate intent to treat; PD=progressive disease; SoD=sum of diameters.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

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Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc., 2021. **2.** Exelixis press release. December 21, 2020. https://ir.exelixis.com/news-releases/news-release-details/exelixis-announces cabozantinib-significantly-improved. **3.** 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;22(8):1126-1138. doi.org/10.1016/S1470-2045(21)00332-6. **4.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

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