



## Exelixis' Partner Ipsen Receives Positive CHMP Opinion for CABOMETYX® (cabozantinib) for Patients with Previously Treated Radioactive Iodine-Refractory Differentiated Thyroid Cancer

March 25, 2022

*– CHMP recommendation follows September 2021 U.S. FDA approval of CABOMETYX in this setting –*

ALAMEDA, Calif.--(BUSINESS WIRE)--Mar. 25, 2022-- [Exelixis, Inc.](#) (Nasdaq: EXEL) today announced that its partner Ipsen received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), for CABOMETYX® (cabozantinib) as a monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy. The European Commission, which has the authority to approve medicines for the European Union, will now review the CHMP recommendation, and a final decision on the application is expected in the coming months.

"The CHMP's recommendation is an important milestone for our partner Ipsen in their efforts to bring CABOMETYX to patients in Europe with radioactive iodine-refractory differentiated thyroid cancer that has progressed following prior systemic therapy," said Vicki L. Goodman, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer at Exelixis. "These patients have a poor prognosis, and there are currently no standard treatment options approved in Europe following progression on anti-VEGFR therapy. We look forward to hearing the European Commission's decision in the coming months, with the hope that a new therapy will soon be available to these patients and their caregivers."

The CHMP recommendation is based on results from COSMIC-311, the phase 3 pivotal trial that demonstrated significant improvement in progression-free survival (PFS) with CABOMETYX versus placebo in patients with RAI-refractory DTC who progressed after up to two prior VEGFR-targeted therapies. COSMIC-311 was the basis for the U.S. Food and Drug Administration (FDA) approval of CABOMETYX in September 2021 for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following VEGFR-targeted therapy and who are RAI-refractory or ineligible. CABOMETYX is currently approved in the European Union as a monotherapy for the treatment of advanced renal cell carcinoma (RCC) in adults who have received prior VEGF-targeted therapy, for previously untreated intermediate- or poor-risk advanced RCC and for hepatocellular carcinoma (HCC) in adults who have been previously treated with sorafenib. CABOMETYX in combination with OPDIVO® (nivolumab) is approved as a first-line treatment for advanced RCC.

### **About COSMIC-311**

COSMIC-311 was a multicenter, randomized, double-blind, placebo-controlled phase 3 pivotal trial that enrolled 258 patients at 164 sites globally. Patients were randomized in a 2:1 ratio to receive either CABOMETYX 60 mg or placebo once daily. The primary endpoints were PFS and objective response rate. Exelixis is sponsoring COSMIC-311, and Ipsen is co-funding the trial. More information about this trial is available at [ClinicalTrials.gov](#).

### **About DTC**

In 2020, over 580,000 new cases of thyroid cancer were diagnosed worldwide.<sup>1</sup> Approximately 44,000 new cases of thyroid cancer will be diagnosed in the U.S. in 2022. Nearly three out of four of these cases will be in women, and the disease is more commonly diagnosed at a younger age compared with most other adult cancers. Cancerous thyroid tumors include differentiated, medullary and anaplastic forms DTC makes up about 90% of cases and includes papillary, follicular and Hürthle cell cancer.<sup>2</sup> DTC is typically treated with surgery followed by ablation of the remaining thyroid with RAI, but approximately 5% to 15% of cases are resistant to RAI treatment.<sup>3,4</sup> For these patients, life expectancy is only three to six years from the time metastatic lesions are detected.<sup>5,6,7</sup>

### **About CABOMETYX® (cabozantinib)**

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC; for the treatment of patients with HCC who have been previously treated with sorafenib; for patients with advanced RCC as a first-line treatment in combination with nivolumab; and for 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. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the U.S. and Japan. Under the terms of the license agreement with Ipsen, Exelixis is eligible to receive development, regulatory and sales milestone payments from Ipsen and further receive royalties on net sales of cabozantinib by Ipsen outside of the U.S. and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited for the commercialization and further clinical development of cabozantinib for all future indications in Japan. Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the U.S.

## **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.

**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.

**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.

**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  $\leq$  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.

**Hepatotoxicity:** CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST  $>3$  times ULN (Grade  $\geq 2$ ) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade  $\geq 2$  increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade  $\geq 2$  increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

**Adrenal Insufficiency:** CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

**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  $\leq$  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.

**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 ( $\geq 20\%$ ) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

## 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.

**Please see accompanying full Prescribing Information** <https://www.cabometryx.com/downloads/CABOMETRYXUSPI.pdf>.

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

## About Exelixis

Founded in 1994, Exelixis, Inc. (Nasdaq: EXEL) is a commercially successful, oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Following early work in model system genetics, we established a broad drug discovery and development platform that has served as the foundation for our continued efforts to bring new cancer therapies to patients in need. Our discovery efforts have resulted in four commercially available products, CABOMETYX<sup>®</sup> (cabozantinib), COMETRIQ<sup>®</sup> (cabozantinib), COTELLIC<sup>®</sup> (cobimetinib) and MINNEBRO<sup>®</sup> (esaxerenone), and we have entered into partnerships with leading pharmaceutical companies to bring these important medicines to patients worldwide. Supported by revenues from our marketed products and collaborations, we are committed to prudently reinvesting in our business to maximize the potential of our pipeline. We are supplementing our existing therapeutic assets with targeted business development activities and internal drug discovery — all to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. Exelixis is a member of the Standard & Poor's (S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. For more information about Exelixis, please visit [www.exelixis.com](http://www.exelixis.com), follow @ExelixisInc on Twitter or like [Exelixis, Inc.](https://www.facebook.com/ExelixisInc) on Facebook.

## Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of CABOMETYX as a monotherapy for patients with RAI-refractory DTC that has progressed following prior systemic therapy; the regulatory review process in the European Union, including the expected timing for a final decision from the European Commission; and Exelixis' plans to reinvest in its business to maximize the potential of the company's pipeline, including through targeted business development activities and internal drug discovery. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and are based upon Exelixis' current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: complexities and the unpredictability of the regulatory review and approval processes in the European Union and elsewhere, including the risk that the European Commission may not approve CABOMETYX as a monotherapy for patients with previously treated RAI-refractory DTC in a timely fashion, if at all; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; Exelixis' dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for partnered compounds in new indications and their adherence to their obligations under relevant collaboration agreements; the continuing COVID-19 pandemic and its impact on Exelixis' product development and commercial activities; Exelixis' ability to protect its intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of CABOMETYX; changes in economic and business conditions; and other factors affecting Exelixis and its partners to obtain regulatory approval for cabozantinib in new indications discussed under the caption "Risk Factors" in Exelixis' Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 18, 2022, and in Exelixis' future filings with the SEC. All forward-looking statements in this press release are based on information available to Exelixis as of the date of this press release, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein, except as required by law.

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<sup>1</sup> Sung, H et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal For Clinicians. doi: 10.3322/caac.21660.

<sup>2</sup> American Cancer Society. About Thyroid Cancer. Available at: <https://www.cancer.org/cancer/thyroid-cancer/about.html>. Accessed March 2022.

<sup>3</sup> UpToDate. Differentiated thyroid cancer: Overview of management. Available at: <https://www.uptodate.com/contents/differentiated-thyroid-cancer>

[overview-of-management](#). Accessed March 2022.

<sup>4</sup> Worden F. 2014. Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. *Ther Adv Med Oncol*. 6:267–279.

<sup>5</sup> Xing M, Haugen BR, Schlumberger M. 2013. Progress in molecular-based management of differentiated thyroid cancer. *Lancet*. 381:1058–1069.

<sup>6</sup> Pacini F, et al. 2012. Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. *Expert Rev Endocrinol Metab*. 7:541–554.

<sup>7</sup> Durante C, et al. 2006. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab*. 91:2892–2899.

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