



## Exelixis Announces Positive Results from Phase 3 CABINET Pivotal Trial Evaluating Cabozantinib in Advanced Pancreatic and Extra-Pancreatic Neuroendocrine Tumors

August 24, 2023

*– CABINET trial will be unblinded and stopped early due to a dramatic improvement in efficacy per a unanimous recommendation by The Alliance for Clinical Trials in Oncology independent Data and Safety Monitoring Board –*

*– Based on positive results, findings will be discussed with the U.S. Food and Drug Administration –*

ALAMEDA, Calif.--(BUSINESS WIRE)--Aug. 24, 2023-- [Exelixis, Inc.](#) (Nasdaq: EXEL) today announced that the Alliance for Clinical Trials in Oncology independent Data and Safety Monitoring Board (DSMB) unanimously recommended to unblind and stop the phase 3 CABINET pivotal trial early due to a dramatic improvement in efficacy that was observed at an interim analysis. CABINET is evaluating cabozantinib (CABOMETYX<sup>®</sup>) compared with placebo in patients with either advanced pancreatic neuroendocrine tumors (pNET) or advanced extra-pancreatic neuroendocrine tumors (also referred to as carcinoid tumors) who experienced progression after prior systemic therapy. Cabozantinib substantially prolonged the time without disease progression or death in both of the trial's cohorts. CABINET is sponsored by the National Cancer Institute (NCI) and is led by The Alliance for Clinical Trials in Oncology. Detailed findings will be presented at an upcoming medical meeting and discussed with the U.S. Food and Drug Administration (FDA).

"As there is no standard of care for patients with advanced pancreatic or extra-pancreatic neuroendocrine tumors whose disease has progressed after prior therapy, we are pleased to see that cabozantinib improved outcomes for two additional patient populations living with advanced, difficult-to-treat cancers," said Will Berg, M.D., Senior Vice President, Medical Affairs, Exelixis. "We are grateful for the recommendation of the Data and Safety Monitoring Board to unblind the CABINET study early due to a dramatic improvement in efficacy and look forward to discussing these findings with the U.S. Food and Drug Administration."

The safety profile of cabozantinib observed in the trial was consistent with its known safety profile, and no new safety signals were identified.

"Patients with progressive neuroendocrine tumors have limited treatment options. At present, after progression on previous therapies, the treatment path is unclear, underscoring the need for additional options for this disease that is rising in incidence," said Jennifer Chan, M.D., M.P.H., study chair for the CABINET trial and Clinical Director of the Gastrointestinal Cancer Center and Director of the Program in Carcinoid and Neuroendocrine Tumors at Dana-Farber Cancer Institute. "These promising findings from the CABINET trial, in which cabozantinib showed an efficacy benefit for patients with pancreatic and extra-pancreatic neuroendocrine tumors, are welcome news and show the potential for cabozantinib to address important unmet needs for this community."

### About CABINET (A021602)

CABINET (Randomized, Double-Blinded Phase III Study of **C**abozantinib versus Placebo **I**n Patients with Advanced **N**euroendocrine **T**umors After Progression on Prior Therapy) is sponsored by the NCI, part of the National Institutes of Health, and is being led and conducted by the NCI-funded Alliance for Clinical Trials in Oncology with participation from the NCI-funded National Clinical Trials Network as part of Exelixis' collaboration with the NCI's Cancer Therapy Evaluation Program. CABINET is a multicenter, randomized, double-blinded, placebo-controlled phase 3 pivotal trial that enrolled a total of 290 patients in two separate cohorts (pNET, n=93; extra-pancreatic NET, n=197) in the U.S. Patients were randomized 2:1 into the cabozantinib or placebo arms of the study in each of the two cohorts. Patients must have had measurable disease per RECIST 1.1 criteria and must have experienced disease progression after at least one FDA-approved line of prior therapy other than somatostatin analogs. The primary endpoint was progression-free survival in each cohort. Upon confirmation of disease progression, patients were unblinded, and those receiving placebo were permitted to cross over to open-label therapy with cabozantinib. Secondary endpoints included overall survival, radiographic response rate and safety. More information about this trial is available at [ClinicalTrials.gov](#).

### About NET

NET refer to cancers that begin in the specialized cells of the body's neuroendocrine system. <sup>1</sup> These cells have traits of both hormone-producing endocrine cells and nerve cells. <sup>1</sup> In the U.S., more than 12,000 people are diagnosed with NET each year and approximately 171,000 people are living with the disease. <sup>2</sup> The number of people diagnosed with NET each year has been increasing. <sup>2</sup> NET are classified as functional or non-functional. <sup>1</sup> Functional NET release peptide hormones that can cause debilitating symptoms and necessitate treatment, while symptoms of non-functional NET are related primarily to tumor growth. <sup>1,3,4</sup> Most NET take years to develop and grow slowly, but some grow quickly. <sup>5</sup> NET can develop in any part of the body, but most commonly start in the gastrointestinal (GI) tract or in the lungs – these historically have been referred to as carcinoid tumors. <sup>5</sup> The five-year survival rates for advanced GI-NET and lung carcinoid tumors are 68% and 55%, respectively. <sup>6,7</sup> NET can also start in the pancreas. <sup>8</sup> While less common, these NET can be more aggressive and the five-year survival rate for advanced pNET is only 23%. <sup>8,9</sup> Surgery to remove the tumor and prevent it from spreading is the typical first approach to treatment for both carcinoid tumors and pNET. <sup>10</sup> For more advanced disease, options include somatostatin analogs, targeted therapy, peptide-receptor radionuclide therapy and chemotherapy. <sup>10</sup>

### About CABOMETYX<sup>®</sup> (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced renal cell carcinoma (RCC); for the treatment of patients with hepatocellular carcinoma (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 differentiated thyroid

cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-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 Pharma SAS exclusive rights for the commercialization and further clinical development of cabozantinib outside of the U.S. and Japan. In 2017, Exelixis granted exclusive rights to Takeda 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.

CABOMETYX is not indicated as a treatment for NET.

## 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

Exelixis is a globally ambitious oncology company innovating next-generation medicines and regimens at the forefront of cancer care. Powered by bi-coastal centers of discovery and development excellence, we are rapidly evolving our product portfolio to target an expanding range of tumor types and indications with our clinically differentiated pipeline of small molecules, antibody drug conjugates and other biotherapeutics. This comprehensive approach harnesses decades of robust investment in our science and partnerships to advance our investigational programs and extend the impact of our flagship commercial product, CABOMETYX<sup>®</sup> (cabozantinib). Exelixis is driven by a bold scientific pursuit to create transformational treatments that give more patients hope for the future. For information about the company and its mission to help cancer patients recover stronger and live longer, visit [www.exelixis.com](http://www.exelixis.com), follow [@ExelixisInc](https://twitter.com/ExelixisInc) on Twitter, like [Exelixis, Inc.](https://www.facebook.com/Exelixis.Inc) on Facebook and follow [Exelixis](https://www.linkedin.com/company/exelixis) on LinkedIn.

## Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of cabozantinib to reduce the risk of disease progression or death for patients with advanced pancreatic neuroendocrine tumors or advanced extra-pancreatic neuroendocrine tumors who experienced progression after prior systemic therapy; Exelixis' plans to discuss the trial data from CABINET with the U.S. Food and Drug Administration; and Exelixis' scientific pursuit to create transformational treatments that give more patients hope for the future. 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 U.S. and elsewhere; Exelixis' continuing compliance with applicable legal and regulatory requirements; Exelixis' dependence on its relationships with its cabozantinib commercial collaboration partners; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; 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 development programs discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 1, 2023 and Annual Report on Form 10-K filed with the SEC on February 7, 2023, 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.

*Exelixis, the Exelixis logo and CABOMETYX are registered U.S. trademarks of Exelixis.*

- <sup>1</sup> Neuroendocrine Tumors: Introduction. [Cancer.Net](https://www.cancer.net/cancer-types/neuroendocrine-tumors/introduction) website. Available at: <https://www.cancer.net/cancer-types/neuroendocrine-tumors/introduction>. Accessed August 2023.
- <sup>2</sup> Neuroendocrine Tumors: Statistics. [Cancer.Net](https://www.cancer.net/cancer-types/neuroendocrine-tumors/statistics) website. Available at: <https://www.cancer.net/cancer-types/neuroendocrine-tumors/statistics>. Accessed August 2023.
- <sup>3</sup> Pancreatic Neuroendocrine Tumors (Islet Cell Tumors) Treatment (PDQ®)—Patient Version. NCI website. Available at: <https://www.cancer.gov/types/pancreatic/patient/pnet-treatment-pdq>. Accessed August 2023.
- <sup>4</sup> Neuroendocrine Tumors: Types of Treatment. [Cancer.Net](https://www.cancer.net/cancer-types/neuroendocrine-tumors/types-treatment) website. Available at: <https://www.cancer.net/cancer-types/neuroendocrine-tumors/types-treatment>. Accessed August 2023.
- <sup>5</sup> Neuroendocrine Tumor of the Gastrointestinal Tract: Introduction. [Cancer.Net](https://www.cancer.net/cancer-types/neuroendocrine-tumor-gastrointestinal-tract/introduction) website. Available at: <https://www.cancer.net/cancer-types/neuroendocrine-tumor-gastrointestinal-tract/introduction>. Accessed August 2023.
- <sup>6</sup> Survival Rates for Gastrointestinal Carcinoid Tumors. ACS website. Available at: <https://www.cancer.org/cancer/types/gastrointestinal-carcinoid-tumor/detection-diagnosis-staging/survival-rates.html>. Accessed August 2023.
- <sup>7</sup> Survival Rates for Lung Carcinoid Tumors. ACS website. Available at: <https://www.cancer.org/cancer/types/lung-carcinoid-tumor/detection-diagnosis-staging/survival-rates.html>. Accessed August 2023.
- <sup>8</sup> Neuroendocrine Tumor of the Pancreas: Statistics. [Cancer.Net](https://www.cancer.net/cancer-types/neuroendocrine-tumor-pancreas/statistics) website. Available at: <https://www.cancer.net/cancer-types/neuroendocrine-tumor-pancreas/statistics>. Accessed August 2023.
- <sup>9</sup> Survival Rates for Pancreatic Neuroendocrine Tumor. ACS website. Available at: <https://www.cancer.org/cancer/types/pancreatic-neuroendocrine-tumor/detection-diagnosis-staging/survival-rates.html>. Accessed August 2023.
- <sup>10</sup> Neuroendocrine Tumor (NET). NCI website. Available at: <https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-endocrine-tumor/carcinoid-tumor>. Accessed August 2023.

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