



Exelixis' Partner Ipsen Receives European Commission Approval for CABOMETYX® (cabozantinib) in Combination with OPDIVO® (nivolumab) as First-Line Treatment for Patients with Advanced Renal Cell Carcinoma

March 31, 2021

– Approval based on CheckMate -9ER trial, in which CABOMETYX in combination with OPDIVO doubled progression-free survival and objective response rate while significantly improving overall survival versus sunitinib –

ALAMEDA, Calif.--(BUSINESS WIRE)--Mar. 31, 2021-- [Exelixis, Inc.](#) (Nasdaq: EXEL) today announced its partner Ipsen received approval from the European Commission (EC) for CABOMETYX® (cabozantinib) in combination with OPDIVO® (nivolumab) as a first-line treatment for advanced renal cell carcinoma (RCC). This approval allows for the marketing of CABOMETYX in combination with OPDIVO in this indication in all 27 member states of the European Union, Norway, Iceland and Liechtenstein.

"We are excited that CABOMETYX in combination with OPDIVO will now be available in Europe, where newly diagnosed kidney cancer patients are in need of additional options that have shown consistent superiority compared to sunitinib across all key efficacy endpoints of progression-free survival, objective response rate and overall survival with a low rate of treatment discontinuations due to side effects," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "We look forward to continuing our collaboration with Ipsen with the shared goal of improving treatment outcomes for people with cancer."

The EC approval is based on results of the phase 3 CheckMate -9ER pivotal trial, in which the combination regimen doubled progression-free survival (PFS) and objective response rate (ORR) while significantly improving overall survival (OS) compared with sunitinib. The combination regimen was generally well tolerated and reflected the known safety profiles of the tyrosine kinase inhibitor and immunotherapy components in previously untreated advanced RCC.

CABOMETYX is also approved in the European Union as a monotherapy for the treatment of advanced 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. The EC approval of CABOMETYX in combination with OPDIVO follows the U.S. Food and Drug Administration's (FDA) approval of the combination regimen for the first-line treatment of advanced RCC in January 2021.

About the CheckMate -9ER Trial

CheckMate -9ER is an open-label, randomized (1:1), multi-national phase 3 trial evaluating patients with previously untreated advanced or metastatic renal cell carcinoma with a clear cell component. A total of 651 patients (22% favorable risk, 58% intermediate risk, 20% poor risk; 25% PD-L1 $\geq 1\%$) were randomized to CABOMETYX at an oral dose of 40 mg once-daily in combination with OPDIVO administered intravenously at a dose of 240 mg every 2 weeks (n = 323) versus sunitinib administered orally at a dose of 50 mg once daily for 4 weeks, followed by 2 weeks off (6-week cycle) (n = 328). The primary efficacy analysis compares the doublet combination regimen of CABOMETYX and OPDIVO versus sunitinib in all randomized patients. Secondary endpoints include OS and ORR. The trial is sponsored by Bristol Myers Squibb and Ono Pharmaceutical Co. and co-funded by Exelixis, Ipsen and Takeda.

About RCC

The American Cancer Society's 2021 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.¹ Clear cell RCC is the most common form of kidney cancer in adults.² If detected in its early stages, the five-year survival rate for RCC is high; for patients with advanced or late-stage metastatic RCC, however, the five-year survival rate is only 13%.¹ Approximately 32,000 patients in the U.S. and 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2021.³

About 70% of RCC cases are known as "clear cell" carcinomas, based on histology.⁴ The majority of clear cell RCC tumors have below-normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.^{5,6} These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.^{7,8,9,10} MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.^{6,7}

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 hepatocellular carcinoma who have been previously treated with sorafenib; and for patients with advanced RCC as a first-line treatment in combination with OPDIVO. 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 United States 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 United States.

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 and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. 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 36% (17% 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. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% 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 ≥ 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 ≥ 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 ≥ 2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

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 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 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. 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.

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 is observed. 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.

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, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

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://cabometyx.com/downloads/CABOMETYXUSPI.pdf>.

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.

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[®] (cabozantinib), COMETRIQ[®] (cabozantinib), COTELLIC[®] (cobimetinib) and MINNEBRO[®] (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. In November 2020, the company was named to *Fortune's* 100 Fastest-Growing Companies list for the first time, ranking 17th overall and the third-highest biopharmaceutical company. For more information about Exelixis, please visit www.exelixis.com, follow [@ExelixisInc](https://twitter.com/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 and commercial potential of CABOMETYX in combination with OPDIVO as a treatment for kidney cancer patients in Europe; Exelixis' and Ipsen's shared goal of improving treatment outcomes for people with cancer; 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: the degree of market acceptance that the combination of CABOMETYX and OPDIVO may achieve in the European Union; Exelixis' dependence on its relationship with Ipsen, including Ipsen's investment in the resources necessary to successfully commercialize CABOMETYX in the European Union; Exelixis' and Ipsen's ability to maintain and scale adequate sales, marketing, market access and product distribution capabilities for CABOMETYX or to enter into and maintain agreements with third parties to do so; Exelixis' and Ipsen's continuing compliance with applicable legal and regulatory requirements; the continuing COVID-19 pandemic and its impact on Exelixis' and Ipsen's commercial activities; Exelixis' ability to protect its intellectual property rights; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; 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 commercial programs and partnerships discussed under the caption "Risk Factors" in Exelixis' Annual Report on Form 10-K submitted to the Securities and Exchange Commission (SEC) on February 10, 2021, 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, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks. MINNEBRO is a Japanese trademark.

OPDIVO[®] is a registered trademark of Bristol-Myers Squibb Company.

¹ American Cancer Society: Cancer Facts & Figures 2021. Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf>. Accessed March 2021.

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³Decision Resources Report: Renal Cell Carcinoma. October 2014 (internal data on file).

⁴American Cancer Society: What is Kidney Cancer? Available at: <https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html>. Accessed March 2021.

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Source: Exelixis, Inc.