Exelixis Announces U.S. FDA Approval of CABOMETYX® (cabozantinib) in Combination with OPDIVO® (nivolumab) as a First-Line Treatment for Patients with Advanced Renal Cell Carcinoma

January 22, 2021

– FDA approval based on CheckMate -9ER trial, in which the combination of CABOMETYX and OPDIVO significantly improved overall survival while doubling progression-free survival and objective response rate versus sunitinib as a first-line treatment for patients with advanced RCC –

– Exelixis prepared to fully support expanded indication immediately –

– Application approved prior to Prescription Drug User Fee Act action date of February 20, 2021 and reviewed under the Real-Time Oncology Review pilot program –

ALAMEDA, Calif.--(BUSINESS WIRE)--Jan. 22, 2021-- Exelixis, Inc. (NASDAQ: EXEL) today announced that the U.S. Food and Drug Administration (FDA) approved CABOMETYX® (cabozantinib) for patients with advanced renal cell carcinoma (RCC) as a first-line treatment in combination with OPDIVO® (nivolumab). RCC is the most common form of kidney cancer, which is among the 10 most frequently diagnosed cancers in the U.S. annually.[1]

“This combination of cabozantinib and nivolumab significantly improved key efficacy measures compared to sunitinib – progression-free survival, overall survival and objective response rate – while showing a low rate of treatment discontinuations due to side effects. The therapeutic benefit demonstrated in CheckMate -9ER and quality of life measures explored emphasize the role of this combination for patients with advanced kidney cancer,” said Dr. Toni Choueiri, Director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute and the Jerome and Nancy Kohlberg Professor of Medicine at Harvard Medical School. “With this important FDA approval, the combination is poised to become a standard in newly diagnosed metastatic kidney cancer.”

The approval is based on results from CheckMate -9ER, a phase 3 pivotal trial evaluating the combination of CABOMETYX and OPDIVO compared with sunitinib in previously untreated advanced or metastatic RCC. These results were presented during the European Society of Medical Oncology Virtual Congress 2020 in September. The FDA reviewed the application for CABOMETYX and OPDIVO under the Real-Time Oncology Review (RTOR) pilot program and Fast Track designation. The RTOR pilot program, which allows an applicant to pre-submit components of the application to allow the FDA to review clinical trial data before the complete filing is submitted, aims to explore a more efficient review process to ensure safe and effective treatments are available to patients sooner.

“As the only combination treatment regimen to double median progression-free survival and objective response rate compared with sunitinib while also significantly improving overall survival, we are excited that CABOMETYX in combination with OPDIVO is now available for the first-line treatment of patients with advanced kidney cancer,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. “This approval is a meaningful milestone for this patient community and speaks to the broad potential of CABOMETYX as we continue to generate important clinical trial results supporting its use in combination with immune checkpoint inhibitors to benefit patients with other difficult-to-treat cancers. We would like to thank the clinical trial participants, the physicians and their staff who participated in the CheckMate -9ER trial and to acknowledge the team at the FDA for their collaboration during the review of our application.”

In CheckMate -9ER, the combination regimen significantly improved overall survival (OS) compared with sunitinib (HR= 0.60, 98.89% CI 0.40-0.89; p=0.001). Median OS has not yet been reached in either treatment arm. Median progression-free survival (PFS) was doubled at 16.6 months for CABOMETYX in combination with OPDIVO compared with 8.3 months for sunitinib (HR 0.51, 95% CI 0.41-0.64; p<0.0001). Objective response rate (ORR) was also doubled: 56% with CABOMETYX in combination with OPDIVO and 27% with sunitinib (p<0.0001). Consistent results for PFS were observed across subgroups of International Metastatic RCC Database Consortium risk status and PD-L1 tumor expression with CABOMETYX in combination with OPDIVO.

CABOMETYX in combination with OPDIVO was generally well tolerated and reflected the known safety profiles of the tyrosine kinase inhibitor and immunotherapy components in previously untreated advanced RCC. The most common adverse reactions reported in at least 20% of patients treated with CABOMETYX in combination with OPDIVO were diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysesthesia, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough and upper respiratory tract infection. The discontinuation rate due to all causality adverse events in the CABOMETYX in combination with OPDIVO arm was 20% for either CABOMETYX or OPDIVO (8% for CABOMETYX only, 7% for OPDIVO only and 6% for both CABOMETYX and OPDIVO due to the same adverse event at the same time).

“While significant progress has been made in the treatment landscape for advanced kidney cancer over the last several years, patients still need more therapeutic options to treat this disease as we search for a possible cure,” said Bryan Lewis, President and Co-founder of KidneyCAN. “As patients are living longer with advanced kidney cancer, focusing on the safety and effectiveness of new treatments has become even more important. The findings for the combination of CABOMETYX and OPDIVO in the CheckMate -9ER trial make the FDA approval of this combination a notable development for the patient community.”

Exelixis’ partner Ipsen Pharma SAS (Ipsen), which has exclusive rights to commercialize and develop CABOMETYX outside of the U.S. and Japan, and Bristol-Myers Squibb Company (BMS) each submitted type II variation applications for CABOMETYX in combination with OPDIVO to the European Medicines Agency (EMA). On September 12, 2020, the EMA validated the type II variations, confirming the submissions are complete and beginning the EMA’s centralized review process. On October 27, 2020 Takeda Pharmaceutical Company Limited (Takeda), Exelixis’ partner responsible for the clinical development and commercialization of CABOMETYX in Japan, and Ono Pharmaceuticals Co., Ltd., BMS’ development and

commercialization partner in Japan, submitted a supplemental application to the Japanese Ministry of Health, Labour and Welfare for manufacturing and marketing approval of CABOMETYX in combination with OPDIVO for the treatment of patients with unresectable, advanced or metastatic RCC.

About CheckMate -9ER

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 ≥1%) were randomized to CABOMETYX at a dose of 40 mg QD and OPDIVO (n = 323) versus sunitinib (n = 328). The primary endpoint is PFS. Secondary endpoints include OS and ORR. The primary efficacy analysis compares the doublet combination regimen of CABOMETYX and OPDIVO versus sunitinib in all randomized patients. The trial is sponsored by BMS 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 type 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 HCC who have been previously treated with sorafenib; and for patients with advanced RCC as a first-line treatment in combination with OPDIVO (nivolumab). 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 (≥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,

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Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the potential for the combination of CABOMETYX and OPDIVO to become a standard of care in newly diagnosed metastatic kidney cancer; the broad therapeutic potential of CABOMETYX in combination with immune checkpoint inhibitors to benefit patients with other difficult-to-treat cancers; 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 any territories where it may be approved, and Exelixis' ability to obtain or maintain coverage and reimbursement for CABOMETYX; Exelixis' ability to maintain and scale adequate sales, marketing, market access and product distribution capabilities for its products or to enter into and maintain agreements with third parties to do so; Exelixis' continuing compliance with applicable legal and regulatory requirements; the continuing COVID-19 pandemic and its impact on Exelixis' 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' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 5, 2020, 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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