Exelixis Announces Partner Takeda Receives Approval in Japan for CABOMETYX® (cabozantinib) for the Treatment of Unresectable Hepatocellular Carcinoma That Has Progressed After Prior Systemic Therapy

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—Approval based on results of two clinical trials in patients with advanced hepatocellular carcinoma who had received prior systemic therapy —

ALAMEDA, Calif.--(BUSINESS WIRE)--Nov. 27, 2020-- Exelixis, Inc. (NASDAQ: EXEL) today announced that Takeda Pharmaceutical Company Limited (Takeda), its partner responsible for the clinical development and commercialization of CABOMETYX® (cabozantinib) in Japan, received approval from the Japanese Ministry of Health, Labor and Welfare to manufacture and market CABOMETYX as a treatment for patients with unresectable hepatocellular carcinoma (HCC) that has progressed after prior systemic therapy.

Takeda's application is based on the results of two clinical trials in patients with advanced HCC who had received prior systemic therapy: CELESTIAL (XL184-309), a global, randomized, placebo-controlled, double-blind phase 3 clinical trial, and Cabozantinib-2003, a phase 2 clinical trial conducted in Japan. The CELESTIAL trial was the basis for the CABOMETYX approvals in the U.S. and the EU for the treatment of patients with HCC who have been previously treated with sorafenib.

"Hepatocellular carcinoma causes approximately 30,000 deaths in Japan each year and is a leading cause of cancer-related death worldwide," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "The approval of CABOMETYX in Japan is an exciting next step toward bringing this treatment to liver cancer patients who otherwise have limited treatment options following prior systemic therapy. We're proud to collaborate with Takeda as we work to bring this treatment to patients in Japan."

Per the terms of Exelixis and Takeda's collaboration and license agreement, Exelixis is eligible to receive a $15 million milestone payment from Takeda upon the first commercial sale of CABOMETYX for unresectable HCC, which is expected to occur in the fourth quarter of 2020. In January 2020, Takeda's application for approval to manufacture and sell CABOMETYX as a treatment for patients with unresectable HCC that had progressed after prior systemic therapy in Japan triggered a $10 million milestone payment. Exelixis continues to be eligible to receive additional development, regulatory and first-sale milestones for potential future cabozantinib indications and is also eligible for sales revenue milestones and royalties on net sales of cabozantinib in Japan.

Takeda fully funds cabozantinib development activities that are exclusively for the benefit of Japan and has the opportunity to share the costs associated with global cabozantinib clinical trials, providing the company opts into those trials.

About HCC

Liver cancer is a leading cause of cancer death worldwide, accounting for more than 700,000 deaths and 800,000 new cases each year.[1] In the U.S., the incidence of liver cancer has more than tripled since 1980.[2] HCC is the most common form of liver cancer, making up about three-fourths of the estimated 43,000 new cases in the U.S. in 2020.[2] HCC is the fastest-rising cause of cancer-related death in the U.S.[3] Without treatment, patients with advanced HCC usually survive less than 6 months.[4]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with HCC who have been previously treated with sorafenib. 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.

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 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: Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, 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 event requiring medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred 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.

Proteinuria: Proteinuria occurred 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 commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.

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. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information https://cabometyx.com/downloads/CABOMETYXUSPI.pdf**.**

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. For more information about Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. on Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of CABOMETYX for patients with liver cancer and Exelixis' and Takeda's collaboration to bring CABOMETYX to HCC patients in Japan; Exelixis' eligibility to receive a $15 million milestone payment from Takeda upon Takeda's first commercial sale of CABOMETYX for unresectable HCC, which is expected to occur in the fourth quarter of 2020; Exelixis' eligibility for future development, regulatory and first-sale milestones, plus sales revenue milestones and royalties on net sales under its collaboration with Takeda; 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 of CABOMETYX in Japan; Exelixis' dependence on its relationship with Takeda, including Takeda's investment in the resources necessary to successfully commercialize CABOMETYX in Japan; Exelixis' and Takeda's ability to maintain and scale adequate sales, marketing, market access and product distribution capabilities for their products or to enter into and maintain agreements with third parties to do so; Exelixis' and Takeda's continuing compliance with applicable legal and regulatory requirements; the continuing COVID-19 pandemic and its impact on Exelixis' and Takeda'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' 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.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks. MINNEBRO is a Japanese trademark.

[1] International Agency for Research on Cancer. GLOBOCAN 2018. Liver Fact Sheet. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed November 2020.

[2] American Cancer Society: Cancer Facts & Figures 2020. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed November 2020.

[3] Siegel R, Miller K, Jemal A: Cancer Statistics, 2020. CA: A Cancer Journal for Clinicians. Volume 70, Issue 1: 7-30. Available at: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590. Accessed November 2020.

[4] Weledji E, Orock G, Ngowe M, NsaghaD. How grim is hepatocellular carcinoma? *Ann Med Surg*. 2014. 3:71-76.

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