Exelixis Announces Partner Takeda Receives Approval in Japan for CABOMETYX® (cabozantinib) Tablets for the Treatment of Curatively Unresectable or Metastatic Renal Cell Carcinoma

March 25, 2020

ALAMEDA, Calif.--(BUSINESS WIRE)--Mar. 25, 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 curatively unresectable or metastatic renal cell carcinoma (RCC).

The approval is based on the results of three clinical trials: METEOR, the Exelixis-sponsored phase 3 pivotal trial of cabozantinib versus everolimus in patients with advanced RCC that experienced disease progression following treatment with at least one prior VEGF receptor tyrosine kinase inhibitor (VEGFR-TKI); CABOSUN, the Alliance for Clinical Trials in Oncology-sponsored phase 2 trial comparing cabozantinib with sunitinib in patients with previously untreated advanced RCC with intermediate- or poor-risk disease; and Cabozantinib-2001, a Takeda-sponsored phase 2 trial in 35 Japanese patients with advanced RCC who had progressed after prior VEGFR-TKI therapy.

“Nearly 17,000 new cases of renal cell carcinoma are estimated to be diagnosed in Japan annually, and since many cases are diagnosed at an advanced stage, the prognosis remains poor for these patients,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. “The approval of CABOMETYX is an important milestone for people with kidney cancer in Japan, and we are excited to continue our collaboration with Takeda as we work to bring more options to patients who need novel therapies.”

Per the terms of Exelixis and Takeda’s collaboration and license agreement, Exelixis is eligible to receive a $31 million milestone payment from Takeda upon the first commercial sale of CABOMETYX for unresectable or metastatic RCC. In January 2020, Takeda applied for approval to manufacture and sell cabozantinib as a treatment for patients with unresectable hepatocellular carcinoma (HCC) that had progressed after prior systemic therapy in Japan, which triggered a $10 million milestone payment. Exelixis will also be eligible to receive further development, regulatory and first-sale milestone payments of up to $45 million from Takeda related both to previously treated and untreated RCC and previously treated HCC. 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 is responsible for 20% of the costs associated with global cabozantinib clinical trials, providing the company opts into those trials.

About RCC
The American Cancer Society’s 2020 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer in the U.S. and estimate nearly 74,000 cases will be diagnosed this year.[1] The most common type of kidney cancer in adults is RCC, which accounts for about 90% of cases.[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 12%, with no identified cure.[1] Approximately 32,000 patients in the U.S. and 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2020, with an estimated 15,000 patients in the U.S. in need of a first-line treatment.[3]

About 70% of RCC cases are known as “clear cell” carcinomas, based on histology. [2] 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.[4,5] These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.[6,7,8,9] MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.[5,6]

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.

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 number of new cases of RCC estimated to be diagnosed in Japan annually; the therapeutic potential of CABOMETYX for patients with kidney cancer in Japan; the potential for the collaboration between Exelixis and Takeda to bring more options to patients who need novel therapies; Exelixis' eligibility to receive a $31 million milestone payment upon the first commercial sale of CABOMETYX for unresectable or metastatic RCC; Exelixis' eligibility for future development, regulatory and first-sale milestone payments, 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, and Takeda's ability to obtain or maintain coverage and reimbursement for this product; 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 continuing compliance with applicable legal and regulatory requirements; Exelixis' ability to protect its intellectual property rights; Exelixis' dependence on third-party vendors for the 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 the ability of Exelixis and its commercial programs and partnerships discussed under the caption "Risk Factors" in Exelixis' Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 25, 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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[1] 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 March 2020.

[2] American Cancer Society: What is Kidney Cancer? Available at: https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html. Accessed March 2020.

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

[4] Harshman, L., and Choueiri, T. Targeting the hepatocyte growth factor/c-Met signaling pathway in renal cell carcinoma. *Cancer J*. 2013; 19:316-323.

[5] Rankin, et al. Direct regulation of GAS6/AXL signaling by HIF promotes renal metastasis through SRC and MET. *Proc Natl Acad Sci USA*. 2014; 111:13373-13378.

[6] Zhou, L., Liu, X-D., Sun, M., et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. *Oncogene*. 2016; 35:2687-2697.

[7] Koochekpour, et al. The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. *Mol Cell Biol*. 1999; 19:5902–5912.

[8] Takahashi, A., Sasaki, H., Kim, S., et al. Markedly increased amounts of messenger RNAs for vascular endothelial growth factor and placenta growth factor in renal cell carcinoma associated with angiogenesis. *Cancer Res*. 1994; 54:4233-4237.

[9] Nakagawa, M., Emoto, A., Hanada, T., Nasu, N., Nomura, Y. Tubulogenesis by microvascular endothelial cells is mediated by vascular endothelial growth factor (VEGF) in renal cell carcinoma. *Br J Urol*. 1997; 79:681-687.

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Investors Contact:
Susan Hubbard
EVP, Public Affairs and
Investor Relations
Exelixis, Inc.
(650) 837-8194
shubbard@exelixis.com

***M*edia Contact:**
Lindsay Treadway
Senior Director, Public Affairs
and Advocacy Relations
Exelixis, Inc.
(650) 837-7522
ltreadway@exelixis.com

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