Exelixis' Partner Takeda Announces Filing of New Drug Application in Japan for CABOMETYX® (Cabozantinib) for Advanced Renal Cell Carcinoma

April 25, 2019

-- Regulatory submission triggers $10 million milestone payment to Exelixis under collaboration and license agreement with Takeda --

-- Submission based on METEOR and CABOSUN trials as well as Takeda bridging study --

ALAMEDA, Calif.--(BUSINESS WIRE)--Apr. 25, 2019-- Exelixis, Inc. (Nasdaq: EXEL) today announced that Takeda Pharmaceutical Company Limited (Takeda), its partner responsible for the clinical development and commercialization of cabozantinib in Japan, has applied to the Japanese Ministry of Health, Labor and Welfare (MHLW) for approval to manufacture and sell CABOMETYX® (cabozantinib) as a treatment for unresectable and metastatic renal cell carcinoma (RCC) in the country. As a result of the submission, Exelixis will receive a $10 million milestone payment from Takeda, anticipated to be received in the second quarter of 2019.

Takeda's application 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. Takeda's phase 2 trial was the subject of a late-breaking abstract at the 107th Annual Meeting of the Japanese Urological Society on April 18, 2019.

"Takeda has proven to be a very effective partner in cabozantinib's development program in Japan since the signing of our collaboration and licensing agreement in early 2017," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "This Japanese regulatory filing is an important milestone on the path toward offering CABOMETYX as a new therapeutic option for patients with unresectable, metastatic renal cell carcinoma in Japan. We congratulate our Takeda colleagues on the filing and look forward to further progress."

Per the terms of Exelixis and Takeda's collaboration and license agreement, Exelixis received a $50 million upfront payment at the time of signing. Following the milestone associated with this regulatory filing, Exelixis will be eligible to receive from Takeda further development, regulatory and first-sale milestone payments of up to $80 million related both to previously treated and previously untreated RCC and previously treated hepatocellular carcinoma (HCC), as well as additional development, regulatory and first-sale milestones for potential future cabozantinib indications. Exelixis 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. As of today, Takeda has opted into and is co-funding CheckMate 9ER, the ongoing phase 3 pivotal trial of cabozantinib plus nivolumab versus sunitinib in previously untreated advanced RCC.

About RCC

The American Cancer Society's 2019 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 12 percent, with no identified cure for the disease.[1] Approximately 32,000 patients in the U.S. and 70,000 globally require treatment, and an estimated 15,000 patients in the U.S. each year are in need of a first-line treatment for advanced kidney cancer.[3]

The majority of clear cell RCC tumors have lower than 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 for the commercialization and further clinical development of cabozantinib for all future indications in Japan.

U.S. Important Safety Information

- **Hemorrhage:** Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. 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 fistula that cannot be appropriately managed 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 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.
- **Wound Complications:** Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding 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.
- **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.
- **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 genetic systems, 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 approved 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 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: Exelixis' timing for receipt of a $10 million milestone payment from Takeda for Takeda's submission of an application to the Japanese MHLW for approval to manufacture and sell CABOMETYX as a treatment for unresectable and metastatic RCC in Japan; the potential for CABOMETYX as a new therapeutic option for patients with unresectable and metastatic RCC in Japan; 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: risks and uncertainties related to regulatory review and approval processes, including that the Japanese MHLW may not approve CABOMETYX as a treatment for unresectable and metastatic RCC; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; Exelixis' dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for cabozantinib in new indications; Exelixis' ability to protect its intellectual property rights; market competition; changes in economic and business conditions; and other factors affecting the ability of Exelixis and its partners to obtain regulatory approval for cabozantinib in new indications discussed under the caption "Risk Factors" in Exelixis' Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 22, 2019, 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.

[1]American Cancer Society: Cancer Facts & Figures 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed April 2019.

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[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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