# Exelixis Announces Results from the Dose-Escalation Stage of the Phase 1b COSMIC-021 Study of Cabozantinib in Combination with Atezolizumab in Previously Untreated Advanced Renal Cell Carcinoma

October 22, 2018

*– Combination of cabozantinib and atezolizumab is well tolerated and shows promising anti-tumor activity –*

*– Safety and efficacy data support 18 expansion cohorts evaluating the combination in 12 different tumor types –*

ALAMEDA, Calif.--(BUSINESS WIRE)--Oct. 22, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced results from the dose-escalation stage of the phase 1b COSMIC-021 study of cabozantinib in combination with atezolizumab in previously untreated advanced renal cell carcinoma (RCC). The primary objective of the dose-escalation stage of the trial was to determine the recommended dose of cabozantinib in combination with the standard dose of atezolizumab for the expansion stage of the trial. The findings demonstrate encouraging clinical activity for the combination, supporting further evaluation of the 40 mg dose of cabozantinib in combination with the standard dose of atezolizumab in the ongoing expansion phase of the trial. The findings were presented during a poster session (abstract 872P) on Monday, October 22 at the European Society for Medical Oncology (ESMO) 2018 Congress, which is being held October 19-23, 2018 in Munich, Germany.

Twelve patients with previously untreated advanced RCC including ten patients with clear cell RCC and two patients with non-clear cell RCC were treated in the dose-escalation stage, with six patients at each cabozantinib dose level — 40 mg or 60 mg daily — in combination with the standard dosing regimen of atezolizumab (1,200 mg infusion once every three weeks).

As of the August 21, 2018 data cut-off, all patients remained on treatment. Median follow-up was 33.4 weeks. Eight of the ten (80 percent) clear cell RCC patients achieved a response per RECIST 1.1. Among all 12 patients enrolled, including the 2 non-clear cell RCC patients, the response rate was 67 percent. The disease control rate (ORR plus stable disease) for all 12 patients was 100 percent.

No dose-limiting toxicities or serious adverse events were noted at either cabozantinib dose. Dose reductions and higher grade AEs were less frequent with the 40 mg cabozantinib dosing cohort. Grade 3 adverse events (83 percent of patients) in the 40 mg cabozantinib dose cohort included hypertension (50 percent), hypophosphatemia (17 percent), hyperglycemia (17 percent), gamma glutamyltransferase increased (17 percent) and muscular weakness (17 percent). Grade 3 adverse events (100 percent of patients) in the 60 mg cabozantinib dose cohort included diarrhea (33 percent), hypertension (33 percent), aspartate aminotransferase increased (17 percent), alanine aminotransferase increased (17 percent), lymphopenia (17 percent), hypophosphatemia (17 percent) and lipase increased (17 percent). No Grade 4 or 5 adverse events were observed.

“These early stage results demonstrate that the combination of cabozantinib and atezolizumab was well tolerated and showed promising anti-tumor activity in advanced kidney cancer,” said Sumanta Kumar Pal, M.D., associate clinical professor, Department of Medical Oncology and Therapeutics Research, co-director, Kidney Cancer Program, City of Hope. “We look forward to continuing to advance this trial to understand whether this combination may benefit patients with multiple tumor types.”

“As we explore cabozantinib in combination with a variety of immune checkpoint inhibitors in a broad spectrum of tumor types, we are pleased with the initial results in the dose-escalation phase of COSMIC-021,” said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. “This combination is being studied across 12 different tumor types in the expansion phase, and we are excited to see how it may improve outcomes for this range of patients.”

As previously announced, the cabozantinib starting dose for the expansion phase is 40 mg. The expansion phase includes multiple solid tumor types, including RCC. More information about this trial is available at ClinicalTrials.gov.

Please see Important Safety Information below and full U.S. prescribing information at **https://cabometyx.com/downloads/CABOMETYXUSPI.pdf**.

**About the COSMIC-021 Study**

COSMIC-021 is a multicenter, phase 1b, open-label study that is divided into two parts: a dose-escalation phase and an expansion cohort phase. The dose-escalation phase was designed to enroll patients either with advanced RCC with or without prior systemic therapy or with inoperable, locally advanced, metastatic or recurrent UC (including renal, pelvis, ureter, urinary bladder and urethra) after prior platinum-based therapy. Ultimately, all patients enrolled in this stage of the trial were patients with advanced RCC. The dose-escalation phase of the study determined the optimal dose of cabozantinib to be 40 mg daily when given in combination with atezolizumab (1200 mg infusion once every 3 weeks).

In the expansion phase, the trial is enrolling 18 expansion cohorts in 12 tumor types: RCC, urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), castration-resistant prostate cancer, triple-negative breast cancer, epithelial ovarian cancer, endometrial cancer, hepatocellular carcinoma (HCC), gastric or gastroesophageal junction adenocarcinoma, colorectal adenocarcinoma, head and neck cancer, and differentiated thyroid cancer. Up to a total of 1,000 patients may enroll in this phase of the trial: each expansion cohort will initially enroll approximately 30 patients; up to 80 patients may enroll in up to eight of those cohorts, including the cohorts with UC or NSCLC patients who have been previously treated with an immune checkpoint inhibitor; and in two exploratory cohorts, approximately 30 patients in each cohort will be treated with cabozantinib as a single-agent.

**About Advanced Renal Cell Carcinoma**

The American Cancer Society's 2018 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 30,000 patients in the U.S. and 68,000 globally require treatment, and an estimated 14,000 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)**

CABOMETYX tablets are approved in the United States for the treatment of patients with advanced RCC. CABOMETYX tablets are also approved in: the European Union, Norway, Iceland, Australia, Switzerland, South Korea and Canada for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy, and in the European Union for previously untreated intermediate- or poor-risk advanced RCC. In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC. In May 2018, the FDA accepted Exelixis' supplemental New Drug Application for CABOMETYX as a treatment for patients with previously treated HCC and assigned it a Prescription Drug User Fee Act action date of January 14, 2019. On March 28, 2018, Ipsen announced that the European Medicines Agency validated its application for a new indication for cabozantinib as a treatment for previously treated advanced HCC in the European Union; on September 20, 2018 the CHMP provided a positive opinion for CABOMETYX as a monotherapy for the treatment of HCC in adults who have been previously treated with sorafenib. 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.

The combination of cabozantinib and atezolizumab is not indicated for previously untreated advanced RCC.

**U.S. Important Safety Information**

- **Hemorrhage**: Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.
- **Hypertension and Hypertensive Crisis:** CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.
- **Diarrhea:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased

appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.

- **Strong CYP3A4 Inhibitors**: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to 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. We discovered our three commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib) and COTELLIC® (cobimetinib), and 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. In July 2018, Exelixis was added to 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 Statement Disclaimer**

This press release contains forward-looking statements, including, without limitation, statements related to: the further evaluation of the combination of cabozantinib with the standard dose of atezolizumab as part of the expansion phase of COSMIC-021; the potential of the combination of cabozantinib and atezolizumab to benefit patients with multiple tumor types; 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 and Exelixis' compliance with applicable legal and regulatory requirements; the potential failure of the combination of cabozantinib and atezolizumab to demonstrate safety and/or efficacy in COSMIC-021; uncertainties inherent in the product development process; the costs of conducting clinical trials, including the ability or willingness of Exelixis' collaboration partners to invest in the resources necessary to complete the trials, as well as Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; Exelixis' ability to protect its intellectual property rights; market competition; changes in economic and business conditions; and other factors affecting Exelixis and its development programs discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission ( SEC) on August 1, 2018, 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.

*Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks.*

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[1] American Cancer Society: Cancer Facts and Figures 2018. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed October 2018.

[2] Jonasch, E., Gao, J., Rathmell, W. Renal cell carcinoma. *BMJ*. 2014; 349:g4797.

[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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