Exelixis Announces Results from Two Analyses Evaluating Effect of PD-L1 Expression or Prior Treatment with Checkpoint Inhibitors on Efficacy of Cabozantinib in Patients with Advanced Renal Cell Carcinoma

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– Cabozantinib was associated with improved overall survival and progression-free survival irrespective of PD-L1 expression in CABOSUN and METEOR trials –

– Cabozantinib also demonstrated activity in patients previously treated with immune checkpoint inhibitors –

– Findings presented this week at ESMO 2018 –

ALAMEDA, Calif.--(BUSINESS WIRE)--Oct. 20, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced results from two analyses evaluating the effect of PD-L1 expression or prior treatment with immune checkpoint inhibitors on the efficacy of cabozantinib in patients with advanced renal cell carcinoma (RCC). The findings are being presented this week at the European Society for Medical Oncology (ESMO) 2018 Congress being held October 19–23 in Munich, Germany.

An analysis of data from the CABOSUN and METEOR trials demonstrated that cabozantinib improved clinical outcomes regardless of PD-L1 status in patients with advanced RCC, relative to sunitinib or everolimus, the respective comparator arms for each trial. The late-breaking abstract [LBA 34] is being presented today in the Genitourinary Tumors, Non Prostate poster discussion session starting at 2:45 p.m. CEST (local Munich time).

Tumor tissue from 110 patients in the CABOSUN trial and 306 patients in the METEOR trial were evaluated to determine whether PD-L1 expression (≥1% of tumor cells) predicted outcomes or response to treatment. The findings showed that PD-L1 expression was associated with shorter median progression-free survival (PFS) and overall survival (OS) in both METEOR and CABOSUN. Treatment with cabozantinib, however, improved PFS and OS compared with everolimus (METEOR) and sunitinib (CABOSUN) in both PD-L1 positive and PD-L1 negative patients.

“As cabozantinib has become a new standard of care for the treatment of advanced kidney cancer, there is great interest in identifying biomarkers to help select for patients who would potentially derive the most clinical benefit,” said Toni Choueiri, M.D., Director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, and lead investigator. “While evidence suggests that patients who are negative for PD-L1 have less benefit with immune checkpoint inhibitors, this analysis demonstrated that cabozantinib may be an effective treatment option regardless of PD-L1 status for patients with advanced kidney cancer.”

An additional analysis evaluating the activity of cabozantinib in 69 patients with advanced RCC who progressed on immune checkpoint inhibitors [abstract 879P] will be presented by lead investigator Bradley McGregor, M.D., Dana-Farber Cancer Institute, at ESMO on Monday, October 22 in a poster display session at 12:45 p.m. CEST. This retrospective analysis found that cabozantinib was active in patients previously treated with immune checkpoint inhibitors, either alone or in combination with anti-VEGF or other therapies. At a median follow-up of 12 months, objective response rate was 33 percent, disease control rate was 79 percent and the one-year overall survival rate was 53 percent.

“With a growing number of options available for advanced kidney cancer, physicians need to consider multiple factors when selecting and sequencing treatments for patients,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. “The findings from these additional analyses demonstrate the potential benefit with cabozantinib for patients regardless of PD-L1 expression as well as after treatment with immune checkpoint inhibitors, reinforcing its role as the TKI of choice for advanced kidney cancer.”

About the CABOSUN Study

On May 23, 2016, Exelixis announced that the phase 2 CABOSUN study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS compared with sunitinib in patients with advanced intermediate- or poor-risk RCC as determined by investigator assessment. The CABOSUN study was conducted by The Alliance for Clinical Trials in Oncology and was sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) under the Cooperative Research and Development Agreement with Exelixis for the development of cabozantinib. These results were first presented by Dr. Toni Choueiri at the European Society for Medical Oncology (ESMO) 2016 Congress and published in the *Journal of Clinical Oncology* (Choueiri, *JCO*, 2016).[1] In June 2017, a blinded independent radiology review committee (IRC) confirmed that cabozantinib provided a clinically meaningful and statistically significant improvement in the primary efficacy endpoint of investigator-assessed PFS. Results from the IRC review were presented by Dr. Toni Choueiri at the ESMO 2017 Congress.

CABOSUN was a randomized, open-label, active-controlled phase 2 trial that enrolled 157 patients with advanced RCC determined to be intermediate- or poor-risk by the IMDC criteria. Patients were randomized 1:1 to receive cabozantinib (60 mg once daily) or sunitinib (50 mg once daily, 4 weeks on followed by 2 weeks off). The primary endpoint was PFS. Secondary endpoints included overall survival, objective response rate and safety. Eligible patients were required to have locally advanced or metastatic clear-cell RCC, ECOG performance status 0-2 and had to be intermediate- or poor-risk per the IMDC criteria (Heng, *JCO*, 2009).[2] Prior systemic treatment for RCC was not permitted.

About the METEOR Study

METEOR was an open-label, event-driven trial of 658 patients with advanced RCC who had failed at least one prior VEGFR TKI therapy. The primary endpoint was PFS in the first 375 patients treated. Secondary endpoints included OS and objective response rate in all enrolled patients. The trial was conducted at approximately 200 sites in 26 countries, and enrollment was weighted toward Western Europe, North America, and Australia. Patients were randomized 1:1 to receive 60 mg of CABOMETYX daily or 10 mg of everolimus daily and were stratified based on the number of prior VEGFR TKI therapies received and on MSKCC risk criteria. No cross-over was allowed between the study arms.

METEOR met its primary endpoint of significantly improving PFS and significantly improved the objective response rate compared with everolimus. These data were presented at ESMO 2015 and published in *The New England Journal of Medicine*.[3] CABOMETYX also demonstrated a statistically significant and clinically meaningful increase in OS in the METEOR trial. Cabozantinib benefit in OS was robust and consistent across all pre-specified subgroups. In particular, benefit was observed regardless of risk category, location and extent of tumor metastases, and tumor MET expression level. These results were presented on June 5, 2016 at the ASCO Annual Meeting and concurrently published in *The Lancet Oncology*.[4]

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.[5] Clear cell RCC is the most common type of kidney cancer in adults.[6] 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.[5] 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. [7]

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.[8,9] These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.[10,11,12,13] MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.[9,10]

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.

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 potential of cabozantinib to be an effective treatment option for patients with advanced RCC, regardless of their PD-L1 expression, as well as after treatment with immune checkpoint inhibitors; 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 and the availability of sufficient coverage and adequate reimbursement for this product; Exelixis' ability to invest in the resources necessary to successfully commercialize its compounds in the territories where they are approved and to execute its commercial strategy; Exelixis' continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib to continue to demonstrate improved outcomes for patients who participated in METEOR and CABOSUN; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; Exelixis' ability to protect its intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of Exelixis' marketed products; changes in economic and business conditions; and other factors affecting Exelixis and its commercial 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.

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[1] Choueiri, T.K., et al. Cabozantinib versus Sunitinib as Initial Targeted Therapy for Patients with Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *Am J Clin Oncol*. 2016; 35:591-597.

[2] Heng D.Y., Xie W., Regan M.M., et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. *Am J Clin Oncol*. 2009; 27:5794-5799.

[3] Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015; 373(19):1814-1823.

[4] Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Onc. 2016 Jun 5; S1470-2045(16)30107-3.

[5] 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.

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

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

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

[9] 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.

[10] 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.

[11] 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.

[12] 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.

[13] 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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