Exelixis Announces Positive Phase 2 Results for CABOMETYX® (cabozantinib) in Combination with OPDIVO® (nivolumab) in Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma at ASCO 2021

June 4, 2021

– CABOMETYX in combination with OPDIVO demonstrated an objective response rate of 47.5% in a cohort of patients with certain histologies of advanced or metastatic nccRCC –

– Data to be presented during the 2021 American Society of Clinical Oncology's Annual Meeting –

ALAMEDA, Calif.--(BUSINESS WIRE)--Jun. 4, 2021-- Exelixis, Inc. (NASDAQ: EXEL) today announced promising phase 2 results for CABOMETYX® (cabozantinib) in combination with Bristol Myers Squibb's OPDIVO ® (nivolumab) in patients with advanced or metastatic non-clear cell renal cell carcinoma (nccRCC) from an investigator-sponsored trial. The combination regimen showed promising efficacy and an acceptable safety profile in patients with metastatic nccRCC with papillary, unclassified or translocation-associated histologies. The data will be presented as part of the Poster Discussion Session: Genitourinary Cancer – Kidney and Bladder at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting, which is being held virtually, June 4-8, 2021. All posters will be available on demand beginning at 6:00 a.m. PT on Friday, June 4.

"The strong objective response rate associated with cabozantinib in combination with nivolumab in this trial is a meaningful finding for this patient community, who are typically not the focus of major clinical trials for kidney cancer," said Dr. Chung-Han Lee, medical oncologist at Memorial Sloan Kettering Cancer Center, and principal investigator for the study. "We look forward to building on these results with additional insights into which types of non-clear cell renal cell carcinoma may be most likely to respond to this combination regimen."

This single-institution, non-randomized, open-label, investigator-sponsored, phase 2 trial of CABOMETYX 40 mg in combination with OPDIVO (240 mg every two weeks or 480 mg every four weeks) was conducted by Memorial Sloan Kettering Cancer Center. The trial enrolled patients with advanced or metastatic nccRCC who had not received prior immune checkpoint inhibitor (ICI) therapy. A total of 47 patients were treated; 40 patients with papillary, unclassified, or translocation-associated RCC in cohort 1, and seven patients with chromophobe histology in cohort 2. Median follow-up was 13.1 months.

In cohort 1, CABOMETYX in combination with OPDIVO demonstrated an objective response rate (ORR) of 47.5% (95% confidence interval [CI]: 31.5–63.9). Among the 32 patients with papillary histology, ORR was 47% (95% CI: 29–65). Objective responses were seen in five of six patients with NF2 mutations, four of five patients with FH mutations and one of six patients with SETD2 mutations. Median duration of response was 13.6 months. Median progression-free survival was 12.5 months (95% CI: 6.3–15.9), and median overall survival was 28 months (95% CI: 16.3–non-estimable). A best response of stable disease was observed for five of seven patients in cohort 2.

"Following the recent FDA approval of CABOMETYX in combination with OPDIVO as a first-line treatment for patients with advanced renal cell carcinoma, we're excited to see these new data specifically in non-clear cell RCC, a heterogeneous group of kidney cancers," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "These positive phase 2 results build on our understanding of CABOMETYX's potential use in papillary RCC, one of these subtypes, and may help physicians choose an appropriate first-line systemic therapy for their patients with advanced non-clear cell renal cell carcinoma."

CABOMETYX or OPDIVO was discontinued due to adverse events in 17% and 13% of patients, respectively. Both therapies were discontinued due to adverse events in 9% of patients. Grade 3/4 treatment-related adverse events were observed in 32% of patients. The most common grade 3/4 treatment-related adverse events were hypertension (13%) and diarrhea (6%).

More information about this trial (NCT03635892) is available at ClinicalTrials.gov.

About RCC

The American Cancer Society's 2021 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] 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 13%.[1] Approximately 32,000 patients in the U.S. and 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2021.[2]

About 70% of RCC cases are known as "clear cell" carcinomas, based on histology. [3] Other subtypes, collectively grouped as nccRCC, constitute a diverse mixture of malignancies.[4] Papillary histology accounts for about 15% of all renal cell carcinomas.[5,6] Genomic and molecular characterization of papillary RCC has implicated MET signaling as a key driver of this cancer.[6,7] Targeting VEGFR and other tyrosine kinases, including MET and AXL, has led to improved outcomes in RCC compared with sunitinib and further supported the investigation of MET-targeting tyrosine kinase inhibitors in nccRCC.

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC; for the treatment of patients with HCC who have been previously treated with sorafenib; and for patients with advanced RCC as a first-line treatment in combination with OPDIVO. 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.

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

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

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed 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 common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

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. Avoid CABOMETYX in patients with severe hepatic impairment.

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

Dr. Lee has provided advisory services to Exelixis and Bristol Myers Squibb.

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. In November 2020, the company was named to *Fortune*'s 100 Fastest-Growing Companies list for the first time, ranking 17th overall and the third-highest biopharmaceutical company. 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 presentation of data from a phase 2 investigator-sponsored trial evaluating CABOMETYX in combination with OPDIVO in patients with advanced or metastatic nccRCC at ASCO 2021; the therapeutic potential of the combination of CABOMETYX and OPDIVO for patients with certain histologies of nccRCC and future insights into which types of nccRCC may be most likely to respond to the combination regimen; 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 availability of data at the referenced times; complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' and BMS' continuing compliance with applicable legal and regulatory requirements; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating the combination of CABOMETYX and OPDIVO; Exelixis' dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for partnered compounds in new indications and their adherence to their obligations under relevant collaboration agreements; 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 CABOMETYX; changes in economic and business conditions, including as a result of the COVID-19 pandemic; 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 May 6, 2021, 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.

[1] American Cancer Society: Cancer Facts & Figures 2021. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf. Accessed June 2021.

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

[3] American Cancer Society: What is Kidney Cancer? Available at: https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html. Accessed June 2021.

[4] Sankin A, Hakimi A, Hsieh J, Molina A. Metastatic Non-Clear Cell Renal Cell Carcinoma: An Evidence Based Review of Current Treatment Strategies. Front Oncol 2015;5:67.

[5] Zhang T, Gong J, Maia MC, Pal SK. Systemic Therapy for Non-Clear Cell Renal Cell Carcinoma. Am Soc Clin Oncol Educ Book 2017;37:337–42.

[6] Cancer Genome Atlas Research Network, Linehan WM, Spellman PT, et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med* 2016;374(2):135–45.

[7] Pal SK, Ali SM, Yakirevich E, et al. Characterization of Clinical Cases of Advanced Papillary Renal Cell Carcinoma via Comprehensive Genomic Profiling. *Eur Urol* 2018;73(1):71–8.

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