Exelixis Announces Phase 1b Results from Cohort 6 of COSMIC-021 Trial in Patients with Metastatic Castration-Resistant Prostate Cancer

May 24, 2021

– The combination of cabozantinib and atezolizumab evaluated in cohort 6 of the COSMIC-021 phase 1b trial resulted in objective response rates of 27% and 18% per investigator assessment and Blinded Independent Radiology Committee, respectively –

– Exelixis intends to discuss the results with the U.S. FDA to determine next steps toward a regulatory submission for the combination regimen for patients with high-risk metastatic CRPC –

– Phase 3 CONTACT-02 trial underway for metastatic CRPC –

ALAMEDA, Calif.--(BUSINESS WIRE)--May 24, 2021-- Exelixis, Inc. (NASDAQ: EXEL) today announced results from the metastatic castration-resistant prostate cancer (CRPC) cohort 6 of COSMIC-021, the phase 1b trial of cabozantinib (CABOMETYX®) in combination with atezolizumab in patients with locally advanced or metastatic solid tumors. Cohort 6 included patients with metastatic CRPC who had been previously treated with enzalutamide and/or abiraterone acetate.

Upon enrollment, patients had to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1) per investigator assessment, had progressed on prior novel hormonal therapy, and could have received prior docetaxel for hormone-sensitive disease. The analysis included 132 patients, 101 of whom had high-risk disease, defined as measurable visceral and/or extra-pelvic lymph node metastases. The group with high-risk disease is the patient population for which Exelixis would pursue a U.S. regulatory filing. The median follow-up for the high-risk patients was 15.8 months. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v. 1.1.

In the high-risk population, the investigator-assessed ORR was 27%, including 2% complete responses (CR) and 25% partial responses (PR). The Blinded Independent Radiology Committee (BIRC)-assessed ORR was 18%, all of which were partial responses. The disease control rate (CR + PR + stable disease) was 88% and 84% per investigator and BIRC assessment, respectively. Other radiographic endpoints, namely progression-free survival and duration of response, were similar between the investigator and BIRC assessment. Detailed results of the trial will be presented at a medical meeting in the second half of 2021.

An interim analysis of the initial 44 patients enrolled in the cohort was previously presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.

“These results from cohort 6 of COSMIC-021 suggest cabozantinib in combination with atezolizumab holds promise as a potential new treatment option in metastatic castration-resistant prostate cancer, a difficult-to-treat tumor type that typically has a poor prognosis,” said Neeraj Agarwal, M.D., Professor of Medicine, Huntsman Cancer Institute, University of Utah and an investigator of the trial. “There is a significant need for more options beyond chemotherapy once patients progress on androgen-deprivation therapy, so it is encouraging to see the response rates, disease control and tolerable safety profile associated with cabozantinib in combination with atezolizumab in this trial.”

The adverse event profile observed in the study was reflective of the known safety profile for each single agent. No new safety signals were identified in this expanded combination cohort. Discontinuation of treatment due to adverse events unrelated to disease progression was 12%.

In continuation of prior regulatory interaction and feedback from the U.S. Food & Drug Administration (FDA), Exelixis intends to discuss the results with the FDA to determine next steps toward a regulatory submission for the combination regimen for patients with high-risk metastatic CRPC. The global phase 3 trial, CONTACT-02, initiated enrollment in June 2020 and is evaluating cabozantinib in combination with atezolizumab versus a second novel hormonal therapy in patients with metastatic CRPC who have been previously treated with one novel hormonal therapy.

“Many patients with metastatic castration-resistant prostate cancer who have progressed on a novel hormonal therapy wish to avoid or delay chemotherapy. These results of the COSMIC-021 cohort 6 suggest the combination of cabozantinib and atezolizumab may offer this patient population a new treatment option,” said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. “We look forward to building on these results with the phase 3 CONTACT-02 trial in our continued effort to bring cabozantinib to many more patients in need.”

More information about this trial (NCT03170960) is available at ClinicalTrials.gov.

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 renal cell carcinoma (RCC) with or without prior systemic therapy or with inoperable, locally advanced, metastatic or recurrent urothelial carcinoma (UC), (including renal, pelvis, ureter, urinary bladder and urethra) after prior platinum-based therapy. Ultimately, all 12 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 24 cohorts in 12 tumor types: RCC, UC, non-small cell lung cancer (NSCLC), CRPC, hepatocellular carcinoma (HCC), triple-negative breast cancer, epithelial ovarian cancer, endometrial cancer, gastric or gastroesophageal junction adenocarcinoma, colorectal adenocarcinoma, head and neck cancer, and differentiated thyroid cancer.

Four of the cohorts are exploratory: three are enrolling approximately 30 patients each with advanced UC, CRPC or NSCLC to be treated with

cabozantinib as a single-agent, and one is enrolling approximately 10 patients with advanced CRPC to be treated with single-agent atezolizumab. Exploratory cohorts have the option to be expanded up to 80 patients (cabozantinib) and 30 patients (atezolizumab) total.

Exelixis is the study sponsor of COSMIC-021. Both Ipsen Pharma SAS (Ipsen) and Takeda Pharmaceutical Company Limited (Takeda) have opted in to participate in the trial and are contributing to the funding for this study under the terms of the companies' respective collaboration agreements with Exelixis. Roche is providing atezolizumab for the trial.

About CRPC

According to the American Cancer Society, in 2021, approximately 250,000 new cases of prostate cancer will be diagnosed, and 34,000 people will die from the disease.[1] Prostate cancer that has spread beyond the prostate and does not respond to androgen-suppression therapies — a common treatment for prostate cancer — is known as metastatic CRPC.[2] Researchers estimate that in 2020, 43,000 people were diagnosed with metastatic CRPC, which has a median survival of less than two years.[3,4,5]

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 nivolumab. 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.

CABOMETYX is not indicated as a treatment for metastatic CRPC.

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.

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 clinical and therapeutic potential of the combination of cabozantinib and atezolizumab as a treatment for patients with metastatic CRPC and the potential for the combination to be a new treatment option in the metastatic CRPC setting; Exelixis' intention to discuss the results of Cohort 6 of COSMIC-021 with the FDA to determine next steps toward a regulatory submission for the combination of cabozantinib and atezolizumab for patients with high-risk metastatic CRPC; Exelixis' plan

to build on the results of Cohort 6 of COSMIC-021 with CONTACT-02 in an effort to bring cabozantinib to more patients in need; 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: complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' and Roche's continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib in combination with atezolizumab to demonstrate continued safety and efficacy in clinical testing; 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; the continuing COVID-19 pandemic and its impact on Exelixis' research and development operations; 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; 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.

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[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 May 2021.

[2] American Society of Clinical Oncology. Cancer.Net. Treatment of Metastatic Castration-Resistant Prostate Cancer. September 8, 2014. Available at: https://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer. Accessed May 2021.

[3] Scher, H.I., Solo, K., Valant, J., Todd, M.B., Mehra, M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. *PLOS ONE*. 2015; 10: e0139440.

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[5] Moreira, D. M., Howard, L. E., Sourbeer, K. N., et al. Predicting Time From Metastasis to Overall Survival in Castration-Resistant Prostate Cancer: Results From SEARCH. *Clin Genitourin Cancer*. 2017; 15: 60–66.e2.

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Source: Exelixis, Inc.