Exelixis Announces Detailed Results from Phase 3 COSMIC-313 Pivotal Trial in Patients with Previously Untreated Advanced Kidney Cancer at ESMO 2022

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– Cabozantinib in combination with nivolumab and ipilimumab significantly reduced the risk of disease progression or death compared with the combination of nivolumab and ipilimumab –

– Median progression-free survival was not yet reached with the combination of cabozantinib, nivolumab and ipilimumab versus 11.3 months with nivolumab combined with ipilimumab –

ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 7, 2022-- Exelixis, Inc. (Nasdaq: EXEL) today announced detailed results from COSMIC-313, an ongoing phase 3 pivotal trial evaluating the combination of cabozantinib (CABOMETYX®), nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab in patients with previously untreated advanced intermediate- or poor-risk renal cell carcinoma (RCC). The data, including detailed results of the primary endpoint of progression-free survival (PFS), are being presented during the Presidential Symposium III (LBA8) on Monday, September 12 at 4:30 p.m. CEST at the 2022 European Society of Medical Oncology (ESMO) Congress.

"I look forward to presenting detailed results from COSMIC-313, which provide a clear look at the efficacy and safety profile for this combination of cabozantinib plus dual checkpoint inhibition," said Toni Choueiri, M.D., Director of the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute and the Jerome and Nancy Kohlberg Chair and Professor of Medicine at Harvard Medical School. "As the first trial with a control arm of nivolumab plus ipilimumab, COSMIC-313 was designed to answer an important question of whether adding cabozantinib to dual checkpoint inhibition can improve outcomes for this poor- and intermediate-risk renal cell carcinoma patient population. I am pleased that the trial demonstrated a significant progression-free survival benefit in patients receiving the triplet combination."

Eligible patients in the trial had intermediate- or poor-risk advanced RCC according to the International Metastatic RCC Database Consortium with a clear-cell component and Karnofsky performance status ≥70%. Of the 855 patients that were randomized, 75% were intermediate-risk and 25% were poor-risk.

As previously announced, the primary endpoint of PFS per Response Evaluation Criteria in Solid Tumors version 1.1, as assessed by Blinded Independent Radiology Committee (BIRC), demonstrated that cabozantinib in combination with nivolumab and ipilimumab significantly reduced the risk of disease progression or death compared with the combination of nivolumab and ipilimumab (hazard ratio: 0.73; 95% confidence interval [CI]: 0.57-0.94; P=0.013). At a prespecified interim analysis for the secondary endpoint of overall survival (OS), the combination of cabozantinib, nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab did not demonstrate a significant benefit. Therefore, the trial will continue to the next analysis of OS.

"We are pleased to share a more detailed picture of this triplet combination of cabozantinib, nivolumab and ipilimumab in patients with advanced kidney cancer at ESMO this year, reinforcing our longstanding commitment to this patient community," said Vicki L. Goodman, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. "We plan to discuss these findings from COSMIC-313 with U.S. regulators and will provide further updates, including the analysis of overall survival, when available."

The new results being presented at the 2022 ESMO Congress demonstrate that median PFS was not reached for the combination of cabozantinib, nivolumab and ipilimumab (95% CI: 14.0-not estimable) and was 11.3 months for the combination of nivolumab and ipilimumab (95% CI: 7.7-18.2). Objective response rates in the PFS intent-to-treat population as assessed by BIRC were 43% (95% CI: 37.2-49.2) and 36% (95% CI: 30.1-41.8), respectively. The median duration of response was not reached in either treatment arm. PFS subgroup analyses will also be presented.

The safety profile observed in the trial was reflective of the known safety profiles for each single agent as well as the combination regimens used in this study. No new safety signals were identified. Grade 3/4 treatment-emergent adverse events (AEs) occurred in 73% of patients treated with the combination of cabozantinib, nivolumab and ipilimumab and in 41% of patients treated with the combination of nivolumab and ipilimumab. Three patients (1%) in each arm had a grade 5 treatment-related AE. Discontinuation of all treatments due to treatment-emergent AEs occurred in 12% and 5% of patients, respectively.

About COSMIC-313

COSMIC-313 is a multicenter, randomized, double-blinded, controlled phase 3 pivotal trial that enrolled 855 patients at 177 sites globally. Patients were randomized 1:1 into the experimental or control arms of the study. Patients in the experimental arm received cabozantinib (40 mg, once daily) in combination with nivolumab (3 mg/kg infusion, once every 3 weeks for 4 doses total) and ipilimumab (1 mg/kg infusion, once every 3 weeks for 4 doses total) followed by cabozantinib (40 mg, once daily) and nivolumab (480 mg/kg flat dose infusion, once every 4 weeks for up to 2 years). Patients in the control arm received cabozantinib-matched placebo in combination with nivolumab (3 mg/kg infusion, once every 3 weeks for 4 doses total) and ipilimumab (1 mg/kg infusion, once every 3 weeks for 4 doses total) followed by cabozantinib-matched placebo and nivolumab (480 mg/kg flat dose infusion, once every 4 weeks for up to 2 years). The primary endpoint is PFS; the secondary endpoint is OS. Exelixis is funding the trial, and Bristol Myers Squibb is providing nivolumab and ipilimumab for use in this trial. More information about this trial is available at ClinicalTrials.gov.

About RCC

The American Cancer Society's 2022 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 14%.[1] Approximately 33,000

patients in the U.S. and over 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2022, with over 15,000 patients in need of a first-line treatment in the U.S.[3]

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 hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; for patients with advanced RCC as a first-line treatment in combination with nivolumab; and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. In 2016, Exelixis granted Ipsen Pharma SAS exclusive rights for the commercialization and further clinical development of cabozantinib outside of the U.S. 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 U.S.

CABOMETYX in combination with nivolumab and ipilimumab is not indicated as a treatment for previously untreated advanced RCC.

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, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. 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 37% (16% 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. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% 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. Withhold and resume at a reduced dose based on severity.

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 and resume CABOMETYX at a reduced dose 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 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. 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, resume at a reduced dose.

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. 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.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

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, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

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. 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' plans to present data, including detailed results of PFS, during the Presidential Symposium III at the 2022 ESMO Congress; the therapeutic potential of the triplet combination of cabozantinib, nivolumab and ipilimumab as a first-line treatment option for RCC patients with intermediate- or poor-risk disease; Exelixis' plans to discuss the trial results with U.S. regulators and provide further updates, including the analysis of OS, when available; 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' continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib in combination with nivolumab and ipilimumab to demonstrate safety and/or efficacy in clinical testing; 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 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 global events; 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 9, 2022, 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 2022. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf. Accessed September 2022.

[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).

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