Exelixis Announces Detailed Results from Phase 3 COSMIC-312 Pivotal Trial of Cabozantinib in Combination with an Immune Checkpoint Inhibitor in Patients with Previously Untreated Advanced Liver Cancer at ESMO Asia Virtual Oncology Week 2021

November 20, 2021

– Exelixis intends to submit a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) in early 2022 following the final overall survival analysis –

ALAMEDA, Calif.--(BUSINESS WIRE)--Nov. 20, 2021-- Exelixis, Inc. (Nasdaq: EXEL) today announced detailed results from the first planned analysis of COSMIC-312, the ongoing phase 3 pivotal trial evaluating cabozantinib (CABOMETYX®) in combination with atezolizumab versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma (HCC). The data are being presented at 7:00 p.m. SGT (6:00 a.m. EST, 3:00 a.m. PST) on Saturday, November 20 in the Virtual Plenary Session during the European Society for Medical Oncology (ESMO) Asia Virtual Oncology Week 2021.

As announced in June and presented today, at a median follow-up of 15.8 months, the primary analysis showed the primary endpoint of progression-free survival (PFS) per RECIST 1.1 by blinded independent review committee (BIRC) was met; in the PFS intent-to-treat (PITT) population, cabozantinib in combination with atezolizumab significantly reduced the risk of disease progression or death by 37% compared with sorafenib (hazard ratio [HR]: 0.63; 99% confidence interval [CI]: 0.44-0.91; P=0.0012; pre-specified critical p-value of 0.01). Median PFS was 6.8 months for cabozantinib in combination with atezolizumab (n=250) versus 4.2 months for sorafenib (n=122).

New results presented during the 2021 ESMO Virtual Plenary include detailed data for a prespecified interim analysis for the primary endpoint of overall survival (OS) in the intent-to-treat (ITT) population, which was conducted at the same time as the primary analysis for PFS in the PITT population. At a median follow-up of 13.6 months, the interim OS analysis in the ITT population showed a trend that favored cabozantinib in combination with atezolizumab but did not reach statistical significance (HR: 0.90; 96% CI: 0.69-1.18; P=0.438). Median OS was 15.4 months for cabozantinib in combination with atezolizumab (n=432) versus 15.5 months for sorafenib (n=217). The trial is continuing as planned to the final analysis of OS, anticipated in early 2022.

“We are encouraged by the significant improvement in progression-free survival observed in COSMIC-312, suggesting cabozantinib in combination with atezolizumab holds potential as a treatment to reduce the risk of disease progression or death for patients with advanced liver cancer,” said R. Kate Kelley, M.D., Professor of Clinical Medicine, Division of Hematology/Oncology, University of California, San Francisco, and lead investigator on COSMIC-312. “Patients with this aggressive form of cancer, who may also have other comorbid conditions due to liver disease, face a poor prognosis and are in need of additional approaches to treatment.”

Subgroup analyses of PFS in the PITT population and preliminary interim OS results in the ITT population were performed by disease etiology:

- Median PFS in hepatitis B virus patients (n=109): 6.7 months for patients treated with cabozantinib in combination with atezolizumab compared with 2.7 months for sorafenib (HR: 0.46; 95% CI: 0.29–0.73).
- Median OS in hepatitis B virus patients (n=191): 18.2 months for patients treated with cabozantinib in combination with atezolizumab compared with 14.9 months for sorafenib (HR: 0.53; 95% CI: 0.33–0.87).
- Median PFS in hepatitis C virus patients (n=105): 7.9 months for patients treated with cabozantinib in combination with atezolizumab compared with 5.6 months for sorafenib (HR: 0.64; 95% CI: 0.38–1.09).
- Median OS in hepatitis C virus patients (n=203): 13.6 months for patients treated with cabozantinib in combination with atezolizumab compared with 14.0 months for sorafenib (HR: 1.10; 95% CI: 0.72–1.68).
- Median PFS in non-viral patients (n=158): 5.8 months for patients treated with cabozantinib in combination with atezolizumab compared with 7.0 months for sorafenib (HR: 0.92; 95% CI: 0.60–1.41).
- Median OS in non-viral patients (n=255): 15.2 months for patients treated with cabozantinib in combination with atezolizumab, and not reached for sorafenib (HR: 1.18; 95% CI: 0.78–1.79).

In an interim analysis of the secondary endpoint of PFS per RECIST 1.1 by BIRC performed to determine the contribution of cabozantinib to the combination with atezolizumab, cabozantinib monotherapy reduced the risk of disease progression or death in the ITT population by 29% versus sorafenib (HR: 0.71; 99% CI: 0.51-1.01; P=0.0107; pre-specified critical p-value of 0.00451). Median PFS was 5.8 months for cabozantinib (n=188) versus 4.3 months for sorafenib (n=217).

Objective response rates per RECIST 1.1 by BIRC in the ITT population were 11% for cabozantinib in combination with atezolizumab, 3.7% for sorafenib and 6.4% for cabozantinib monotherapy. Disease control rates (complete response + partial response + stable disease) were 78%, 65% and 84%, respectively.

“Exelixis has a longstanding commitment to patients with liver cancer, and we are pleased to present more detailed efficacy and safety data during this ESMO Virtual Plenary Session reinforcing the potential of cabozantinib in combination with atezolizumab for patients with this disease who are in need of additional first-line treatment options,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer, Exelixis. “We look forward to the final COSMIC-312 overall survival analysis in early 2022 and to submitting an sNDA to the FDA at that time.”

The safety profile for cabozantinib in combination with atezolizumab was consistent with those previously observed for each single agent, and no new

safety signals were identified. The most common grade 3 or higher adverse events (AEs) for cabozantinib in combination with atezolizumab were palmar-plantar erythrodysesthesia (7.9% versus 8.2% for sorafenib and 8.5% for cabozantinib monotherapy), hypertension (7.0%, 6.3% and 11.0%, respectively), aspartate aminotransferase increased (6.5%, 2.4% and 5.3%) and alanine aminotransferase increased (6.3%, 1.9% and 5.9%).

Rates of grade 3/4 treatment-related AEs were 51% for cabozantinib and atezolizumab, 30% for sorafenib and 52% for cabozantinib monotherapy. Rates of grade 5 treatment-related AEs were 1.9% for cabozantinib and atezolizumab, 0.5% for sorafenib and 0.5% for cabozantinib monotherapy. Treatment discontinuations due to treatment-related AEs in the combination arm were 6.1% for the combination of cabozantinib and atezolizumab and 14.0% for either cabozantinib and/or atezolizumab. The treatment-related discontinuation rate for sorafenib was 7.7% and for cabozantinib monotherapy was 8.5%.

About COSMIC-312

COSMIC-312 is a global, multicenter, randomized, controlled phase 3 pivotal trial that enrolled 837 patients at 281 study centers globally. Nine enrolled patients were from Mainland China, 232 were from elsewhere in Asia, and 596 were from outside Asia. An extension phase in China is ongoing and is not included in this current analysis. Patients were randomized approximately 2:1:1 to one of three arms: cabozantinib (40 mg) in combination with atezolizumab (n=432), sorafenib (n=217) or cabozantinib (60 mg; n=188). Exelixis is sponsoring COSMIC-312, and Ipsen is co-funding the trial. Genentech, a member of the Roche Group, is providing atezolizumab for use in this trial. More information about COSMIC-312 is available at ClinicalTrials.gov.

About HCC

More than 900,000 new cases of liver cancer, 90% of which are HCC, are diagnosed worldwide each year.[1,2] HCC is a leading cause of cancer-related death, expected to cause 1 million global deaths annually by 2030.[3] In the U.S., HCC is the fastest-rising cause of cancer-related death.[4] Median survival for patients with symptomatic advanced HCC who are treated with systemic therapies is just 1 to 1.5 years.[2] Research has shown that gastrointestinal varices – which are associated with a higher risk of death from bleeding – occur in about 60-75% of patients with advanced HCC, the presence of which can impact the therapies available to these patients.[5,6]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced renal cell carcinoma (RCC); for the treatment of patients with 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 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 is not indicated as a treatment for previously untreated advanced HCC.

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: the presentation of data from COSMIC-312 in the Virtual Plenary Session during the ESMO Asia Virtual Oncology Week 2021; the therapeutic potential of cabozantinib in combination with atezolizumab to reduce the risk of disease progression or death for patients with advanced liver cancer who are in need of additional first-line treatment options; addressing unmet needs for patients with liver cancer and plans to submit an sNDA to the FDA in early 2022 following the final OS analysis; 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 Roche's continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib in combination with atezolizumab 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 cabozantinib 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' and Roche's ability to protect their respective 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 November 2, 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 International Agency for Research on Cancer. GLOBOCAN 2020. Liver Fact Sheet. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed November 2021.

2 Llovet, J.M., Kelley, R.K., Villanueva, A. et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6.

3 Kim, E., Viatour, P. Hepatocellular carcinoma: old friends and new tricks. *Exp Mol Med.* 2020;52:1898–1907.

4 Rawla, P., Sunkara, T., Muralidharan, P., et al. Update in global trends and aetiology of hepatocellular carcinoma. *Contemporary oncology (Pozn).* 2018;22(3):141–150.

5 Giannini, E.G., Risso, D., Testa, R., et al. Prevalence and prognostic significance of the presence of esophageal varices in patients with hepatocellular carcinoma. *Clin Gastro Hep.* 2006;4:1378-1384.

6 Boregowda, U., Umapathy, C., Halim, N., etc. Update on the management of gastrointestinal varices. *World J Gastrointest Pharmacol Ther*. 2019;10(1):1-21.

View source version on businesswire.com: https://www.businesswire.com/news/home/20211120005130/en/

Investors Contact:
Susan Hubbard
EVP, Public Affairs and
Investor Relations
Exelixis, Inc.
(650) 837-8194
shubbard@exelixis.com

Media Contact:

Lindsay Treadway
Executive Director,
Public Affairs and
Advocacy Relations
Exelixis, Inc.
(650) 837-7522
ltreadway@exelixis.com

Source: Exelixis, Inc.