Exelixis Announces Results from Phase 2 Trial of Cabozantinib in Combination with Pembrolizumab in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma at ASCO 2022

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– Results demonstrated an objective response rate of 54% and an overall clinical benefit rate of 91% –

ALAMEDA, Calif.--(BUSINESS WIRE)--May 26, 2022-- Exelixis, Inc. (Nasdaq: EXEL) today announced results from a phase 2, investigator-sponsored trial of cabozantinib (CABOMETYX®) in combination with pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). The data will be presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting during Oral Abstract Session: Head and Neck Cancer on Friday, June 3 beginning at 2:45 p.m. CT.

The trial met its primary endpoint of objective response rate per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at 54%. The overall clinical benefit rate was 91%. At a median follow-up of 10.6 months, the one-year progression-free survival rate was 54.0% (95% confidence interval [CI]: 31.5-72.0%), and median progression-free survival was 14.6 months. The one-year overall survival (OS) rate was 68.4% (95% CI: 45.1-83.5%; median OS: 22.3 months). For the 17 patients with a PD-L1 combined positive score (CPS) under 20, the one-year OS rate was 54.9% (95% CI: 24.5-77.5%; median OS: 14.6 months). For the 17 patients with a CPS score of 20 or more, the one-year OS rate was 83.6% (95% CI: 48.0-95.7%; median OS: 32.9 months).

“Metastatic head and neck cancer is a challenging disease to treat, particularly following disease progression after definitive therapy, meaning patients need additional options beyond radiation and chemotherapy,” said Nabil F. Saba, M.D., Professor and Vice Chair, Hematology and Medical Oncology, The Lynne and Howard Halpern Chair in Head and Neck Cancer Research, Co-Director of Head and Neck Cancer Multidisciplinary Program, Winship Cancer Institute, Emory University, and primary investigator of the investigator-sponsored trial. “These results showing promising clinical activity of cabozantinib in combination with pembrolizumab are encouraging to these patients who face poor outcomes.”

In this phase 2 trial, eligible patients had recurrent or metastatic HNSCC that was deemed inoperable, with measurable disease per RECIST version 1.1, a life expectancy of at least 3 months and an Eastern Cooperative Group Performance Status of 0 or 1. Of the 36 evaluable patients, 61% had cancer in the oropharynx, 16% in the nasopharynx, 11% in the larynx, 6% in the hypopharynx and 6% in the oral cavity. Eighty-nine percent of patients had received prior radiation therapy and all had received prior chemotherapy.

The most frequent adverse events (AEs) were fatigue (44.4%), diarrhea (33.3%), hypothyroidism (33.3%), constipation (30.6%), dry mouth (27.8%), anorexia (25.0%), headache (25.0%), hypertension (25.0%), hyponatremia (25.0%) and oral mucositis (25.0%). Grade 3/4 treatment-related AEs were aspartate aminotransferase (AST) increase (8.3%), hyponatremia (8.3%), gamma-glutamyl transferase increase (5.6%), lipase increase (5.6%), oral mucositis (5.6%), alanine transaminase/AST increase (2.8%), bilirubin increase (2.8%) and hypertension (2.8%). Dose reductions occurred in 47.2% of patients, and AEs leading to discontinuation occurred in 25.0% of patients.

“Treatment options for patients with metastatic head and neck squamous cell carcinoma are limited, leaving a critical unmet need for this community,” said Vicki L. Goodman, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. “These data support the further development of a combination regimen of cabozantinib and an immune checkpoint inhibitor in patients with metastatic head and neck carcinoma and we are pleased to share these data at ASCO. Through our research, including our investigator-sponsored trials program, we continue to advance toward our goal of bringing new treatment options to people with difficult-to-treat cancers.”

About HNSCC

HNSCC comprises head and neck cancers that begin in the squamous cells that line the mucosal surfaces of the head and neck.[1] Accounting for about 90% of all head and neck cancers, HNSCC is classified by its location: it can occur in the oral cavity, oropharynx, nasal cavity and paranasal sinuses, nasopharynx, larynx or hypopharynx.[1,2] Oral cavity and larynx cancers are generally associated with tobacco consumption, alcohol abuse or both, whereas pharynx cancers are increasingly attributed to infection with human papillomavirus (HPV), primarily HPV-16.[3] About 50,000 new cases of HNSCC are diagnosed in the U.S. every year.[1] HNSCC is more common among men and people over the age of 50.[4] Depending on the site of the cancer and level of metastases, the five-year survival rate for metastatic HNSCC ranges from 4-35%.[5]

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 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 vascular endothelial growth factor receptor (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 is not indicated as a treatment for recurrent or metastatic HNSCC.

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 a phase 2 investigator-sponsored trial evaluating cabozantinib in combination with pembrolizumab in patients with metastatic HNSCC during an oral abstract session at ASCO 2022; the therapeutic potential of cabozantinib in combination with immune checkpoint inhibitors to help patients with metastatic HNSCC and Exelixis' goal of bringing new treatment options to people with difficult-to-treat cancers; 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 atezolizumab or in combination with durvalumab 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; the costs of conducting clinical trials, including the ability or willingness of Exelixis' collaboration partners or investigator sponsors to invest in the resources necessary to complete the trials; 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 May 10, 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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