Exelixis Announces Initiation of the STELLAR-305 Phase 2/3 Pivotal Trial Evaluating Zanzalintinib in Combination with Pembrolizumab in Patients with Previously Untreated Recurrent or Metastatic Head and Neck Cancer

December 4, 2023

– STELLAR-305 is Exelixis' first pivotal study in squamous cell carcinoma of the head and neck –

– Trial will evaluate the potential of inhibition of VEGF, MET and AXL, which are elevated in these tumors –

ALAMEDA, Calif.--(BUSINESS WIRE)--Dec. 4, 2023-- Exelixis, Inc. (Nasdaq: EXEL) today announced the initiation of STELLAR-305, a phase 2/3 pivotal trial evaluating zanzalintinib in combination with pembrolizumab versus pembrolizumab alone in patients with previously untreated PD-L1-positive recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).

"We are excited to progress zanzalintinib, our next-generation multi-targeted tyrosine kinase inhibitor, into this population of patients who otherwise are relegated to immunotherapy plus chemotherapy, but may benefit from a chemo-free option," said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. "This study is based on encouraging data from a phase 2 investigator-initiated trial of cabozantinib and pembrolizumab and demonstrates our agility to move quickly into indications with sound rationale from our flagship asset."

STELLAR-305 is a global, multicenter, randomized, double-blind phase 2/3 study that will enroll patients with PD-L1-positive recurrent or metastatic SCCHN that is incurable with local therapies. Patients must not have received prior systemic therapy for recurrent or metastatic disease. Patients will be randomized 1:1 to receive zanzalintinib in combination with pembrolizumab or placebo in combination with pembrolizumab. The primary endpoints of the study are progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by Blinded Independent Radiology Committee (BIRC) and overall survival. Secondary endpoints include PFS per RECIST 1.1 by investigator and objective response rate and duration of response per RECIST 1.1 by BIRC and by investigator.

STELLAR-305 is sponsored by Exelixis. More information about STELLAR-305 is available at ClinicalTrials.gov.

About Zanzalintinib

Zanzalintinib is a next-generation oral tyrosine kinase inhibitor that inhibits the activity of receptor tyrosine kinases implicated in cancer growth and spread, including VEGF receptors, MET, AXL and MER. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis and resistance to multiple therapies, including immune checkpoint inhibitors. With zanzalintinib, Exelixis sought to build upon its extensive experience with the target profile of cabozantinib, the company's flagship medicine, while improving key characteristics, including pharmacokinetic half-life. Zanzalintinib is currently being developed for the treatment of advanced solid tumors, including genitourinary, colorectal and head and neck cancers.

About SCCHN

SCCHN 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, SCCHN 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] Approximately 50,000 new cases of SCCHN are diagnosed in the U.S. every year.[1] SCCHN 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 SCCHN ranges from 4-35%.[5]

CABOMETYX 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, and 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

Exelixis is a globally ambitious oncology company innovating next-generation medicines and regimens at the forefront of cancer care. Powered by bi-coastal centers of discovery and development excellence, we are rapidly evolving our product portfolio to target an expanding range of tumor types and indications with our clinically differentiated pipeline of small molecules, antibody-drug conjugates and other biotherapeutics. This comprehensive approach harnesses decades of robust investment in our science and partnerships to advance our investigational programs and extend the impact of our flagship commercial product, CABOMETYX® (cabozantinib). Exelixis is driven by a bold scientific pursuit to create transformational treatments that give more patients hope for the future. For information about the company and its mission to help cancer patients recover stronger and live longer, visit www.exelixis.com, follow @ExelixisInc on X (Twitter), like Exelixis, Inc. on Facebook and follow Exelixis on LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of zanzalintinib in combination with pembrolizumab as a chemo-free option to improve outcomes for patients with previously untreated PD-L1-positive recurrent or metastatic SCCHN, including specifically the clinical potential of zanzalintinib's inhibition of VEGF, MET and AXL, which are elevated in these tumors; and Exelixis' scientific pursuit to create transformational treatments that give more patients hope for the future. 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' continuing compliance with applicable legal and regulatory requirements; the potential failure of zanzalintinib in combination with pembrolizumab to demonstrate safety and/or efficacy in STELLAR-305 and in future clinical testing; uncertainties inherent in the product development process, including evolving regulatory requirements, slower than anticipated patient enrollment or inability to identify a sufficient number of clinical trial sites; the costs of conducting clinical trials; Exelixis' dependence on third-party vendors for the development, manufacture and supply of zanzalintinib; Exelixis' ability to protect its intellectual property rights; market competition; changes in economic and business conditions; and other factors affecting Exelixis and its development programs detailed from time to time under the caption "Risk Factors" in Exelixis' most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q, and in Exelixis' future filings with the Securities and Exchange Commission. 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] Head and neck squamous cell carcinoma. MedlinePlus website. Available at: https://medlineplus.gov/genetics/condition/head-and-neck-squamous-cell-carcinoma/. Accessed December 2023.

[2] Squamous cell carcinoma of the head and neck. Penn Medicine website. Available at: https://www.pennmedicine.org/cancer/types-of-cancer/squamous-cell-carcinoma/types-of-squamous-cell-carcinoma/squamous-cell-carcinoma-of-the-head-and-neck. Accessed December 2023.

[3] Johnson, DE, Burtness, B, Leemans, CR, et al. Head and neck squamous cell carcinoma. *Nat Rev Dis Primers.* November 2020;6(1):92.

[4] Head and neck cancers. NCI website. Available at: https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet#how-common-are-head-and-neck-cancers. Accessed December 2023.

[5] Beckham, TH, Leeman, JE, Xie, P, et al. Long-term survival in patients with metastatic head and neck squamous cell carcinoma treated with metastasis-directed therapy. *Br J Cancer.* November 2019;121(11):897-903.

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

Media Contact:
Stekki Millman
Senior Director, Public Affairs
Exelixis, Inc.
(650) 837-7187
smillman@exelixis.com

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