Exelixis Announces CELESTIAL Phase 3 Pivotal Trial Results Published in The New England Journal of Medicine

July 4, 2018

– Trial results formed the basis of regulatory filings in the U.S. and European Union for CABOMETYX® (cabozantinib) for previously treated advanced hepatocellular carcinoma –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jul. 4, 2018-- Exelixis, Inc. (Nasdaq: EXEL) today announced that *The New England Journal of Medicine* (*NEJM*) published results from the CELESTIAL phase 3 pivotal trial of cabozantinib in patients with previously treated advanced hepatocellular carcinoma (HCC).[1] The data, originally presented at the 2018 American Society of Clinical Oncology's Gastrointestinal Cancers Symposium (ASCO-GI) in January, demonstrate that cabozantinib provided a statistically significant and clinically meaningful improvement in overall survival (OS) versus placebo.

"Patients with this form of advanced liver cancer have very limited treatment options once their disease progresses following treatment with sorafenib," said Ghassan K. Abou-Alfa, M.D., Memorial Sloan Kettering Cancer Center, New York and lead investigator on CELESTIAL. "These results suggest that, if approved, cabozantinib could become an important addition to the treatment landscape that may help slow disease progression and, critically, improve survival for these patients."

Exelixis announced in May 2018 that the U.S. Food and Drug Administration (FDA) accepted the company's supplemental New Drug Application (sNDA) for CABOMETYX® (cabozantinib) tablets as a treatment for patients with previously treated HCC. The filing has been assigned a Prescription Drug User Fee Act action date of January 14, 2019. Exelixis' partner Ipsen received validation by the European Medicines Agency in March 2018 for its application for variation to the CABOMETYX marketing authorization to include the new indication for patients with previously treated advanced HCC.

"The publication of the CELESTIAL trial results in a peer-reviewed publication as prestigious as *NEJM* further validates the importance of these data for the advanced liver cancer community," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "We're working closely with the FDA as they review our sNDA in order to bring CABOMETYX to this growing patient population as quickly as possible."

Median OS in CELESTIAL was 10.2 months with cabozantinib versus 8.0 months with placebo (HR 0.76, 95 percent CI 0.63-0.92; p=0.0049). Median progression-free survival (PFS) was more than doubled, at 5.2 months with cabozantinib and 1.9 months with placebo (HR 0.44, 95 percent CI 0.36-0.52; p<0.0001). Objective response rates per RECIST 1.1 were 4 percent with cabozantinib and 0.4 percent with placebo (p=0.0086). Disease control (partial response or stable disease) was achieved by 64 percent of patients in the cabozantinib group compared with 33 percent of patients in the placebo group.

In a subgroup analysis of patients whose only prior therapy for advanced HCC was sorafenib (70 percent of patients in the study), median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (HR 0.70, 95 percent CI 0.55-0.88). Median PFS in the subgroup was 5.5 months with cabozantinib versus 1.9 months with placebo (HR 0.40, 95 percent CI 0.32-0.50).

Adverse events were consistent with the known safety profile of cabozantinib. The most common (≥10 percent) grade 3 or 4 adverse events in the cabozantinib group compared to the placebo group were palmar-plantar erythrodysesthesia (17 percent vs. 0 percent), hypertension (16 percent vs. 2 percent), increased aspartate aminotransferase (12 percent vs. 7 percent), fatigue (10 percent vs. 4 percent) and diarrhea (10 percent vs. 2 percent). Treatment-related grade 5 adverse events occurred in six patients in the cabozantinib group (hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism and hepatorenal syndrome) and in one patient in the placebo group (hepatic failure). Sixteen percent of patients in the cabozantinib arm and three percent of patients in the placebo arm discontinued treatment due to treatment-related adverse events.

About the CELESTIAL Study

CELESTIAL is a randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC conducted at more than 100 sites globally in 19 countries. The trial was designed to enroll 760 patients with advanced HCC who received prior sorafenib and may have received up to two prior systemic cancer therapies for HCC and had adequate liver function. Enrollment of the trial was completed in September 2017. Patients were randomized 2:1 to receive 60 mg of cabozantinib once daily or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia versus other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms during the blinded treatment phase of the trial. The primary endpoint for the trial is OS, and secondary endpoints include objective response rate and PFS. Exploratory endpoints include patient-reported outcomes, biomarkers and safety.

In October 2017, Exelixis announced that the independent data monitoring committee for the CELESTIAL study recommended that the trial be stopped for efficacy following review at the second planned interim analysis, with cabozantinib providing a statistically significant and clinically meaningful improvement in OS compared with placebo in patients with previously treated advanced HCC. In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC.

About HCC

Liver cancer is the second-leading cause of cancer death worldwide, accounting for more than 700,000 deaths and nearly 800,000 new cases each year.[2] In the U.S., the incidence of liver cancer has more than tripled since 1980.[3] HCC is the most common form of liver cancer, making up about three-fourths of the estimated nearly 42,000 new cases in the U.S. in 2018.[3] HCC is the fastest-rising cause of cancer-related death in U.S.[4] Without treatment, patients with advanced HCC usually survive less than 6 months.[5]

About CABOMETYX® (cabozantinib)

CABOMETYX tablets are approved in the United States for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX tablets are also approved in the European Union, Norway, Iceland, Australia, Switzerland and South Korea for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy, and in the European Union for previously untreated intermediate- or poor-risk advanced RCC. On March 28, 2018, Ipsen announced that the European Medicines Agency validated its application for a new indication for cabozantinib as a treatment for previously treated advanced HCC in the European Union. 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, including RCC.

CABOMETYX is not indicated for previously treated advanced HCC.

Please see Important Safety Information below and full U.S. prescribing information at **https://cabometyx.com/downloads/CABOMETYXUSPI.pdf**.

U.S. Important Safety Information

- **Hemorrhage**: Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.
- **Hypertension and Hypertensive Crisis:** CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.
- **Diarrhea:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.
- **Strong CYP3A4 Inhibitors**: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.

- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information

https://cabometyx.com/downloads/CABOMETYXUSPI.pdf.

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 genetic systems, 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. We discovered our three commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib) and COTELLIC® (cobimetinib), and 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. In July 2018, Exelixis was added to 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.

Exelixis Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of cabozantinib as a treatment option for patients with previously treaded advanced HCC, if approved; the regulatory review process, including Exelixis' intent to continue to work closely with the FDA as they review the application for cabozantinib as a treatment for patients with previously treated advanced HCC; 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; and Exelixis' mission to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. Words such as "could" "may," "commitment," "potential," "intend," or other similar expressions identify forward-looking statements, but the absence of these words does not necessarily mean that a statement is not forward-looking. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements 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: risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; market acceptance of CABOMETYX, COMETRIQ, and COTELLIC and the availability of coverage and reimbursement for these products; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX, COMETRIQ, and COTELLIC; risks related to the potential failure of cabozantinib and cobimetinib to demonstrate safety and efficacy in clinical testing; Exelixis' ability and the ability of its collaborators to conduct clinical trials of cabozantinib and cobimetinib, both alone and in combination with other therapies, sufficient to achieve a positive completion; Exelixis' dependence on its relationships with its collaboration partners, including, the level of their investment in the resources necessary to successfully commercialize partnered products in the territories where they are approved; the level of costs associated with Exelixis' commercialization, research and development, in-licensing or acquisition of product candidates, and other activities; Exelixis' dependence on third-party vendors for the development, manufacture and supply of its products; Exelixis' ability to protect the company's intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of Exelixis' marketed products; changes in economic and business conditions, and other factors discussed under the caption "Risk Factors" in Exelixis' annual report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 2, 2018, and in Exelixis' future filings with the SEC. The forward-looking statements made in this press release speak only as of the date of this press release. Exelixis expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Exelixis' expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks.

References:

[1] Abou-Alfa, G, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018. 379:54-63.

[2] Cancer Incidence and Mortality Worldwide. Liver Cancer. International Agency for Research on Cancer, GLOBOCAN 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed July 2018.

[3] American Cancer Society: Cancer Facts and Figures 2018. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed July 2018.

[4] Mittal S, El-Serag HB. Epidemiology of HCC: Consider the Population. *J Clin Gastroenterol*. 2013. 47:S2-S6.

[5] Weledji E, Orock G, Ngowe M, NsaghaD. How grim is hepatocellular carcinoma? *Ann Med Surg*. 2014. 3:71-76.

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