Exelixis Announces Results for Combination of Cabozantinib and Nivolumab With or Without Ipilimumab in Advanced Hepatocellular Carcinoma

January 24, 2020

– Data from the CheckMate 040 trial presented at the 2020 American Society of Clinical Oncology's Gastrointestinal Cancers Symposium –

ALAMEDA, Calif.--(BUSINESS WIRE)--Jan. 24, 2020-- Exelixis, Inc. (NASDAQ: EXEL) today announced phase 1/2 clinical trial results from the combination of cabozantinib (CABOMETYX®) and nivolumab (*Opdivo*®) with or without ipilimumab (*Yervoy*®) in advanced hepatocellular carcinoma (HCC). Data from the cabozantinib combination cohort of the CheckMate 040 trial will be presented on Friday, January 24 during Rapid Abstract Session B from 7:00 – 7:45 a.m. PT at the 2020 American Society of Clinical Oncology's Gastrointestinal Cancers Symposium (ASCO GI), which is being held in San Francisco, California, January 23-25, 2020. The data will also be included in Poster Session B from 12:00 – 1:30 p.m. PT and 4:30 – 5:30 p.m. PT on January 24.

CheckMate 040 is a phase 1/2 study that includes an exploratory cohort of patients with advanced HCC who were either treatment naïve (41%) or who were intolerant to or had progressed on prior sorafenib therapy (59%). For the 36 patients treated with the combination of cabozantinib and nivolumab (17 treatment naïve [47%] and 19 with prior sorafenib therapy [53%]), the investigator-assessed objective response rate (ORR) was 19%, and disease control rate (DCR) was 75%. Median progression-free survival (PFS) was 5.4 months, and median overall survival was 21.5 months. For the 35 patients treated with the combination of cabozantinib, nivolumab and ipilimumab (12 treatment naïve [34%] and 23 with prior sorafenib therapy [66%]), the investigator-assessed ORR was 29%, and DCR was 83%. Median PFS was 6.8 months, and median overall survival had not yet been reached.

"We are pleased to report clinically meaningful responses from CheckMate 040 cohort 6 in advanced liver cancer patients treated with these cabozantinib combinations," said Thomas Yau, M.D., Clinical Associate Professor, Department of Medicine, The University of Hong Kong, and a lead investigator of the trial. "Patients with advanced liver cancer need new and effective treatment options. Based on the cohort six findings, cabozantinib in combination with immunotherapy offers a potentially powerful and attractive new treatment approach that warrants further study in advanced liver cancer populations."

No new safety signals were identified in this combination cohort. Treatment-related grade 3 or 4 adverse events were observed in 47% of the cabozantinib and nivolumab group; events occurring in more than 5% of patients were hypertension (11%), diarrhea (11%), aspartate aminotransferase (AST) increase (8%) and lipase increase (6%). Treatment-related grade 3 or 4 adverse events were observed in 71% of the cabozantinib, nivolumab and ipilimumab group; events occurring in more than 5% of patients were AST increase (23%), lipase increase (17%), ALT increase (17%), hypertension (17%) and palmar-plantar erythrodysaesthesia (9%). Discontinuation rates due to treatment-related adverse events were 11% for the cabozantinib and nivolumab group and 20% for the cabozantinib, nivolumab and ipilimumab group.

"As we just marked one year since CABOMETYX was approved for the treatment of patients with advanced hepatocellular cancer who have previously received sorafenib, it's exciting to be sharing new data featuring cabozantinib as part of a combination with immunotherapies," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "The promising clinical activity observed for these cohorts in CheckMate 040 suggests combination therapy with cabozantinib and immunotherapy may potentially benefit patients with this aggressive disease."

More information about this trial is available at ClinicalTrials.gov.

About CheckMate 040

CheckMate 040 is a phase 1/2, open-label trial investigating nivolumab or nivolumab-based combinations in patients with advanced HCC with and without chronic viral hepatitis who are naïve, intolerant to or who have progressed during sorafenib therapy. Patients in the cabozantinib combination cohort were randomized 1:1 to receive either nivolumab plus cabozantinib or nivolumab plus cabozantinib and ipilimumab. Primary endpoints include ORR (investigator assessed using RECIST v1.1) and safety/tolerability. The trial is sponsored by Bristol-Myers Squibb. Exelixis is co-funding the trial and providing cabozantinib. Ipsen has opted in to participate in the trial and is contributing to the funding for this study under the terms of our collaboration agreement.

About HCC

Liver cancer is a leading cause of cancer death worldwide, accounting for more than 700,000 deaths and 800,000 new cases each year.[1] In the U.S., the incidence of liver cancer has more than tripled since 1980.[2] HCC is the most common form of liver cancer, making up about three-fourths of the estimated 43,000 new cases in the U.S. in 2020.[2] HCC is the fastest-rising cause of cancer-related death in the U.S.[3] Without treatment, patients with advanced HCC usually survive less than 6 months.[4]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with HCC who have been previously treated with sorafenib. 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 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.

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 occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.
- **Perforations and Fistulas:** Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed 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 event requiring medical intervention.
- **Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% 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. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.
- **Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.
- **Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% 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.
- **Proteinuria:** Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. 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 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.
- **Wound Complications:** Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding 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.
- **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 commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.
- **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.
- **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. 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 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' expectation that data from the cabozantinib cohort of the CheckMate 040 trial will be presented at the 2020 ASCO GI; the potential for cabozantinib in combination with immunotherapy to offer a powerful and attractive new approach in the treatment of advanced HCC; 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; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the potential failure of the combination of cabozantinib and nivolumab with or without ipilimumab to demonstrate safety and/or efficacy in future trials; uncertainties inherent in the product development process; the costs of conducting clinical trials, including the ability or willingness of Exelixis' collaboration partners 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; 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 October 30, 2019, 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.

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Opdivo® and Yervoy® are registered trademarks of Bristol-Myers Squibb Company.

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[1] International Agency for Research on Cancer. GLOBOCAN 2018. Liver Fact Sheet. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed January 2020.

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[3] Siegel R, Miller K, Jemal A: Cancer Statistics, 2020. CA: A Cancer Journal for Clinicians. Volume 70, Issue 1: 7-30. Available at: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590. Accessed January 2020.

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

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