Exelixis Announces Positive Preliminary Data From an Investigator-Sponsored Phase 1 Trial of XL888 and Vemurafenib

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– Combination Generally Well Tolerated; 92% Objective Response Rate Observed –

– Investigators Plan Phase 1b Triple-combination Trial of XL888, Vemurafenib, and Cobimetinib –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Nov. 16, 2014-- Exelixis, Inc. (NASDAQ:EXEL) today announced preliminary results from a phase 1 investigator-sponsored trial (IST) evaluating the safety and activity of XL888, an Exelixis-discovered small molecule oral inhibitor of Heat Shock Protein 90 (HSP90), in combination with vemurafenib in patients with unresectable stage III/IV BRAF V600 mutation-positive melanoma. Safety and efficacy results support the further investigation of 90 mg of XL888 twice weekly (BIW) and vemurafenib 960 mg twice daily (BID) in additional studies that would include a third agent.

The trial results were presented today by Keiran Smalley, Ph.D., an investigator on the trial and an associate professor at H. Lee Moffitt Cancer Center, Tampa, Florida, in a late-breaking oral presentation session at the Society for Melanoma Research 2014 International Congress, which is taking place November 13-16, 2014, in Zurich, Switzerland. Based on these results, as well as findings from coBRIM, the phase 3 pivotal trial of cobimetinib, an Exelixis-discovered MEK inhibitor, and vemurafenib in previously untreated metastatic melanoma patients with a BRAF V600 mutation, the Moffitt Center plans to initiate a phase 1b IST of the triple combination of vemurafenib, cobimetinib, and XL888 in a similar patient population.

“The BRAF inhibitor vemurafenib is active in BRAF-mutated malignant melanoma, but development of resistance is common. Preclinical studies led by Keiran Smalley, Ph.D. suggested that most BRAF inhibitor resistance mechanisms involve proteins that are clients of HSP90, and the preclinical evaluation of XL888 showed that it is highly active in vemurafenib-resistant melanoma models,” said Jeffrey Weber, MD, Ph.D., director of the Donald A. Adam Comprehensive Melanoma Research Center at the Moffitt Cancer Center and Research Institute in Tampa, FL. “The current phase 1 data show that both drugs can be given together, and compelling initial response results suggest potential cooperative activity.”

“About half of metastatic melanoma patients whose tumors harbor a BRAF V600 mutation respond to vemurafenib, but most of them develop resistance and their tumors begin to regrow,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “Multiple mechanisms drive this resistance, and the team at Moffitt found that many of them involve upregulation of HSP90 client proteins that are sensitive to XL888. We look forward to supporting the Moffitt team as they continue to evaluate XL888 as part of our IST program.”

Study Design

The phase 1 multi-cohort study is designed to evaluate the combination of vemurafenib plus escalating doses of XL888 in patients with unresectable stage III/IV BRAF V600 mutation-positive melanoma. The trial enrolls four cohorts; patients receive 960 mg of vemurafenib BID along with XL888 BIW at one of four dose levels: 30 mg (cohort 1), 45 mg (cohort 2), 90 mg (cohort 3), or 135 mg (cohort 4). Eligible patients must have a confirmed BRAF V600 mutation and have not received treatment with a BRAF or HSP90 inhibitor. The primary endpoint of the trial is to determine the safety and tolerability of the combination, including a maximum tolerated dose (MTD). Secondary endpoints include objective response rate (RECIST-1 criteria), estimates of progression-free survival (PFS) and overall survival, and analysis of pharmacodynamic biomarkers.

Study Results

The trial had enrolled fifteen subjects (cohorts 1-3, n=3; cohort 4, n=6), and the median age was 60 years. Seventy-three percent of the subjects were male, and the majority of subjects (14/15) were assessed as having the stage IV metastatic form of their disease.

The most common adverse events were consistent with previous studies of vemurafenib and included anorexia, fatigue, arthralgia, and rash. Diarrhea and vision changes were seen at all dose levels, with the highest rates being seen in cohort 4. These events resolved upon dose interruption. Dose-limiting toxicities only occurred in cohort 4 (grade 3 diarrhea and pancreatitis), and an MTD has not yet been established. The trial also reported fewer secondary cutaneous neoplasms in higher XL888 dose cohorts.

At the time of data cut-off, objective tumor regression was observed in 11 of 12 response-evaluable patients (two complete responses and nine partial responses), for an objective response rate of 92%. Additionally, one stage IIIC patient with a partial response underwent resection of residual disease and pathology showed no viable tumor cells. Three patients who did not have post baseline tumor assessments were excluded from the response analysis; two patients elected alternative treatment prior to the first post baseline scan, and the third patient was still in the first cycle of study treatment. The estimated PFS at 6- and 12-months was 63% (95% CI: 28 - 84%) and 39% (95% CI: 11 - 68%), respectively.

About XL888

XL888 is a highly potent and selective ATP-competitive inhibitor of HSP90, a molecular chaperone protein that affects the activity and stability of a range of key regulatory proteins, including kinases such as BRAF, MET, and VEGFR2. In preclinical studies, XL888 has been shown to inhibit the proliferation of a broad panel of human tumor cell lines and induce marked degradation of HSP90 client proteins, which include a number of kinases

implicated in cancer cell growth and survival. After completing phase 1 testing, Exelixis deprioritized XL888 and its other pipeline assets to focus its limited resources on the company's lead compound, cabozantinib. Investigators at the Moffitt Cancer Center conducted preclinical work showing activity of XL888 in vemurafenib-resistant melanoma models. These preclinical results provided the rationale for the current investigator-sponsored phase 1 trial.

About Exelixis

Exelixis, Inc. is a biopharmaceutical company committed to developing small molecule therapies for the treatment of cancer. Exelixis is focusing its development and commercialization efforts primarily on COMETRIQ® (cabozantinib), its wholly-owned inhibitor of multiple receptor tyrosine kinases. Another Exelixis-discovered compound, cobimetinib, a highly selective inhibitor of MEK, is being evaluated by Roche and Genentech, Inc. (a member of the Roche Group) in a broad development program under a collaboration with Exelixis. For more information, please visit the company's web site at www.exelixis.com.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the planned phase 1b triple-combination trial of XL888, vemurafenib and cobimetinib; potential future combination studies with XL888; the clinical and therapeutic potential of XL888; and Exelixis' continued support of the Moffitt team evaluating XL888. Words such as "plan," "further," "would," "can" "look forward," "suggest," "potential," 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 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. Exelixis' 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 related to the potential failure of XL888 to demonstrate safety and efficacy in clinical testing; the clinical, therapeutic and commercial value of XL888; the general sufficiency of Exelixis' capital and other resources; the uncertainty of regulatory approval processes; market competition; changes in economic and business conditions; and other factors discussed under the caption "Risk Factors" in Exelixis' quarterly report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 4, 2014 and in Exelixis' other 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.

Source: Exelixis, Inc.

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