Lilly Reports Results of Phase 3 Soft Tissue Sarcoma Study of LARTRUVO®

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- Study did not meet the primary endpoints of overall survival (OS) in the full study population or in the leiomyosarcoma (LMS) sub-population; there was no difference in survival between the study arms for either population.

- There were no new safety signals identified and the safety profile was comparable between treatment arms.

INDIANAPOLIS, Jan. 18, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today reported that the results of ANNOUNCE, the Phase 3 study of LARTRUVO® (olaratumab), in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma (STS), did not confirm the clinical benefit of LARTRUVO in combination with doxorubicin as compared to doxorubicin, a standard of care treatment. Specifically, the study did not meet the primary endpoints of overall survival (OS) in the full study population or in the leiomyosarcoma (LMS) sub-population; there was no difference in survival between the study arms for either population. LARTRUVO was well tolerated; there were no new safety signals identified and the safety profile was comparable between treatment arms. Lilly plans to present the ANNOUNCE data at an upcoming medical conference and will publish the results in a medical journal.

LARTRUVO in combination with doxorubicin previously showed an OS benefit in STS in a 133-patient, U.S.-only, randomized Phase 2 trial, which led to accelerated approval by the U.S. Food and Drug Administration and conditional marketing authorization by the European Medicines Agency. Continued approval is contingent upon verification of clinical benefit in a confirmatory trial. As ANNOUNCE did not confirm clinical benefit, Lilly is working with global regulators to determine the appropriate next steps for LARTRUVO. While these discussions are ongoing, patients who are currently receiving LARTRUVO may, in consultation with their physician, continue their course of therapy if they are receiving clinical benefit. For patients who have not previously received LARTRUVO, the results of the Phase 3 trial do not support initiating treatment with LARTRUVO in patients with STS, outside of participation in a clinical trial. At this time, Lilly is suspending promotion of LARTRUVO.

"Lilly was surprised and disappointed that LARTRUVO did not improve survival for patients with advanced soft tissue sarcoma in this study," said Anne White, president, Lilly Oncology. "Lilly is committed to helping people who have soft tissue sarcoma and we will carefully study the detailed data in an effort to better understand the different results between the two trials. We are thankful for the patients and physicians who have participated in the ANNOUNCE study."

LARTRUVO is also being studied in an ongoing global, randomized, double-blind, placebo-controlled Phase 2 trial in advanced STS in combination with gemcitabine and docetaxel.

Lilly expects to incur a charge in the first quarter of 2019 related to LARTRUVO. The exact amount of the charge has not yet been determined, but is estimated to be in the range of $70 million to $90 million (pre-tax), or approximately $0.10 per share (after tax).

In addition, the company expects this to have an impact of approximately $0.17 per share on Lilly's full-year 2019 earnings per share guidance. Lilly will provide a full update to its 2019 financial guidance, including the impact of the potential Loxo Oncology acquisition, when it announces Q4 2018 earnings. This announcement does not change Lilly's 2020 minimum financial goals.

About Soft Tissue Sarcoma

Sarcomas are a diverse and relatively rare type of cancer that usually develop in the connective tissue of the body, which include fat, blood vessels, nerves, bones, muscles, deep skin tissues and cartilage. Soft tissue sarcoma (STS) is a complex disease with multiple subtypes, making it hard to diagnose and difficult to treat. According to the American Cancer Society, in 2018, an estimated 13,040 new STS cases will be diagnosed, and more than 5,000 people will not survive their disease in the U.S. alone. For decades, there have been no first-line therapeutic advancements for STS that have improved OS.

About LARTRUVO® (olaratumab)

LARTRUVO is a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody that specifically binds PDGFR-α and prevents receptor activation. LARTRUVO exhibits *in vitro* and *in vivo* anti-tumor activity against selected sarcoma cell lines and disrupted the PDGFR-α signaling pathway in *in vivo* tumor implant models.

Information about additional clinical trials for LARTRUVO in sarcoma can be found at ClinicalTrials.gov (in the search box on the home page, type in "olaratumab").

About the ANNOUNCE Trial

ANNOUNCE is a randomized, double-blind, Phase 3 study of LARTRUVO in combination with doxorubicin, followed by LARTRUVO monotherapy, versus doxorubicin plus placebo followed by placebo, in patients with advanced or metastatic STS. The two primary endpoints are OS in the ITT population and in the LMS sub-population. Patients with locally advanced, unresectable or metastatic STS not amenable to curative treatment were enrolled and were eligible with any prior number of treatment regimens, provided they had not previously received treatment with an anthracycline.

LARTRUVO was administered at a loading dose of 20 mg/kg on days 1 and 8 of cycle 1 and 15 mg/kg on days 1 and 8 of all subsequent cycles in combination with doxorubicin 75 mg/m2 administered on day 1 of each cycle. Placebo was administered in combination with doxorubicin for 8 cycles. LARTRUVO was continued as monotherapy until disease progression.

Key secondary endpoints include safety, progression-free survival, objective response rate, and patient-reported outcomes.

INDICATION
LARTRUVO is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

This indication is approved under Accelerated Approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

IMPORTANT SAFETY INFORMATION FOR LARTRUVO

Warnings and Precautions

Infusion-Related Reactions

- Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.3%) of 485 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest. Infusion-related reactions required permanent discontinuation in 2.3% of patients and interruption of infusion in 10% of patients. All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO; 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N = 485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication. Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR.

Embryo-Fetal Toxicity

- Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

Most Common Adverse Reactions/Lab Abnormalities

- The most commonly reported adverse reactions (all grades; grade 3-4) occurring in ≥20% of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were nausea (73% vs 52%; 2% vs 3%), fatigue (69% vs 69%; 9% vs 3%), musculoskeletal pain (64% vs 25%; 8% vs 2%), mucositis (53% vs 35%; 3% vs 5%), alopecia (52% vs 40%; 0% vs 0%), vomiting (45% vs 19%; 0% vs 0%), diarrhea (34% vs 23%; 3% vs 0%) decreased appetite (31% vs 20%; 2% vs 0%), abdominal pain (23% vs 14%; 3% vs 0%), neuropathy (22% vs 11%; 0% vs 0%), and headache (20% vs 9%; 0% vs 0%).
- The most common laboratory abnormalities (all grades; grade 3-4) occurring in ≥20% of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were lymphopenia (77% vs 73%; 44% vs 37%), neutropenia (65% vs 63%; 48% vs 38%) and thrombocytopenia (63% vs 44%; 6% vs 11%), hyperglycemia (52% vs 28%; 2% vs 3%), elevated aPTT (33% vs 13%; 5% vs 0%), hypokalemia (21% vs 15%; 8% vs 3%), and hypophosphatemia (21% vs 7%; 5% vs 3%).

Use in Specific Populations

- Lactation: Because of the potential risk for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LARTRUVO and for at least 3 months following the last dose.

For more information about LARTRUVO, please see full Prescribing Information at http://pi.lilly.com/us/lartruvo-uspi.pdf**.**

About Lilly Oncology
For more than 50 years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly's commitment to people with cancer, please visit www.LillyOncology.com**.**

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and http://newsroom.lilly.com/social-channels. P-LLY

Lilly Forward-Looking Statement
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about LARTRUVO (olaratumab) as a treatment for patients with advanced soft tissue sarcoma and reflects Lilly's current belief. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date or that discussions with regulatory agencies will result in LARTRUVO (olaratumab) maintaining regulatory approval. There can also be no guarantees that the company has accurately estimated the accounting charge and financial impact of the ANNOUNCE study results. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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