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FDA Approves Lilly's LARTRUVO™ (olaratumab) in Combination with Doxorubicin for Soft Tissue Sarcoma

- LARTRUVO, in combination with doxorubicin, is the first FDA-approved front-line therapy for soft tissue sarcoma in four decades**
- The approval was based on results from the positive Phase 2 JGDG trial**
- LARTRUVO received the FDA's Breakthrough Therapy Designation and was approved under the Agency's Accelerated Approval program**

INDIANAPOLIS, Oct. 19, 2016 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the U.S. Food and Drug Administration (FDA) has granted approval of LARTRUVO™ (olaratumab injection, 10 mg/mL), in combination with doxorubicin, for the treatment of adults 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. LARTRUVO's indication is approved under Accelerated Approval, and is based on data from the Phase 2 portion of the pivotal JGDG trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. LARTRUVO, in combination with doxorubicin, is the first FDA-approved front-line therapy for STS in four decades. The confirmatory Phase 3 trial, ANNOUNCE, is fully enrolled.

"LARTRUVO represents an important step forward in soft tissue sarcoma treatment," said William D. Tap, M.D., chief of the sarcoma medical oncology services at Memorial Sloan Kettering Cancer Center in New York and the principal investigator of the JGDG registration trial. "We are pleased with this approval, which will provide patients with a treatment option that offers new hope in their battle against this difficult disease."

Soft tissue sarcoma is a complex disease with multiple subtypes, making it hard to diagnose and difficult to treat. For decades, there have been no first-line therapeutic advancements for STS that have improved overall survival (OS). According to the American Cancer Society, in 2015, there were an estimated 12,000 new STS cases diagnosed and nearly 5,000 deaths in the U.S. alone, representing an unmet medical need.

LARTRUVO is the first monoclonal antibody approved to treat STS. It also received Fast Track, Orphan Drug and Breakthrough Therapy designations from the FDA for this indication, and was reviewed and approved under the FDA's Accelerated Approval program. This program allows for earlier approval of drugs that treat serious conditions and that fill an unmet medical need.

"The approval of LARTRUVO is based on an encouraging and positive study for patients, and represents progress in soft tissue sarcoma treatment. For the first time in four decades, we now have a combination regimen - LARTRUVO and doxorubicin - that offers progress over doxorubicin alone in the front-line setting, by improving overall survival for people with soft tissue sarcoma," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "This continues our commitment to discovering new ways to treat cancer, including for people who have rare types of cancer."

"The entire sarcoma patient community is excited to have an innovative medicine approved for the treatment of advanced soft tissue sarcoma," said Bert E. Thomas IV, PhD, MBA, CEO of the Sarcoma Foundation of America. "We are confident that the approval of LARTRUVO may help these patients live longer."

The approval of LARTRUVO is based on the results of JGDG, an open-label, randomized, active-controlled study of 133 patients, which compared LARTRUVO, in combination with doxorubicin chemotherapy, to doxorubicin alone in patients with STS with a histologic subtype for which an anthracycline-containing regimen was appropriate and which is not amenable to curative treatment with surgery or radiotherapy. The efficacy outcome measures were OS, progression-free survival (PFS), and objective response rate (ORR).

Median OS was improved by 11.8 months in patients randomized to receive LARTRUVO plus doxorubicin compared to patients randomized to doxorubicin alone, and was statistically significant. Median OS was 26.5 months (95% CI: 20.9, 31.7) on the LARTRUVO-doxorubicin arm compared to 14.7 months (95% CI: 9.2, 17.1) on the doxorubicin-only arm (stratified hazard ratio [HR], 0.52; 95% CI: 0.34, 0.79, < 0.05). The study met its prespecified protocol-defined endpoint for PFS.

Patients treated on the LARTRUVO and doxorubicin arm achieved 8.2 months (95% CI: 5.5, 9.8) of median PFS compared to 4.4 months (95% CI: 3.1, 7.4) on the doxorubicin-only arm (stratified hazard ratio [HR], 0.74; 95% CI: 0.46, 1.19), based on independent review. The number of events at the time of analysis was 37 (56%) on the LARTRUVO-doxorubicin arm and 34 (51%) on the doxorubicin-only arm. The number of deaths at the time of analysis was 39 (59%) on the LARTRUVO-doxorubicin arm and 52 (78%) on the doxorubicin-only arm. Objective response rate (ORR), based on independent review and defined as complete response (CR) plus partial response (PR), was also assessed with an ORR of 18.2 percent (95% CI: 9.8, 29.6) (CR, 4.5%; PR, 13.6%) on the LARTRUVO-doxorubicin arm and 7.5 percent (95% CI: 2.5, 16.6) (CR, 1.5%; PR, 6%) on the doxorubicin-only arm.

The labeling for LARTRUVO contains Warnings and Precautions for infusion-related reactions and embryo-fetal toxicity. The most commonly reported adverse reactions (all grades) occurring in ≥ 20 percent of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were nausea (73% vs 52%), fatigue (69% vs 69%), musculoskeletal pain (64% vs 25%), mucositis (53% vs 35%), vomiting (45% vs 19%), diarrhea (34% vs 23%) and headache (20% vs 9%). The most common laboratory abnormalities (all grades) occurring in $\geq 20\%$ of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were lymphopenia (77% vs 73%), neutropenia (65% vs 63%), thrombocytopenia (63% vs 44%), hyperglycemia (52% vs 28%), elevated aPTT (33% vs 13%), hypokalemia (21% vs 15%) and hypophosphatemia (21% vs 7%). Febrile neutropenia was reported in 13% of LARTRUVO plus doxorubicin-treated patients versus 12% of doxorubicin-treated patients.

Adverse reactions resulting in permanent discontinuation of LARTRUVO occurred in 8% (5/64) of patients. The most common adverse reaction leading to LARTRUVO discontinuation was infusion-related reaction (3%). Dose reductions of LARTRUVO for adverse reactions occurred in 25% (16/64) of patients; the most common adverse reaction leading to dose reduction was Grade 3 or 4 neutropenia (20%). Dose delays of LARTRUVO for adverse reactions occurred in 52% (33/64) of patients; the most common adverse reactions resulting in dose delays were neutropenia (33%), thrombocytopenia (8%) and anemia (5%). See the full Important Safety Information at the end of this press release and the [Prescribing Information](#).

Lilly is committed to helping patients access LARTRUVO and offers support programs for qualified uninsured, underinsured and insured patients who receive LARTRUVO for its FDA-approved indication and who may need assistance with their out-of-pocket prescription medication costs, including a co-pay program where qualified patients pay no more than \$25 per infusion. Patients and healthcare professionals with questions about LARTRUVO should contact The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or visit www.lilly.com.

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").

A Phase 3 trial of LARTRUVO and doxorubicin in advanced STS is fully enrolled (ClinicalTrials.gov Identifier: [NCT02451943](https://clinicaltrials.gov/ct2/show/study/NCT02451943)).

About the JGDG Trial

JGDG was an open-label, randomized, active-controlled study that compared LARTRUVO, in combination with doxorubicin chemotherapy, to doxorubicin alone in patients with unresectable, soft tissue sarcoma (STS).

The study enrolled 133 doxorubicin-naïve patients with STS with a histologic subtype for which an anthracycline-containing regimen was appropriate and which is not amenable to curative treatment with surgery or radiotherapy. Sixty-six patients with an ECOG performance status of 0 - 2 were randomized to the LARTRUVO-doxorubicin arm and 67 to the doxorubicin-only arm.

Patients were randomized to receive LARTRUVO at 15 mg/kg as an intravenous infusion on day one of each 21-day cycle in combination with 75 mg/m² doxorubicin, and LARTRUVO only on day eight. Doxorubicin was administered following LARTRUVO infusion on day one of each 21-day cycle for up to eight cycles. After doxorubicin was discontinued, patients on the LARTRUVO plus doxorubicin arm without evidence of disease progression or unacceptable toxicity could continue to receive LARTRUVO monotherapy until disease progression. All patients received the cardioprotectant dexrazoxane prior to doxorubicin in cycles five to eight.

About Sarcomas

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 is a complex disease with multiple subtypes, making it very hard to diagnose and difficult to treat. For decades, there have been no front-line therapeutic advancements for STS that have improved overall survival. According to the American Cancer Society, in 2015, there were an estimated 12,000 new STS cases diagnosed and nearly 5,000 deaths in the U.S. alone.

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 $\geq 20\%$ 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 $\geq 20\%$ 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](#).

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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 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 newsroom.lilly.com/social-channels. (P-LLY)

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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 the potential of LARTRUVO (olaratumab) as a treatment of advanced soft tissue sarcoma, and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There can be no guarantee that future study results and patient experience will be consistent with the study findings to date. Among other things, there can also be no guarantee that LARTRUVO will receive regulatory approval for any future indications or that it will prove to be commercially successful. 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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The Lilly logo is rendered in a vibrant red, cursive script font. The letters are fluid and interconnected, with a classic, elegant feel. The 'L' is particularly large and prominent, leading into the 'i', 'l', 'l', 'e', and 'y' which follow in a similar flowing style.

Logo - <http://photos.prnewswire.com/prnh/20031219/LLYLOGO>

To view the original version on PR Newswire, visit: <http://www.prnewswire.com/news-releases/fda-approves-lillys-lartruvo-olaratumab-in-combination-with-doxorubicin-for-soft-tissue-sarcoma-300347858.html>

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