SpringWorks Therapeutics Announces Publication of Long-Term Efficacy and Safety Data from the Phase 3 DeFi Trial of OGSIVEO® (nirogacestat) in Adults with Desmoid Tumors in the Journal of Clinical Oncology

October 21, 2025

Long-term continuous OGSIVEO treatment for up to 4 years was associated with further tumor size reductions, increase in objective response rate, sustained improvement in desmoid tumor symptoms and consistent safety profile

STAMFORD, Conn., Oct. 21, 2025 (GLOBE NEWSWIRE) -- SpringWorks Therapeutics, Inc., a healthcare company of Merck KGaA, Darmstadt, Germany, announced today that long-term efficacy and safety data from the Phase 3 DeFi trial of OGSIVEO® (nirogacestat), an oral gamma secretase inhibitor for the treatment of adults with progressing desmoid tumors who require systemic treatment, were published in the *Journal of Clinical Oncology (JCO).* The long-term follow-up data from DeFi, which was a global, randomized, multicenter, double-blind, placebo-controlled trial, were previously presented at the 2024 Connective Tissue Oncology Society Meeting. The new results published in *JCO* utilized a December 2024 data cutoff date (the final data cut of the clinical trial) and showed that longer-term treatment with OGSIVEO was associated with further reductions in tumor size, an increase in objective response rate (ORR) with additional partial responses (PRs) and complete responses (CRs), sustained improvement in patient reported outcomes, and a consistent safety profile compared to the April 2022 data cut off utilized for the primary analysis of the trial. The *JCO* e-publication can be accessed at the following link: https://ascopubs.org/doi/abs/10.1200/JCO-25-00582.

“Desmoid tumors are locally aggressive and complex tumors whose unpredictable growth can cause significant pain, functional impairment, and emotional distress. For many patients, these tumors disrupt daily life in ways that are often underestimated, so advancing treatment options that offer durable symptom relief and tumor control can make a meaningful difference for patients,” said Ravin Ratan, M.D., M.Ed., Associate Professor, Department of Sarcoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center in Houston and lead author of the *JCO* publication. “While the optimal duration of therapy may vary for many patients and is best decided between individual patients and their physicians, the new data published in the *JCO* provide physicians with additional information regarding the long-term safety and efficacy of nirogacestat, and will help inform treatment decisions and improve patient care.”

In the Phase 3 DeFi trial primary analysis, which was previously published in the *New England Journal of Medicine*, OGSIVEO showed significant improvement versus placebo in progression-free survival (PFS), objective response rate (ORR), and patient-reported outcomes (PRO) in adult patients with progressing desmoid tumors (DT; median [range] exposure: 20.6 [0.3-33.6] months).[1] In the *JCO* publication, long-term efficacy and safety were evaluated in patients randomized to OGSIVEO and followed through the final data-cutoff date of December 2024. The median duration of OGSIVEO treatment in these patients was 33.6 (0.3 to 61.8) months.

Objective response rates (ORR) improved with long-term OGSIVEO treatment. While ORR was 34.3% (n = 24) in year 1, it increased to 45.7% (n = 32) in patients who received OGSIVEO for up to 4 years, with three additional complete responses (CRs) and three additional partial responses (PRs) since the primary analysis and yielding 24 (34.3%) PRs and 8 (11.4%) CRs in total. The median best percent reduction from baseline in target tumor size by RECIST 1.1 with continuous OGSIVEO treatment was −32.3% at year one (n=46) and −75.8% (n=15) for patients completing at least four years of treatment. Improvements in patient-reported outcomes (PROs) of pain, desmoid tumor-specific symptom severity, desmoid tumor-specific physical functioning, global health status/quality of life and role functioning occurred early (as early as Cycle 2, the first post-treatment timepoint evaluated as disclosed at the primary analysis) and were sustained with up to 45 months of treatment with OGSIVEO.

Overall, the incidence and severity of frequently reported treatment emergent adverse events (TEAEs) decreased through years two, three and four of treatment. The most common adverse events (≥15%) reported in patients receiving OGSIVEO were diarrhea, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection, and dyspnea. Please see Important Safety Information below, including Warnings & Precautions relating to diarrhea, ovarian toxicity, hepatotoxicity, non-melanoma skin cancers, electrolyte abnormalities, and embryo-fetal toxicity.[2]

“We are pleased that long-term continuous nirogacestat treatment for up to four years was associated with additional late responses and further tumor size reductions,” said Uche Iloeje, M.D., Senior Vice President, Global Head of Medical Affairs at SpringWorks Therapeutics. “These data represent the largest prospective analysis from a randomized controlled clinical trial of long-term exposure to any systemic agent for desmoid tumors and provide valuable insights on the benefits of OGSIVEO for patients with desmoid tumors.”

About the DeFi Trial

DeFi (NCT03785964) was a global, randomized (1:1), multicenter, double-blind, placebo-controlled pivotal Phase 3 trial that evaluated the efficacy, safety and tolerability of nirogacestat in adult patients with progressing desmoid tumors. The double-blind phase of the study randomized 142 patients (nirogacestat, n=70; placebo n=72) to receive 150 mg of nirogacestat or placebo twice daily. Key eligibility criteria included tumor progression by ≥20% as measured by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) within 12 months prior to screening. The primary endpoint was progression-free survival, as assessed by blinded independent central review, or death by any cause. Secondary and exploratory endpoints included safety and tolerability measures, objective response rate, duration of response, changes in tumor volume assessed by magnetic resonance imaging (MRI), and changes in patient-reported outcomes. DeFi also included an open-label extension phase.

About Desmoid Tumors

Desmoid tumors are rare, locally aggressive tumors of the soft tissues that can be serious, debilitating, and, in rare cases when vital structures are

impacted, life-threatening.[3,4]

Desmoid tumors are most commonly diagnosed in patients between the ages of 20 and 44 years, with a two-to-three times higher prevalence in females.[5,6] In the U.S., up to 1650 people are diagnosed with desmoid tumors every year.[5,7,8]

Although desmoid tumors do not metastasize, they can be associated with recurrence rates of up to 77% after surgical resection.[6,9] Desmoid tumor experts and treatment guidelines now recommend systemic therapies as first-line intervention for most tumor locations requiring treatment.[10,11]

About OGSIVEO® (nirogacestat)

OGSIVEO® (nirogacestat) is an oral, selective, small molecule gamma secretase inhibitor approved in the United States and European Union as monotherapy for the treatment of adult patients with progressing desmoid tumors who require systemic treatment.

The FDA and the EMA have granted Orphan Drug designation for OGSIVEO for the treatment of desmoid tumors.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Diarrhea:** Diarrhea occurred in 84% of patients treated with OGSIVEO. Grade 3 events occurred in 16% of patients. Monitor patients and manage using antidiarrheal medications. Modify dose as recommended.
- **Ovarian Toxicity:** Female reproductive function and fertility may be impaired in patients treated with OGSIVEO. Impact on fertility may depend on factors like duration of therapy and state of gonadal function at time of treatment. Long-term effects on fertility have not been established. Advise patients on the potential risks for ovarian toxicity before initiating treatment. Monitor patients for changes in menstrual cycle regularity or the development of symptoms of estrogen deficiency, including hot flashes, night sweats, and vaginal dryness.
- **Hepatotoxicity:** ALT or AST elevations occurred in 30% and 33% of patients, respectively. Grade 3 ALT or AST elevations (>5 × ULN) occurred in 6% and 2.9% of patients. Monitor liver function tests regularly and modify dose as recommended.
- **Non-Melanoma Skin Cancers:** New cutaneous squamous cell carcinoma and basal cell carcinoma occurred in 2.9% and 1.4% of patients, respectively. Perform dermatologic evaluations prior to initiation of OGSIVEO and routinely during treatment.
- **Electrolyte Abnormalities:** Decreased phosphate (65%) and potassium (22%) occurred in OGSIVEO-treated patients. Phosphate <2 mg/dL occurred in 20% of patients. Grade 3 decreased potassium occurred in 1.4% of patients. Monitor phosphate and potassium levels regularly and supplement as necessary. Modify dose as recommended.
- **Embryo-Fetal Toxicity:** Oral administration of nirogacestat to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity at maternal exposures below human exposure at the recommended dose of 150 mg twice daily. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment with OGSIVEO and for 1 week after the last dose.

ADVERSE REACTIONS

- The most common (≥15%) adverse reactions were diarrhea, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection, and dyspnea.
- Serious adverse reactions occurring in ≥2% of patients were ovarian toxicity (4%).
- The most common laboratory abnormalities (≥15%) were decreased phosphate, increased urine glucose, increased urine protein, increased AST, increased ALT, and decreased potassium.

DRUG INTERACTIONS

- **CYP3A Inhibitors and Inducers:** Avoid concomitant use with strong or moderate CYP3A inhibitors (including grapefruit products, Seville oranges, and starfruit) and strong or moderate CYP3A inducers.
- **Gastric Acid Reducing Agents:** Avoid concomitant use with proton pump inhibitors and H2 blockers. If concomitant use cannot be avoided, OGSIVEO can be staggered with antacids (e.g., administer OGSIVEO 2 hours before or 2 hours after antacid use).
- Consult the full Prescribing Information prior to and during treatment for important drug interactions.

To report suspected adverse reactions, contact SpringWorks Therapeutics at 1-888-400-SWTX (1-888-400-7989) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information for OGSIVEO for more information.

About SpringWorks Therapeutics

SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany, is a commercial-stage biopharmaceutical company dedicated to improving the lives of patients with rare tumors. We developed and are commercializing the first and only FDA and EC approved medicine for adults with desmoid tumors and the first and only FDA and EC approved medicine for both adults and children with neurofibromatosis type 1 associated plexiform neurofibromas (NF1-PN). We are also advancing a portfolio of novel targeted therapy product candidates for patients with

additional rare tumors and hematological cancers.

For more information, visit www.springworkstx.com and follow @SpringWorksTx on X, LinkedIn, Facebook, Instagram and YouTube.

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across life science, healthcare and electronics. More than 62,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From providing products and services that accelerate drug development and manufacturing as well as discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2024, Merck KGaA, Darmstadt, Germany, generated sales of € 21.2 billion in 65 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany, operate as MilliporeSigma in life science, EMD Serono in healthcare and EMD Electronics in electronics. Since its founding in 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.

Contacts:

Media
Media@Springworkstx.com

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