Mural Oncology Presents Clinical and Preclinical Data Across its Pipeline at the 39th Annual Meeting of the Society for Immunotherapy of Cancer (SITC)

November 7, 2024

Less frequent IV dosing with nemvaleukin in patients with select advanced solid tumors, including ovarian cancer and mucosal melanoma, showed tumor site-specific pharmacodynamic activity and immune activation

Preclinical data demonstrated durable immune responses and tumor growth inhibition with Mural's IL-18 variants, reinforcing pursuit of IND-enabling studies with candidate nomination anticipated by the end of 2024, and IND submission expected in Q4 2025

Additional preclinical data from Mural's IL-12 program suggest the company's approach may unlock the potential of IL-12 as a therapeutic by mitigating the cytokine's historic toxicity; company continues to expect candidate nomination by the end of 2024

WALTHAM, Mass. and DUBLIN, Nov. 07, 2024 (GLOBE NEWSWIRE) -- Mural Oncology plc (Nasdaq: MURA), a clinical-stage immuno-oncology company developing novel, investigational engineered cytokine therapies designed to address areas of unmet need for patients with a variety of cancers, shared three poster presentations at the 39th Annual Meeting of the Society for Immunotherapy of Cancer (SITC), taking place November 6-10, 2024 in Houston.

Data presented from the ARTISTRY-3 clinical trial of Mural's lead candidate, nemvaleukin alfa (nemvaleukin), showed tumor site-specific pharmacodynamic activity and immune activation in patients with ovarian cancer and mucosal melanoma. In addition, Mural presented preclinical data from its interleukin (IL)-12 and IL-18 programs that supported the company's unique protein engineering capabilities to overcome shortcomings associated with cytokines.

"To date, nemvaleukin, as both a single agent and in combination with PD-1, has shown durable antitumor activities with manageable safety profile in an outpatient setting. In order to make nemvaleukin treatment administration more convenient for both patients and providers, we initiated the ARTISTRY-3 clinical trial to evaluate the effects of a less frequent IV dosing schedule," said Sarina Piha-Paul, MD, Associate Professor, Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center and senior author of the ARTISTRY-3 poster. "The data from ARTISTRY-3 reveal that less frequent IV dosing of nemvaleukin demonstrated tumor-site immune activation dominated by cytolytic effector NK cells and CD8+ T cells and further support the mechanism of action of nemvaleukin."

The details for the presentations are as follows, and all posters are available at muraloncology.com/publications.

Tumor microenvironment pharmacodynamic effect of nemvaleukin less frequent intravenous dosing in multiple solid tumors: results from the phase 1/2 ARTISTRY-3 study (Friday, Nov. 8: Abstract #217)
Nemvaleukin is a novel, engineered fusion protein designed to leverage antitumor effects of the IL-2 pathway while mitigating the hallmark toxicities that have historically limited its use. ARTISTRY-3, a phase 1/2 study, evaluated less frequent intravenous (LFIV) dosing of nemvaleukin in advanced solid tumors.

Paired biopsies were available from 8 patients across the three different dosing schedules of nemvaleukin (Schedule 1: dosing on day 1; Schedule 2: dosing on days 1 and 8; Schedule 3: dosing on days 1 and 4).

Collectively, LFIV nemvaleukin demonstrated tumor-site-specific pharmacodynamic activity and immune activation. Nemvaleukin treatment increased cytolytic NK and CD8 T cell densities in the tumor microenvironment. Density ratios of CD8 and NK cells relative to immune-suppressive T_{regs} were also favorable for the nemvaleukin LFIV regimen. The results were seen in biopsies from both mucosal melanoma and ovarian cancer tumors, supporting the hypothesis that nemvaleukin has the potential to recruit cytolytic effectors to poorly immunogenic tumor sites.

Mural is currently running two late-stage, potentially registrational trials in platinum-resistant ovarian cancer (ARTISTRY-7) and mucosal melanoma (ARTISTRY-6, cohort 2), with data readouts expected in late Q1/early Q2 2025 and Q2 2025, respectively.

Preclinical efficacy and immune activity of half-life extended IL-18 fusion proteins resistant to IL-18BP suppression (Saturday, Nov. 9: Abstract #1340)
IL-18 is a potent immune-stimulating cytokine, but it is limited by IL-18 binding protein (IL-18BP), a secreted high-affinity decoy receptor that neutralizes IL-18, thus limiting its activity over time. Mural's protein engineering aims to address the shortcomings of native IL-18 in two ways. First through the introduction of mutations designed to minimally impact the native structure while eliminating binding to IL-18BP. Secondly, by extending the half-life of IL-18BP via fusion to a protein scaffold to increase the cytokine's exposure, allowing for sustained immune stimulation.

In preclinical models, a weekly dosing regimen in mice provided durable immune responses and tumor growth inhibition. These mouse ortholog variants demonstrated resistance to IL-18BP and increased half-life, with durable expansion of immune-stimulating NK and CD8 T cells.

These studies support pursuit of IND-enabling studies for first-in-human clinical trials. Mural plans to nominate a development candidate for its IL-18 program by the end of 2024 and intends to submit an Investigational New Drug (IND) Application to the FDA in Q4 2025.

Modulation of IL-12p70 exposure and activity following sequential administration of tumor targeted self-assembling split IL-12 subunits (Saturday, Nov. 9: Abstract #1300)
IL-12p70 is a potent stimulator of the immune system with profound anti-tumor activity but very poor tolerability. Mural is developing an innovative

approach to mitigate that toxicity by creating inactive split IL-12 subunits (IL-12p35 and IL-12p40) and assembling functional IL-12p70 predominantly in the tumor and tumor microenvironment.

In murine models, increasing the interval time between subunit injections or reducing the dose level of the second subunit effectively modulated serum drug concentration while maintaining IL-12 levels in the tumor. Pharmacokinetics and pharmacodynamics were also assessed in non-human primates, where the inactive subunits were assembled and formed functional IL-12p70 in the periphery.

Together, these data suggest Mural's novel approach may unlock the potential of IL-12p70 as a therapeutic by mitigating the toxicity associated with systemic administration.

Mural plans to nominate a development candidate for its IL-12 program by the end of 2024.

About Mural Oncology
Mural Oncology is leveraging its novel protein engineering platform to develop cytokine-based immunotherapies for the treatment of cancer. By combining our expertise in cytokine biology and immune cell modulation and our protein engineering platform, we are developing medicines to deliver meaningful and clinical benefits to people living with cancer. Our mission is to broaden the potential, and reach, of cytokine-based immunotherapies to improve the lives of patients. Our lead candidate, nemvaleukin, is currently in potentially registrational trials in platinum-resistant ovarian cancer and mucosal melanoma reading out in the first half of 2025. Mural Oncology has its registered office in Dublin, Ireland, and its primary facilities in Waltham, Mass. For more information, visit Mural Oncology's website at www.muraloncology.com and follow us on LinkedIn and X.

About Nemvaleukin
Nemvaleukin alfa (nemvaleukin) is a novel, engineered fusion protein designed to leverage antitumor effects of the IL-2 pathway while mitigating the hallmark toxicities that limit its use. Nemvaleukin selectively binds to the intermediate-affinity IL-2 receptor (IL-2R) and is sterically occluded from binding to the high-affinity IL-2R. Because of this molecular design, nemvaleukin treatment leads to preferential expansion of antitumor CD8+ T cells and natural killer cells, with minimal expansion of immunosuppressive regulatory T cells. Nemvaleukin is currently being evaluated in two potentially registrational late-stage trials.

About Mural Oncology's IL-18 Program
IL-18 is a potent immune-stimulating cytokine, but its efficacy is blunted by IL-18 binding protein (IL-18BP), a high affinity decoy receptor that neutralizes IL-18, thereby rendering it ineffective. Native IL-18's potency is also limited by its short half-life. Mural's protein engineering aims to address the shortcomings of native IL-18 in two ways. First through the introduction of mutations designed to minimally impact the native structure while eliminating binding to IL-18BP. Secondly, half-life extension via fusion to a protein scaffold increases the cytokine's exposure, allowing for sustained immune stimulation. Together, these have demonstrated more durable immunological effect in preclinical studies. Mural intends to nominate a development candidate for its IL-18 program by the end of 2024 and file an IND submission by Q4 2025.

About Mural Oncology's IL-12 Program
Native IL-12 is a highly potent pro-inflammatory cytokine that has a narrow therapeutic index when administered systemically. To mitigate this toxicity, Mural, through its novel approach to protein engineering, split the IL-12p70 heterodimer into two inactive monomers: IL12p35 and IL-12p40. These individual subunits are then separately fused to antibody fragments and sequentially injected, which deliver and concentrate IL-12 preferentially in the tumor microenvironment to limit systemic exposure. In preclinical studies, Mural's engineered IL-12 achieved the desired reduction in serum while maintaining tumor concentrations providing the potential to reduce systemic toxicities. Mural intends to nominate a development candidate for its IL-12 program by the end of 2024.

Forward-Looking Statements
Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding: the company's pipeline and development programs, including the expected timing of clinical updates from the ARTISTRY-6 and ARTISTRY-7 trials, the expected timing of preclinical updates, candidate nomination, and IND submission, including with respect to the company's IL-18 and IL-12 programs, the potential of the company's product candidates and programs to address unmet medical needs, and the continued progress of its pipeline and programs. Any forward-looking statements in this press release are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include, among others, the inherent risks and uncertainties associated with competitive developments, preclinical development, clinical trials, recruitment of patients, product development activities and regulatory approval requirements; that preclinical or interim results and data from ongoing clinical studies of the company's cytokine programs and product candidates may not be predictive of future or final results from such studies, results of future clinical studies or real-world results; future clinical trials or future stages of ongoing clinical trials may not be initiated or completed on time or at all; the company's product candidates, including nemvaleukin, could be shown to be unsafe or ineffective; changes in the cost, scope and duration of development activities; the U.S. Food and Drug Administration may make adverse decisions regarding the company's product candidates; and those other risks and uncertainties set forth in the company's filings with the Securities and Exchange Commission ("SEC"), including its Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2024 and in subsequent filings the company may make with the SEC. All forward-looking statements contained in this press release speak only as of the date of this press release. The company anticipates that subsequent events and developments will cause its views to change. However, the company undertakes no obligation to update such forward-looking statements to reflect events that occur or circumstances that exist after the date of this press release, except as required by law.

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