Alkermes Advances ALKS 4230 into Monotherapy Expansion Phase of ARTISTRY-1 in Patients With Renal Cell Carcinoma or Melanoma

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-- Initiation of Monotherapy Efficacy Evaluation Follows Selection of Recommended Phase 2 Dose in Dose-Escalation Stage --

-- Proof-of-Mechanism Demonstrated by Desired Expansion of Tumor-Killing Immune Cells While Avoiding Activation of Immunosuppressive Cells --

DUBLIN, June 12, 2019 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced the initiation of the monotherapy expansion stage of its ARTISTRY-1 clinical trial to evaluate the efficacy, safety and tolerability of ALKS 4230 in treating patients with renal cell carcinoma or melanoma. Initiation of this portion of the ongoing study follows the identification of 6 µg/kg/day administered intravenously as the recommended monotherapy dose of ALKS 4230 to evaluate in these select tumor types. The maximum tolerated dose of ALKS 4230 has not yet been reached, and the dose-escalation stage of the ARTISTRY-1 study is continuing. ALKS 4230 is a novel, engineered fusion protein designed to selectively expand tumor-killing immune cells while avoiding the activation of immunosuppressive cells by preferentially binding to the intermediate-affinity interleukin-2 (IL-2) receptor complex.

"At the 6 µg/kg/day dose, data from the dose-escalation stage of ARTISTRY-1 demonstrated the tolerability profile we set out to achieve for ALKS 4230, along with desired lymphocyte cell expansion without corresponding T_{reg} activation. This validates our design rationale for ALKS 4230, and we now look forward to progressing into the expansion stage to evaluate ALKS 4230 as monotherapy in select tumor types," said Craig Hopkinson, M.D., Chief Medical Officer and Senior Vice President of Medicines Development and Medical Affairs at Alkermes. "We plan to present the first efficacy data from across the ALKS 4230 development program at a medical meeting later this year, pending conference acceptance."

Selection of the recommended phase 2 dose of ALKS 4230 as monotherapy was made following the completion of five dose-escalation cohorts, spanning a dose range of 0.1 µg/kg/day to 6 µg/kg/day, in 36 patients who were refractory to prior administered therapies known to demonstrate clinical benefit. Data from the completed cohorts demonstrated dose-dependent pharmacodynamic effects on circulating natural killer (NK) cells and $CD8^+$ T cells, and minimal and non-dose dependent effects on immunosuppressive regulatory T cells (T_{regs}). The newly initiated monotherapy expansion stage will assess objective efficacy measures of ALKS 4230 administered intravenously daily for five consecutive days in up to 105 patients refractory to prior administered therapies with renal cell carcinoma or melanoma, two tumor types for which high-dose IL-2 has demonstrated durable anti-tumor responses as a monotherapy treatment.[1]

Data from the initial four cohorts of the dose-escalation stage of ARTISTRY-1 were presented at the 2018 Society for Immunotherapy of Cancer (SITC) Annual Meeting. Treatment with ALKS 4230 at 3 µg/kg/day resulted in a dose-dependent increase in circulating NK cells and $CD8^+$ T cells with a near 4-fold and 2-fold expansion, respectively, and minimal, non-dose-dependent change in T_{regs}. Further effector-cell expansion was observed in cohort 5 at the 6 µg/kg/day dose, with minimal increase in circulating T_{regs}. No dose-limiting toxicities were observed in cohort 5. Fever and chills were the most common treatment-related adverse events (AEs) for ALKS 4230 across all cohorts, and the safety profile observed with ALKS 4230 was consistent with the known profile of cytokine therapy.

About ALKS 4230

ALKS 4230 is a novel, engineered fusion protein designed to selectively expand tumor-killing immune cells while avoiding the activation of immunosuppressive cells by preferentially binding to the intermediate-affinity interleukin-2 (IL-2) receptor complex. The selectivity of ALKS 4230 is designed to leverage the proven anti-tumor effects of existing IL-2 therapy while mitigating certain limitations.

About the ARTISTRY Clinical Program

ARTISTRY is an Alkermes-sponsored clinical program evaluating ALKS 4230 in patients with advanced solid tumors. ARTISTRY-1 is an ongoing phase 1/2 study in which ALKS 4230 is administered as an intravenous infusion daily for five consecutive days. ARTISTRY-1 has three distinct stages: an ongoing monotherapy dose-escalation stage, the newly initiated monotherapy expansion stage and an ongoing combination therapy stage with the PD-1 inhibitor KEYTRUDA® (pembrolizumab) in patients with select advanced solid tumors.

ARTISTRY-2 is an ongoing phase 1/2 study of ALKS 4230 administered subcutaneously as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors. ARTISTRY-2 is designed to explore the safety, tolerability and efficacy of ALKS 4230 administered subcutaneously and assess once-weekly and once-every-three-week dosing schedules.

About Alkermes

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines for the treatment of central nervous system (CNS) diseases and oncology. The company has a diversified commercial product portfolio and a substantial clinical pipeline of product candidates for chronic diseases that include schizophrenia, depression, addiction, multiple sclerosis and cancer. Headquartered in Dublin, Ireland, Alkermes plc has an R&D center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and a manufacturing facility in Wilmington, Ohio. For more information, please visit Alkermes' website at www.alkermes.com.

Note Regarding Forward-Looking Statements

Certain statements set forth in this press release constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the potential therapeutic value of ALKS 4230; clinical development

plans for ALKS 4230, including details of the ongoing ARTISTRY-1 and ARTISTRY-2 phase 1/2 studies and the company's plans for presentation of data relating to the ARTISTRY development program. You are cautioned that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, many of which are beyond the company's control, which could cause actual results to differ materially from those expressed or implied in the forward-looking statements. These risks and uncertainties include, among others, whether preclinical and early clinical results for ALKS 4230, as a monotherapy or in combination with pembrolizumab, will be predictive of future clinical study results; whether ALKS 4230, as a monotherapy or in combination, could be shown to be unsafe or ineffective; whether future clinical trials or future stages of ongoing clinical trials for ALKS 4230, as a monotherapy or in combination, will be initiated or completed on time or at all; changes in the cost, scope and duration of development activities for ALKS 4230; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2018 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release.

KEYTRUDA® is a registered trademark of Merck & Co., Inc.

[1] Rosenberg S. A. (2014). IL-2: the first effective immunotherapy for human cancer. *Journal of immunology (Baltimore, Md.: 1950)*, *192*(12), 5451–5458. doi:10.4049/jimmunol.1490019

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