Monte Rosa Therapeutics Announces Interim PK/PD and Clinical Data for MRT-2359 in Phase 1/2 Trial for MYC-Driven Solid Tumors

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Optimal levels of degradation of GSPT1 in peripheral blood mononuclear cells and tumors observed at all doses, consistent with preclinical studies

Tumor size reductions observed in patients with biomarker-positive tumors

Safety profile supports further clinical development of MRT-2359

Conference call and webcast at 8:00 a.m. ET today

BOSTON, Oct. 17, 2023 (GLOBE NEWSWIRE) -- Monte Rosa Therapeutics, a clinical-stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today announced interim data from the Phase 1 dose escalation part of its ongoing Phase 1/2 open-label, multicenter study of MRT-2359 in patients with MYC-driven solid tumors, including lung cancers and high-grade neuroendocrine cancer. MRT-2359 is an investigational, orally bioavailable, GSPT1-directed MGD discovered by Monte Rosa Therapeutics. Cancers driven by MYC overexpression have been demonstrated to be dependent on GSPT1, creating a therapeutic opportunity.

Interim clinical data from the MRT-2359 study have demonstrated favorable tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles in heavily pre-treated patients with lung cancers and high-grade neuroendocrine cancer. In addition, MRT-2359 has been observed to significantly reduce GSPT1 protein levels in patient tumors and has shown evidence of tumor size reductions, including partial responses, in heavily pretreated patients with biomarker-positive tumors. Monte Rosa is continuing with dose level and schedule optimization in this ongoing study.

"We're highly encouraged by the safety profile, the depth of pharmacodynamic modulation of GSPT1 in tumors, and even more so by the early evidence of anti-tumor activity of MRT-2359 in patients with biomarker-positive cancers," said Markus Warmuth, M.D., Chief Executive Officer of Monte Rosa Therapeutics. "We believe these results, the first ever to show clinical activity of a rationally designed molecular glue degrader in solid tumors, represent an important advance for the field and underscore the potential for MRT-2359 to benefit patients living with a variety of difficult-to-treat cancers. We are excited to learn more about the clinical profile of MRT-2359 in our ongoing Phase 1/2 clinical study, and early next year we plan to provide further clarity on the expected timing for the full Phase 1 data disclosure in 2024."

Summary of available study results:

- As of the analysis cutoff date of September 7, 2023, 21 patients had been dosed, with 15 of the 21 patients evaluable for efficacy.
- Optimal PD modulation of GSPT1 by MRT-2359 was observed at all dose levels, consistent with its designed activity based on preclinical studies. Following MRT-2359 dosing, approximately 60% reduction in GSPT1 protein expression was observed in peripheral blood mononuclear cells and tumor tissue biopsies. Similar levels of degradation were observed across all dose levels, suggesting saturated PD responses from 0.5 mg to 2 mg and supporting that pharmacodynamically, 0.5 mg is a fully active dose. The level of GSPT1 degradation observed was in line with the levels seen in preclinical studies that were associated with anti-tumor activity.
- Of the 15 evaluable patients that have been administered MRT-2359 across three dose cohorts (0.5 mg, 1 mg, and 2 mg in a 5 days on-drug, 9 days off-drug dosing schedule), six were identified as biomarker-positive in indicated tumor types, specifically N-MYC high non-small cell lung cancer (NSCLC) adenocarcinoma, L-/N-MYC high small cell lung cancer (SCLC), L-/N-MYC high-grade neuroendocrine tumors (prostate, bladder, and others) and neuroendocrine tumors of the lung.
- Clinical activity was seen across all dose levels. Of the six biomarker-positive patients, two achieved a partial response (PR), one confirmed and one unconfirmed, and one patient experienced durable stable disease (SD). Additionally, one patient who had an unevaluable biomarker status also experienced durable SD.
- The MRT-2359 safety profile supports further clinical development, with no signs of hypotension, cytokine release syndrome (CRS) or clinically significant hypocalcemia observed at any dose level, all of which have been reported as safety limitations of other GSPT1 degraders. The 0.5 mg and 1 mg dose levels resulted in Grade 1 or 2 treatment-related adverse events (AEs) only. At the 2 mg dose level, Grade 4 thrombocytopenia (dose-limiting toxicity (DLT), n=2) and Grade 4 neutropenia (non-DLT, n=1) were observed, findings consistent with preclinical toxicology studies. No patients discontinued treatment due to AEs at any dose level, and the Grade 4 AEs observed at the 2 mg dose were transient and resolved with dose reductions.

"Observing clinical activity in multiple patients who have exhausted all other treatment options strengthens our optimism about the potential of MRT-2359 for patients with MYC-driven solid tumors. This represents a sizable patient group, encompassing many cancer types, that currently experience significant unmet need. We continue to explore optimal doses and dosing schedules as we collect clinical data from this ongoing Phase 1/2 study," said Filip Janku, M.D., Ph.D., Chief Medical Officer of Monte Rosa Therapeutics.

Jordi Rodon Ahnert, M.D., Ph.D., Associate Professor, The University of Texas MD Anderson Cancer Center and Principal Investigator on the study, commented: “While the molecular role of MYC as a common driver of numerous cancers has been well appreciated for decades, the development of an effective therapeutic targeting this pathway has remained elusive. An effective drug for MYC-driven cancers could represent an important new therapeutic approach with applicability against many cancers. These early MRT-2359 data suggest that this highly specific MGD is clinically active in a treatment-refractory population and strongly support continued development.”

Monte Rosa Therapeutics is continuing with dose and schedule optimization as well as enrollment of biomarker-positive patients into various backfill cohorts of the Phase I part of the study. The company is currently dosing MRT-2359 at 1.5 mg in a 5 days on-drug, 9 days off-drug dosing schedule and, based on the observed safety profile, is considering a 21 days on-drug, 7 days off-drug dosing regimen.

Conference Call

Monte Rosa Therapeutics will host a conference call and webcast today at 8:00 a.m. ET to discuss the interim PK/PD and clinical data for MRT-2359. To participate via telephone and join the call live, please register in advance here. Upon registration, telephone participants will receive a confirmation email detailing how to join the conference call, including the dial-in number and a unique passcode. A live webcast of the call will also be available on the Investors section of the Monte Rosa website at ir.monterosatx.com, and a replay of the call will be available at the same link approximately two hours after its completion. The replay will be available for at least 30 days following the conclusion of the call.

About MRT-2359

MRT-2359 is a potent, selective, and orally bioavailable investigational molecular glue degrader (MGD) that induces the interaction between the E3 ubiquitin ligase component cereblon and the translation termination factor GSPT1, leading to the targeted degradation of GSPT1 protein. The MYC transcription factors (c-MYC, L-MYC, and N-MYC) are well-established drivers of human cancers that maintain high levels of protein translation, which is critical for uncontrolled cell proliferation and tumor growth. Preclinical studies have shown that this addiction to MYC-induced protein translation creates a dependency on GSPT1. By inducing degradation of GSPT1, MRT-2359 is designed to exploit this vulnerability, disrupting the protein synthesis machinery and leading to anti-tumor activity in MYC-driven tumors.

About the Phase1/2 Study of MRT-2359

The Phase 1/2, open-label, multicenter study is designed to assess the safety, tolerability, PK, PD and preliminary clinical activity of MRT-2359 in patients with previously treated selected solid tumors, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), high-grade neuroendocrine cancer of any primary site, diffuse large B-cell lymphoma (DLBCL) and solid tumors with L-MYC or N-MYC amplification. In the Phase 1 portion of the study, patients receive escalating doses of MRT-2359 to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Once the RP2D is determined, the anti-tumor activity of MRT-2359 will be assessed as part of the Phase 2 portion of the study, which includes molecular biomarkers for stratification and selection.

For more information visit clinicaltrials.gov (Study Identifier: NCT05546268).

About Monte Rosa

Monte Rosa Therapeutics is a clinical-stage biotechnology company developing highly selective molecular glue degrader (MGD) medicines for patients living with serious diseases in the areas of oncology, autoimmune and inflammatory diseases, and more. MGDs are small molecule protein degraders that have the potential to treat many diseases that other modalities, including other degraders, cannot. Monta Rosa’s QuEEN™ (Quantitative and Engineered Elimination of Neosubstrates) discovery engine combines AI-guided chemistry, diverse chemical libraries, structural biology and proteomics to identify degradable protein targets and rationally design MGDs with unprecedented selectivity. The QuEEN discovery engine enables access to a wide-ranging and differentiated target space of well-validated biology across multiple therapeutic areas. Monte Rosa has developed the industry’s leading pipeline of MGDs, which spans oncology, autoimmune and inflammatory disease and beyond. For more information, visit www.monterosatx.com

Forward-Looking Statements

This communication includes express and implied “forward-looking statements,” including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include all statements that are not historical facts and in some cases, can be identified by terms such as “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “continue,” “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained herein include, but are not limited to, statements about our ongoing pre-clinical and clinical development of our GSPT1 degrader referred to as MRT-2359, including our expectations regarding the potential relevance of certain interim clinical data, and our expectations for the nature and timing of our clinical development of MRT-2359, the potential for MRT-2359 to benefit patients living with a variety of difficult-to-treat cancers and MYC-driven solid tumors, our plans to continue the Phase 1/2 Study of MRT-2359, including its anticipated progress, clinical trial design and our ability to enroll the requisite number of patients and dose each dosing cohort in the intended manner, our QuEEN™ discovery engine and our view of its potential to identify degradable protein targets and rationally design MGDs with unprecedented selectivity, our pipeline of MGDs being the industry leader, spanning oncology, autoimmune and inflammatory diseases and beyond, as well as our expectations of success for our programs and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2022, filed with the U.S. Securities and Exchange Commission on March 16, 2023, and any subsequent filings, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward-looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance, or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations, or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated

the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research.

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