Monte Rosa Therapeutics Presents Preclinical Data from GSPT1 Degrader Program Focused on MYC-Driven Cancers at AACR 2023

April 17, 2023

- Preclinical data demonstrate preferential activity of MRT-2359, an orally bioavailable GSPT1-directed molecular glue degrader, in MYC-driven tumor cells
- Phase 1/2 clinical trial of MRT-2359 ongoing in MYC-driven solid tumors, including lung cancer; disclosure of initial data from Phase 1 arm of study expected in second half of 2023

BOSTON, April 17, 2023 (GLOBE NEWSWIRE) -- Monte Rosa Therapeutics, Inc. (NASDAQ: GLUE), a clinical stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today presented preclinical data characterizing MRT-2359, an orally bioavailable GSPT1-directed molecular glue degrader designed for the treatment of MYC-driven solid tumors, including lung cancer. The data were presented at the American Association for Cancer Research (AACR) Annual Meeting in Orlando, FL.

"Our extensive preclinical work on MRT-2359 forms a strong basis for our ongoing clinical trial by providing insight into the effects of GSPT1 degradation on the MYC pathway in cancer. By optimizing selectivity and fine-tuning the degradation rate of the translation termination factor GSPT1, using AI tools built into our QuEEN™ platform, we generated a GSPT1 degrader with preferential effect on MYC-driven tumors, and showed this effect is unique compared to other modalities targeting the protein translation machinery. We look forward to reporting initial data from the Phase 1 arm of the trial later this year," said Owen Wallace, Ph.D., Chief Scientific Officer of Monte Rosa.

A summary of our data and findings includes:

- Anti-tumor activity of MRT-2359 was assessed in >80 lung patient-derived xenografts (PDXs) confirming the preferential anti-tumor activity in PDX models of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) where N- and/or L-MYC expression was high, as well as in PDX models of neuroendocrine (NE) lung cancer. Numerous instances of tumor regressions were observed in these models with MRT-2359 when dosed orally daily or intermittently
- A causal link was established in vitro between N- and L-MYC expression and sensitivity to MRT-2359; other agents targeting the protein translation machinery or MYC transcription (e.g., CDK9 inhibitor) failed to show differential activity
- Treatment with MRT-2359 in the N- or L-MYC high cell lines inhibited protein translation and caused a downmodulation of transcription of MYC target genes
- MRT-2359 had preferential activity over the growth and survival of MYC-driven tumor cells, compared with cell lines with low N- or L-MYC expression, in which little effect was observed following GSPT1 degradation

Collectively, these data support the ongoing clinical evaluation of MRT-2359. Initiated in October 2022, the Phase 1/2 open-label, multicenter study (Identifier: NCT05546268) is primarily assessing the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD) and preliminary clinical activity of MRT-2359 in patients with previously treated selected solid tumors, including NSCLC, 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 are receiving 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 patient stratification and selection.

The preclinical data were presented as follows:

Oral Presentation
Title: New Drugs on the Horizon - Discovery of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for MYC-driven cancers
Session: New Drugs on the Horizon: Part 3
Presenter: Owen Wallace, Ph.D., Chief Scientific Officer of Monte Rosa
Date and Time: Monday, April 17; 10:40 a.m. ET

Oral Presentation
Title: Development of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for the treatment of lung cancers with MYC-induced translational addiction
Session: Mini Symposium
Abstract: 3449
Presenter: Gerald Gavory, Ph.D., Senior Director of Drug Discovery and Translational Research at Monte Rosa
Date and Time: Monday, April 17; 3:10 p.m. ET

About MRT-2359
MRT-2359 is a potent, selective and orally bioavailable 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 exploits this vulnerability, disrupting the protein synthesis machinery and leading to anti-tumor activity in MYC-driven tumors.

About Monte Rosa
Monte Rosa Therapeutics is a biotechnology company developing novel molecular glue degrader (MGD) medicines for patients living with serious diseases such as oncology, autoimmune and inflammatory diseases. MGDs are small molecule protein degraders designed to employ the body's natural mechanisms to selectively eliminate therapeutically relevant proteins. The Company's QuEEN™ (Quantitative and Engineered Elimination of Neosubstrates) platform enables it to rapidly identify protein targets and design highly selective degraders by combining diverse libraries of proprietary MGDs with in-house proteomics, structural biology, AI/machine learning, and computational chemistry capabilities. 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 pre-clinical observations for continued clinical development, and our expectations for the nature and timing of our clinical development of MRT-2359. 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, 2023, filed with the US 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.

Investors Shai Biran, Monte Rosa Therapeutics ir@monterosatx.com Media media@monterosatx.com