Monte Rosa Therapeutics Presents Preclinical Data at the 2024 San Antonio Breast Cancer Symposium on the Potential of its CDK2-directed Molecular Glue Degraders to Treat HR-positive/HER2-negative Breast Cancer

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CDK2-directed MGD drove deep tumor regression in preclinical models of HR-positive/HER2-negative breast cancer when combined with either a CDK4/6 inhibitor or a CDK4/6 inhibitor and endocrine therapy

Potential to provide more sustained responses in a difficult-to-treat patient population, while avoiding toxicities typically associated with limited selectivity of CDK2 inhibitors

BOSTON, Dec. 11, 2024 (GLOBE NEWSWIRE) -- Monte Rosa Therapeutics, Inc. (Nasdaq: GLUE), a clinical-stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today announced the company will present preclinical data on the potential of its highly selective cyclin-dependent kinase 2 (CDK2)-directed molecular glue degrader to treat HR-positive/HER2-negative breast cancer at the 2024 San Antonio Breast Cancer Symposium, held December 10-13 in San Antonio, Texas.

The data demonstrate that the company's CDK2-directed MGD, MRT-9643, has superior selectivity compared to clinical-stage CDK2 inhibitors and induced robust downstream CDK2 pathway suppression. When combined with current standard of care therapies, MRT-9643 drove deep tumor regression in preclinical models of HR-positive/HER2-negative breast cancer.

"Degrading CDK2 in conjunction with CDK4/6 inhibition has the potential to provide more sustained responses in patients with HR-positive/HER2-negative breast cancer. While currently approved CDK4/6 inhibitors offer clinical benefit, patients often relapse as tumors become reliant on the CDK2 pathway. However, attempts to inhibit CDK2 with conventional modalities have led to substantial toxicities, likely due to inadequate target specificity," said Sharon Townson, Ph.D., Chief Scientific Officer of Monte Rosa Therapeutics. "Our results demonstrate that MRT-9643 is a highly selective oral CDK2 degrader that could potentially avoid many of the dose-limiting toxicities associated with less selective CDK2 inhibitors. Additionally, in preclinical models of HR-positive/HER2-negative breast cancer, the combination of our CDK2-targeted MGD with either a CDK4/6 inhibitor or a CDK4/6 inhibitor plus an endocrine therapy drove deep tumor regression. We look forward to advancing our CDK2 MGD program towards a development candidate nomination in H1 2025."

The poster, entitled, "Selective Targeting of CDK2 Using Molecular Glue Degraders for the Treatment of HR-Positive/HER2-Negative Breast Cancer" (Poster Number P5-01-26), will be displayed on Friday, December 13, from 12:30 to 2:00 p.m. CST in Poster Session 5: Developmental Therapeutics Translational Science Tumor Biology. The poster will be presented by William Tahaney, Scientist II, Biology, and Nina Ilic-Widlund, Director, Biology, Monte Rosa Therapeutics.

Summary of findings:

- In cellular assays, MRT-9643 induced deep CDK2 degradation, resulting in CDK2-dependent cancer cell growth inhibition.
- MRT-9643 engages CDK2 through a novel binding mode that does not utilize the catalytic site typically engaged by catalytic-site inhibitors, enabling superior selectivity over conserved CDKs and other kinases.
- MRT-9643 demonstrated superior selectivity as compared to several clinical-stage small molecule CDK2 inhibitors evaluated.
- The combination of MRT-9643 and ribociclib, an FDA-approved CDK4/6 inhibitor, delayed resistance to CDK4/6 inhibition both *in vitro* and *in vivo*.
- When dosed orally in preclinical models of HR-positive/HER2-negative breast cancer, MRT-9643 drove deep tumor regression in combination with a CDK4/6 inhibitor or triple combination with a CDK4/6 inhibitor and endocrine therapy (fulvestrant), resulting in enhanced downstream pathway suppression as compared to a CDK4/6 inhibitor alone.

About CDK2 MGDs and MRT-9643

Cyclin-dependent kinase 2 (CDK2) is a key driver of cell cycle progression in cancer, acting in coordination with CDK4 and CDK6 to drive cell proliferation. CDK4/6 inhibitors, in combination with endocrine therapy, are FDA-approved agents for the treatment of HR-positive/HER2-negative breast cancer, however many patients become resistant because their tumors become reliant on CDK2. Targeting CDK2 in conjunction with CDK4/6 inhibition has the potential to provide more sustained clinical responses. In preclinical studies, Monte Rosa's CDK2-targeted MGD, MRT-9643, has demonstrated highly selective degradation of CDK2, with no detectable off-target activity. MRT-9643 induced robust downstream CDK2 pathway suppression and drove deep tumor regression in preclinical models of HR-positive/HER2-negative breast cancer when combined with either a CDK4/6 inhibitor or a CDK4/6 inhibitor plus an endocrine therapy. Targeting CDK2 with MRT-9643 represents a potentially novel approach to treating

HR-positive/HER2-negative breast cancer in combination with current standard of care therapies.

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. Monte 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. Monte Rosa has a global license agreement with Novartis to advance VAV1-directed molecular glue degraders and a strategic collaboration with Roche to discover and develop MGDs against targets in cancer and neurological diseases previously considered impossible to drug. 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 the therapeutic potential of CDK2 degradation, including using the company's CDK2-directed MGD, MRT-9643, that degrading CDK2 in conjunction with CDK4/6 inhibition has the potential to provide more sustained responses in patients with HR-positive/HER2-negative breast cancer, about preclinical data presented at the 2024 San Antonio Breast Cancer Symposium, held December 10-13 in San Antonio, Texas supporting the potential of its highly selective cyclin dependent kinase 2 (CDK2)-directed molecular glue degrader to treat HR-positive/HER2-negative breast cancer, and about the Potential of CDK2-directed MGDs, including MRT-9643, to provide more sustained responses in a difficult-to-treat patient population while avoiding toxicities typically associated with limited selectivity of CDK2 inhibitors, 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, 2023, filed with the U.S. Securities and Exchange Commission on March 14, 2024, 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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