Monte Rosa Therapeutics Presents Preclinical Data at the 36th EORTC-NCI-AACR Symposium on the Potential of its Cyclin E1-directed Molecular Glue Degraders for the Treatment of CCNE1-Amplified Solid Tumors

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Cyclin E1 molecular glue degraders (MGDs) represent a potential novel therapeutic approach by directly and selectively targeting a frequently amplified non-enzymatic driver oncogene relevant in multiple solid tumors

Cyclin E1 MGD inhibited tumor growth in CCNE1-amplified cancer models in vivo

BOSTON, Oct. 23, 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 at the 36th EORTC-NCI-AACR Symposium (ENA 2024), taking place in Barcelona, Spain from October 23 to 25, on the potential of its cyclin E1 (CCNE1)-directed molecular glue degraders (MGDs) for the treatment of *CCNE1*-amplified solid tumors. *CCNE1* is a well-validated oncogene that is amplified in multiple tumor types, but the corresponding cyclin E1 protein has traditionally been undruggable. The data being presented demonstrate that Monte Rosa's MGD degrades cyclin E1 with a high level of selectivity, sparing other closely related proteins, including other cyclins, and cyclin-dependent kinases (CDKs). The data also showed that a cyclin E1-directed MGD led to downstream pathway inhibition and induced tumor growth suppression and regression preferentially in *CCNE1*-amplified and over-expressing tumor cell lines and xenograft models. The Company continues to perform preclinical research in order to progress the program towards a development candidate nomination.

"Cyclin E1 (CCNE1) has long been a high interest yet undruggable oncology target. By directly and selectively targeting this frequently amplified non-enzymatic driver oncogene, cyclin E1 MGDs represent a potential paradigm shift and novel precision medicine approach," said Sharon Townson, Ph.D., Chief Scientific Officer of Monte Rosa Therapeutics. "Our results demonstrate that our cyclin E1-targeted MGD drives highly selective and potent degradation of cyclin E1, which we believe is important because it could reduce toxicities associated with inhibition of closely related cyclins as well as CDKs. We believe these promising data support continued preclinical development and the potential of cyclin E1-directed MGDs as an important new therapeutic approach for various solid tumors, including ovarian, endometrial, gastric, breast, and other cancers."

The poster, entitled, "Selective Targeting of Cyclin E1 Using Molecular Glue Degraders in *CCNE1* Amplified Solid Malignancies" (Poster Number 511), will be displayed for the duration of the conference in the Late Breaking Posters section and presented each day during the lunchtime period by Ralph Tiedt, Vice President, Biology, Monte Rosa Therapeutics.

Summary of findings:

- In cellular assays, MRT-50969 induced deep cyclin E1 degradation in conjunction with downstream pathway suppression, as evidenced by downmodulation of RB phosphorylation and E2F-driven gene expression.
- MRT-50969 selectively inhibited proliferation and induced G1-S cell cycle arrest and senescence in *CCNE1*-amplified cancer cell lines, while sparing cell lines without amplification.
- When dosed orally as a single agent in preclinical models of *CCNE1*-amplified breast cancer and gastric cancer, the cyclin E1-directed MGD MRT-50969 induced robust tumor growth suppression and regression.
- Unlike CDK2 inhibitors, MRT-50969 inhibited cell proliferation and downstream signaling in an RB-dependent manner, attesting to its higher level of selectivity compared to leading CDK2 inhibitors.
- Cryo-EM analysis showed that cyclin E1 can be engaged by cereblon-based MGDs through a cryptic pocket on the cyclin E1 surface, revealing a previously undescribed binding mode and suggesting that the target space for cereblon is larger than previously thought.

About Cyclin E1 (CCNE1) MGDs
Cyclin E1 (CCNE1) is a critical driver of cell cycle progression and cell proliferation that is frequently amplified or overexpressed in solid malignancies including ovarian, endometrial, gastric, breast, and other cancers. *CCNE1* amplification is associated with poor patient survival. This target has previously been considered undruggable with conventional approaches due to lack of enzymatic activity. In preclinical studies, cyclin E1-targeted MGDs have resulted in deep and highly selective target degradation. When dosed orally as a single agent in *CCNE1*-amplified *in vivo* models, cyclin E1-targeted MGDs induced robust tumor growth suppression and regression. Targeting cyclin E1 with a MGD represents a potentially novel approach to target multiple *CCNE1*-amplified solid malignancies with high unmet medical need, including ovarian, endometrial, gastric, breast and others.

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, and has 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 Cyclin E1 targeting molecular glue degraders ("MGDs") and their potential for use as therapeutics, including for the treatment of cancers and tumors, including CCNE1 amplified solid tumors, and for use in any therapeutic approach that directly and selectively targets CCNE1, the frequency of CCNE1 amplification as a non-enzymatic driver oncogene relevant in multiple solid tumors and the relevance of such tumors for any MGD, the relevance of Cyclin E1 MGD specificity for the treatment of CCNE1 amplified tumors and cancers, the developability and potential of cyclin E1 MGDs as a therapeutic approach for various solid tumors, including ovarian, endometrial, gastric, breast, and other cancers, any advantages of the attributes MRT-50969 for ongoing development, including as compared to other therapeutic approaches, including 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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