Biomea Fusion To Present Two Preclinical Posters at the 114th AACR Annual Meeting

April 13, 2023

- Abstract 473 highlights the dose dependent reduction of menin target genes in *ex vivo* chronic lymphocytic leukemia (CLL) patient samples treated with BMF-219, an investigational covalent inhibitor. BMF-219 showed greater potency and ability to achieve >98% growth inhibition in these CLL patient samples in comparison with reversible BTK inhibitor, pirtobrutinib, and irreversible BTK inhibitor, ibrutinib.
- Abstract 4939 demonstrates the potential utility of combining a covalent menin inhibitor, BMF-219, and a FLT3 covalent inhibitor, BMF-500, to achieve higher cell killing at lower concentrations in preclinical acute myeloid leukemia (AML) models.

REDWOOD CITY, Calif., April 13, 2023 (GLOBE NEWSWIRE) -- Biomea Fusion, Inc. (“Biomea”)(Nasdaq: BMEA), a clinical-stage biopharmaceutical company dedicated to discovering and developing novel covalent small molecules to treat and improve the lives of patients with genetically defined cancers and metabolic diseases, today announced the upcoming presentation of two preclinical abstracts at the American Association for Cancer Research (AACR) Annual Meeting in Orlando, Florida from April 14-19, 2023.

“Building on the preclinical data presented last year, we continued our translational work and are excited to again report the superior potency observed *ex vivo* of BMF-219 in comparison to a new investigational clinical agent for CLL, pirtobrutinib, and the well-profiled first in class irreversible BTK inhibitor, ibrutinib. Treatment with BMF-219 also induced dose-dependent reduction in the expression of menin target genes *MEN1, BCL2* and *MYC* and was observed to alter key pathways in CLL patient samples, thereby providing further support to clinically investigate BMF-219 as a potential novel therapeutic agent,” said Mini Balakrishnan, PhD, Executive Director of Biology at Biomea Fusion.

Biomea’s preclinical posters will be made available at https://biomeafusion.com/publications/ following presentation at the meeting.

Covalent menin inhibitor, BMF-219, impacts key gene signatures and molecular pathways in chronic lymphocytic leukemia patient-derived models

Session Category / Session Title: Experimental and Molecular Therapeutics / Novel Antitumor Agents 1

Session Date and Time: Sunday, April 16, 2023; 1:30 PM -5:00 PM ET

Location: Orange County Convention Center, Poster Section 17

Abstract / Poster: 473 / 4

Abstract Text:

Chronic lymphocytic Leukemia (CLL) is the most common type of adult leukemia characterized by clonal proliferation of malignant B-lymphocytes. Although standard-of-care agents are well tolerated in CLL, patients with certain genetic subsets of the disease continue to display poor response to these therapeutic regimens. Menin is an epigenetic protein that drives oncogenic function through transcriptional regulation directed by its interactions with various protein partners. In the B-cell maturation pathway, menin regulates a distinct set of genes targets (Li et al., 2013). We previously described the potent activity of BMF-219, a selective covalent oral menin inhibitor, against a diverse panel of CLL patient specimens with various cytogenetic and mutational backgrounds, including TP53 and NOTCH1 mutations. We also reported the ability of BMF-219 to downregulate the anti-apoptotic gene, BCL2, an established major driver of CLL, in acute leukemia cells. Here, we provide insights into the molecular impact of BMF-219 in CLL patient samples, as revealed through gene expression profiling of CLL specimens from BTK-inhibitor experienced patients that represent clinical profiles of TP53 mutated and complex cytogenetic backgrounds (del 13q, del 6q). BMF-219 displayed on-target activity through dose dependent reduction of the target gene, MEN1, in the treated patient samples. Differential gene expression analysis revealed alteration of additional novel gene targets, including reduction of BCL2 and genes modulated in response to prior BTK-inhibitor treatment. Gene set enrichment analysis highlighted top altered molecular pathways in BMF-219 treated CLL models. Notably, the KRAS signaling pathway was a top downregulated pathway in the BMF-219 treated CLL samples. We previously reported KRAS to be impacted by BMF-219 in solid tumor indications. Gene ontology analysis of biological processes and molecular function identified additional novel mechanisms elicited by BMF-219 in these treated CLL models. Furthermore, we provide new data demonstrating the superior potency of BMF-219 and ability to achieve >98% growth inhibition in ex vivo cultured CLL patient specimens when compared to new investigational drugs currently in clinical development and established standard-of-care agents for CLL. Collectively, these data demonstrate the mechanistic impact of BMF-219 on key gene targets and molecular pathways modulated by covalent menin inhibition, further highlighting its potential as a novel therapeutic agent in CLL.

Combinatorial approach using covalent menin inhibitor, BMF-219, and/or covalent FLT3 inhibitor, BMF-500, with MEK or BCL2 blockade potentiates therapeutic use in AML

Session Category / Session Title: Experimental and Molecular Therapeutics / Novel Antitumor Agents, PI3K/AKT Inhibitors, Proteasome Inhibitors,

and Topoisomerases

Session Date and Time: Tuesday, April 18, 2023; 1:30 PM -5:00 PM ET

Location: Orange County Convention Center, Poster Section 15

Abstract / Poster: 4939 / 17

Abstract Text:

Introduction:

Acute myeloid leukemia (AML) is a clinically and genetically heterogeneous disease characterized by a highly diverse genomic landscape. Despite recent advances in therapies, treatment outcome remains variable and largely defined by genomic abnormalities such as gene fusions, copy number alterations and point mutations. Mutations in epigenic modifiers, nucleophosmin (NPM1c), signaling and kinase pathway such as KMT2A-re-arrangements (KMT2A-r), internal tandem duplication (ITD) insertions in FLT3, and NRAS mutations are amongst the highest alterations in AML patients with a propensity towards poor response to treatment and overall disease outcome. Such limitations impact the ability to achieve long-lasting response to treatment and result in therapy-induced resistance eventually leading to relapse. Combinatorial strategies are required to combat resistance and maximize duration of antitumor activity.

BCL2 and MEK blockade in combination with menin and/or FLT3 inhibitors potentiates an improved therapeutic strategy to achieve increased antitumor activity and overcome AML resistance. Here we explored the use of our clinical-stage covalent menin inhibitor, BMF-219, and BMF-500, a covalent FLT3 inhibitor, in combination with each other and in combination with BCL2 and MEK inhibitors in MV-4-11 and MOLM-13 cell lines for 4-days, then viability was measured using CellTiter Glo.

Results:

BMF-219 and BMF-500 as single agents induce effective antitumor activity on MOLM-13 and MV-4-11 cells lines. When dosed in combination, BMF-219 and BMF-500 show beneficial effects affording higher cell killing at lower concentrations. Repeated experiments revealed patterns of increased cell killing is achieved when trametinib, MEK inhibitor, and venetoclax, BCL2 inhibitor, are combined with BMF-219 treatment.

Conclusions:

Collectively, our studies demonstrate the utility of combination strategies to achieve higher antileukemic cell killing with reduced concentrations of menin and FLT3 covalent inhibitors. Additionally, we show benefit of combinatorial approaches of menin and FLT3 covalent inhibitors with MEK and BCL2 blockade. These data provide initial pre-clinical evidence for combining pathway specific inhibitors as a promising therapeutic strategy for further investigation in acute leukemia.

About Biomea Fusion

Biomea Fusion is a clinical stage biopharmaceutical company focused on the discovery and development of covalent small molecules to treat patients with genetically defined cancers and metabolic diseases. A covalent small molecule is a synthetic compound that forms a permanent bond to its target protein and offers a number of potential advantages over conventional non-covalent drugs, including greater target selectivity, lower drug exposure, and the ability to drive a deeper, more durable response. The company is utilizing its proprietary FUSION™ System to advance a pipeline of covalent-binding therapeutic agents against key oncogenic drivers of cancer and metabolic diseases. Biomea Fusion's goal is to utilize its capabilities and platform to become a leader in developing covalent small molecules in order to maximize the clinical benefit when treating various cancers and metabolic diseases.

Forward-Looking Statements

Statements we make in this press release may include statements which are not historical facts and are considered forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact, including statements regarding the preclinical, clinical and therapeutic potential of our product candidates and development programs, including BMF-219 and BMF-500, the potential of BMF-219 as a treatment for various types of cancer, including CLL, and diabetes, the potential of BMF-500 as a treatment for various types of cancer and as an FLT3 inhibitor, and diabetes, our research, development and regulatory plans, including the progress of our ongoing COVALENT-101 clinical trial of BMF-219, the availability of data from the trial, and the timing of such events, may be deemed to be forward-looking statements. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act and Section 21E of the Exchange Act and are making this statement for purposes of complying with those safe harbor provisions.

Any forward-looking statements in this press release are based on our current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements, including the risk that we may encounter delays or unforeseen results in preclinical development, patient enrollment and in the initiation, conduct and completion of our ongoing and planned clinical trials and other research, development and regulatory activities. These risks concerning Biomea Fusion's business and operations are described in additional detail in its periodic filings with the U.S. Securities and Exchange Commission (the "SEC"), including its most recent periodic report filed with the SEC and subsequent filings thereafter. Biomea Fusion explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

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