Biomea Fusion to Present New Preclinical Data Showing BMF-219's Strong Activity in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) Tumor Models at ASCO 2022

May 26, 2022

- BMF-219 is the first investigational menin inhibitor in clinical development to show potential as a therapeutic agent for CLL
- BMF-219, a covalent menin inhibitor, demonstrated potency across *ex vivo* CLL tumor models with varying cytogenetic risk profiles and Rai stages, indicating broad activity with over 98% cell lethality in these models
- High- and intermediate-risk cytogenetic profile (*TP53* alterations and *NOTCH1* mutations, respectively) CLL patient samples, which represent a significant unmet clinical need, were highly sensitive to BMF-219 treatment
- BMF-219 was also highly active against samples taken from CLL patients with profiles of resistance to standard-of-care agents, including bendamustine and ibrutinib
- BMF-219 is currently in a Phase I clinical trial (COVALENT-101) in patients with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM).

REDWOOD CITY, Calif., May 26, 2022 (GLOBE NEWSWIRE) -- Biomea Fusion, Inc. (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 it will present new data at the American Society of Clinical Oncology (ASCO) Annual Meeting demonstrating BMF-219's activity in *ex vivo* preclinical models of CLL. In addition, the company will present a Trial In Progress (TIP) poster presentation detailing the design of COVALENT-101. Once released at the ASCO Annual Meeting, the preclinical and TIP presentations can be viewed on Biomea's website at https://biomeafusion.com/publications.

"Given our leadership team's involvement with the discovery and development of ibrutinib and, thus, its demonstrated efficacy in CLL, we were highly encouraged to see BMF-219 demonstrate greater activity than ibrutinib *ex vivo*, especially in patient samples with *TP53* alterations and *NOTCH1* mutations," said Thomas Butler, Biomea's Chief Executive Officer and Chairman of the Board. "BMF-219's powerful cell-killing activity across *ex vivo* CLL models as a single agent, at similar concentrations as our prior experiments of BMF-219 in ex vivo models of other cancer types, is a very important finding. We are eager and very excited to fully explore the clinical potential of a covalent menin inhibitor across multiple liquid and solid tumor types."

BMF-219 demonstrated potency across *ex vivo* CLL tumor models with varying cytogenetic risk profiles and Rai stages, indicating broad activity with over 98% cell lethality in all of these models. Additionally, BMF-219 showed consistently strong activity compared to venetoclax (used as a positive control) and significantly greater activity than a clinical non-covalent (reversible) menin inhibitor. Additionally, BMF-219 exhibited robust growth inhibition in patient samples that were less responsive to bendamustine and ibrutinib.

Poster Presentation Details:

Preclinical activity of irreversible Menin inhibitor, BMF-219, in chronic lymphocytic leukemia. (Abstract #7541)
Session Title: Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
Session Date and Time: Saturday, June 4, 2022, 8:00 AM-11:00 AM CDT
Full Text:
Background: Menin is a scaffold protein that drives oncogenic function through transcriptional modulation directed by its various cofactors. A previous report demonstrated that menin regulates a distinct set of gene targets independent of its function with the MLL proteins in hematopoiesis and is essential for B-cell maturation (Li et al.*Blood*.2013;122(12):2039-46.). Chronic Lymphocytic Leukemia (CLL) is a disease of malignant B lymphocytes, for which standard-of-care agents are generally well tolerated; however, CLL patients with certain genetic backgrounds demonstrate inferior outcomes to these regimens. A major driving feature of CLL is overexpression of the anti-apoptotic marker, BCL2. We previously reported the ability of BMF-219, a selective, irreversible menin inhibitor, to downregulate the expression of BCL2 in acute leukemia cells. Additionally, we have reported the synergy of BCL2-targeted agent, venetoclax, with BMF-219 in potent cell killing of diffuse large B-cell lymphoma (DLBCL) preclinical models, prompting our exploration of BMF-219 activity in CLL. Here, we provide the first preclinical evidence for menin as a therapeutic target in CLL, by demonstrating high potency of BMF-219 against a diverse collection of CLL patient specimens.

Methods: A comprehensive panel of CLL samples isolated from patients with Rai Stages 1 to 3 disease, including relapsed or refractory disease, were cultured *ex vivo* in the presence of BMF-219 or clinical reversible menin inhibitors to assess the antileukemic activity of the compounds. Samples were analyzed for differential gene expression of select targets in response to treatment.

Results: BMF-219 demonstrated high potency, achieving >98% cell lethality at 1 μM exposure in all patient samples tested, with IC_{50} values in the range of 0.1 to 0.38 μM. Specimens isolated from patients with clinical profiles of high-risk genetic backgrounds associated with inferior outcomes to standard therapy, such as mutations in TP53 and NOTCH1, and chromosomal aberrations such as del(13q), trisomy 12 and complex karyotype, exhibited high sensitivity to BMF-219 treatment. BMF-219 was also highly effective against patient samples with clinical profiles of resistance to bendamustine, ibrutinib and venetoclax therapy. In comparison, clinical reversible menin inhibitors demonstrated no significant activity across all

patient samples tested, with incalculable IC_{50} values and <15% reduction in cell viability at 1 μM exposure. Expression of select target genes in treated CLL cell lines was explored and will be reported.

Conclusions: Collectively, our data demonstrate the potent preclinical activity of BMF-219 against CLL patient specimens harboring various mutational and cytogenetic backgrounds, including categories of high-risk. These data highlight the unique potential of irreversible menin inhibition as a novel therapeutic option for patients with CLL.

COVALENT-101: A phase 1 study of BMF-219, a novel oral irreversible menin inhibitor, in patients with relapsed/refractory (R/R) acute leukemia (AL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM). (Abstract #TPS7064)
Session Title: Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant
Session Date and Time: Saturday, June 4, 2022, 8:00 AM-11:00 AM CDT
Full Text:
Background: Menin, a protein involved in transcriptional regulation, impacting cell cycle control, apoptosis, and DNA damage repair, plays a direct role in oncogenic signaling in multiple cancers. Inhibition of menin is therefore a novel approach to cancer treatment. Preclinical data of BMF-219, a highly selective, orally bioavailable, small-molecule irreversible inhibitor of menin, show sustained potent abrogation of menin-dependent oncogenic signaling in vitro and in vivo. BMF-219 exhibited a strong anti-proliferative effect on various menin-dependent acute myeloid leukemia (AML) cell lines, DLBCL lines representing Double/Triple Hit Lymphoma (DHL/THL) and Double Expressor Lymphoma (DEL), and MM cell lines with diverse mutational backgrounds. BMF-219 also showed high potency *ex vivo* in patient samples from MLL-rearranged and NPM1-mutant AML, THL and MYC-amplified DLBCL, and bone marrow mononuclear cells from treatment-naive and R/R MM.

Methods: COVALENT-101 (NCT05153330) is an open-label, multi-cohort, non-randomized, multicenter Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of once daily oral BMF-219 in patients with R/R AL, DLBCL and MM who have received standard therapy. Utilizing an accelerated titration design, doses of BMF-219 will be escalated in single-subject cohorts independently for each indication until 1 subject experiences either a ≥ Grade 2 related-adverse event or dose limiting toxicity (DLT). At that point, the cohort will switch to a classical “3 +3” design. Treatment will continue in 28-day cycles until progression or intolerability. Expansion cohorts for each indication will enroll patients to obtain further safety and efficacy data. Patients with R/R AL, R/R DLBCL ≥ 2 but ≤ 5 therapies, and R/R MM who received ≥ 3 therapies and failed or are ineligible for any standard therapies are eligible. Patients must have ECOG PS ≤ 2, and adequate organ function. Key exclusion criteria include known CNS disease involvement, prior menin inhibitor therapy, and clinically significant cardiovascular disease.

The primary objective is to determine independently for each cohort/indication the optimal biological dose (OBD)/ recommended Phase 2 dose (RP2D) of BMF-219 oral monotherapy. Key secondary objectives include further evaluation of safety and tolerability, characterization of the pharmacodynamics and pharmacokinetics of BMF-219, and assessment of its antitumor activity based on best overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and time to progression (TTP) per disease-specific response criteria as assessed by the investigator. Food-effect studies will be performed in DLBCL and MM patients at certain dose levels. The enrollment commenced in January 2022. Clinical trial information: NCT05153330.

About Chronic Lymphocytic Leukemia (CLL)

CLL is a chronic leukemia that progresses relatively slowly and typically impacts older adults. In the United States, approximately 20,000 patients are diagnosed with CLL each year. While the existing treatments options produce 5-year survival outcomes greater than 87%, there is an unmet need for patients that have high- or medium-risk cytogenetic profiles and those that are relapsed or refractory to existing treatments.

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 our cash runway, the clinical and therapeutic potential of our product candidates and development programs, including BMF-219, the potential of BMF-219 as a treatment for various types of cancer, including CLL, and diabetes, our research, development and regulatory plans, the progress of our COVALENT-101 Phase 1 clinical trial, including ongoing enrollment in 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, IND-filing and acceptance, patient enrollment and in the initiation, conduct and completion of our 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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