Biomea Fusion Announces Upcoming Presentations of Preclinical Data in Diffuse Large B-Cell Lymphoma, Multiple Myeloma, and Several KRAS Mutant Solid Tumors for BMF-219 at AACR Annual Meeting 2022

March 8, 2022

- Irreversible covalent menin inhibitor, BMF-219, exhibited high potency and complete growth inhibition in high-grade B-cell lymphoma and multiple myeloma (MM) preclinical patient derived *ex vivo* models
- BMF-219 demonstrated high potency in various KRAS-mutant cell lines, as well as potential advantages over the KRAS-targeted inhibitor sotorasib in multiple cell lines
- BMF-219 showed strong potency in *ex vivo* preclinical models of colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and pancreatic cancer

REDWOOD CITY, Calif., March 08, 2022 (GLOBE NEWSWIRE) -- Biomea Fusion, Inc. (“Biomea”) (Nasdaq: BMEA), a clinical-stage biopharmaceutical company dedicated to the discovery and development of novel irreversible covalent small molecules to treat and improve the lives of patients with genetically defined cancers and metabolic diseases, today announced that two abstracts on BMF-219 have been accepted for poster presentation at the upcoming American Association for Cancer Research (AACR) Annual Meeting 2022. The AACR Annual Meeting will be held from April 8-13, 2022, at the Ernest N. Morial Convention Center in New Orleans, LA. BMF-219, Biomea’s lead program, is an irreversible covalent menin inhibitor, currently in a Phase I study for the treatment of patients with relapsed/refractory acute leukemias, including those with the MLL1/KMT2A gene rearrangements and NPM1 mutations. BMF-219 is the first and only irreversible covalent menin inhibitor in the clinic.

“The preclinical data we will present at AACR further validate our planned development of BMF-219 in KRAS- and MYC-dependent solid tumors and highlight the potential anti-cancer benefits of inhibiting menin, achieved via irreversible covalency,” said Thomas Butler, Biomea’s CEO and Chairman of the Board. “In preclinical models, BMF-219 demonstrated near complete tumor growth inhibition in both MYC-dependent and pan-KRAS mutant cancers. These mutations are broadly manifested in numerous tumor types and are generally considered categories of very high unmet need. We are excited with the potential benefits BMF-219 may bring to patients across a spectrum of multiple liquid and solid cancers, and we look forward to seeing the results in the clinic.”

Biomea plans to initiate enrollment of patients with MM and diffuse large B-cell lymphoma (DLBCL) in the ongoing Phase I clinical trial of BMF-219 in the first half of 2022. The company anticipates submitting an investigational new drug (IND) application for BMF-219 in KRAS-mutant solid tumors, including patients with NSCLC, CRC, and pancreatic cancer in the fourth quarter of 2022.

Poster Presentation Details

Biomea abstracts are now available on the AACR website, www.aacr.org. Details for the upcoming presentations are as follows:

Anti-tumor activity of irreversible menin inhibitor, BMF-219, in high-grade B-cell lymphoma and multiple myeloma preclinical models (Abstract #1205)

Session Category: Experimental and Molecular Therapeutics
Session Title: Novel Targets and Pathways
Session Date and Time: Tuesday, April 12, 2022 9:00 AM - 12:30 PM
Location: New Orleans Convention Center, Exhibit Halls D-H, Poster Section 24
Poster Board Number: 23
Permanent Abstract Number: 2654
Full Text of Abstract:

Double/Triple Hit Lymphoma (DHL/THL) and Double Expressor Lymphoma (DEL) are high-grade B-cell lymphomas (HGBCL) that exhibit low responses to standard therapeutic regimens resulting in poor prognosis. DHL harbor translocations in MYC and BCL2 or BCL6, THL contain translocations in MYC/BCL2/BCL6, and DEL are characterized by high expression of MYC and BCL2. Menin is a scaffold protein that drives oncogenic function through its regulation of genes such as *HOXA9*, with distinct effects on transcription that are directed by various cofactors. A recent study reported that knockdown of *HOXA9* resulted in marked growth inhibition of multiple myeloma (MM) cells (Chapman et al., 2017).

We previously reported the ability of irreversible menin inhibitor, BMF-219, to modulate MYC expression and exhibit high potency against DHL DLBCL preclinical models. Moreover, we demonstrated that MYC and its co-factor MAX, regulate differential gene expression in BMF-219-treated leukemia cells. Here, we demonstrate the anti-tumor activity of BMF-219 in HGBCL and MM preclinical models harboring various mutational backgrounds.

BMF-219 exhibited high potency against THL and DEL cell lines, with IC_{50} values of 0.27 μM and 0.37 μM, respectively. Both models achieved >90% growth inhibition with single-agent treatment. Notably, BMF-219 was multi-fold more potent and exerted dramatically greater growth inhibition

compared to clinical reversible menin inhibitors in all DLBCL cell lines tested, including an expanded panel of DHL cell lines. In *ex vivo* studies, an R-CHOP refractory THL patient sample and an R-EPOCH refractory MYC-amplified DLBCL patient sample were highly sensitive to BMF-219 treatment, with IC_{50} values of 0.15 μM and 0.2 μM, respectively, and demonstrated complete growth inhibition at 1 μM exposure. In contrast, two clinical reversible menin inhibitors demonstrated much lower potency (IC_{50} = 0.96 μM and 6.3 μM in the MYC-amplified model, and IC_{50} = 5.63 μM and not calculable for the second reversible inhibitor in the THL model). MM cell lines harboring mutations in TP53, KRAS and NRAS were all sensitive to BMF-219 with IC_{50} values in the range of 0.25 μM to 0.5 μM and achieved 100% growth inhibition at 1 μM exposure. Combination treatments of BMF-219 with standard-of-care agents in MM cell lines were also tested. Notably, BMF-219 demonstrated single-agent efficacy (IC_{50} values between 0.1 μM and 0.3 μM) against a panel of newly diagnosed and R/R *ex vivo* MM samples, including a p53- deleted clinical profile.

Collectively, our data demonstrate the novel and robust anti-tumor activity of BMF-219 in HGBCL and MM preclinical models that represent categories of high unmet need. BMF-219 exhibits multi-fold higher potency and complete growth inhibition in these preclinical models compared to clinical reversible menin inhibitors, demonstrating its unique anti-tumor potential in these cancers.

Irreversible menin inhibitor, BMF-219, inhibits the growth of KRAS-mutated solid tumors (Abstract #1202)

Session Category: Experimental and Molecular Therapeutics
Session Title: Signaling Pathway Inhibitors
Session Date and Time: Tuesday, April 12, 2022 9:00 AM - 12:30 PM
Location: New Orleans Convention Center, Exhibit Halls D-H, Poster Section 25
Poster Board Number: 8
Permanent Abstract Number: 2665
Full Text of Abstract:

Introduction:
KRAS (Kirsten rat sarcoma virus) is the most frequently mutated isoform amongst RAS oncogenes in human solid tumors being present in a high percentage of colorectal cancers (CRC), non-small cell lung cancers (NSCLC), and pancreatic cancers. With only one approved KRAS G12C inhibitor for NSCLC, KRAS driven tumors continue to represent a significant unmet medical need where novel effective therapies are highly desired. Menin is a required co-factor of oncogenic transcriptional proteins with functional interactions that are critical for various malignancies including acute leukemia. We previously reported that BMF-219, a novel irreversible menin inhibitor, exhibits strong potency on acute leukemia (MOLM-13) and KRAS-mutant (MiaPaCa-2) cells. Results from MiaPaCa-2 cells prompted our exploration of the effects of BMF-219 in an expanded panel of KRAS-mutant solid tumors through in vitro and ex vivo preclinical models.

Methods:
BMF-219, clinical reversible menin inhibitors, or clinically approved KRAS G12C inhibitor, sotorasib, were cultured with CRC, NSCLC and pancreatic cancer cell lines for 4-days. Human ex vivo preclinical models harboring KRAS mutations were cultured with BMF-219 and reversible menin for 6-days. Cell viability was measured using CellTiter Glo and IC_{50} values were calculated. MiaPaCa-2 cells incubated with BMF-219 were analyzed by RNA-seq on the Illumina NextSeq 550 platform.

Results:
MiaPaCa-2, a KRAS G12C-mutant cell line, showed marked reduction of KRAS expression levels following 24 hours of BMF-219 treatment at 0.5 μM. An expanded panel of 14 CRC, NSCLC and pancreatic KRAS-mutant cell lines harboring G12C, G12D, G12V, and Q61L revealed single-agent BMF-219 activity after a 4-day treatment. Majority of the cell lines tested exhibited >90% inhibition of growth, independent of KRAS mutation type. Sotorasib reached a maximum of 90-93% growth inhibition in three of eight cell lines. By contrast, BMF-219 inhibited cell viability ≥ 90% in six of eight KRAS G12C lung cancer lines. Human CRC, NSCLC and pancreatic ex vivo preclinical models with G12C, G12D, and G12V KRAS mutations were all sensitive to BMF-219 after a 6-day treatment. Complete abrogation of growth was observed in all samples with IC_{50} values ranging between 0.2 μM - 0.6 μM.

Conclusion:
KRAS-mutant CRC, NSCLC, pancreatic cancer cell lines and ex vivo preclinical models are highly sensitive to irreversible menin inhibitor, BMF-219, where clinical reversible menin inhibitors displayed limited activity. High potency of BMF-219 was observed amongst various KRAS-mutant cell lines suggesting that BMF-219 broadly inhibits these tumors. As an irreversible menin inhibitor, BMF-219, manifests advantages over the KRAS-targeted inhibitor sotorasib in multiple cell lines tested, and displays unique potency compared with clinical reversible menin inhibitors in ex vivo preclinical models of CRC, NSCLC, and pancreatic cancer.

About Biomea Fusion

Biomea Fusion is a biopharmaceutical company focused on the discovery and development of irreversible small molecules to treat patients with genetically defined cancers and metabolic diseases. An irreversible small molecule is a synthetic compound that forms a permanent bond to its target protein and offers a number of potential advantages over conventional reversible 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 irreversible-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 irreversible 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 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 and diabetes, our research, development and regulatory plans, including our plans to initiate

clinical development of BMF-219 in up to seven distinct tumor types, as well as diabetes, and the timing of such events, including the timing of patient enrollment, data presentations, candidate selection, IND submissions and trial initiations, 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 in patient enrollment and in the initiation, conduct and completion of our planned clinical trials. These risks concerning Biomea Fusion's business and operations are described in additional detail in its periodic filings with 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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