UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 8, 2022

Biomea Fusion, Inc.
(Exact name of Registrant as Specified in Its Charter)

Delaware	001-40335	82-2520134
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(IRS Employer Identification No.)

650 Main Street Redwood City, CA	94063
(Address of Principal Executive Offices)	(Zip Code)

Registrant's Telephone Number, Including Area Code: (650) 980-9099

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value	**BMEA**	**The Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01. Other Events.

On April 8, 2022, Biomea Fusion, Inc. (the "Company") issued a press release titled, "Biomea Fusion Reports Preclinical Data on BMF-219 and Trial in Progress Presentations at AACR 2022 Annual Meeting." The information described in the press release is also being presented in poster presentations at the American Association for Cancer Research (AACR) 2022 Annual Meeting on April 12, 2022.

Copies of the press release and the Company's poster presentations are attached to this Current Report on Form 8-K as Exhibits 99.1 through 99.4 and incorporated herein by reference.

Forward-Looking Statements

Statements made or incorporated by reference in this Current Report on Form 8-K 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 the Company's product candidates and development programs, including BMF-219, the potential of BMF-219 as a treatment for various types of cancer and diabetes, the Company's research, development and regulatory plans, and the timing of such events, may be deemed to be forward-looking statements. The Company intends 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 is making this statement for purposes of complying with those safe harbor provisions.

Any forward-looking statements made or incorporated by reference in this Current Report on Form 8-K are based on the Company's current expectations, estimates and projections only as of the date of this Current Report on Form 8-K 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 the Company may encounter delays in patient enrollment and in the initiation, conduct and completion of its planned clinical trials and other research and development activities. These risks concerning the Company'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. The Company explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press release titled, "Biomea Fusion Reports Preclinical Data on BMF-219 and Trial in Progress Presentations at AACR 2022 Annual Meeting."
99.2	Poster presentation titled, "Irreversible Menin Inhibitor, BMF-219, Exhibits Potent Cytotoxicity in KRAS-Mutated Solid Tumors."
99.3	Poster presentation titled, "Anti-tumor Activity of Irreversible Menin Inhibitor, BMF-219, in High Grade B-Cell Lymphoma and Multiple Myeloma Preclinical Models."
99.4	Poster presentation titled, "A Phase 1 study of BMF-219, a novel oral irreversible menin inhibitor, as a single agent in patients with relapsed/refractory (R/R) acute lymphocytic/acute myeloid leukemia (ALL/AML), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM)."
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

BIOMEA FUSION, INC.

Date: April 8, 2022

By: /s/ Thomas Butler

Thomas Butler
Principal Executive Officer

Biomea Fusion Reports Preclinical Data on BMF-219 and Trial in Progress Presentations at AACR 2022 Annual Meeting

April 8, 2022

- Covalent menin inhibitor BMF-219 showed strong cytotoxic activity as a single agent at similar concentrations across multiple preclinical patient derived (PDX) models *ex vivo*, including diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and pancreatic cancer
- Single agent BMF-219 demonstrated pronounced anti-cancer activity *in vitro* across KRAS G12C, G12D, G13D, and G12V mutant cell lines, including higher cell killing in comparison to commercially available KRAS G12C inhibitors and other clinical menin reversible inhibitors
- BMF-219 was multi-fold more potent and exerted greater cytotoxicity compared to clinical reversible menin inhibitors in DLBCL patient-derived *ex vivo* samples and over 99% cell lethality in MM cell lines with RAS mutations as a single agent
- A Phase I study (COVALENT-101) of BMF-219 is currently enrolling patients with relapsed / refractory acute leukemias, DLBCL, and MM

REDWOOD CITY, Calif., April 08, 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 presented new data at the American Association of Cancer Research (AACR) Annual Meeting demonstrating BMF-219's potent and highly effective activity in multiple preclinical models of DLBCL, MM, and KRAS human *ex vivo* tumor models and cell lines in poster presentations. In addition, the company presented a Trial In Progress (TIP) poster presentation detailing the design of Biomea's ongoing Phase I clinical trial (COVALENT-101).

The preclinical and TIP presentations can be viewed on Biomea's website at https://biomeafusion.com/publications.

"Today, we unveiled a dataset in which single agent BMF-219 demonstrated pronounced cytotoxic activity across multiple liquid and solid tumor types that we will be pursuing in the clinic. These data clearly show BMF-219's powerful cell-killing activity in a broad spectrum of tumor types, including a very robust pan-KRAS effect," said Steve Morris, MD, Biomea's Chief Medical Officer. "In liquid and solid tumor preclinical studies, BMF-219 has demonstrated a highly differentiated profile from both non-covalent menin inhibitors as well as clinical-stage and FDA-approved covalent KRAS G12C inhibitors. We are very excited to see how this differentiated profile translates in the clinical setting across multiple liquid and solid tumors."

In comparison to two highly specific KRAS G12C inhibitors, BMF-219 exhibited broader potency across KRAS-mutated cell lines (G12C, G12D, G13D, and G12V) and *ex vivo* PDX tumor models indicating pan-KRAS activity with over 90% growth inhibition in most of these models. Additionally, BMF-219 showed the potential to increase the depth of response across G12C cell lines, notably achieving a higher percentage of cell killing in G12C colorectal cancer cells compared to the commercially available KRAS inhibitor sotorasib and another clinical-stage KRAS inhibitor. Additionally, BMF-219 exhibited robust growth inhibition as a single agent against high-grade B-cell lymphoma cell lines that are known to have low response to standard of care, as well as in multiple MM cells with TP53 and RAS mutations at similar drug concentrations.

A targeted pan-KRAS inhibitor has the potential to treat the 25-35% of NSCLC, 40-45% of CRC, and ~90% of pancreatic cancer patients who have KRAS-mutant tumors. If approved, BMF-219 could be an effective treatment for relapsed/refractory DLBCL and MM, where patients have a significant unmet need despite a large armamentarium of therapeutic options. Additionally, we believe BMF-219 has the potential to be an effective therapeutic option for menin-dependent acute leukemias, including the >45% of AML patients that are believed to have menin-dependent disease.

Poster Presentation Details

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

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

COVALENT-101: A Phase 1 study of BMF-219, a novel oral irreversible menin inhibitor, as a single agent in patients with relapsed/refractory (R/R) acute lymphocytic/acute myeloid leukemia (ALL/AML), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM) (NCT05153330) (Abstract #7613)

Session Category: Clinical Trials
Session Title: Phase I Trials in Progress 1
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 34
Poster Board Number: 10
Permanent Abstract Number: CT210

About Biomea Fusion

Biomea Fusion is a 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 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, the progress of our COVALENT-101 Phase I clinical 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 in patient enrollment and in the initiation, conduct and completion of our planned clinical trials and other research and development 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.

Contact:

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Abstract 2665 AACR April 8 – 13, 2022

Irreversible Menin Inhibitor, BMF-219, Exhibits Potent Cytotoxicity in KRAS-Mutated Solid Tumors

Brian Law, BS[1], Daniel Lu, MS[1], Priyanka Somanath, PhD[1], James T. Palmer, PhD[1], Lekha Kumar, MS[1], Tripta Rughwani, MS[1], Tenley Archer, PhD[1], Taisei Kinoshita, PhD[1], Mini Balakrishnan, PhD[1] and Thomas Butler, MSc MBA[1]

[1]Biomea, Fusion, Inc. Redwood City, CA

We Aim to Cure™

Introduction

- Kirsten rat sarcoma virus (KRAS) alterations are amongst the top oncogenic drivers and account for approximately one in seven of all human cancer. Within the US, KRAS mutations are most frequently found in high percentages of colorectal cancer (CRC), non-small cell NSCLC cancer (NSCLC) and pancreatic cancer.[1] These cancers respond poorly to standard-of-care agents, progress, and their management has been hindered by a lack of effective targeted therapies.
- BMF-219, is an orally bioavailable, selective irreversible inhibitor of menin, an important transcriptional regulator known to play a direct role in oncogenic signaling in multiple cancers.
- Preclinical data of BMF-219 show sustained potent abrogation of menin-dependent oncogenic signaling in vitro and in vivo.
- Results from Mia PaCa-2 cells prompted our exploration of the effects of BMF-219 in an expanded panel of KRAS-mutated solid tumors through in vitro, ex vivo PDX models, and KRAS-mutated gene expression.

Table 1. Estimated Target Population[1]

KRAS Type	Estimated Frequency of US Cases
CRC	~45%
NSCLC	~20%
Pancreatic	~90%

Methods

- Mia PaCa-2 cells were incubated with BMF-219 for 24 hours and analyzed by RNA-seq on the Illumina NextSeq 550 platform.
- BMF-219, clinical reversible menin inhibitor, or commercially available standard of care KRAS G12C inhibitor, sotorasib, were cultured with CRC, NSCLC, and pancreatic cancer cell lines for 4-days. Cell viability was measured using CellTiter Glo.
- Human ex vivo PDX tumor models harboring KRAS mutations were cultured with BMF-219 and clinical reversible menin inhibitors for 6-days. Cell viability was measured using CellTiter Glo.

Results

- Mia PaCa-2, a KRAS G12C mutated cell line, showed marked reduction of KRAS and MEN1 expression levels in MiaPaCa-2 cells at 0.5 µM and 1 µM after 24 hours BMF-219 treatment.
- An expanded panel of 14 CRC, NSCLC and pancreatic KRAS-mutated cell lines revealed single agent BMF-219 activity after a 4-day treatment. Most of the cell lines tested exhibited > 90% inhibition of growth, independent of KRAS mutation type. Sotorasib reached a maximum of 86-93% growth inhibition in three of ten G12C cell line. By contrast, BMF-219 inhibited cell viability ≥ 90% in seven of ten KRAS G12C NSCLC cancer lines.
- Human CRC, NSCLC and pancreatic ex vivo preclinical models with G12C and G12D KRAS mutations were all sensitive to BMF-219 6-day treatment. Complete abrogation of growth was observed in all samples with GI_{50} values ranging between 0.2 µM – 0.7 µM. Clinical reversible menin inhibitors were inactive in all preclinical models tested.

In Vitro Results

Figure 1. BMF-219 Cell-Killing in Mia PaCa-2 KRAS G12C cell line

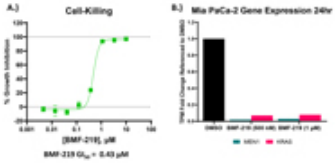


Figure 1. A.) BMF-219 induces cell killing of KRAS-mutated G12C cell line Mia PaCa-2 (Pancreatic cancer). Cells were treated with BMF-219 for 4 days and cell killing measured by Cell Titer Glo. Representative dose response curve is shown. GI_{50} is averaged from 2 independent experiments. **B.) BMF-219 treatment induced changes in KRAS and MEN1 in the KRAS-mutated cell line.** Each bar in the figure represents the Transcripts Per Million (TPM) normalized expression of MEN1 or KRAS genes colored by gene. Bar plots display the distribution of data referenced to the respective cell line DMSO controls.

Figure 2. Growth Inhibition In Vitro of KRAS Mutant Cell Lines at 1.1µM

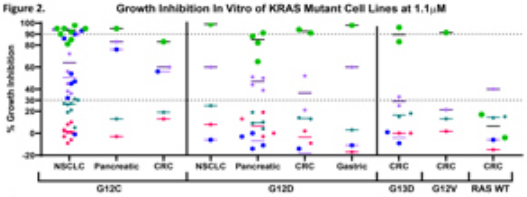


Figure 2. BMF-219 inhibits KRAS mutant cell growth in vitro. Observed max % inhibition of KRAS mutant cell lines representing lung (NSCLC), pancreatic, colorectal (CRC), gastric cancers were treated with 1.1 µM of BMF-219, two clinical reversible menin inhibitors, and two clinical irreversible KRAS G12C inhibitors. Cells were treated with compounds at a starting concentration of 10 µM to generate GI_{50} values. Each data point is an average of technical duplicates from 2 or 3 independent repeats.

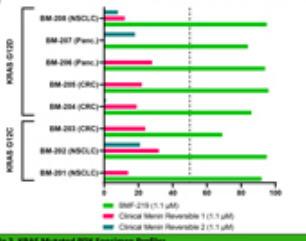
Table 2. KRAS Mutant Cell Line GI_{50} Summary

Tumor Type Type	KRAS-G12C GI_{50} (µM)			KRAS G12D-GI_{50} (µM)				KRAS-G13D GI_{50} (µM)	KRAS-G12V GI_{50} (µM)	RAS WT GI_{50} (µM)
	NSCLC (8)	Pancreatic (1)	CRC (1)	NSCLC (1)	Pancreatic (4)	CRC (2)	Gastric (1)	CRC (2)	CRC (1)	CRC (2)
BMF-219	0.36 - 0.57	0.43	0.57	0.29	0.43-0.83	0.42	0.34	0.37-0.57	0.45	1.6, LR
Clinical Menin Reversible 1	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
Clinical Menin Reversible 2	1.8 - 6.2, LR	3.1	6.9	2.0	4.1-7.2	6.5	3.8	3.9-6.3	3.2	3.1, LR
Clinical KRAS-G12C Irreversible	0.026 - 4.7	0.0038	0.017	0.84	1.1-4.0	1.1	0.70	1.4-2.3	1.8	1.3
Sotorasib KRAS-G12C	0.033 - 5.6, LR	0.0054	0.035	LR	6.7, LR	LR	LR	LR	LR	LR

Limited Response (LR) = % growth inhibition < 30 %. Values next to tumor cell type (#) are numbers of unique cell lines tested. Data represents mean of 2 or 3 independent repeats.

Ex Vivo Results

Figure 3. % Growth Inhibition of Ex Vivo PDX Tumors



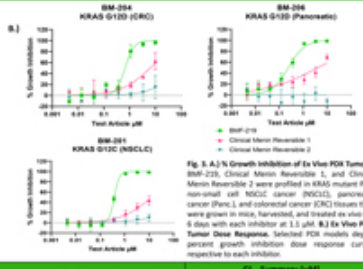


Fig. 3. A.) % Growth Inhibition of Ex Vivo PDX Tumors. BMF-219, Clinical Menin Reversible 1, and Clinical Menin Reversible 2 were profiled in KRAS mutant PDX non-small cell NSCLC cancer (NSCLC), pancreatic cancer (Panc.), and colorectal cancer (CRC) tissues that were grown in mice, harvested, and treated ex vivo for 6 days with each inhibitor at 1.1 µM. **B.) Ex Vivo PDX Tumor Dose Response.** Selected PDX models depict percent growth inhibition dose response curves respective to each inhibitor.

Table 3. KRAS Mutated PDX Specimen Profiles

Patient Clinical Stage at Collection	Prior Therapy	KRAS Mutation	Specimen Type	GI_{50} Summary (µM)		
				BMF-219	Clinical Menin Reversible 1	Clinical Menin Reversible 2
BM-207 (Not Available)	N/A	G12D	Pancreatic	0.559	LR	LR
BM-206 (Not Available)	N/A	G12D	Pancreatic	0.244	4.27	LR
BM-204 (Stage IV)	1) 5-FU/Oxaliplatin; 2) 5-FU/Irinotecan/Bevacizumab; 3) 5-FU/Panitumumab	G12D	CRC	0.671	6.32	LR
BM-205 (Stage IV)	1) 5-FU/Oxaliplatin/Bevacizumab (mixed response) 2) Capecitabine/Irinotecan/Bevacizumab 3) Irinotecan/Cetuximab/Capecitabine (responded, progression unknown)	G12D	CRC	0.298	9.98	LR
BM-203 (Stage IV)	1) 5-FU/Oxaliplatin	G12C	CRC	0.624	8.23	LR
BM-208 (Stage IV)	1) Cisplatin/Etoposide (mixed response) 2) Carboplatin/Premetrexed (mixed response) 3) Ramucirumab/Docetaxel (mixed response)	G12D	NSCLS	0.480	7.39	LR
BM-201 (Stage III)	1) Carboplatin/Nab-paclitaxel; 2) Carboplatin/Docetaxel	G12C	NSCLS	0.384	LR	LR
BM-202 (Not Available)	1) Cisplatin/Bevacizumab	G12C	NSCLS	0.352	7.76	LR

Conclusion

- Single agent treatment of BMF-219 in vitro at 1 µM in KRAS-mutated cell lines demonstrated higher cell killing in comparison to commercially available standard of care KRAS G12C inhibitor, sotorasib, and clinical KRAS G12C irreversible.
- MEN1 and KRAS gene expression dramatically decreased after 24-hour treatment with BMF-219 in KRAS-mutated G12C cell line Mia PaCa-2 (Pancreatic cancer).
- BMF-219 achieves high cell killing broadly across KRAS-mutated ex vivo treated patient derived CRC, NSCLC, and pancreatic models.
- In comparison to two highly specific KRAS G12C inhibitors, BMF-219 exhibited potency broadly across KRAS-mutated cell lines and PDX tumor models indicating BMF-219 may provide therapeutic advantages over these KRAS mutation-specific inhibitors for use in CRC, NSCLC, and pancreatic cancers.
- At clinically relevant concentrations, potent clinical KRAS inhibitors like sotorasib are highly efficacious up to 50 % inhibition. However, at these concentrations BMF-219 is more proficient, achieving higher percent of cell killing, suggests that BMF-219 produces an increase in the depth of response.

References

1. Hofmann, M. H., Gerlach, D., Misale, S., et al. Expanding the Reach of Precision Oncology by Drugging All KRAS Mutants. Cancer Discov (2022) doi:10.1158/2159-8290.cd-21-1331.
2. Hallin J, Engstrom LD, Hargis L, et al. The KRASG12C Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov. 2020 Jan;10(1):54-71. doi: 10.1158/2159-8290.CD-19-1167. Epub 2019 Oct 28. PMID: 31658955; PMCID: PMC6954325.
3. Chester E. Chamberlain, et al. Menin Determines K-RAS Proliferative Outputs in Endocrine Cells. J Clin Invest. 2014;124(9):4093-4101. https://doi.org/10.1172/JCI69004.

Acknowledgements - We would like to acknowledge the support received from Arpeggio Biosciences for generating RNAseq data, analysis of gene expression data, and database management. We also would like to acknowledge the support received from Champions Oncology for generating human PDX KRAS-mutated models in mice and ex vivo data.

Abstract 2654 AACR April 8 – 13, 2022

biomea FUSION

Anti-tumor Activity of Irreversible Menin Inhibitor, BMF-219, in High Grade B-Cell Lymphoma and Multiple Myeloma Preclinical Models

We Aim to Cure™

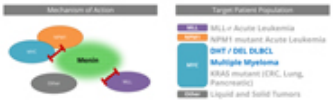
Priyanka Somanath, PhD[1], Daniel Lu, MS[1], Brian Law, BS[1], Lekha Kumar, MS[1], Angela Lu[1], James T. Palmer, PhD[1], Taisei Kinoshita, PhD[1], Mini Balakrishnan, PhD[1] and Thomas Butler, MSc MBA[1]

[1]Biomea Fusion, Inc. Redwood City, CA

INTRODUCTION

- Double/Triple Hit Lymphoma (DHL/THL) and Double Expresser Lymphoma (DEL) are high-grade B-cell lymphomas (HGBL) 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 Diffuse Large B-Cell Lymphoma (DLBCL) preclinical models (Somanath et al., 2021).

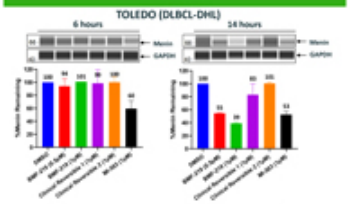
- Here, we demonstrate the anti-tumor activity of BMF-219 in HGBL and MM preclinical models harboring various mutational backgrounds.



METHODS

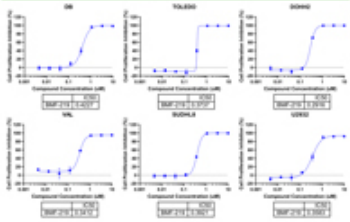
- AML and DLBCL cell lines were cultured in the presence of BMF-219 or clinical reversible menin inhibitors for 14 hours. Menin protein expression was measured by the Wes system and analyzed using the Compass software (automated western blotting, Protein Simple). Signal was normalized to GAPDH and referenced to DMSO control.
- DLBCL and MM cell lines were cultured in the presence of BMF-219 or bortezomib (PS-341) for 4 days and cell proliferation was measured by Cell Titer Glo.
- Patient-derived DLBCL PDX models and MM patient derived BMMCs were cultured *ex vivo* in the presence of BMF-219 or PS-341 for 6 days and cell proliferation was measured by Cell Titer Glo.

RESULTS



BMF-219 reduces menin protein in DLBCL cells. Quantitation of menin protein expression in TOLEDO (DLBCL, DHL) cell line treated with BMF-219, clinical reversible menin inhibitors or preclinical reversible menin inhibitor, MI-503, for 14 hours.

BMF-219 exerts potent cell lethality in DLBCL cell lines

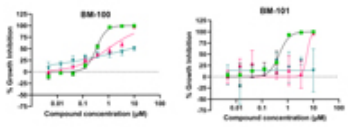


DLBCL Cell Line	Category	Translocation	Average % Max Inhibition by BMF-219	Average IC_{50} ± Standard Deviation (µM)
DB	DHL	MYC/BCL2	98.5	0.407 ± 0.067
Toledo	DHL	MYC/BCL2	98.8	0.315 ± 0.065
DOHH2	DHL	MYC/BCL2	99.7	0.323 ± 0.031
VAL	THL	MYC/BCL2/BCL6	97.1	0.271 ± 0.070
U2932	DEL-ABC	MYC/BCL2 Overexpression	92.4	0.370 ± 0.012
SUDHL8	GCB	-	99.6	0.601 ± 0.209
Pfeiffer	GCB	-	99.6	0.167 ± 0.040
OCI-LY7	GCB	-	99.6	0.650 ± 0.260

Potent killing activity of BMF-219 at clinically relevant concentrations in representative DLBCL cell lines. Cell lines from DHL (DB, Toledo, DOHH2), THL (VAL), DEL (U2932), and GCB (SUDHL8) subtypes were cultured in the presence of BMF-219 at 8 dose concentrations ranging from 0.005 µM to 10 µM for 4 days and cell killing measured by Cell Titer Glo. Representative dose response curves are shown on the top. Average IC_{50} values of at least two experiments, maximal percentage cell killing and cytogenetic background of DLBCL cell lines are summarized in the table.

BMF-219 exerts pronounced lethality in DLBCL PDX models *ex vivo*

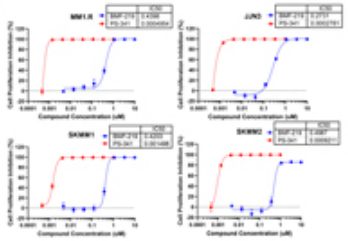
THL- Responded, then progressed on R-EPOCH | **MYC Amplified- Responded, then progressed on R-CHOP**



Treatment	Growth Inhibition IC_{50} (µM)	
	BM-100	BM-101
BMF-219	0.250	0.101
Clinical Reversible-1	0.969	5.63
Clinical Reversible-2	0.31	Max killing <50%

Growth inhibition of patient-derived DLBCL Triple Hit Lymphoma (THL) and MYC-amplified PDX samples treated with BMF-219 or clinical reversible menin inhibitors after 6 days of treatment.

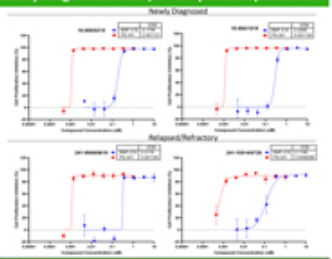
BMF-219 exerts >99% lethality against MM cell lines



MM Cell Line	Translocation	Mutation	Average % Max Inhibition by BMF-219	Average IC_{50} ± Standard Deviation (µM)
MM1.S	t(14;16)	KRAS G12A	99.5	0.467 ± 0.17
MM1.R	t(14;16)	KRAS G12A	99.6	0.462 ± 0.17
SKMM1	t(14;20)	NRAS G12A	99.2	0.467 ± 0.05
SKMM2	t(11;14)	TP53	80.2	0.654 ± 0.15
JJN3	t(14;16)	NRAS Q61K	99.2	0.289 ± 0.02

Potent killing activity of BMF-219 at clinically relevant concentrations in representative MM cell lines. MM1.R, JJN3, SKMM1 and SKMM2 cell lines were cultured in the presence of BMF-219 (blue) or PS-341 (red) at 8 dose concentrations ranging from 0.005 µM to 10 µM for four days and cell killing measured by Cell Titer Glo. Representative dose response curves are shown on the top. Average IC_{50} values of at least two experiments, maximal percentage cell killing, and cytogenetic background of MM cell lines are summarized in the table.

BMF-219 dramatically reduces growth of both newly diagnosed and R/R MM patient specimens



Multiple Myeloma Specimen ID	Stage at Diagnosis	Treatment Status	Prior Therapy and Response	Translocation
16-669/0219	IIIA	Newly Diagnosed	None	No data
16-684/1019	IIIA	Newly Diagnosed	None	No data
241-9945/06-19	IIIA	Refractory	VCD N-4 (resistant)	p53 deletion
241-10514/0720	IIIA	Refractory	VCD N-4 (responded) High dose CPH (SC-mobilization) (responded) Consolidation (AutoSCT, double transplant) Bortezomib- maintenance (resistant) RVD #4 (resistant) PRD #4 (resistant)	p53 deletion-negative

Growth inhibition of newly diagnosed (A-B) and R/R (C-D) MM patient-derived bone marrow mononuclear cells (BMMCs) after 6 days of treatment with BMF-219 (blue) or PS-341 (red). Clinical profiles of MM patient-derived BMMC specimens are summarized in the table.

CONCLUSIONS

- BMF-219 exhibited high potency as a single agent against DHL, THL and DEL DLBCL cell lines, with IC_{50} values of 0.27 µM and 0.37 µM, respectively.
- In *ex vivo* studies, BMF-219 was highly effective against R-CHOP and R-EPOCH refractory patient samples with THL and MYC-amplified genetic backgrounds.
- BMF-219 was multi-fold more potent and exerted dramatically greater growth inhibition compared to clinical reversible menin inhibitors in DLBCL patient-derived *ex vivo* samples.
- BMF-219 achieved >99% cell lethality in MM cell lines with RAS mutations.
- 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.

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Abstract 7613

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COVALENT-101

(NCT05153330)

A Phase 1 study of BMF-219, a novel oral irreversible menin inhibitor, as a single agent in patients with relapsed/refractory (R/R) acute lymphocytic/acute myeloid leukemia (ALL/AML), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM)

We Aim to Cure™

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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 a novel approach to cancer treatment.[1]

BMF-219

- BMF-219, is an orally bioavailable, potent and selective irreversible covalent inhibitor of menin, an important transcriptional regulator known to play a direct role in oncogenic signaling in multiple cancers.
- Preclinical data of BMF-219 show sustained potent abrogation of menin-dependent oncogenic signaling in vitro and in vivo.
- BMF-219 demonstrates a strong anti-proliferative effect on various menin-dependent acute myeloid leukemia (AML) cell lines, DLBCL cell lines representing Double/Triple Hit Lymphoma(DHL/THL), Double Expressor Lymphoma (DEL), and MM cell lines harboring diverse mutational backgrounds.
- BMF-219 also exhibits 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.[2]
- BMF-219 is currently supplied as 25 and 100 mg strength capsules for oral administration.

COVALENT-101 (BF-MNN-101) STUDY OVERVIEW

- COVALENT-101 is a prospective, open-label, multi-cohort, non-randomized, multicenter, first-in-human Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of oral BMF-219 administered once daily in patients with R/R ALL, AML, DLBCL and MM who have received standard therapy.
- Approximately 20 clinical sites in the United States.

OBJECTIVES & ENDPOINTS

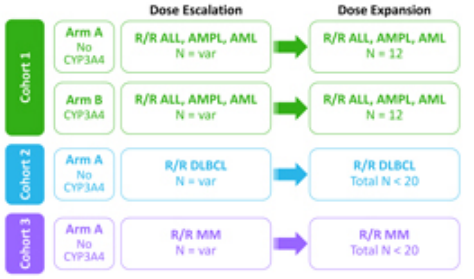
Primary	Determine OBD & RP2D of BMF-219 for each Cohort (1, 2 & 3) and Arm (A & B)	• OBD/RP2D will be determined based on PK/PD/Safety/Efficacy
Secondary	Further evaluate Safety and tolerability of BMF-219	• TEAE / SAE incidence • C_{max}, T_{max} and $AUC_{0-\infty}$ of BMF-219
	PK/ PD evaluation of BMF-219 Additional Evidence of Efficacy of antitumor activity	• Cohort 1: CRR*↗ • Cohort 2: ORR↗ • Cohort 3: ORR◊ } & other efficacy parameters per investigator assessment
Exploratory	To characterize the PD effects of BMF-219 for each cohort independently	• Changes in gene expression • Explore predictive and pharmacodynamic markers

* Based on European LeukemiaNet (ELN) 2017 Recommendation for diagnosis and management of AML or the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, ALL (Version 2. 2021)

↗ Revised criteria for response assessment of lymphoma (Cheson, 2014)

◊ International Myeloma Working Group (IMWG) response criteria (Kumar, 2016)

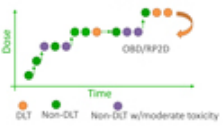
Study Design



Dose Escalation Scheme

Dose Level (DL)	Fibonacci Factor	ARM A Fibonacci Cal. Dose (mg)	ARM A Suggested Clinical Dose (mg)	ARM B Fibonacci Cal. Dose (mg)	ARM B Suggested Clinical Dose (mg)
DL 1	1	100	100	25	25
DL 2	2	200	200	50	50
DL 3	1.67	334	325	83.5	75
DL 4	1.5	501	500	125.25	125
DL 5	1.33	666.33	650	166.58	175

Accelerated titration design followed by 3+3



- Doses of BMF-219 will be escalated in single-subject cohorts independently for each indication until 1 subject experiences either any ≥ Grade 2 related-TEAE which does not meet DLT criteria, or a DLT in the first cycle.
- At that point, the dose level for the specific cohort will follow a classical "3 + 3" dose escalation design.

Study Flowchart

Screening	• Up to 28 days from consent
Treatment	• Daily treatment with BMF-219 in 28-day cycles
Post Tx Follow-Up	• Regular post-tx efficacy assessment visits
Post HSCT Treatment	• Post adequate response to BMF-219 patient may proceed with HSCT and then resume BMF-219
Long Term Follow-Up	• Survival follow-up calls

Key Eligibility Criteria

Inclusion Criteria

- ≥ 18 years with ECOG performance status of 0-2 and an estimated life expectancy of > 3 months
- Adequate liver function: Bilirubin ≤ 1.5 ULN; ALT/AST ≤ 2.0 ULN
- Adequate renal function: estimated creatinine clearance (eCrCl) ≥ 60 mL/min (Cohort 1) or eCrCl ≥ 30 mL/min (Cohorts 2 & 3) using the Cockcroft-Gault equation
- Prior treatment-related toxicities resolved to ≤ Grade 2 prior to enrollment
- Adequate washout from prior therapies (e.g., ≥ 60 days from RT; ≥ 60 days from stem cell infusion; ≥ 7 days from biologics or steroids; ≥ 21 days from prior immunotherapy; ≥ 14 days from completion of last chemotherapy)

Indication & Prior Regimen Criteria

Cohort	Arm	Indication	Prior treatment regimens	*CYP3A4 inhibitors
1	A	R/R ALL, AMPL, AML agnostic of mutation	No limit, includes prior HSCT	No
1	B	R/R ALL, AMPL, AML agnostic of mutation	No limit, includes prior HSCT	Yes
2	A	R/R DLBCL / DLBCL transformed from previously indolent lymphoma (e.g., follicular lymphoma)	≥ 2 but ≤ 5 with at least 1 course of anthracycline-based chemotherapy & at least 1 course of anti-CD20 immunotherapy	No
3	A	R/R MM	≥ 3 but ≤ 6 including proteosome inhibitor	No

* Subjects are receiving concomitant medications considered to be strong or moderate inhibitors of CYP3A4

Exclusion Criteria

- Known CNS disease involvement
- Prior menin inhibitor therapy
- Clinically significant cardiovascular disease; LVEF < 45%
- Mean QTcF or QTcB of > 470 millisecond (ms)
- Acute or chronic GVHD except disease limited to skin with adequate control using topical steroids
- Concurrent malignancy in the previous 2 years

References

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2. Anti-tumor activity of irreversible menin inhibitor, BMF-219, in High Grade B-Cell Lymphoma and Multiple Myeloma Preclinical Models. AACR 2022, Abstract 2654.