COVALENT-102: A phase 1/1b dose finding study of BMF-219, an oral covalent menin inhibitor, in patients with metastatic non-small cell lung cancer (NSCLC), pancreatic cancer (PDAC), & colorectal cancer (CRC) with activating KRAS mutations

Stacey A Cohen, MD[1]; Christos Fountzilas, MD[2]; David Sommerhalder, MD[3]; Saba Radhi, MD[4]; Sandip Patel, MD[5]; Al Benson, MD[6]; Kai He, MD[7]; Apar Ganti, MD[8]; Alex Spira, MD[9]; Bhagyashree Yadav, MD[10]; Alex Cacovean, MD[10]; Steve Morris, MD[10]; Thomas Butler, MS, MBA[10]; David Hong, MD[11]

[1]Fred Hutchinson Cancer Center, Seattle, WA; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, [3]NEXT Oncology, San Antonio, TX; [4]Cancer Treatment Centers of America, Phoenix, AZ; [5]University of California, San Diego, CA; [6]Northwestern Medical Group, Chicago, IL; [7]Ohio State University, Columbus, OH; [8]University of Nebraska, Omaha, NE; [9]NEXT Oncology, Virginia, Fairfax, VA; [10]Biomea Fusion, Inc., Redwood City, CA; [11]MD Anderson Cancer Center, Houston, TX

BMF-219 BACKGROUND

- BMF-219 is a selective covalent inhibitor of menin, a transcriptional regulator of oncogenic signaling pathways in multiple cancers, that inhibits the menin/MYC interaction and downregulates the expression of MYC and MYC target genes, including KRAS.[1,2]
- In addition to MYC disruption, inhibition of the Menin-MLL complex by BMF-219 alters JunD genomic function, a crucial factor for KRAS-driven tumorigenesis.[3]
- Inhibition of the Menin-MLL complex suppresses expression of Rasgrf1, which is essential for generation of the active RAS-GTP conformation of KRAS, activation of downstream pathways, and tumorigenesis.[4]
- Preclinically, BMF-219 shows sustained potent abrogation of menin-dependent oncogenic signaling.
- BMF-219 exerts pan-mutant KRAS anticancer activity that is independent of the specific KRAS-activating mutation.[5]

COVALENT-102 STUDY OVERVIEW

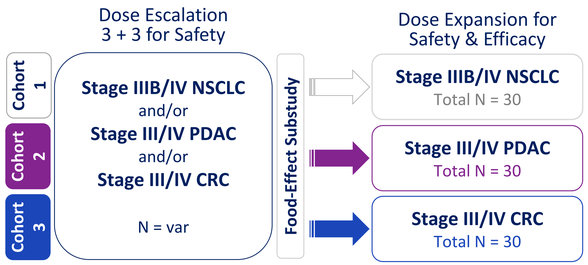
- COVALENT-102 (NCT05631574) is a prospective, open-label, multicenter, dose finding study evaluating the safety, tolerability, and clinical activity of escalating doses of BMF-219 administered daily in patients with unresectable, locally advanced, or metastatic NSCLC (Cohort 1), PDAC (Cohort 2) & CRC (Cohort 3) with activating KRAS mutations who have received standard therapy.
- Approximately 20-30 clinical sites in the United States, EU & S. Korea.
- COVALENT-102 began accruing patients in January 2023; enrollment is ongoing

OBJECTIVES & ENDPOINTS

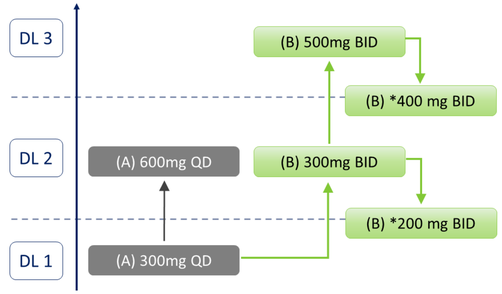
Primary	Determine the optimal biological dose(s) (OBDs) and recommended Phase 2 dose(s) (RP2Ds) of BMF-219 monotherapy in subjects with unresectable, locally advanced, or metastatic NSCLC, PDAC and CRC	• OBD/RP2D will be determined based on PK/PDn/Safety/Tolerability & ORR
Secondary	Further evaluate Safety and tolerability of BMF-219 PK evaluation of BMF-219 Evaluate Efficacy* of BMF-219 monotherapy in subjects with unresectable, locally advanced, or metastatic NSCLC, PDAC and CRC	• TEAEs / SAEs • C_{max}, T_{max}, and AUC_{last} of BMF-219 • DOR, DCR
Exploratory	Time to clinical events of interest Characterize pharmacodynamic (PDn) effects of BMF-219 in subjects with unresectable, locally advanced, or metastatic NSCLC, PDAC and CRC Measure biomarkers of the menin-regulated pathways Assess the effects of BMF-219 on glycemic biomarkers in subjects with diabetes Assess the effect of food on the PK exposure of BMF-219	• Explore progression-free survival (PFS), overall survival (OS), time to response (TTR) • Explore early clinical activity and the prognostic and predictive relationship of PDn markers in BMF-219-treated tumor cells • Measure the gene expression and protein changes in plasma and tissue • Assess target engagement • Changes in blood glucose, HbA1c levels, and blood C-peptide levels in diabetic patients • AUC_{last}, AUC_t, t_{max}, C_{max}, and $t_{1/2}$

* Efficacy is per RECIST 1.1 criteria as assessed by the Investigator

STUDY DESIGN

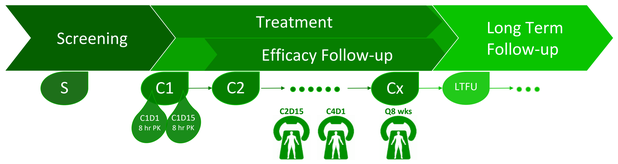


Dose Escalation Scheme



* If ≥ 33% of subjects in Arm B experience a DLT (e.g., > 1 out of 3 or > 2 out of 6 subjects) at DL2 or DL3, dosing will transition to 200 mg BID or 400 mg BID, respectively.

Study Flowchart



Screening	• Up to 28 days from consent
Treatment	• Daily treatment with BMF-219 in 28-day cycles
Post Tx Follow-Up	• Regular efficacy assessment visits
Long Term Follow-Up	• Survival follow-up calls

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- ≥ 18 years with ECOG performance status of 0-2 (NSCLC, CRC) or ECOG 0-1 (PDAC) and an estimated life expectancy of > 3 months
- Activating KRAS mutation
- Radiologic progression & ≥ 1 measurable lesion
- Adequate liver function: Bilirubin ≤ 1.5 ULN; ALT/AST ≤ 2.0 ULN
- Adequate renal function: estimated creatinine clearance (eCrCl) ≥ 60 mL/min using the Cockcroft-Gault equation
- Adequate washout from prior therapies
- Prior KRAS inhibitor exposure allowed

Indication & Prior Regimen Criteria

Cohort	Indication	Prior treatment regimens
1	NSCLC	≥ 2 but ≤ 4 prior tx including CPI &/or platinum-based chemo ± bevacizumab
2	PDAC	≥ 1 prior tx including either FOLFIRINOX or gemcitabine/nab-paclitaxel (± platinum-based chemo)
3	CRC	≥ 1 prior tx including FOLFOX or FOLFIRI ± bevacizumab (prior ICI if MSI-H/dMMR)

Exclusion Criteria

- Symptomatic &/ or untreated CNS metastasis
- Pre-existing interstitial lung disease (ILD), or pericardial/ pleural effusion of ≥ Gr 2 or require chronic O_2 tx for COPD or pleural effusions
- Prior menin inhibitor therapy
- Strong or moderate CYP3A inhibitor/inducer (subjects may qualify if they are able to discontinue within 7 days of enrollment)
- Clinically significant cardiovascular disease; LVEF < 45%
- Mean QTcF or QTcB of > 470 millisecond (ms)
- Concurrent malignancy in the previous 2 years

References

1. Somanath P, et al. Anti-tumor activity of irreversible menin inhibitor, BMF-219, in high-grade B-cell lymphoma and multiple myeloma preclinical models [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; *Cancer Res* 2022;82(12_Suppl):Abstract nr 2654. https://doi.org/10.1158/1538-7445.AM2022-2654
2. Somanath P, et al. Novel Irreversible Menin Inhibitor, BMF-219, Shows Potent Single Agent Activity in Clinically Relevant DLBCL Cells. *Blood* 2021; 138 (Supplement 1): 4318. https://doi.org/10.1182/blood-2021-148045
3. Ruiz E J, et al. JunD, not c-Jun, is the AP-1 transcription factor required for Ras-induced lung cancer. *JCI Insight*. 2021;6(13):e12498.5 https://doi.org/10.1172/jci.insight.124985
4. Zhu LY, et al. Loss of MLL Induces Epigenetic Dysregulation of Rasgrf1 to Attenuate Kras-Driven Lung Tumorigenesis. *Cancer Res* (2022) 82 (22): 4153–4163. https://doi.org/10.1158/0008-5472.CAN-22-1475
5. Law B, et al. Irreversible menin inhibitor, BMF-219, inhibits the growth of KRAS-mutated solid tumors [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; *Cancer Res* 2022;82(12_Suppl):Abstract nr 2665. https://doi.org/10.1158/1538-7445.AM2022-2665