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

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**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-MKL complex by BMF-219 alters JUN genomic function, a crucial factor for KRAS-driven tumorigenesis.3
- Inhibition of the Menin-MKL 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

**OBJECTIVES & ENDPOINTS**

- To determine the biological disposition (dose)-response (DRS) and recommend Phase 2 dose(s) (RD2) of BMF-219 monotherapy in subjects with unresectable, locally advanced, or metastatic NSCLC (Cohort 1), PDAC (Cohort 2) & CRC (Cohort 3) with activating KRAS mutations who have received standard therapy.
- To approximately 20-30 clinical sites in the United States, EU & S. Korea.
- COVALENT 102 began accruing patients in January 2022; enrollment is ongoing.

**STUDY DESIGN**

**Stage III/IV NSCLC**

- **Dose Escalation**
  - Dose Escalation 3 + 3 for Safety
  - Stage III/IV NSCLC Total N = 30
- **Expansion & Safety/Efficacy**
  - Stage III/IV NSCLC Total N = 30
- **Dose Escalation Scheme**
  - DL 1 (a) 20mg BID
  - (b) 40mg BID
  - DL 2 (a) 80mg BID
  - (b) 160mg BID
  - DL 3 (a) 200mg BID
  - (b) 400mg BID

**Screening**

- Up to 28 days from consent
- Daily treatment with BMF-219 in 28-day cycles
- Regular efficacy assessment visits
- 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 function: Bilirubin ≤ 1.5 ULN; ALAT/ASAT ≤ 2 ULN
  - Renal function: estimated creatinine clearance (eCrCl) ≥ 60 ml/min using the Cockcroft-Gault equation
  - Adequate washout from prior therapies
  - Prior KRAS inhibitor exposure allowed

**Exclusion Criteria**

- Symptomatic &/or untreated CNS metastasis
- Pre-existing intestinal lung disease (ILD), or pericardial/ pleural effusion of ≥ Gr 2 or require chronic O2 therapy
- 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; UEF < 45%
- Mean QTcF > 500 ms or QT intervals (ms):
  - Concurrent malignancy in the previous 2 years

**References**