A Phase Ila/IIb, open-label trial of the MDM2–p53 antagonist BI 907828 in advanced biliary tract carcinoma, pancreatic ductal adenocarcinoma or other solid tumors: Brightline-2

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Introduction
Mechanism of action of BI 907828, an MDM2–p53 antagonist:
- Inactivation of p53 is a key mechanism by which tumors promote survival and proliferation1
- MDM2, an E3 ubiquitin ligase, is an endogenous negative regulator of p53.2 Blocking the MDM2–p53 interaction in TP53 wild-type tumors represents a potential therapeutic strategy
- BI 907828 blocks the interaction between p53 and its negative regulator MDM2. This stabilizes p53, permitting p53 target gene induction, leading to cell cycle arrest or apoptosis in TP53 wild-type tumor cells3

MDM2 amplification prevalence
- MDM2 is amplified in a range of tumor types, including biliary tract carcinoma and pancreatic ductal adenocarcinoma2,5

Trial design
Brightline-2 (NCT05512377): a multicenter, open-label, single-arm, Phase IIa/IIb trial, assessing the efficacy and safety of BI 907828, an MDM2–p53 antagonist

Cohort 1
- Biliary tract cancer
- Pancreatic ductal adenocarcinoma
- Lung adenocarcinoma
- Bladder cancer

Inclusion and exclusion criteria
Inclusion
- Locally advanced or metastatic: Biliary tract carcinoma; Pancreatic ductal adenocarcinoma; Lung adenocarcinoma; Bladder cancer

Exclusion
- Previous administration of BI 907828 or any other MDM2–p53 or MDMX (MDM4)–p53 antagonist
- Major surgery performed ≤ 54 weeks prior to treatment on trial or planned ≤ 6 months after screening
- Previous or concomitant malignancies that may affect treatment efficacy or trial outcome
- Receipt of appropriate prior standard-of-care therapy
- Written report confirming MDM2 amplification (copy number ≥ 28)
- TP53 wild-type
- ≥ 1 measurable lesion (RECIST v1.1)
- ECOG performance status of 0/1

Trial rationale
- Biliary tract carcinoma and pancreatic ductal adenocarcinoma are associated with a median survival of ~1 year in the advanced stages, and effective therapies are needed4-7
- In two ongoing Phase I trials (1403-0001, 1403-0002), treatment with BI 907828 ± ezabenlimab (an anti-PD-1 monoclonal antibody) showed antitumor activity in selected TP53 wild-type advanced/metastatic solid tumors

Efficacy summary in patients with biliary tract carcinoma treated in two Phase Ia/b trials
- Ten patients with biliary tract carcinoma received BI 907828 as monotherapy (1403-0001) or in combination with ezabenlimab (1403-0002). Five patients achieved partial response and three patients achieved stable disease as best response8,9

Monotherapy, N=6 (Trial 1403-0001)

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Combination, N=4 (Trial 1403-0002)

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References

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