p53 is known as the **'guardian of the genome'** and plays a key role in regulating cell proliferation and apoptosis

Inactivation of **p53** is a central mechanism for tumors to escape cell death

Brigimadlin is a potent, orally available small molecule investigational drug that binds to MDM2 and blocks the MDM2–p53 interaction, restoring p53 function

Targeting MDM2 with brigimadlin

Brigimadlin blocks the interaction between **p53** and its negative regulator **MDM2**

↓

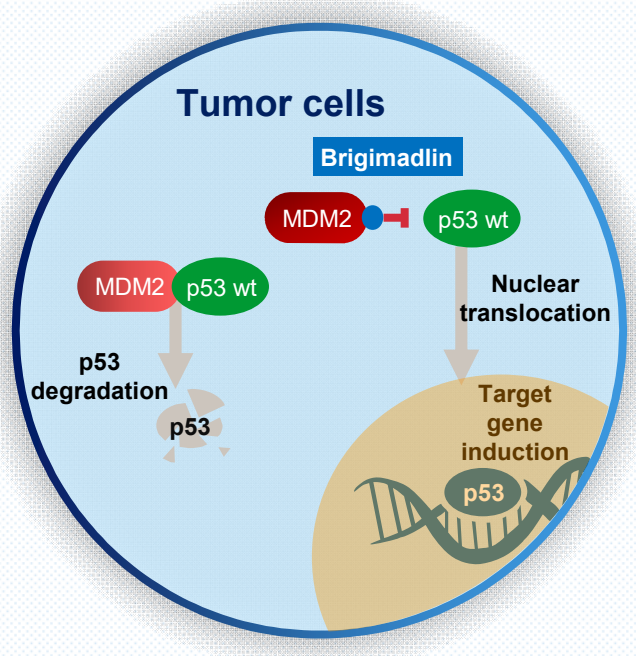
Restoration of **p53** function

↓

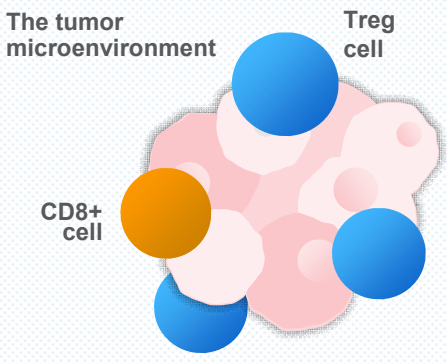
p53 induces target genes

↓

Cell cycle arrest or apoptosis in tumor cells with ***TP53*** **wild-type status**

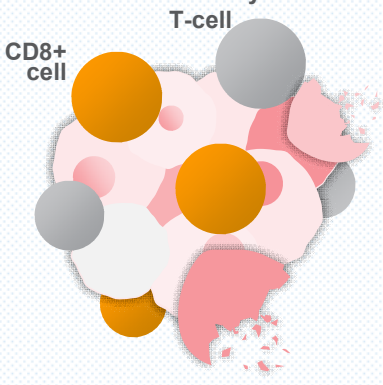


Brigimadlin may also promote a pro-immunogenic tumor microenvironment to help immune destruction of tumor cells



Brigimadlin has potential immunomodulatory properties

Preclinical data suggest this effect may be potentiated by combining **brigimadlin** with **immune checkpoint inhibitors** such as BI 754091 (ezabenlimab; a PD-1 inhibitor)



Here we present data from the first 12 patients with biliary tract cancer (BTC) treated with brigimadlin in two ongoing Phase Ia/Ib studies (data cut-off: Patients 1–10, December 2022; Patients 11–12, February 2023), and safety results in the overall populations

What are the aims of the two studies?

Assess safety, tolerability, and RP2D of **brigimadlin,** both as a monotherapy and in combination with ezabenlimab

Investigate antitumor activity in patients with advanced ***TP53*wt**, ***MDM2*-amplified** tumors (*TP53*wt only for Cohort 1 in 1403-0002)

What are the study designs?

Study 1403-0001 (monotherapy)

Phase Ia: dose escalation

Arm A	**Arm B**
Brigimadlin on D1 Q3W (10–80 mg) 29 pts	Brigimadlin on D1/D8 Q4W (5–60 mg) 25 pts

Primary endpoint: MTD based on DLTs
Secondary endpoints: PK, safety, efficacy

↓

Phase Ib: dose expansion (150 pts)

*TP53*wt *MDM2*-amplified sarcomas	Other *TP53*wt *MDM2*-amplified tumor types

Study 1403-0002 (combination)

Phase Ia: dose escalation

Brigimadlin (10–45 mg D1 Q3W) + ezabenlimab (240 mg D1 Q3W) + BI 754111 (600 mg D1 Q3W)

↓

Brigimadlin (restart escalation 45 mg D1 Q3W) + ezabenlimab (240 mg D1 Q3W)

Primary endpoint: MTD based on DLTs
Secondary endpoints: PK, safety, efficacy

↓

Phase Ib: dose expansion (95 pts)

*TP53*wt soft tissue sarcoma	Other *TP53*wt *MDM2*-amplified tumor types

Patients with BTC who have been enrolled

A total of **12 patients** with BTC have been enrolled across both trials:

Monotherapy

Combination

Median age, years:
70.5 **62.5**

Male:
67% **67%**

Tumor type

- Ampullary carcinoma (n=3)
- Intrahepatic cholangiocarcinoma (n=4 and n=1)
- Cholangiocarcinoma (n=2)
- Gall bladder carcinoma (n=2)

■ Monotherapy study (Q3W) ■ Combination study

Safety profile of brigimadlin +/- ezabenlimab

Overall, in the two trials, **102/110 (92.7%)** and **39/42 (92.9%)** experienced **≥1 TRAE**

Patients with AEs leading to:

- Dose reduction: 29.1% / 26.2%
- Discontinuation: 5.5% / 4.8%

In the two trials, **44.5%** and **50.0%** of patients had a **grade ≥3 TRAE**
The most common were:

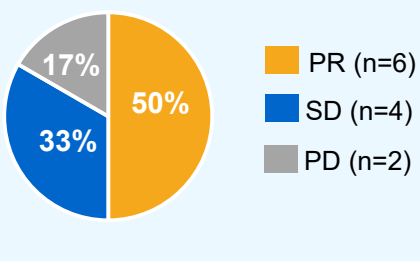
Thrombocytopenia	Neutropenia	Reduced WBC count	Anemia
23.6% **19.0%**	**21.8%** **19.0%**	**10.9%** **16.7%**	**10.0%** **11.9%**

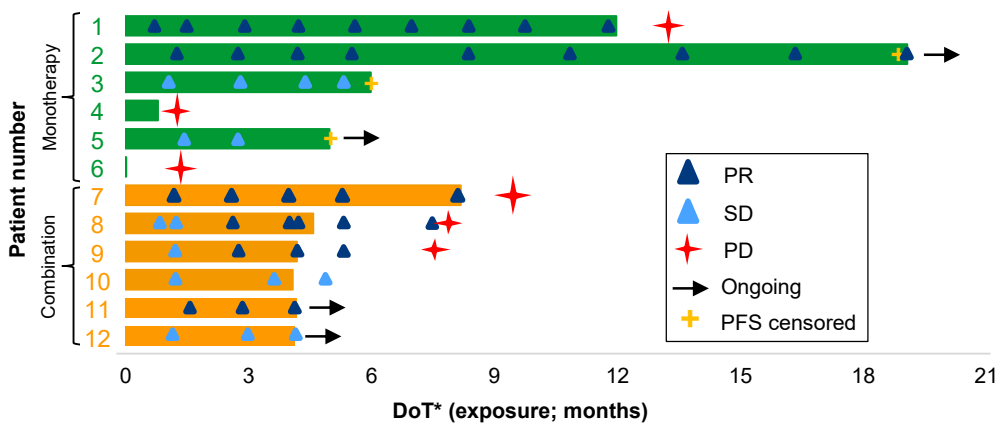
■ Monotherapy study (Q3W) ■ Combination study

Data from **patients with BTC** treated with **brigimadlin are consistent with the safety profile** seen in the overall population

Efficacy of brigimadlin +/- ezabenlimab in patients with BTC

Best response among patients with BTC who received either **brigimadlin** as monotherapy, or in combination with ezabenlimab **(n=12)**





*Time from first to last drug administration (D1Q3W); dose could be delayed due to AE up to 63 days.

In summary

Treatment of brigimadlin +/- ezabenlimab in patients with BTC showed:

A tolerable safety profile

Promising preliminary antitumor activity

Brightline-2, a Phase IIa/b trial in patients with BTC, is currently open for recruitment (NCT05512377)

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Disclosures
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Acknowledgments
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Supplementary Figure 1. An infographic summary of the case series manuscript entitled 'Efficacy and safety of the MDM2–p53 antagonist brigimadlin (BI 907828) in patients with advanced biliary tract cancer'.

Abbreviations: AEs, adverse events; BTC, biliary tract cancer; CD8, cluster of differentiation 8; DoT, duration of treatment; D1/8, Day 1/8; DLT, dose-limiting toxicity; MDM2, murine double minute 2 homolog; MTD, maximum tolerated dose; p53, protein 53; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; pts, patients; Q3W, every three weeks; RP2D, recommended Phase II dose; SD, stable disease; TP53, tumor protein 53; TRAE, treatment-related AE; Treg, regulatory T-cell; WBC, white blood cell; wt, wild-type