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BL-B01D1, an EGFR x HER3 Bispecific Antibody-drug Conjugate (ADC), in Patients with Locally Advanced or Metastatic Biliary Tract Carcinoma (BTC)

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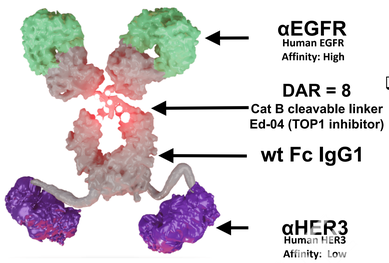
Background



- BL-B01D1, a potentially first-in-class EGFR×HER3 bispecific antibody-drug conjugate[1].
- Here, we present the safety and efficacy data in biliary tract carcinoma (BTC) from a phase I study (BL-B01D1-103), which enrolled patients with gastrointestinal cancer and other solid tumors.
- Clinical trial identification: NCT05262491.

Objectives

- Phase Ia: to observe the safety and tolerability of BL-B01D1 in patients with locally advanced or metastatic gastrointestinal cancer and other solid tumors, to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of BL-B01D1.
- Phase Ib: to observe the safety and tolerability of BL-B01D1 at the recommended dose of Phase Ia, to determine the recommended phase 2 dose (RP2D).

Methods

- This phase I study enrolls patients with locally advanced or metastatic gastrointestinal cancer and other solid tumors.
- This open-label, Phase I study was designed to evaluate BL-B01D1 safety, tolerability, pharmacokinetic characteristics, and preliminary efficacy in patients with locally advanced or metastatic gastrointestinal cancer and other solid tumors. Dose-escalation phase referred to BL-B01D1-101 study (NCT05194982)[2] and dose-expansion phase is being investigated. During dose-expansion, subjects with different tumor types were treated with BL-B01D1 at 2.0, 2.5, 3.0, 3.5mg/kg D1D8 Q3W and 3.0, 5.0mg/kg D1 Q3W.
- The primary endpoints of the study are dose limiting toxicities (DLT), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D). Secondary endpoints are treatment emergent adverse events (TEAE), pharmacokinetics parameters, objective response rate (ORR), disease control rate (DCR), duration of response (DOR).
- Exploratory endpoints are progression free survival (PFS), overall survival (OS), biomarker, and neutralizing antibodies (NAb).

Declaration of interest

- Jun Zhou has nothing to declare.

Study Design of BTC

Key Eligibility criteria:

- Locally advanced or metastatic BTC
- Previously treated with at least one line of therapy
- ECOG performance status of 0-1
- At least one measurable lesion per RECIST v1.1
- Adequate organ and marrow function

→ 2.5 mg/kg D1D8 Q3W
→ 3.0 mg/kg D1D8 Q3W
→ 3.5 mg/kg D1D8 Q3W

→ Treatment until disease progression or intolerable toxicity

→ **Primary endpoints**: DLT, MTD, RP2D

Secondary endpoints: ORR, DCR, DOR, Safety

Exploratory endpoints: PFS, OS, Biomarker, NAb

* We only illustrated design for BTC cohort. All patients with BTC were enrolled in D1D8 Q3W schedule.

Enrollment

- As of June 30th, 2024, 44 BTC patients were enrolled in D1D8 Q3W regimens, with 31 patients treated at 2.5mg/kg, 3 patients treated at 3.0 mg/kg and 10 patients treated at 3.5 mg/kg.
- More than half of the patients received at least 2 prior lines of systemic treatment.
- The median follow up was 5.9 months.

Table 1. Patient Characteristics

	ALL (N=44)	2.5mg/kg (N=31)	3.0mg/kg (N =3)	3.5mg/kg (N =10)
Age, median (range)	60.0 (31~75)	59.0 (31~70)	70.0 (61~75)	60.0 (44~73)
Sex (Male), n(%)	29/44 (65.9%)	22/31 (71.0%)	3/3 (100%)	4/10 (40.0%)
BMI, mean (range)	23.0 (16.4~33.8)	23.6 (17.4~33.8)	24.1 (20.9~27.5)	20.7 (16.4~24.2)
ECOG, n(%)				
0	6/44 (13.6%)	6/31 (19.4%)	0	0
1	38/44 (86.4%)	25/31 (80.6%)	3/3 (100%)	10/10 (100%)
Prior line of therapy, n(%)				
0	1/44 (2.3%)	0	0	1/10 (10.0%)
1	20/44 (45.5%)	16/31 (51.6%)	0	4/10 (40.0%)
2	10/44 (22.7%)	7/31 (22.6%)	1/3 (33.3%)	2/10 (20.0%)
≥3	13/44 (29.5%)	8/31 (25.8%)	2/3 (66.7%)	3/10 (30.0%)
Prior anti-PD(L)-1, n(%)	35/44 (79.5%)	23/31 (75.2%)	3/3 (100%)	9/10 (90.0%)

Safety

- The most common ≥Grade 3 treatment-related adverse events (TRAEs) were thrombocytopenia (31.8%), anemia (27.3%), leukopenia (20.5%) and neutropenia (18.2%)
- No interstitial lung disease (ILD) was observed.
- No new safety signals were observed.

Table 2. TRAE Summary (freq ≥ 20%)

	BTC (N=44)	
Preferred Term (PT), n(%)	All Grade	≥G3
Hematological AE		
Anemia	36 (81.8)	12 (27.3)
Thrombocytopenia	33 (75.0)	14 (31.8)
Leukopenia	26 (59.1)	9 (20.5)
Neutropenia	17 (38.6)	8 (18.2)
Lymphocyte count decreased	10 (22.7)	2 (4.5)
Non-Hematological AE		
Nausea	19 (43.2)	0
Aspartate aminotransferase increased	15 (34.1)	1 (2.3)
Alanine aminotransferase increased	11 (25.0)	1 (2.3)
Diarrhea	13 (29.5)	1 (2.3)
Stomatitis	11 (25.0)	1 (2.3)
Weight decreased	10 (22.7)	0
Hypoalbuminemia	9 (20.5)	1 (2.3)
Blood bilirubin increased	9 (20.5)	0
Alopecia	9 (20.5)	0

Efficacy

- Among the 44 enrolled patients, 36 were evaluable for efficacy. The ORR was 38.9% (14/36), cORR was 22.2% (8/36), DCR was 88.9% (32/36), mPFS was 4.3 months, and and mDOR was 7.3 months.
- A total of 25 patients were evaluable for efficacy in the 2.5 mg/kg D1D8 Q3W regimen. The ORR was 32.0% (8/25), cORR was 20.0% (5/25), DCR was 88.9% (22/25), mPFS was 4.3 months, and mDOR was 7.3 months.

Table 3. Efficacy by Dose

	Total (N=36)	2.5mg/kg D1D8Q3W (N=25)	3.0mg/kg D1D8Q3W (N=3)	3.5mg/kg D1D8Q3W (N=8)
Prior treatment line, median (range)	2 (0-5)	2 (1-5)	3 (2-4)	2 (0-4)
Best Overall Response (BOR), n				
CR	1	1	0	0
PR	13	7	2	4
cPR	7	4	0	3
PR→Onging	2	2	0	0
SD	18	14	1	3
PD	4	3	0	1
ORR, % (95% CI)	38.9% (23.1-56.5)	32.0% (14.9-53.5)	66.7 (9.4-99.2)	50.0% (15.7-84.3)
cORR, % (95% CI)	22.2% (10.1-39.2)	20.0% (6.8-40.7)	0% (0.0, 70.8)	37.5% (8.5-75.5)
DCR, % (95% CI)	88.9% (73.9-96.9)	88.0% (68.8-97.5)	100% (29.2-100.0)	87.5% (47.3~99.7)
mPFs (months, 95% CI)	4.2 (2.8, 7.1)	4.3 (2.7, NR)	3.5 (2.8, NR)	3.4 (1.3, 7.1)
mDOR (months, 95% CI)	5.9 (4.2, NR)	7.3 (NR, NR)	NE	5.8 (4.2, NR)

Figure 1. Waterfall plot

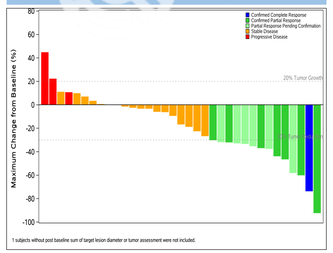


Figure 2. Spider plot

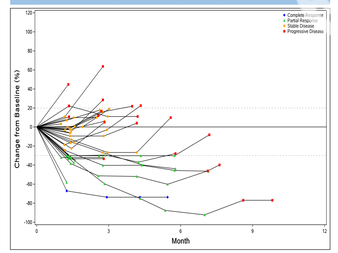
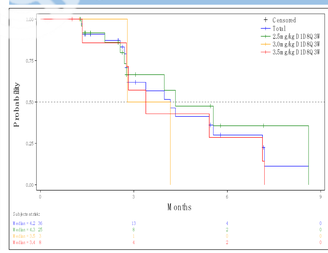


Figure 3. PFS K-M Plot



Conclusions

- In patients with locally advanced or metastatic BTC, BL-B01D1 demonstrated manageable safety with encouraging antitumor activity.
- Further evaluation of BL-B01D1 in this patient population is ongoing.

Reference

[1]. https://doi.org/10.1158/1538-7445.AM2023-2642
[2]. DOI: 10.1200/JCO.2023.41.16_suppl.3001

Acknowledgments

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