FPN:1426P

BL-B01D1, an EGFR x HER3 Bispecific Antibody-drug Conjugate (ADC), in Patients with Locally Advanced or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

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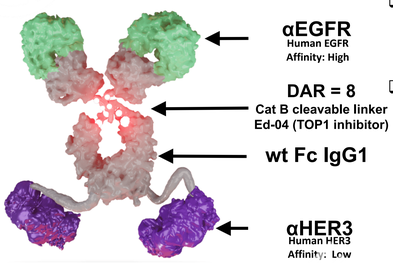
Background



- BL-B01D1, an EGFR×HER3 bispecific antibody-drug conjugate[1].
- Here, we present the safety and efficacy data in esophageal squamous cell carcinoma (ESCC) 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

- Chang Liu has nothing to declare.

Study Design of ESCC*

Key Eligibility criteria:

- Locally advanced or metastatic ESCC
- 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

→ **2.0 mg/kg D1D8 Q3W**
→ **2.5 mg/kg D1D8 Q3W**
→ **3.0 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 ESCC cohort treated under D1D8 Q3W schedule, as the patients with ESCC were mainly enrolled in D1D8 Q3W schedule. Here we present the data from 2.0m and 2.5 mg/kg D1D8 Q3W.

Enrollment

- As of June 30th, 2024, 83 previously treated ESCC patients were enrolled in Q3W D1D8 regimens with 22 patients treated at 2.0 mg/kg, 60 patients at 2.5mg/kg and 1 patient at 3.0mg/kg. Among the enrolled ESCC patients, 97.6% (81/83) had received anti-PD-1/L1 and platinum-based chemotherapy (PBC) in combination or sequentially.
- More than half of the patients received at least 2 prior lines of systemic treatment.
- The median follow up was 10.5 months.

Table 1. Patient Characteristics

	Total (N=83*)	2.0mg/kg (N =22)	2.5mg/kg (N =60)
Age, median (range)	62.0 (45~75)	63.5 (51~73)	61.0 (45~75)
Sex (Male), n(%)	73/83 (88.0%)	21/22 (95.5%)	51/60 (85.0)
BMI, mean (range)	20.0 (13.2 - 31.6)	20.6 (15.9, 26.4)	19.8 (13.2, 31.6)
ECOG, n(%)			
0	15/83 (18.1%)	4/22 (18.2%)	10/60 (16.7%)
1	68/83 (81.9%)	18/22 (81.8%)	50/60 (83.3%)
Prior line of therapy, n(%)			
1	31/83 (37.3%)	8/22 (36.4%)	23/60 (38.3%)
2	27/83 (32.5%)	4/22 (18.2%)	23/60 (38.3%)
≥3	25/83 (30.1%)	10/22 (45.5%)	14/60 (23.3%)
Prior anti-PD(L)-1, n(%)	81/83 (97.6%)	22/22 (100%)	58/60 (96.7%)

* including one patient treated at 3.0mg/kg D1D8Q3W.

Safety

- At dose level 2.5 mg/kg D1D8 Q3W, the most common ≥Grade 3 treatment-related adverse events (TRAEs) were anemia (28.3%), leukopenia (18.3%), thrombocytopenia (18.3%), neutropenia (16.7%), etc.
- Two cases (1/2 G2, 1/2 G3) of interstitial lung disease (ILD) by investigator's adjudication were observed at 2.5mg/kg D1D8 Q3W dose level.
- No new safety signals were observed.

Table 2. TRAE Summary (freq ≥ 15%)

	ESCC at 2.5mg/kg D1D8 Q3W (N=60)	
Preferred Term (PT), n(%)	All Grade	≥G3
Hematological AE		
Anemia	50 (83.3)	17 (28.3)
Leukopenia	34 (56.7)	11 (18.3)
Thrombocytopenia	35 (58.3)	11 (18.3)
Neutropenia	28 (46.7)	10 (16.7)
Lymphocyte count decreased	18 (30.0)	9 (15.0)
Non-Hematological AE		
Nausea	28 (46.7)	0
Asthenia	23 (38.3)	1 (1.7)
Decreased appetite	15 (25.0)	0
Vomiting	14 (23.3)	0
Weight decreased	13 (21.7)	0
Hypoalbuminemia	13 (21.7)	0
Hyponatremia	13 (21.7)	0
Hypokalemia	12 (20.0)	2 (3.3)
Blood alkaline phosphatase increased	12 (20.0)	0
Alanine aminotransferase increased	10 (16.7)	1 (1.7)
Albumin urine present	9 (15.0)	0
Stomatitis	9 (15.0)	0

Efficacy

- Among the enrolled patients, 74 patients were evaluable for efficacy. The ORR was 35.1% (26/74), cORR was 32.4% (24/74), DCR was 73.6% (53/74), mPFS was 4.3 months, mDOR was 6.5 months.
- A total of 52 patients were evaluable for efficacy in 2.5mg/kg D1D8 Q3W regimen. The ORR was 44.2% (23/52), cORR was 40.4% (21/52), DCR was 80.8% (42/52), mPFS was 5.4 months, and mDOR was 6.6 months.

Table 3. Efficacy by Dose

	Total (N=74)	2.0mg/kg D1D8Q3W (N=22)	2.5mg/kg D1D8Q3W (N=52)
Prior treatment line, median (range)	2 (1-7)	2 (1-7)	2 (1-4)
Best overall response (BOR), n			
CR	1	1	0
PR	25	2	23
Confirmed PR	23	2	21
SD	26	7	19
PD	19	9	10
NE	3	3	0
ORR, 95%CI (%)	35.1% (24.4, 47.1)	13.6% (2.9, 34.9)	44.2% (30.5, 58.7)
cORR,95%CI (%)	32.4% (22.0, 44.3)	13.6% (2.9, 34.9)	40.4% (27.0, 54.9)
DCR, 95%CI (%)	70.3% (58.5, 80.3)	45.5% (24.4, 67.8)	80.8% (67.5, 90.4)
Median PFS (months) (95% CI)	4.3 (3.3, 5.5)	2.7 (1.4, 3.6)	5.4 (4.0, 6.8)
Median DOR (months) (95% CI)	6.5 (4.5, 12.4)	4.5 (2.8, NR)	6.6 (5.6, 12.4)

Figure 1. Waterfall plot

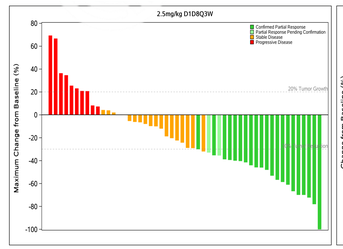


Figure 2. Spider plot

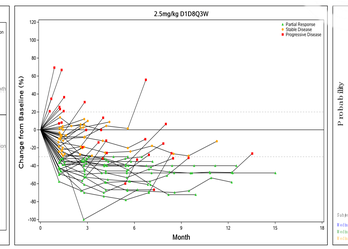
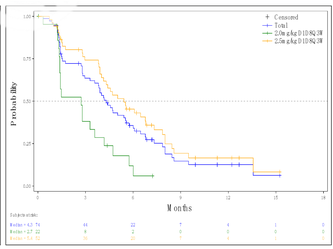


Figure 3. PFS K-M Plot



Conclusions

- In patients with heavily pretreated ESCC, BL-B01D1 demonstrated manageable safety with encouraging antitumor activity.
- Phase III study of BL-B01D1 monotherapy in ESCC is ongoing (NCT06304974).

Reference

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

Acknowledgments

We thank all the patients and their families for their participation. We also thank all the investigators, study nurses, and other study staffs for their contributions.