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BL-M07D1, a novel HER2 antibody-drug conjugate, in subjects with locally advanced or metastatic HER2 expressing breast cancer and other solid tumors: Results from a phase 1 study

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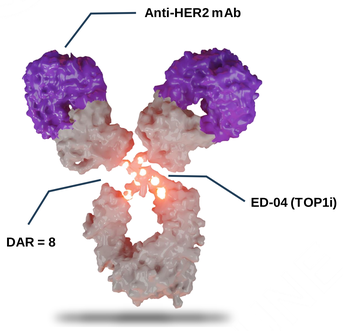
Background



- BL-M07D1, a HER2 antibody-drug conjugate[1].
- Currently, 5 phase I or phase Ib/II clinical studies of BL-M07D1 are being conducted in different carcinomas. The indication in this study (BL-M07D1-101) is HER2 expressing breast cancer and other solid tumors.
- Clinical trial information: NCT05461768.

Objectives

- Phase Ia: To observe the safety and tolerability of BL-M07D1 in patients with locally advanced or metastatic HER2-positive/low-expressing breast cancer (BC) and other solid tumors in order to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of BL-M07D1.
- Phase Ib: To observe the safety and tolerability of BL-M07D1 at the recommended dose of Phase Ia and determine the recommended Phase II dose (RP2D).

Methods

- This phase I study enrolled patients with locally advanced or metastatic HER2-positive/low-expressing breast cancer and other solid tumors.
- This open-label, two cohorts Phase I study is designed to evaluate BL-M07D1 safety, tolerability, pharmacokinetic characteristics, and initial efficacy in patients with locally advanced or metastatic HER2 expressing breast cancer and other solid tumors, as determined by Immunohistochemistry(IHC). Dose-escalation and dose-expansion phases are being investigated. During dose-escalation, subjects will receive BL-M07D1 in 2 different schedule (Cohort A: 1.0mg/kg D1/D8 Q3W; Cohort B: 2.6~7.4mg/kg D1 Q3W). In the dose-expansion phase, one or several dosages will be chosen for further evaluation .
- 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), overall survival(OS), progression free survival(PFS), duration of response(DOR). Exploratory endpoints are biomarker assessment, and neutralizing antibodies.

Acknowledgments

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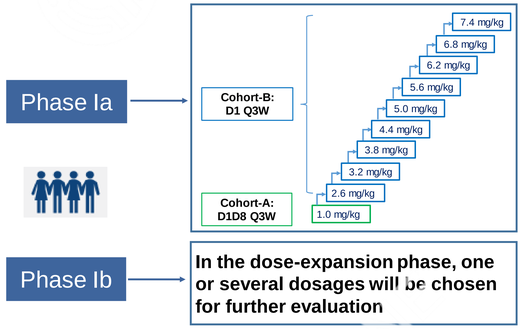
Reference

[1]. Weili Wan, et al. BL-M07D1, a novel HER2-targeting ADC, demonstrates potent anti-tumor efficacy in preclinical pharmacodynamic models [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2023; Part 1 (Regular and Invited Abstracts); 2023 Apr 14-19; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2023; 83(7_Suppl): Abstract nr 2643.

Study Design

Eligibility criteria

- Locally advanced or metastatic HER2-positive/low-expressing breast cancer and other solid tumors
- Previously treated with at least one line of therapy
- Eastern Cooperative Oncology Group performance status of 0-1
- At least one measurable lesion per RECIST v1.1
- Adequate organ and marrow function
- Either no brain metastases or stable brain metastases at screening



Primary endpoints: DLT, MTD, RP2D
Secondary endpoints: ORR, DCR, OS, PFS, DOR, safety

Enrollment

- As of September 30th, 2023, a total of 130 patients were treated with at least one dose, with 23 patients in the Dose-Escalation (D-ESC) phase and 107 in the Dose-Expansion (D-EXP) phase. The median follow-up time was 3.9 months.

Table 1. Patient enrollment

Dose and Freq	HER2+ BC	HER2-Low BC	Other	Total
D1D8Q3W_1.0 mg/kg	1	0	0	1
D1Q3W_2.6 mg/kg	2	1	0	3
D1Q3W_3.2 mg/kg	1	1	1	3
D1Q3W_3.8 mg/kg	8	9	0	17
D1Q3W_4.4 mg/kg	40	24	7	71
D1Q3W_5.0 mg/kg	7	7	6	20
D1Q3W_5.6 mg/kg	3	3	5	11
D1Q3W_6.2 mg/kg	1	1	2	4
Total	63	46	21	130

Table 2. Patient Demographic

	ALL (N=130)
Age (Median, Range)	54.0 (31.0 - 75.0)
Sex (Male)	13/130 (10%)
Weight (Mean, Range)	59.2 (33.5 - 85.0)
BMI (Mean, Range)	23.5 (15.3 - 33.3)
ECOG	
0	22/130 (17%)
1	105/130 (81%)
UNK (0 or 1)	3/130 (2%)
Prior treatment line	
1	25/130 (19%)
2	35/130 (27%)
≥3	70/130 (54%)

Safety

- The most common Grade ≥3 treatment-related adverse events (TRAEs) were neutropenia (42%), leukopenia (28%), anemia (23%), and thrombocytopenia (17%).
- One G2 interstitial lung disease (ILD) was observed.
- One DLT was observed with G3 febrile neutropenia and G4 thrombocytopenia lasting > 7days at 6.2 mg/kg D1Q3W.
- No drug-related death was observed.

Table 3. TRAE Summary (Freq ≥ 10%)

	BL-M07D1-101 (N=130)			
PT Term	G1	G2	≥G3	All
Leukopenia[1]	12 (9%)	44 (34%)	37 (28%)	93 (72%)
Anaemia[2]	26 (20%)	34 (26%)	30 (23%)	90 (69%)
Neutropenia[3]	5 (4%)	25 (19%)	55 (42%)	85 (65%)
Nausea	23 (18%)	44 (34%)	2 (2%)	69 (53%)
Thrombocytopenia[4]	29 (22%)	15 (12%)	21 (17%)	66 (51%)
Vomiting	19 (15%)	19 (15%)	5 (4%)	43 (33%)
Decreased appetite	19 (15%)	19 (15%)		38 (29%)
Alopecia	18 (14%)	18 (14%)		36 (28%)
Lymphocyte count decreased	8 (6%)	15 (12%)	11 (8%)	34 (26%)
Asthenia	21 (16%)	12 (9%)		33 (25%)
GGT increased	19 (15%)	4 (3%)	1 (<1%)	24 (18%)
AST increased	20 (15%)	3 (2%)		23 (18%)
Stomatitis[5]	9 (7%)	12 (9%)		21 (16%)
ALT increased	17 (13%)	2 (2%)	1 (<1%)	20 (15%)
Blood ALP increased	18 (14%)	2 (2%)		20 (15%)
Hypokalaemia	15 (12%)	3 (2%)	2 (2%)	20 (15%)
Weight decreased	12 (9%)	7 (5%)	1 (<1%)	20 (15%)
Diarrhoea	11 (8%)	8 (6%)		19 (15%)
Dizziness	14 (11%)	4 (3%)		18 (14%)
Constipation	11 (8%)	6 (5%)		17 (13%)
Hypoalbuminaemia	11 (8%)	6 (5%)		17 (13%)
Occult blood positive	15 (12%)			15 (12%)
Peripheral sensory neuropathy	12 (9%)	1 (<1%)		13 (10%)

[1] Leukopenia combined white blood cell count decreased and leukopenia;
[2] Anemia combined anemia and hemoglobin count decreased;
[3] Neutropenia combined neutrophil count decreased, neutropenia, and febrile neutropenia;
[4] Thrombocytopenia combined platelet count decreased and thrombocytopenia;
[5] Stomatitis combined stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

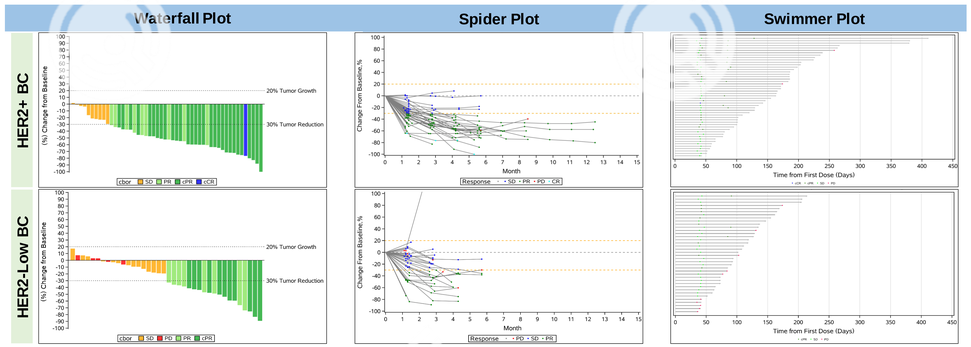
Efficacy

- Among the 130 enrolled patients, 88 BC patients were evaluable for efficacy. The ORR (n/N, [95%CI]) was 67.0% (59/88, [56.2-76.7]), cORR was 47.7% (42/88 [37.0-58.6]),DCR was 94.3% (83/88, [87.2, 98.1]) (Table 3). The median PFS and median DOR have not reached.
- In HER2+BC, 50 patients were evaluable for efficacy. The ORR was 80.0% (40/50, [66.3, 90.0]), DCR was 100% (50/50) (Table 3). 18/50 patients had received other HER2-ADC prior to BL-M07D1, the ORR was 77.8% (14/18, [52.4-93.6]), cORR was 50.0% (9/18, [26.0-74.0]), DCR 100% (18/18) (Table 3). The median PFS and median DOR have not reached.
- In HER2-Low BC, 38 patients were evaluable for efficacy. The ORR was 50.0% (19/38, [33.4, 66.6]), DCR was 86.8% (33/38, [71.9-95.6]). The median PFS and median DOR have not reached.

Table 4. Efficacy by Tumor subtype

BOR, n	HER2+ BC (N=50)	HER2+ BC Prior HER2-ADC[1] (n=18)	HER2-Low BC (N=38)	All (N=88)
Prior treatment line median (range)	3 (1-13)	4 (2-13)	3 (1-10)	3 (1-13)
cCR	1	0	0	1
PR	39	14	19	58
cPR	30	9	11	41
PR→Onging	8	4	7	15
PR→PD	/	/	1	1
PR→Other	1	1	/	1
SD	10	4	14	24
SD-(ongoing and TL shrinkage)	7	3	10	17
PD	0	0	5	5
ORR, % (95% CI)	80.0% (66.3-90.0)	77.8% (52.4-93.6)	50.0% (33.4-66.6)	67.0% (56.2-76.7)
cORR, % (95% CI)	62.0% (47.2-75.3)	50.0% (26.0-74.0)	28.9% (15.4-45.9)	47.7% (37.0-58.6)
DCR, % (95% CI)	100%	100%	86.8% (71.9-95.6)	94.3% (87.2-98.1)

[1] 17/18 patients had received HER2-ADC with microtubule inhibitor prior to BL-M07D1; 1/18 had received HER2-ADC with TOPI inhibitor prior to BL-M07D1.



Conclusions

- BL-M07D1 demonstrated promising preliminary antitumor activity in patients with HER2+ breast cancer and HER2-Low breast cancer.
- BL-M07D1 demonstrated comparable antitumor activity in patients with HER2-positive breast cancer who had previously been treated with other HER2-ADCs.
- The MTD for BL-M07D1 was not reached. The observed toxicities were predominantly hematologic, and notably, there was a low incidence of interstitial lung disease (ILD) identified.
- Further investigations and clinical trials are warranted to fully assess the efficacy and safety profile of BL-M07D1 in a larger and more diverse patient population.