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BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate, in patients with Locally Advanced or Metastatic Breast Cancer and other Solid Tumor: Updated results from a Phase I study

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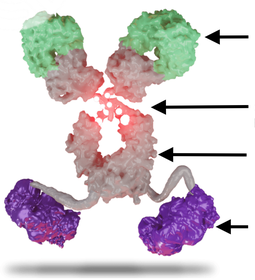
Background



- BL-B01D1, an EGFR×HER3 bispecific antibody-drug conjugate[1].
- The preliminary data of BL-B01D1 in breast cancer was published in 2023 SABCS[2]. The updated safety/efficacy results from phase I study of BL-B01D1 in breast cancer (BL-B01D1-104) are presented.
- Clinical trial information: NCT05470348.

Primary Objectives

- Phase Ia: To observe the safety and tolerability of BL-B01D1 in patients with locally advanced or metastatic breast cancer and other solid tumors in order 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 and determine the recommended phase II dose (RP2D).

Methods

- This phase I study enrolled patients with locally advanced or metastatic breast cancer and other solid tumors.
- This open-label, phase I study was designed to evaluate BL-B01D1 safety, tolerability, pharmacokinetic characteristics, and initial efficacy in patients with locally advanced or metastatic breast cancer and other solid tumors. Dose-escalation phase referred to BL-B01D1-101 (NCT05194982)[2] and dose-expansion phase is being investigated. During the dose-expansion phase, subjects were treated with BL-B01D1 at 2.5mg/kg D1D8 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 (TEAEs), pharmacokinetics parameters, objective response rate (ORR), disease control rate (DCR), and duration of response (DOR).
- Exploratory endpoints are progression free survival (PFS), overall survival (OS), biomarker, and neutralizing antibodies (NAb).

Acknowledgments

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Reference

[1]. https://doi.org/10.1158/1538-7445.AM2023-2642

[2]. https://doi.org/10.1158/1538-7445.SABCS23-PS08-07

Study Design

Eligibility criteria

- Locally advanced or metastatic breast cancer and other solid tumors
- Previously treated with standard therapy
- Eastern Cooperative Oncology Group performance status of 0-1
- At least one measurable lesion per RECIST v1.1
- Adequate organ and marrow function

Phase Ia (referred to BL-B01D1-101)
- Cohort A D1D8 Q3W: 3.5 mg/kg, 3.0 mg/kg, 2.5 mg/kg
- Cohort B D1 Q3W: 7.0 mg/kg, 6.0 mg/kg, 5.0 mg/kg

Phase Ib
- In the dose-expansion phase, subjects received BL-B01D1 in 2.5mg/kg D1D8 Q3W.

Primary endpoints: DLT, MTD (or MAD), RP2D
Secondary endpoints: ORR, DCR, DOR, Safety
Exploratory endpoints: PFS, OS, Biomarker, NAb

Enrollment

- As of September 30th, 2024, a total of 162 breast cancer patients were treated with 2.5 mg/kg on the D1D8 Q3W schedule regardless of the EGFR/HER3 expression.
- Among the 162 patients, 41 patients were with HER2+ BC, 77 patients were with HR+HER2- BC, and 44 patients were with TNBC.

Table 1. Patient Baseline Characteristics

	Total (N = 162)	HER2+ BC (N = 41)	HR+HER2- BC (N = 77)	TNBC (N = 44)
Age (years)				
Median	52	51	55	47
Min, Max	26, 75	33, 70	26, 75	30, 64
Gender, n(%)				
Female	162 (100)	41 (100)	77 (100)	44 (100)
ECOG-PS Score, n(%)				
0	17 (10.5)	3 (7.3)	9 (11.7)	5 (11.4)
1	145 (89.5)	38 (92.7)	68 (88.3)	39 (88.6)
# of metastatic organs				
Median	2	2	3	2
Min, Max	1, 9	1, 5	1, 9	1, 5
Prior line of therapy, n(%)				
0L	2 (1.2)	1 (2.4)	1 (1.3)	0
1L	20 (12.3)	2 (4.9)	8 (10.4)	10 (22.7)
2L	27 (16.7)	4 (9.8)	10 (13.0)	13 (29.5)
≥3L	113 (69.8)	34 (82.9)	58 (75.3)	21 (47.7)
Prior line of chemotherapy, n(%)				
0L	15 (9.3)	2 (4.9)	13 (16.9)	0
1L	47 (29.0)	7 (17.1)	29 (37.7)	11 (25.0)
2L	45 (27.8)	13 (31.7)	17 (22.1)	15 (34.1)
≥3L	55 (34.0)	19 (46.3)	18 (23.4)	18 (40.9)
Prior PBC, n(%)				
Yes	55 (34.0)	8 (19.5)	21 (27.3)	26 (59.1)
Prior paclitaxel, n(%)				
Yes	147 (90.7)	36 (87.8)	68 (88.3)	43 (97.7)
Prior anti-PD-1/PD-L1, n(%)				
Yes	30 (18.5)	3 (7.3)	13 (16.9)	14 (31.8)
Prior CDK4/6 inhibitors, n(%)				
Yes	58 (35.8)	5 (12.2)	50 (64.9)	3 (6.8)

HER2+ defined as IHC 3+ or IHC 2+/in situ hybridization (ISH)+;
HER2- defined as IHC 0, 1+, 2+/ISH-.

Safety

- The most common Grade ≥3 treatment-related adverse events (TRAEs) were anemia (41.4%), leukopenia (42.6%), neutropenia (52.5%), thrombocytopenia (26.5%).
- One drug-related death (febrile neutropenia) was observed.
- No interstitial lung disease (ILD) was observed.

Table 2. TRAE Summary (Freq ≥ 20%)

	Total (N = 162)	
Preferred Term (PT), n(%)	**All Grade**	**Grade ≥G3**
Anemia	149 (92.0)	67 (41.4)
Leukopenia	145 (89.5)	69 (42.6)
Neutropenia	141 (87.0)	85 (52.5)
Thrombocytopenia	111 (68.5)	43 (26.5)
Nausea	96 (59.3)	6 (3.7)
Stomatitis	79 (48.8)	9 (5.6)
Aspartate aminotransferase increased	78 (48.1)	0
Asthenia	75 (46.3)	17 (10.5)
Alanine aminotransferase increased	73 (45.1)	0
Vomiting	69 (42.6)	1 (0.6)
Hypertriglyceridaemia	62 (38.3)	2 (1.2)
Alopecia	55 (34.0)	0
Hypokalaemia	55 (34.0)	6 (3.7)
Decreased appetite	54 (33.3)	1 (0.6)
Hyperglycaemia	50 (30.9)	0
Constipation	44 (27.2)	1 (0.6)
Hyponatraemia	43 (26.5)	2 (1.2)
Hypoalbuminemia	42 (25.9)	0
Hypercholesterolemia	41 (25.3)	0
Urinary tract infection	38 (23.5)	1 (0.6)
Weight decreased	38 (23.5)	0
Blood alkaline phosphatase increased	36 (22.2)	0
Diarrhea	35 (21.6)	3 (1.9)
Blood lactate dehydrogenase increased	33 (20.4)	0

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

Efficacy

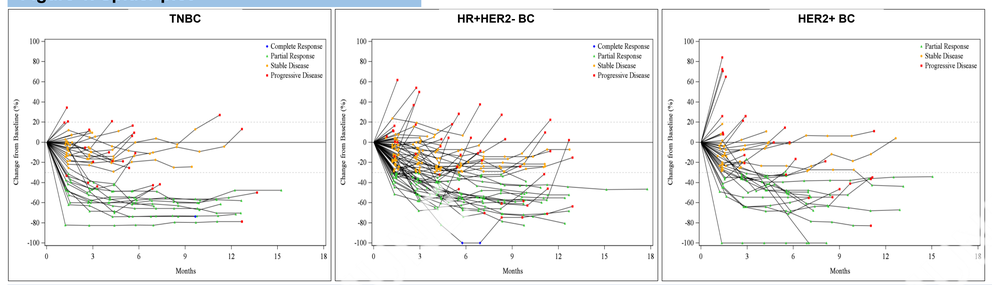
- As of September 30th, 2024, the study has enrolled 162 BC patients with median follow-up 11.6 months. The analysis was based on ITT population except for one patient with HER2+ BC due to insufficient follow-up.
- In TNBC, the median follow up was 11.9 months, cORR was 34.1%, mDOR was 11.5 months, mPFS was 5.8 months. For 26 patients with prior 1-2L chemotherapy, the median follow up was 12.3 months,, cORR was 50.0%, mDOR was 11.5 months, mPFS was 6.9 months.
- In HR+ HER2- BC, the median follow up was 11.7 months, cORR was 37.7%, mDOR was 7.4 months, mPFS was 7.0 months. For 46 patients with prior 1-2L chemotherapy, the median follow up was 12.1 months, cORR was 45.7%, mDOR was 7.1 months, mPFS was 8.3 months.
- In HER2+ BC, 40 patients were efficacy evaluable, one patient without sufficient follow-up was excluded. The median follow up was 8.7 months, cORR was 47.5%, mDOR was 7.4 months, mPFS was 7.0 months.

Table 3. Efficacy by Tumor subtype

	TNBC		HR+HER2- BC		HER2+ BC
	Total	Prior 1-2L chemotherapy	Total	Prior 1-2L chemotherapy	Total
	(N = 44)	(N = 26)	(N = 77)	(N = 46)	(N = 40)
Median prior line of therapy (Range)	2 (1-10)	2 (1-3)	3 (0-13)	3 (1-7)	4 (0-8)
Best Overall Response (BOR), n					
CR	1*	1*	1#	1#	0
PR	14	12	35	24	19
cPR	15	13	28	20	19
SD	21	7	25	13	13
PD	4	2	9	6	7
NE	4	4	7	2	1
ORR, % (95%CI)	34.1% (20.5, 49.9)	50.0% (29.9, 70.1)	46.8% (35.3, 58.5)	54.3% (39.0, 69.1)	47.5% (31.5, 63.9)
ORR confirmed, % (95%CI)	34.1% (20.5, 49.9)	50.0% (29.9, 70.1)	37.7% (26.9, 49.4)	45.7% (30.9, 61.0)	47.5% (31.5, 63.9)
DCR, % (95%CI)	81.8% (67.3, 91.8)	76.9% (56.4, 91.0)	79.2% (68.5, 87.6)	82.6% (68.6, 92.2)	80.0% (64.4, 91.0)
Median DOR (months) (95% CI)	11.5 (4.6, NR)	11.5 (4.6, NR)	7.4 (5.6, NR)	7.1 (5.4, 9.8)	7.4 (4.6, 9.8)
Median PFS (months) (95% CI)	5.8 (4.3, 12.7)	6.9 (4.0, 13.7)	7.0 (5.5, 8.5)	8.3 (5.7, 11.1)	7.0 (3.2, 9.0)
6-month PFS rate (%) (95% CI)	48.4 (31.5, 63.4)	58.2 (34.8, 75.8)	58.1 (45.2, 69.0)	66.8 (49.6, 79.4)	55.2 (37.5, 69.8)
Median OS (months) (95% CI)	NR (13.2, NR)	NR (13.2, NR)	NR (NR, NR)	NR (NR, NR)	NR (15.1, NR)
12-month OS rate (%) (95% CI)	68.9 (51.4, 81.2)	74.0 (50.6, 87.5)	67.7 (54.4, 77.9)	74.0 (56.2, 85.4)	78.9 (54.6, 91.1)

* CR was confirmed as cPR, but was not confirmed as cCR as of cutoff date but was confirmed as of October 10th, 2024. # CR was confirmed as of cutoff date.

Figure 1. Spider plot



Conclusions

- BL-B01D1 has demonstrated encouraging efficacy in previously treated patients with metastatic and locally advanced breast cancer, particularly in earlier line setting.
- The safety and tolerability of BL-B01D1 are consistent with previously published data.
- Phase III studies of BL-B01D1 in TNBC and HR+HER2-BC were on-going (NCT06382142 and NCT06343948).