BL-M07D1, a novel HER2-targeting ADC, demonstrates potent anti-tumor efficacy in preclinical pharmacodynamic models

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Weili Wan, Shuwen Zhao, Shi Zhuo, Yong Zhang, Lan Chen, Gangrui Li, Jahan Salar Khalili, Sa Xiao, Yongqi Yan, Xuejiao Shen, Yi Zhu. Sichuan Baili Pharmaceutical Co., Ltd., Chengdu, China, SystImmune Inc., Redmond, WA

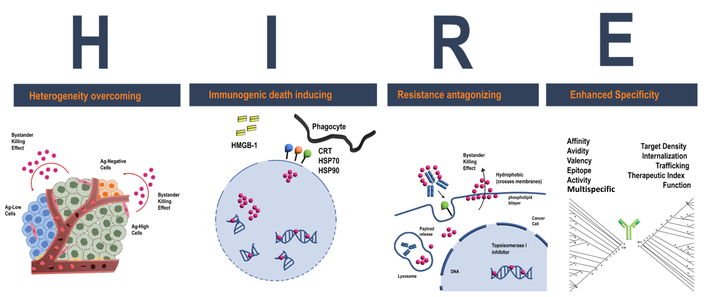
Abstract

HER2 is a member of the epidermal growth factor receptor family. Activation of the HER2 signaling pathway has been shown to strongly promote carcinogenesis. It is therapeutically targeted in cancer owing to its overexpression and pathway dependence in a variety of human carcinomas, especially human breast cancers. We created a promising therapeutic anti-tumor agent, BL-M07D1, an anti-HER2-Ed-04 ADC. It is comprised of a humanized anti-HER2 antibody Trastuzumab, a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04), which is a derivative of the alkaloid camptothecin, driving cell cycle arrest at the S phase and subsequent apoptosis. The BL-M07D1 drug-to-antibody-ratio is 8:1 (DAR=8), similar to Trastuzumab Deruxotecan (DS-8201), while possessing a more stable linker.

To evaluate the pharmacological potential of BL-M07D1, xenograft tumor inhibition assays were used to compare BL-M07D1 with the commercialized HER2-targeting ADCs, T-DM1 and DS-8201, which have been approved worldwide for patients with HER2-expressing tumors. Results from the in vivo murine studies show that BL-M07D1 has strong tumor inhibition effects in multiple cell line-derived xenograft (CDX) tumor models. 1) BL-M07D1 exhibited better anti-tumor efficacy than DS-8201 in CDX with low HER2 expression, human epidermal cancer A431 and human non-small cell lung cancer NCI-H1975. Both models are considered be T-DM1-insensitive. 2) BL-M07D1 exhibited better anti-tumor efficacy in comparison to either T-DM1 or DS-8201 in a CDX with JIMT-1, a HER2-positive human breast cancer cell line. 3) BL-M07D1 exhibits potent bystander effects in a heterogeneous xenograft model of HER2-positive and HER2-negative tumor cells composed of NCI-N87 and MDA-MB-468 cells. In this model, BL-M07D1 exhibited stronger tumor inhibition than T-DM1, consistent with bystander effects that are also exhibited by DS-8201.

In conclusion, in vivo studies suggest that BL-M07D1, a novel HER2-targeting ADC, is potentially more efficacious in a broader patient population than T-DM1, and mediate superior anti-tumor efficacy than DS-8201. The clinical phase I is under way and the available data exhibit excellent efficacy in breast cancer therapy with acceptable tolerability.

Therapeutic Mechanism of Action



BL-M07D1 Cell Binding to HER2 Expressing Cells

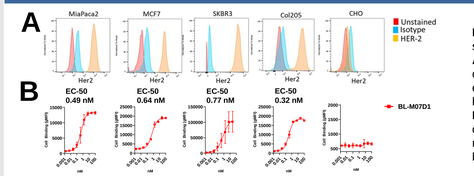
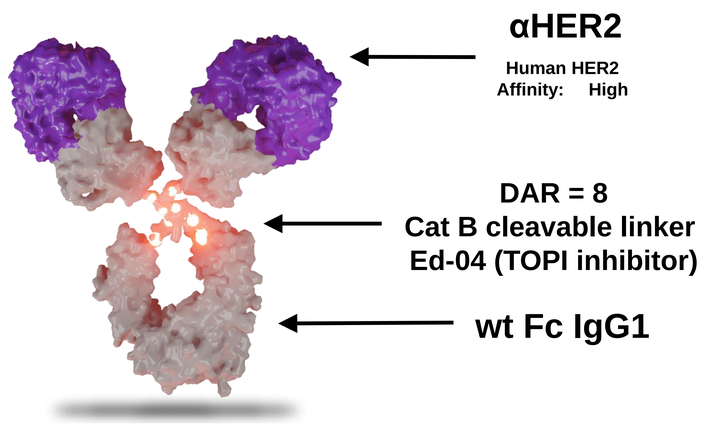


Figure 1. BL-M07D1 structure mediates specific antigen binding.
A) MiaPaca 2 cells, MCF-7 cells, SK-BR-3 cells, Colo-205 cells and CHO cells were evaluated for HER2 expression, indicated by orange histogram on x-axis.
B) Data points of BL-M07D1 binding gMFI of indicated cancer cell lines and CHO cells representing the binding to HER2. Error bars represent SEM.

BL-M07D1: HER2 ADC



Proliferation inhibition *in vitro*

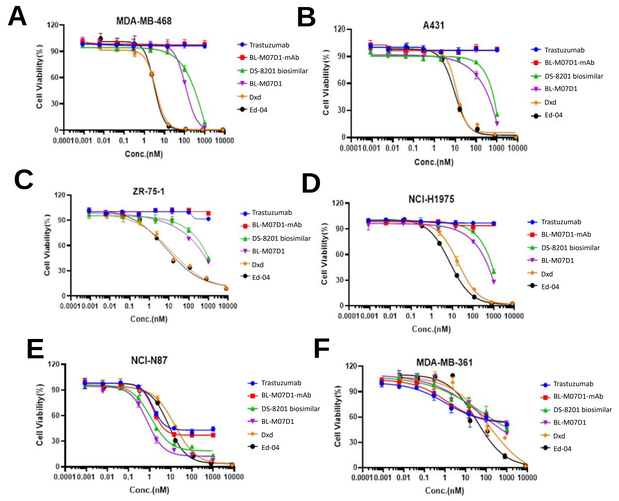


Figure 2. Impact of BL-M07D1 on cancer cell proliferation
Cancer cells were evaluated for their proliferative ability in the presence BL-M07D1 (purple curve), Transtuzumab (blue curve), BL-M07D1 mAb (red curve), DS-8201 (green curve), Dxd (orange curve) and Ed-04 (black curve). Error bars represent SEM.

- **BL-M07D1 shows greater potency that DS-8201 biosimilar inhouse *in vitro***
- **ED-04 warhead superior to Dxd**
- **Data suggests BL-M07D1 enhanced activity is based on payload activity *in vitro***

BL-M07D1 Xenograft Tumor inhibition *in vivo*

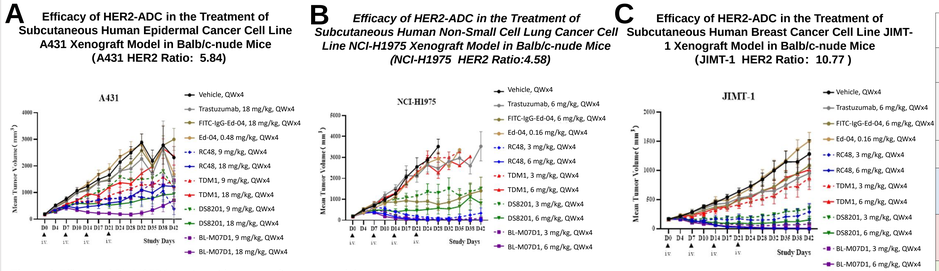


Figure 3.Efficacy of BL-M07D1 treatment in xenograft mouse model
Balb/c-nude mice were implanted with A) A431, B) NCI-1975 or C)JIMT-1 tumor xenografts to measure reduction in tumor volume during treatment with multiple doses of BL-M07D1 (purple curve), DS-8201 (green curve), T-DMI (red curve), RC48 (blue curve), Ed-04 (light brown curve), FITC-IgG1-Ex0115 (dark brown curve), Trastuzumab (grey curve) and vehicle (black curve). Treatments were administrated by intravenous injections at 9 mg/kg and 18 mg/kg on Day 0, Day 7, Day 14 and Day 21. The models was evaluated for 42 days. Error bars represent SEM.

- BL-M07D1 exhibits strong inhibition in multiple cell line-derived xenograft (CDX) tumor models
- BL-M07D1 exhibited better anti-tumor efficacy than T-DM1 in CDX with low HER2 expression, human epidermal cancer A431 and human non-small cell lung cancer NCI-H1975

BL-M07D1 Xenograft Tumor bystander inhibition *in vivo*

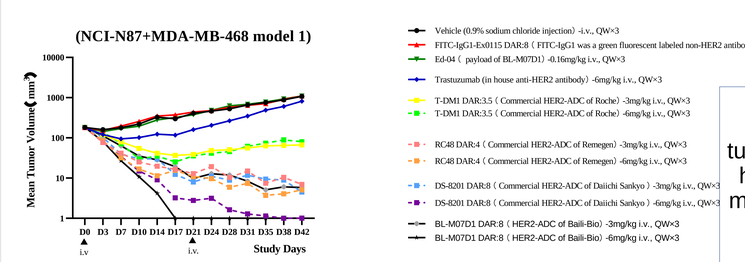


Figure 4. BL-M07D1 bystander inhibition in xenograft mouse tumor

In vivo, BL-M07D1 exhibited superior anti-tumor activity to T-DM1 in a heterogeneous xenograft model composed of HER2-high and HER-low xenograft model.

Summary

- BL-M07D1 exhibited better anti-tumor efficacy than DS-8201 in CDX with low HER2 expression, human epidermal cancer A431 and human non-small cell lung cancer NCI-H1975. Both models are considered be T-DM1-insensitive.
- BL-M07D1 exhibited better anti-tumor efficacy in comparison to either T-DM1 or DS-8201 in a CDX with JIMT-1, a HER2-positive human breast cancer cell line.
- BL-M07D1 exhibits potent bystander effects in a heterogeneous xenograft model of HER2-positive and HER2-negative tumor cells composed of NCI-N87 and MDA-MB-468 cells. In this model, BL-M07D1 exhibited stronger tumor inhibition than T-DM1, consistent with bystander effects that are also exhibited by DS-8201.
- BL-M07D1, a novel HER2-targeting ADC, is potentially more efficacious in a broader patient population than T-DM1, and mediate superior anti-tumor efficacy than DS-8201.

Acknowledgments

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References

BL-M07D1 clinical trials:

A Study of BL-M07D1 in Patients With Locally Advanced or Metastatic HER2 Positive/Low Expression Breast Cancer and Other Solid Tumors https://ClinicalTrials.gov/show/NCT05461768

Phase I Clinical Study of BL-M07D1 in Locally Advanced or Metastatic Digestive Tract Tumors and Other Solid Tumors https://ClinicalTrials.gov/show/NCT05631964