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 cancers, especially human breast cancers. We created a promising therapeutic anti-tumor agent, BL-M07D1, an anti-HER2-Ed-D4 ADC. It is comprised of a humanized anti-HER2 antibody Trastuzumab, a cathepsin B cleavable linker, and a novel topoisomerase II inhibitor agent (Ed-D4), which is a derivative of the alkylating camptothecin, driving cell cycle arrest at the S phase and subsequent apoptosis. The BL-M07D1 drug-to-antibody ratio is 1:1 (DAR=8), similar to Trastuzumab Deruxtecanc (DS-8201), while possessing a more stable linker.

To evaluate the pharmaceutical 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 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 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.

**Abstract**

**BL-M07D1: HER2 ADC**

- **aHER2**
  - Human HER2 Affinity: High
- **DAR = 8**
  - Cat B cleavable linker
  - Ed-04 (TOPI inhibitor)
- **wt Fc IgG1**

**BL-M07D1 Xenograft Tumor inhibition in vivo**

- BL-M07D1 exhibits stronger inhibition in multiple cell line-derived xenograft (CDX) tumor models:
  - BL-M07D1 exhibited better anti-tumor efficacy than T-DM1 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.

**Proliferation inhibition in vitro**

**In vivo**

- BL-M07D1 exhibited superior anti-tumor activity to T-DM1 in a heterogeneous xenograft model composed of HER2-positive and HER2-low xenograft model.

**Summary**

- 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.

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**References**

A Study of BL-M07D1 in Patients With Locally Advanced or Metastatic HER2-Positive/Over-Expressed Breast Cancer and Other Solid Tumors. Phase I Clinical Trial of BL-M07D1 in Locally Advanced or Metastatic EGFRT Positive Non-Small Cell Lung Cancer. Phase I Clinical Study of BL-M07D1 in Locally Advanced or Metastatic EGFRT Positive Non-Small Cell Lung Cancer.