BL-M02D1, a novel Trop2-targeting ADC, demonstrates robust anti-tumor efficacy in preclinical evaluation

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**Abstract**

Trop2, also known as trophoblast antigen 2, is a transmembrane glycoprotein. It is therapeutically targeted in cancer due to its over-expression in a variety of human carcinomas. To develop a promising therapeutic anti-tumor agent, we generated BL-M02D1, an anti-Trop2-Ed-04 ADC. It is comprised of a novel monoclonal antibody against Trop2 (huT4D3), a cetuximab B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04). The novel Ed-04 is a derivative of the alkyd camptothecin and mediates cell cycle arrest at the S phase and subsequent apoptosis. BL-M02D1 achieves a high drug-to-toxin ratio (DAR=8) with a highly stable linker.

The antitumor efficacy of BL-M02D1 was evaluated in comparison to a commercialized Trop2-targeting ADC, IMMU-132, in xenograft tumor models. BL-M02D1 exhibited stronger tumor inhibition capacity than IMMU-132 at lower doses in the gastric cancer cell line NCI-N87, the breast cancer cell line MDA-MB-231, and the non-small cell lung cancer line HCC827 xenograft models. BL-M02D1 exhibited potent bystander effects, exemplified by strong tumor inhibition in a heterogeneous xenograft model of Trop2-positive and Trop2-negative tumor cells (A431 and SW620). This characteristic of BL-M02D1 was also compared to IMMU-132. In the heterogeneous Trop2 xenograft model (A431 and SW620), BL-M02D1 exhibited higher tumor inhibition capacity than IMMU-132, indicating that BL-M02D1 possesses a more potent bystander effect than IMMU-132.

In summary, these studies suggest BL-M02D1, a novel Trop2-targeting ADC, is potentially more efficacious in the treatment of Trop2-expressing carcinomas than IMMU-132. The clinical phase I has been progressing and the available data exhibit excellent efficacy in breast cancer therapy with manageable toxicity.

**Therapeutic Mechanism of Action**

**BL-M02D1: TROP2 ADC**

- **αTROP2** Human TROP2 Affinity: Intermediate
- **DAR = 8** Cat B cleavable linker Ed-04 (TOPI inhibitor)
- **wt Fc IgG1**

**BL-M02D1 Proliferation inhibition in vitro**

- **BL-M02D1** structure mediated cytotoxicity enhancements in gastric cancer NCI-N87, breast cancer MDA-MB-231, and non-small cell lung cancer HCC827 xenograft models. BL-M02D1 achieves strong tumor inhibition capacity than IMMU-132 at lower doses in the gastric cancer cell line NCI-N87, the breast cancer cell line MDA-MB-231, and the non-small cell lung cancer line HCC827 xenograft models. BL-M02D1 exhibits a high drug-to-toxin ratio (DAR=8) with a highly stable linker.

**BL-M02D1 Cell Binding to TROP2 expressing cells**

**BL-M02D1 Bystander-based cytotoxicity inhibition in vitro**

- **BL-M02D1** anti-tumor efficacy in heterogeneous TROP2 expression model was superior to IMMU-132 and DS-1062 bispecific (inhouse).
- **Dramatic potency difference is evident at 3 mg/kg dose level but also at 6 mg/kg dose level**

**Summary**

- BL-M02D1 exhibited stronger tumor inhibition capacity than IMMU-132 at lower doses in the gastric cancer NCI-N87, the breast cancer MDA-MB-231, and the non-small cell lung cancer HCC827 xenograft models.
- BL-M02D1 exhibited potent bystander effects, exemplified by strong in vitro activity with Trop2-positive and Trop2-negative tumor lines (A431 [TROP2 ratio 187.64] and SW620 [TROP2 ratio 1.49]).
- In the heterogeneous Trop2 xenograft model (A431 [TROP2 ratio 187.64] and SW620 [TROP2 ratio 1.49]), BL-M02D1 exhibited higher tumor inhibition capacity than IMMU-132, indicating that BL-M02D1 possess a more potent bystander effect than IMMU-132 and biosimilar DS-1062 (inhouse).
- These results suggest BL-M02D1 is potentially more efficacious in the treatment of Trop2-expressing carcinomas than IMMU-132.

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**References**

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