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

SYSTIMMUNE

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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 (hu4D3), a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04). The novel Ed-04 is a derivative of the alkaloid camptothecin and mediates cell cycle arrest at the S phase and subsequent apoptosis. BL-M02D1 achieves a high drug-to-antibody-ratio (DAR=8) with a highly stable linker.

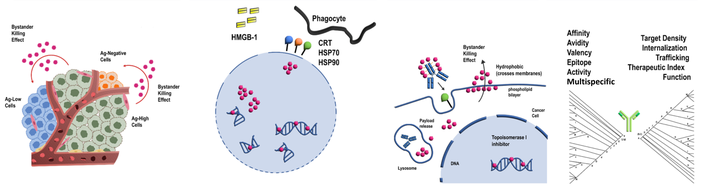
The antitumor efficacy of BL-M02D1 was evaluated in comparison to a commercialized Trop2-targeting ADC, IMMU-132, in xenograft tumor models. BL-M02D1 exhibited stronger tumor inhibition capacity than IMMU-132 at lower doses in the gastric cancer cell line NCI-N87, the breast cancer cell line MDA-MB-231, and the non-small cell lung cancer cell 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 possess 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

H I R E

Heterogeneity overcoming | Immunogenic death inducing | Resistance antagonizing | Enhanced Specificity



BL-M02D1 Cell Binding to TROP2 expressing cells

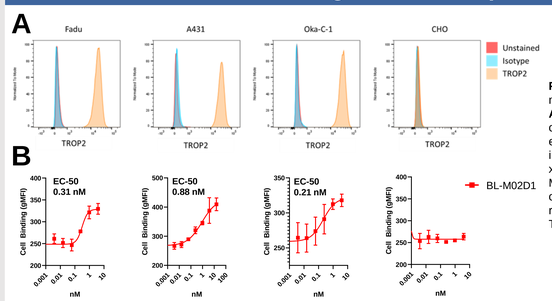
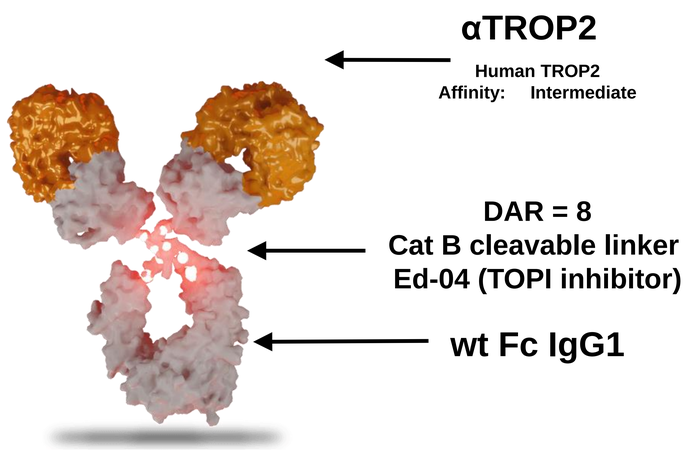


Figure 1. BL-M02D1 structure mediates specific antigen binding. **A)** Fadu cells, A431 cells, Oka-C1 cells, and CHO cells were evaluated for HER2 expression, indicated by orange histogram on x-axis. **B)** Data points of BL-M02D1 binding gMFI of indicated cancer cell lines and CHO cells representing the binding to TROP2.

BL-M02D1: TROP2 ADC



BL-M02D1 Proliferation inhibition *in vitro*

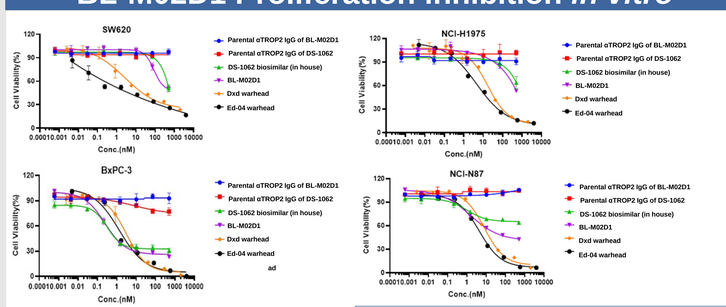


Figure 2. BL-B02D1 structure mediated cytolytic function.
SW620, NCI-H1975, BxPC-3, and NCI-N87 treated with indicated agents and viability assessed relative. Data plotted relative to untreated controls.

- Warhead: Ed-04 more potent than Dxd
- BL-M02D1 more effective than DS-106 biosimilar (inhouse)

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

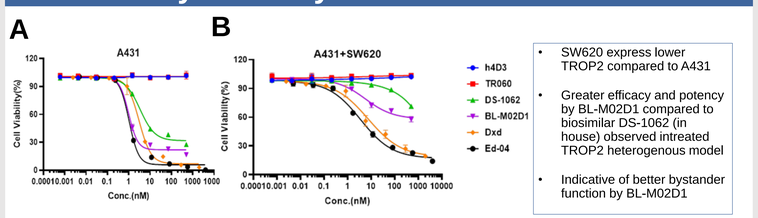


Figure 3. BL-B02D1 structure mediated cytolytic function by bystander action.
A431 (TROP2 high) cells treated with indicated agents and viability assessed. (**A**) A431 and SW620 (TROP2 low) cells treated with indicated agents and viability assessed. Data plotted relative to untreated controls. (**B**)

- SW620 express lower TROP2 compared to A431
- Greater efficacy and potency by BL-M02D1 compared to biosimilar DS-1062 (in house) observed intreated TROP2 heterogenous model
- Indicative of better bystander function by BL-M02D1

BL-M02D1 Xenograft Tumor inhibition *in vivo*

Efficacy of TROP2-ADC in the Treatment of Subcutaneous Human Gastric Cancer Cell Line NCI-N87 Xenograft Model in Balb/c-nude Mice (NCI-N87 TROP2 Ratio: 74.23)

Efficacy of TROP2-ADC in the Treatment of Subcutaneous Human Non-Small Cell Lung Cancer Cell Line HCC827 Xenograft Model in Balb/c-nude Mice (HCC827 TROP2 Ratio: 129.83)

Efficacy of TROP2-ADC in the Treatment of Subcutaneous Human Breast Cancer Cell Line MDA-MB-231 Xenograft Model in Balb/c-nude Mice (MDA-MB-231 TROP2 Ratio: 6.08)

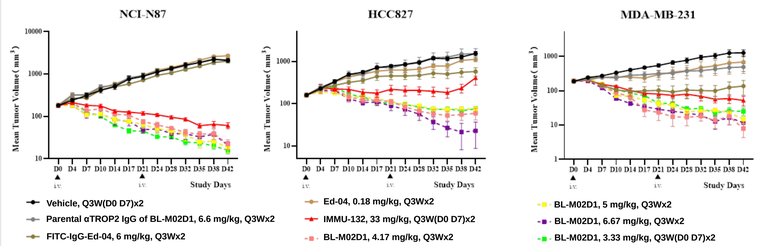


Figure 4. BL-M02D1 mediates direct anti tumor efficacy toward TROP2+ tumor xenografts in vivo

Treatment
Vehicle (0.9% sodium chloride injection)
hu4D3 (in house anti-TROP2 antibody)
FITC-IgG1-Ex0115 (DAR=8) （FITC-IgG1 was a green fluorescent labeled non-TROP2 antibody）
Ed-04 （ payload of BL-M07D1）
IMMU-132（DAR=8) （Commercial TROP2-ADC of Immunomedics）
BL-M02D1（DAR=8) （TROP2-ADC of BioKin）

BL-M02D1 bystander-based cytotoxicity inhibition *in vivo*

Efficacy of TROP2-ADC in the Treatment of Subcutaneous Human Epidermal Cancer Cell Line A431 and Human Colon Cancer Cell Line SW620 Heterogeneous Xenograft Model in Balb/c-nude Mice (A431_Trop2 Ratio:187.64;(P7) SW620_Trop2 Ratio: 1.49(P9);)

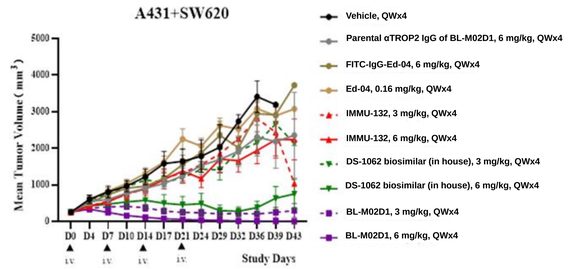


Figure 5. BL-B02D1 comparison with other TROP2 specific ADC in TROP2 heterogeneous bystander tumor model

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

Treatment
Vehicle (0.9% sodium chloride injection)
hu4D3 (in house anti-TROP2 antibody)
FITC-IgG1-Ex0115 (DAR=8) （FITC-IgG1 was a green fluorescent labeled non-TROP2 antibody）
Ed-04 （ payload of BL-M07D1）
IMMU-132（DAR=8) （Commercial TROP2-ADC of Immunomdecis）
DS-1062 （DAR=4) （in house TROP2-ADC of Daiichi Sankyo ）
BL-M02D1（DAR=8) （TROP2-ADC of Baili-Bio）

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

Acknowledgments

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References

BL-M02D1 clinical trials:

A Study of BL-M02D1 in Patients With Locally Advanced or Metastatic Gastrointestinal Tumors or Other Solid Tumors https://ClinicalTrials.gov/show/NCT05385692

A Study of BL-M02D1 in Patients With Locally Advanced or Metastatic Triple Negative Breast Cancer or Other Solid Tumors https://ClinicalTrials.gov/show/NCT05339685