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

SYSTIMMUNE
Abstract Number: 2644

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

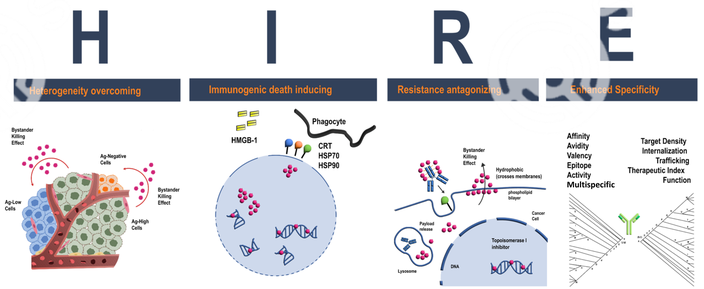
Abstract

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



BL-M02D1 Cell Binding to TROP2 expressing cells

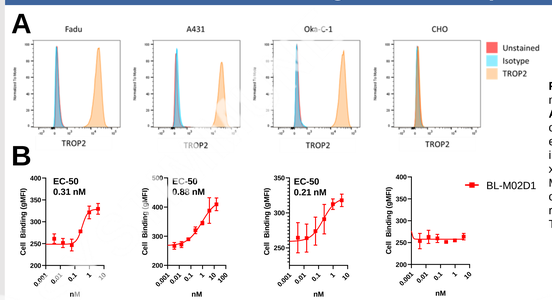
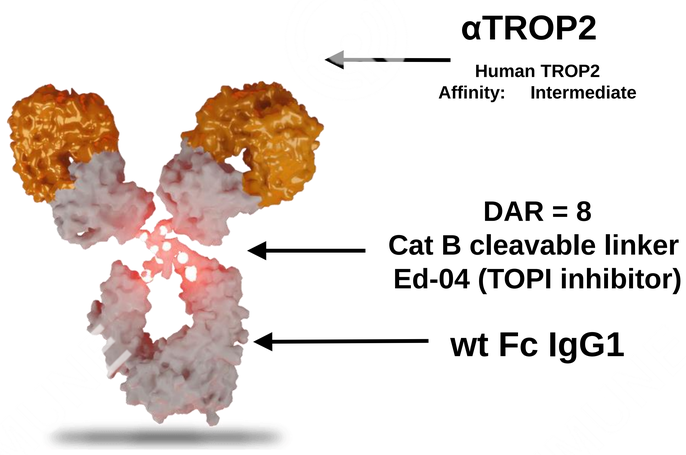


Figure 1. BL-M02D1 structure mediates specific antigen binding. **A)** Fadu cells, A431 cells, Oka-C1 cells, and CHO cells were evaluated for HER2 expression, indicated by orange histogram on x-axis. **B)** Data points of BL-M02D1 binding gMFI of indicated cancer cell lines and CHO cells representing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

BL-M02D1: TROP2 ADC



BL-M02D1 Proliferation inhibition *in vitro*

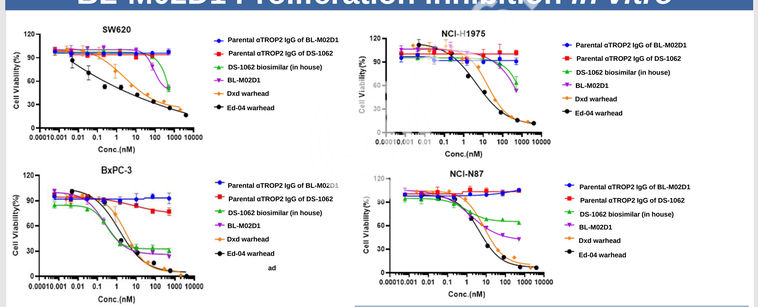


Figure 2. BL-B02D1 structure mediated cytolytic function.
SW620, NCI-H1975, BxPC-3, and NCI-N87 treated with indicated agents and viability assessed relative. Data plotted relative to untreated controls.

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

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

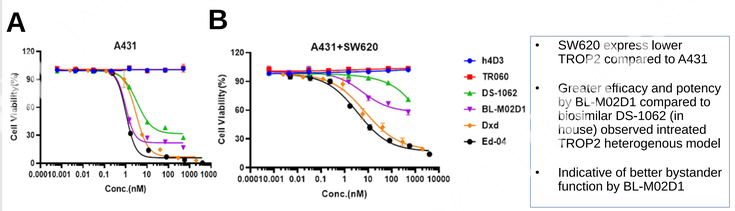


Figure 3. BL-B02D1 structure mediated cytolytic function by bystander action.
A431 (TROP2 high) cells treated with indicated agents and viability assessed. (**A**) A431 and SW620 (TROP2 low) cells treated with indicated agents and viability assessed. Data plotted relative to untreated controls. (B)

- 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)

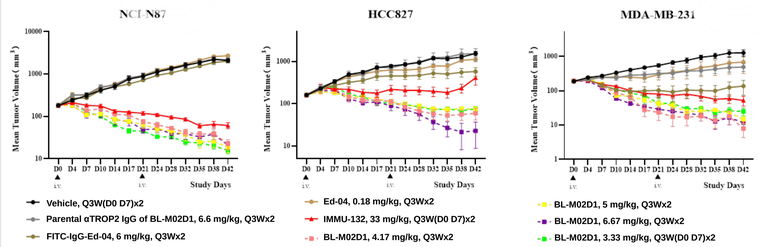
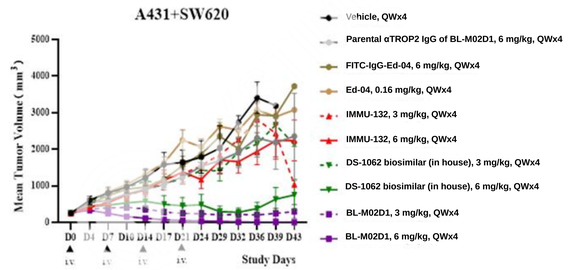


Figure 4. BL-M02D1 mediates direct anti tumor efficacy toward TROP2+ tumor xenografts in vivo

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);)



- 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)

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

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 biosimiiar DS-1062 (inhouse)
- These results suggest BL-M02D1 is potentially more efficacious in the treatment of Trop2-expressing carcinomas than IMMU-132

Acknowledgments

The authors acknowledge the efforts and contributions of numerous staff of Systimmune Inc. and Baili Pharmaceuticals who worked on the development of BL-M02D1

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