BL-B01D1, a novel EGFR×HER3-targeting ADC, demonstrates robust anti-tumor efficacy in preclinical evaluation

Wellin Wan, Shuwen Zhao, Shi Zhuo, Yong Zhang, Lan Chen, Gangrui Li, Blair Renshaw, Jahan Salar Khalili, Sa Xiao, Yi Zhu. Sicuhan Baili Pharmaceutical Co., Ltd., Chengdu, China, Systimmune Inc., Redmond, WA

**Abstract**

EGFR and HER3, members of the human epidermal growth factor receptor (ErbB) family, are targeted in cancer therapy due to their over-expression and pathway dependence in common human epithelial carcinoma tumors. To develop a promising therapeutic anti-tumor agent, we generated BL-B01D1, an EGFR×HER3-targeting ADC, which binds to EGFR and/or HER3 positive cells and is expected to be superior to anti-EGFR and anti-HER ADCs. It is comprised of a bispecific antibody against EGFR/HER3 (SI-B001), a chothepsin 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. BL-B01D1 achieves a high drug-to-antibody-ratio (DAR=8) with a highly stable linker.

The pharmacological potential of this ADC was evaluated in comparison to its parental single antigen-targeting ADCs in xenograft models composed of either the human colorectal cancer cell line SW620 or pancreatic cancer cell line BiPC3. The tumor inhibition activity of BL-B01D1 was compared with ADCs prepared from each parental anti-EGFR or anti-HER3 mAb conjugated with the same linker and payload. The bispecific ADC, BL-B01D1 exhibited stronger tumor inhibition capacity than the anti-EGFR ADC and the anti-HER3 ADC separately.

The preclinical studies suggest BL-B01D1, as an EGFR×HER3-targeting ADC, might be a promising novel agent with activity toward a broad range of human cancers. The clinical phase I has been progressing and the available data exhibit excellent efficacy but low levels of targeted toxicity in the non-small cell lung cancer (NSCLC) treatment setting. Overall, these data suggest BL-B01D1 has potential to serve as a novel, efficacious therapeutic agent for NSCLC with similar therapeutic impact as DS-8201 has in breast cancer treatment.

**Therapeutic Mechanism of Action**

**BL-B01D1 Bi-specific ADC**

- qEGFR
  - Human EGFR
  - Affinity: High
- qHER3
  - Human HER3
  - Affinity: Low

**BL-B01D1 proliferation inhibition is mediated by EGFR and HER3 binding and Ed-04 specific cytotoxicity**

- Cetuximab Sensitive Cell Lines
- Cetuximab Insensitive Cell Lines

**BL-B01D1 Cell Binding is determined by EGFR and not HER3**

**Heterogenous EGFR Xenograft Tumor Control by BL-B01D1 in vivo**

![Graphs and data showing tumor control by BL-B01D1 in vivo](Image)

**Summary**

- **BL-B01D1, an EGFR×HER3-targeting ADC, which can bind to EGFR and/or HER3 positive cells**
- **BL-B01D1 is comprised of a bispecific antibody against EGFR/HER3 (SI-B001), a chothepsin B cleavable linker, and a novel topoisomerase I inhibitor agent (Ed-04) with a drug-to-antibody-ratio of 8 (DAR=8)**
- **Ed-04 is a derivative of the alkaloid camptothecin, driving cell cycle arrest at the S phase and subsequent apoptosis showing superior bystander activity compared to Daichi payload (in house)**
- **BL-B01D1 exhibited stronger tumor inhibition capacity than the parental anti-EGFR ADC and the anti-HER3 ADC in colorectal cancer SW620 and pancreatic cancer BiPC3 xenograft models**
- **As an EGFR×HER3-targeting ADC, BL-B01D1 might be a promising, novel agent, with activity toward a broad range of human cancers**

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**References**

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