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**A NOVEL BISPECIFIC ANTIBODY-DRUG CONJUGATE
TARGETING PTK7 AND TROP2, BCG033,
DEMONSTRATES PRECLINICAL EFFICACY AGAINST
TRIPLE-NEGATIVE BREAST CANCER XENOGRAPTS**

Sufei Yao, Chengzhang Shang, Gao An, W Frank An, Chaoshe Guo*, Yi Yang. *Biocytogen Pharmaceuticals (Beijing) Co., Ltd., Beijing, China*

Background Patients with metastatic triple-negative breast cancer (TNBC) have low rates of overall survival, indicating the need to develop novel treatments. Although the TROP2-targeting ADC sacituzumab govitecan was recently granted accelerated approval from the FDA for treating patients with metastatic TNBC,¹ the on-target toxicity of this single-targeting agent has limited clinical efficacy.² We sought to improve the specificity of future TNBC-targeting therapies by generating a bispecific antibody-drug conjugate (BCG033) targeting TROP2 and PTK7, another tumor-associated antigen highly expressed in TNBC that is correlated with poor prognosis and metastatic disease.³

Methods Fully human bispecific antibodies (BsAbs) targeting PTK7 and TROP2 were assessed for reactivity to human and cynomolgus monkey antigens by surface plasmon resonance. Binding to several cell lines was also examined by flow cytometry. The drug-to-antibody ratio (DAR) of BCG033 candidates conjugated with monomethyl auristatin E was evaluated by hydrophobic interaction chromatography (HIC). Internalization of BCG033 in TNBC cell lines was assessed by flow cytometry, and killing of HCC70 cells or MDA-MB-468 cells was examined by IncuCyte imaging. The *in vivo* efficacy of BCG033 was subsequently evaluated in several cell line-derived xenografts and TNBC xenografts.

Results PTK7 x TROP2 BsAbs exhibited reactivity to human and cynomolgus monkey antigens, and demonstrated enhanced internalization *in vitro* compared with parental PTK7 antibodies. HIC assessments indicated a DAR of 4 for both BsADC candidates. In cell line-derived xenografts, BCG033 demonstrated superior activity to benchmark and parental ADCs. BCG033 also demonstrated superior efficacy to PTK7 benchmark in patient-derived xenografts, including TNBC xenografts with varying PTK7 expression levels, and non-TNBC breast cancer xenografts.

Conclusions BCG033 is a novel bispecific antibody-drug conjugate that targets PTK7 and TROP2. BCG033 demonstrates promising preclinical efficacy *in vivo*, suggesting it may offer new treatment options for TNBC or other solid tumors expressing PTK7 and TROP2 in the future.

REFERENCES

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Ethics Approval All animal studies were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Biocytogen Beijing Co., Ltd.

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