BG-C477, a novel topoisomerase 1 inhibitor-based ADC, exhibits antitumor activity in carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-expressing preclinical models

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Abstract

CEACAM5 (CEA) is a cell surface glycoprotein highly expressed in many cancers, including colorectal cancer (CRC), gastric cancer (GC), lung and pancreatic cancers. BG-C477 is a novel ADC that is composed of a CEACAM5-specific antibody conjugated to Top1i payloads (drug-to-antibody ratio = 8) via a cleavable linker. It remains stable in human plasma and mice blood circulation. BG-C477 showed specific binding to CEA-expressing MKN45 cells and stronger internalization activity compared to anti-CEA DM4 ADC. BG-C477 exhibited robust and CEA-dependent cytotoxicity in cell lines with different CEA expression levels. A potent bystander effect of BG-C477 was observed in co-culture killing assay with mixed CEA-positive MKN45 and -negative HCT116 cells, indicating the potential to treat tumors with heterogeneous CEA expression. In the animal studies, BG-C477 demonstrated potent and dose-associated single-agent efficacy in multiple CEA-expressing cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models. Moreover, BG-C477 exhibited superior antitumor efficacy in GC and CRC PDX models that anti-CEA DM4 ADC was ineffective.

In summary, BG-C477 is a promising CEA targeting ADC with great anti-tumor activity across multiple types of tumors. The first in human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of BG-C477 is ongoing (NCT06596473).