BGB-C354, a novel B7H3 ADC with high DAR stability and strong bystander effect, demonstrates robust antitumor activity in preclinical models

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Abstract

B7H3 is a type I transmembrane protein belonging to the B7 immunoregulatory family. B7H3 is overexpressed on a wide range of solid tumors such as lung cancers, gastrointestinal cancers and gynecological cancers, but its expression is absent or low in normal tissues, making it an attractive target for anticancer therapies.

BGB-C354 is a B7-H3-targeting antibody-drug conjugate (ADC) composed of a humanized anti-B7-H3 monoclonal antibody conjugated via a cleavable linker to a novel TOP1i payload, and the drug to antibody ratio (DAR) is approximately 8. Utilizing a stable ring-open conjugator, BGB-C354 demonstrated improved ADC stability and sustained high DAR in vivo, which may enable more efficient payload delivery to B7H3-expressing tumors.

In nonclinical pharmacological studies, BGB-C354 exhibited strong target binding activity, high target-dependent internalization, and potent cytotoxicity toward B7H3-expressing tumor cells. In addition, BGB-C354 demonstrated strong bystander killing effect in the presence of B7H3-expressing cell lines to potentially overcome the tumor heterogeneity. Notably, robust anti-tumor activity was observed in a panel of cell-derived xenograft (CDX) models with varying levels of B7-H3 expression, as well as in patient-derived xenograft (PDX) models. Consistent with its mechanism of action, DNA damage and apoptosis biomarker changes were induced by BGB-C354 in a dose-dependent manner after single dosing in preclinical models. Recently, a phase I study of BGB-C354 has been initiated to investigate its potential safety and preliminary efficacy in patients with B7H3-expressing advanced solid tumors (NCT06422520).