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).

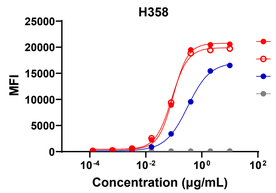
Potent binding activity and good internalization

A

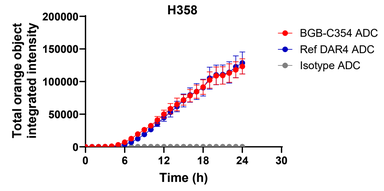
Target binding by SPR

ADC	Antigen	K_D (M)
BGB-C354	Human 4-Ig B7H3	1.13E-10
	Human 2-Ig B7H3	8.38E-10
	Cynomolgus monkey 4-Ig B7H3	1.19E-10
	Rat 2-Ig B7H3	ND
	Mouse 2-Ig B7H3	ND

B **Cellular binding**



C **Internalization**

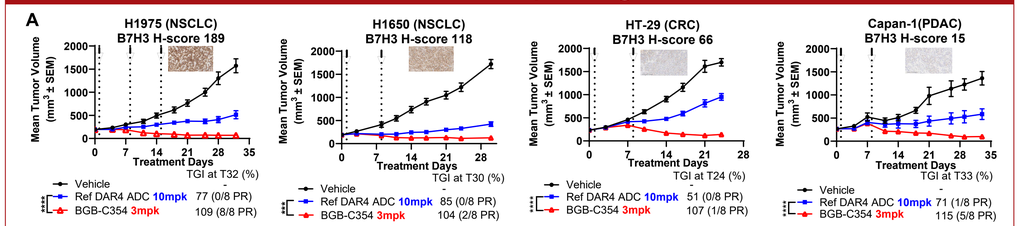


Abbreviations: ADC, antibody-drug conjugate; FACS, fluorescence-activated cell sorting; K_D, equilibrium dissociation constant; MFI, mean fluorescence intensity; ND: not detectable; SPR, surface plasmon resonance.
Note: Data are shown as mean ± SD.

Figure 2. Target binding activity of BGB-C354
(A) BGB-C354 showed strong binding to human B7H3 and good cyno monkey cross-reactivity measured by SPR. (B) BGB-C354 showed strong cellular binding measured by FACS. (C) BGB-C354 showed strong internalization in B7H3-positive H358 cell line.

Robust antitumor effect in B7H3-expressing CDX and PDX models

A



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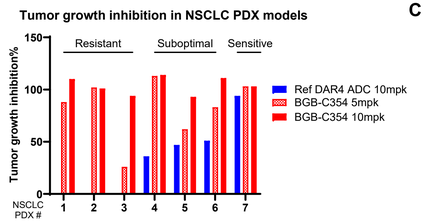

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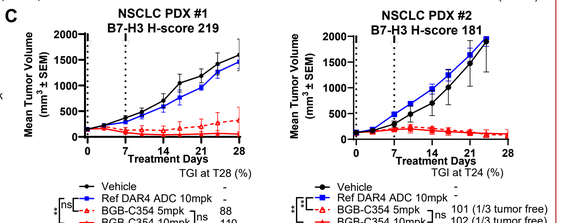


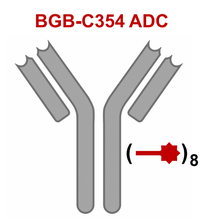
Abbreviations: CDX, cell-derived xenograft; CRC, colorectal cancer; IHC, immunohistochemistry; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; PR, partial response; SEM, standard error of the mean; TGI, tumor growth inhibition; NSCLC, non-small cell lung cancer.
Note: Dashed line with arrow indicates drug treatment. PR was considered as tumor volume smaller than 50% of that on the first day of dosing in three consecutive measurements.
Tumor volumes on indicated days were compared. p < 0.05 were considered statistically significant. *, p < 0.05; **, p < 0.01; ***, p < 0.005; ****, p < 0.001; ns, not significant.

Figure 4. Antitumor activity of BGB-C354 in xenograft models
BGB-C354 demonstrated robust antitumor effects in (A) CDX models covering low-to-high B7H3 expression levels and (B) NSCLC PDX models representing varied sensitivity to ref DAR4 ADC. (C) Representative data of tumor growth inhibition in 2 PDX models which are B7H3^{high} but primarily resistant to the ref DAR4 ADC.

High DAR stability

A

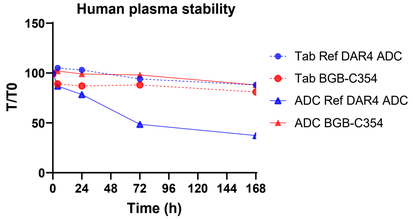
BGB-C354 ADC



Key attributes

- Proprietary hIgG1 mAb with strong binding and good internalization
- Cleavable and stable linker with ring-open process
- Optimized DAR for better potency and CMC robustness
- Potent TOP1i-based payload with strong bystander and ICD effect

B



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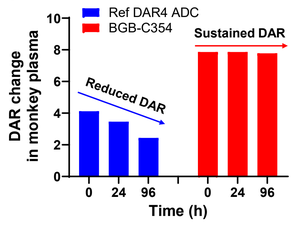
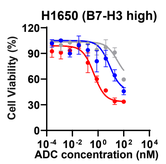


Abbreviations: ADC, antibody-drug conjugate; DAR, drug antibody ratio; ICD, immunogenic cell death; IgG1, immunoglobulin G 1; mAb, monoclonal antibody; Tab, total antibody; TOP1i, topoisomerase I inhibitor.
Note: Reference ADC (ref ADC) is an internally generated B7H3 DAR4 ADC using GGFG-DXd as the linker-payload.

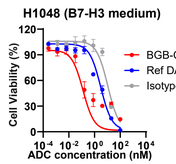
Figure 1. Key molecular feature of BGB-C354
(A) Illustration and key attributes of BGB-C354. (B) BGB-C354 showed improved ADC stability than ref DAR4 ADC in human plasma *ex vivo* after incubation for 7 days. (C) BGB-C354 showed sustained high DAR in cyno monkey *in vivo* when treated with 10mpk ADC.

Strong target mediated killing effect and bystander killing effect

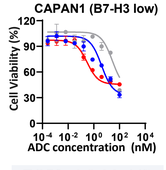
A **Target mediated killing**



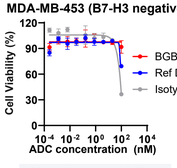
EC50: **17-fold** shift



EC50: **25-fold** shift

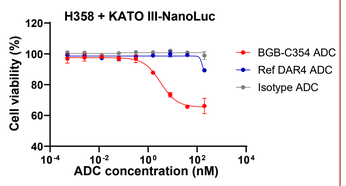


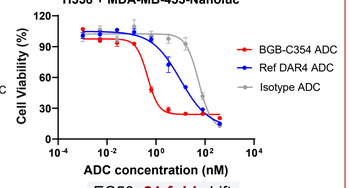
EC50: **4-fold** shift



No off-target killing

B **Bystander killing**





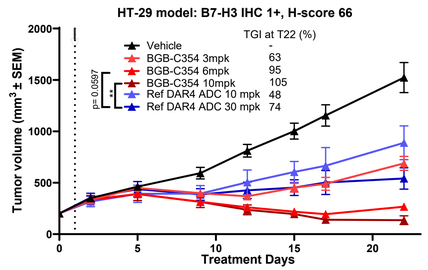
EC50: **21-fold** shift

Abbreviations: EC50, half maximal effective concentration; NanoLuc, NanoLuc luciferase.
Note: KATO III and MDA-MB-453 are B7H3 negative cell lines with NanoLuc overexpression. Luciferase signal was used as the readout to monitor the bystander killing effect to B7H3 negative cells. Data are shown as mean ± SD.

Figure 3. *In vitro* cytotoxicity of BGB-C354
(A) BGB-C354 showed strong target mediated killing effect in a panel of cancer cell lines with different B7H3 expression levels. (B) BGB-C354 demonstrated strong bystander killing effect to B7H3 negative cells in the presence of B7H3 positive cells.

Dose- and time-dependent PD biomarker change

A



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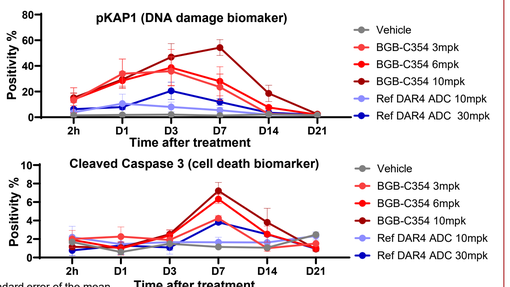

Abbreviations: IHC, immunohistochemistry; PD, pharmacodynamic; pKAP1, phospho-KAP1; SEM, standard error of the mean
Note: Dashed line with arrow indicates drug treatment. (B) Data are shown as mean ± SD.
Tumor volumes on indicated days were compared. p < 0.05 were considered statistically significant. *, p < 0.05; **, p < 0.01; ***, p < 0.005; ****, p < 0.001; ns, not significant.

Figure 5. Mechanism of action of BGB-C354
(A) BGB-C354 induced a dose-dependent anti-tumor effect in B7H3^{low} HT-29 CDX model, which was better than ref DAR4 ADC. (B) Consistent with the superior anti-tumor efficacy, more significant induction of DNA damage and apoptosis PD biomarkers were observed in a dose- and time-dependent manner, supporting the mechanism of action of TOP1 inhibition.

Conclusion

BGB-C354 is a novel TOP1i based B7-H3-targeting ADC using ring-open linker design for improved DAR stability.

- Sustained high DAR to enhance payload delivery to tumor
- Strong bystander effect to address tumor heterogeneity
- Robust anti-tumor activity in reference DAR4 ADC primarily resistant PDX models

With a strong preclinical activity and good tolerability in cyno monkey, a phase I clinical study in advanced solid cancers with BGB-C354 is in progress (NCT06422520).