

Clinical breakthroughs of B7-H3-targeted antibody-drug conjugates in solid tumors

Rongzhen Huang,¹ Lunlang Zhou,¹ and Haiwen Chen^{2,*}

¹First Clinical College, Guangzhou Medical University, Guangzhou 511436, China

²State Key Laboratory of Respiratory Disease, National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China

*Correspondence: 2021390052@gzhmu.edu.cn

Received: April 7, 2026; Accepted: September 22, 2026; Published Online: September 24, 2026; <https://doi.org/10.59717/j.xinn-oncol.2026.100034>

© 2026 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

Citation: Huang R., Zhou L. and Chen H. (2026). Clinical breakthroughs of B7-H3-targeted antibody-drug conjugates in solid tumors. *The Innovation Oncology* 1:100034.

THE THERAPEUTIC OPPORTUNITY OF B7-H3 IN SOLID TUMORS

B7-H3 (CD276), a B7 immune checkpoint family member, has emerged as a highly promising therapeutic target in oncology.¹ Unlike the PD-1/PD-L1 axis, which revolutionized immunotherapy yet benefits only a subset of patients, B7-H3 is broadly overexpressed in lung, nasopharyngeal, prostate, and head and neck cancers but shows limited expression in normal tissues. Despite possessing a short intracellular domain without known signaling motifs, B7-H3 overexpression has been linked to the activation of JAK2/STAT3, NF- κ B, and PI3K/AKT signaling in various tumor contexts, correlating with increased proliferation, migration, invasion, and treatment resistance. This tumor-selective expression, together with its involvement in both immune regulation and tumor progression, renders B7-H3 an ideal target for precision therapeutics.^{1,2} Although early monoclonal antibody and bispecific approaches achieved limited clinical success, antibody-drug conjugate (ADC) technology has fundamentally transformed this landscape by enabling targeted delivery of potent cytotoxic payloads to tumor cells while sparing healthy tissues.¹

CLINICAL BREAKTHROUGHS: YL201, HS-20093 AND I-DXD

Phase I/II trials of YL201, HS-20093, and I-DXd have established clinical proof-of-concept for B7-H3-targeted ADCs in solid tumors.¹⁻³ The phase I/II YL201 trial enrolled 312 patients across multiple tumor types, representing the largest B7-H3 ADC cohort evaluated to date. YL201 employs a topoisomerase I inhibitor delivered via MediLink's TMALIN platform, which enables dual payload release in the tumor microenvironment and intracellularly. In heavily pretreated extensive-stage small cell lung cancer (ES-SCLC) (95.8% prior anti-PD-1/PD-L1 exposure), YL201 achieved an objective response rate (ORR) of 63.9% (95% CI: 51.7–74.9) and median progression-free survival (mPFS) of 6.3 months. In platinum- and immunotherapy-refractory nasopharyngeal carcinoma (NPC), the ORR was 48.6% (including two complete responses) with mPFS of 7.8 months. Safety was predictable, with grade $\geq$ 3 hematologic toxicities as the primary adverse events (neutropenia 31.7%, leukopenia 29.5%, anemia 25.0%) and low rates of interstitial lung disease (1.3%) and infusion reactions (0.3%).¹

The phase I ARTEMIS-001 trial of HS-20093 corroborated these findings in 306 patients with lung cancer. HS-20093 achieved confirmed ORRs of 52.3% in ES-SCLC and 22.4% in non-small cell lung cancer (NSCLC), with comparable efficacy at 8.0 and 10.0 mg/kg. The maximum tolerated dose was 12.0 mg/kg, with 8.0 mg/kg selected for phase III based on favorable benefit-risk assessment. High in vivo stability and minimal systemic payload exposure supported its predictable safety profile.²

Concurrently, ifinatamab deruxtecan (I-DXd; DS-7300a) demonstrated efficacy in the phase II IDEATE-Lung01 trial (NCT05280470).³ I-DXd, which uses a cleavable tetrapeptide linker and DXd payload, achieved a confirmed ORR of 48.2% (95% CI: 39.6–56.9) and mPFS of 4.9 months at 12 mg/kg in 137 previously treated ES-SCLC patients, with higher efficacy in the second-line setting (ORR 56.3%). Its safety profile was consistent with the deruxtecan class, including adjudicated treatment-related interstitial lung disease in 12.4% of patients—a key distinction from YL201 and HS-20093. I-DXd received FDA Breakthrough Therapy designation in August 2025 and is now in phase III development. As topoisomerase I inhibitor-based ADCs, all three warrant caution in frail patients, particularly those with ES-SCLC, where substantial hematologic toxicities may necessitate dose modifications.

CHALLENGING THE CONVENTIONAL BIOMARKER PARADIGM

Perhaps the most intriguing finding from these trials is the lack of correla-

tion between B7-H3 expression and clinical response. In the YL201 study, immunohistochemical analysis of 152 pretreatment specimens showed no significant relationship between B7-H3 H-scores and objective response across ES-SCLC, NPC, lymphoepithelioma-like carcinoma, and esophageal squamous cell carcinoma, and soluble B7-H3 in peripheral blood lacked predictive value.¹ The HS-20093 trial independently confirmed this observation, with waterfall plots demonstrating equivalent response distributions regardless of baseline B7-H3 H-score.² Similarly, exploratory analyses from IDEATE-Lung01 revealed no clinically meaningful association between B7-H3 expression and antitumor response in I-DXd-treated patients, despite high median baseline expression.³

This apparent biomarker-independent efficacy challenges conventional ADC development paradigms. First, B7-H3 expression may enable initial tumor targeting, yet the therapeutic window appears sufficiently broad to accommodate heterogeneous antigen density. Second, the TMALIN platform's dual-release mechanism—activating payload in the tumor microenvironment independent of internalization¹—may reduce dependency on high-level target expression. Third, these findings preliminarily hint at the potential for broader applicability across antigen-heterogeneous tumor types.¹⁻³

Nevertheless, the interpretation of these findings requires caution. While the aforementioned mechanisms provide biological plausibility for biomarker-independent activity, several caveats remain. Phase I/II trials lacked statistical power for biomarker subgroup analyses, and the absence of detected correlation in underpowered cohorts does not exclude its existence. The membrane-permeable topoisomerase I inhibitor payloads diffuse into neighboring antigen-negative or low-expressing cells upon release, decoupling cell-surface antigen density from tumor response through a chemical bystander effect. Additionally, B7-H3 undergoes constitutive internalization and recycling, rendering pretreatment biopsies potentially unrepresentative of dynamic antigen availability during therapy; moreover, single-site H-scores fail to capture intratumoral or inter-lesional heterogeneity. Thus, this observation remains a hypothesis requiring confirmation in adequately powered studies with predefined biomarker analysis plans. Whole-body imaging modalities, such as ⁸⁹Zr-DFO-anti-B7-H3 PET, may further clarify the antigen density–response relationship by noninvasively quantifying total tumor burden and overcoming sampling bias inherent to biopsy-based assessments.⁴

EXPANDING THE THERAPEUTIC ARSENAL: BEYOND ADCS

The clinical success of B7-H3-targeted ADCs has validated this target as therapeutically viable with a favorable safety window.¹⁻³ Confirmation that normal tissue expression is sufficiently low to permit safe targeting provides a strong rationale for exploring alternative modalities, encompassing bispecific T-cell engagers (BiTEs), chimeric antigen receptor T-cell (CAR-T) therapy, and radiolabeled antibody constructs (Figure 1).

Bispecific T-cell engagers bridge tumor B7-H3 to T-cell CD3, activating cytotoxicity independent of MHC presentation. Unlike ADCs, BiTEs lack chemical bystander effects and depend on direct T cell–tumor cell engagement, making their efficacy potentially more sensitive to target expression levels. B7-H3-directed BiTEs are in early-stage development, and their combination with PD-1/PD-L1 blockade may alleviate microenvironmental immunosuppression.

CAR-T therapy represents another promising frontier. B7-H3-targeted CAR-T constructs have demonstrated clinical activity in the phase I BrainChild-03 trial (NCT04185038). CAR-T cells lack bystander effects and depend on immunological synapse formation, potentially rendering low B7-H3 expres-

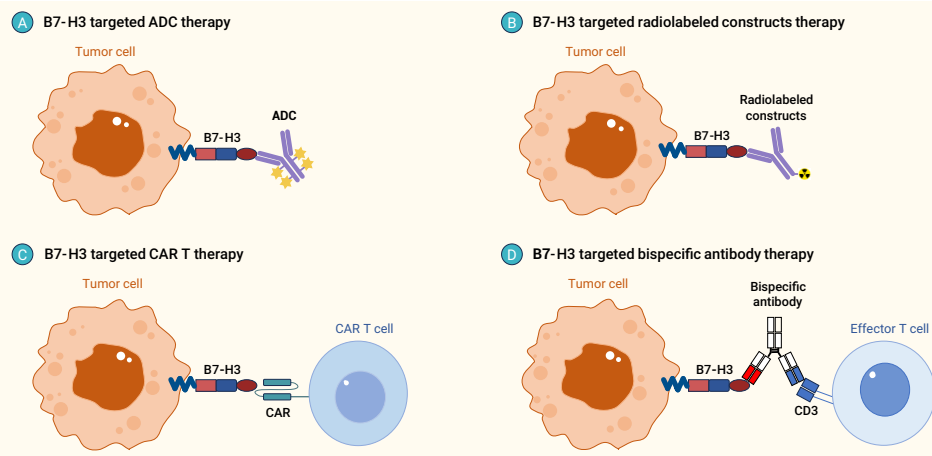


Figure 1. Schematic representation of B7-H3-targeted therapeutic strategies for solid tumors B7-H3 represents a clinically validated target in solid tumor oncology. B7-H3-targeted antibody–drug conjugates (ADCs; e.g., YL201, HS-20093) have demonstrated promising response rates and a predictable safety profile in patients with refractory disease. This figure illustrates four core B7-H3-directed therapeutic modalities: (A) ADC therapy, which delivers cytotoxic payloads to B7-H3-expressing tumor cells; (B) radiolabeled construct therapy, enabling targeted radiation delivery to B7-H3-positive tumor cells; (C) chimeric antigen receptor (CAR)-T cell therapy, utilizing engineered T cells to eliminate B7-H3-expressing malignant cells; and (D) bispecific antibody therapy, which bridges B7-H3 on tumor cells and CD3 on T cells to potentiate anti-tumor immunity.

sion a barrier to efficacy. Furthermore, the immunosuppressive tumor microenvironment and poor T-cell infiltration have historically constrained CAR-T success in solid tumors. To overcome these challenges, B7-H3 CAR-T cells may be engineered to enhance tumor penetration and potency, for example by modifying the extracellular matrix, blocking immunosuppressive signaling, and arming with cytokines or chemokines.

Radiolabeled antibody constructs (e.g., ^{131}I -omburtamab) offer a distinct mechanism: radionuclide-conjugated antibodies deliver ionizing radiation via β -particles that penetrate several millimeters, producing a physical crossfire effect capable of killing neighboring antigen-negative cells. However, this modality remains at the proof-of-concept stage, constrained by delivery challenges and myelosuppression concerns, and has not yet achieved the clinical maturity of late-phase ADCs.

CLINICAL DEVELOPMENT STRATEGY AND FUTURE DIRECTIONS

Recently, YL201 showed positive results in relapsed ES-SCLC (NCT06612151; YL201 vs topotecan: median overall survival 13.3 vs 9.4 months; mPFS 7.4 vs 2.8 months; ORR 59.1% vs 9.7%; grade ≥ 3 adverse events 55.4% vs 77.9%).⁵ Additional phase III trials are underway: YL201 is being evaluated in NPC at 2.4 mg/kg; HS-20093 is being compared to standard second-line therapy in small cell lung cancer (SCLC) at 8.0 mg/kg (NCT06498479); and I-DXd is being assessed at 12.0 mg/kg versus physician's choice in previously treated ES-SCLC (NCT06203210). These dose differentials—ranging from 2.0 to 12.0 mg/kg across agents—likely reflect distinct linker-payload platforms, drug-to-antibody ratios, and pharmacokinetic profiles, highlighting the importance of platform-specific rather than universal dosing strategies.^{1–3}

Three urgent clinical priorities require attention. First, the optimal sequencing of B7-H3-targeted therapies must be defined, particularly with respect to prior topoisomerase I inhibitor exposure. All three studies indicate reduced efficacy following prior topotecan or irinotecan treatment,^{1–3} likely driven by payload-specific resistance mechanisms with direct implications for patient stratification, warranting prospective validation to inform clinical decision-making. Second, combination strategies require exploration, including ADC plus immunotherapy to exploit potential immunogenic cell death and epitope spreading, or ADC plus targeted agents for molecularly defined subpopulations. Third, predictive biomarkers beyond simple antigen quantification—such as tumor microenvironment characteristics (e.g., cancer-associated fibroblast density and extracellular matrix stiffness), DNA damage response signatures, and circulating tumor DNA dynamics—may enable precision patient selection.

Mechanistically, the biomarker-independent efficacy observed invites further investigation. Whether this reflects bystander effects from payload release in the tumor microenvironment, differential antigen internalization kinetics, or alternative uptake mechanisms remains to be elucidated. Understanding these processes could inform the design of next-generation ADCs with enhanced therapeutic indices.

CONCLUSION

The clinical validation of B7-H3-targeted ADCs marks a pivotal development in advanced solid tumor treatment. Response rates approaching or

exceeding 50% in refractory settings, coupled with predictable, predominantly hematologic toxicities, establish B7-H3 as a therapeutic priority. This has catalyzed development beyond ADCs, encompassing bispecific T-cell engagers, CAR-T therapies, and radiolabeled antibody constructs. However, the dissociation between B7-H3 expression and clinical response challenges antigen density as a universal predictive biomarker. Consequently, elucidating payload-mediated bystander effects, B7-H3 internalization kinetics, and biopsy-related spatial heterogeneity is essential for platform-specific patient selection. Moving forward, the field should transition from static immunohistochemistry to integrative biomarker frameworks encompassing tumor microenvironment architecture, DNA damage response status, circulating tumor DNA dynamics, and B7-H3-directed immuno-PET for real-time target quantification. This is essential to translate platform-specific activity into durable, precision-guided outcomes across modalities.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used DeepSeek in order to polish the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

REFERENCES

- Ma Y., Yang Y., Huang Y., et al. (2025). A B7H3-targeting antibody–drug conjugate in advanced solid tumors: A phase 1/1b trial. *Nat. Med.* **31**:1949–1957. DOI:10.1038/s41591-025-03600-2
- Duan J., Sun Y., Wang Q., et al. (2026). HS-20093, a B7-H3-targeted antibody–drug conjugate in lung cancer: Results from the ARTEMIS-001 phase 1a/b trial. *Cancer Cell* **44**:846–857. DOI:10.1016/j.ccell.2026.02.006
- Rudin C.M., Johnson M.L., Paz-Ares L., et al. (2026). Ifinotamab deruxtecan in patients with extensive-stage small cell lung cancer: Primary analysis of the phase II Ideate-Lung01 trial. *J. Clin. Oncol.* **44**:261–273. DOI:10.1200/JCO-25-02142
- Qiu Y., Gu T., Wang T., et al. (2026). Integrated radio-theranostics using a [^{68}Zr]/[^{177}Lu]Lu-labeled B $_7$ -H $_3$ antibody–drug conjugate for prostate cancer. *Theranostics* **16**:6132–6144. DOI:10.7150/thno.125878
- Zhao Y., Liu H., Meng X., et al. (2026). Tambotatug pelitecan in small-cell lung cancer after platinum-based therapy. *N. Engl. J. Med.* Published online September 12:2026. DOI:10.1056/NEJMoa2610229

FUNDING AND ACKNOWLEDGMENTS

This work was supported by grants from the Natural Science Foundation of Guangdong Province (No. 2026A1515012452 to H.W. C.) and the National Natural Science Foundation of China (No. 82203640 to H.W. C.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests. None of the authors have any conflicts of interest related to MediLink Therapeutics, Hansoh Pharmaceutical, Daiichi Sankyo, Merck Sharp & Dohme LLC, or any other companies developing the ADCs discussed in this manuscript. The authors declare no conflicts of interest.