

Review Article

A B7-H3-Targeting Antibody–Drug Conjugate in Advanced Solid Tumors: Insights from a Phase 1/1b Clinical Trial

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Abstract: Antibody-drug conjugates (ADCs) have emerged as a powerful new class of targeted cancer therapeutics, leveraging the specificity of monoclonal antibodies to deliver highly potent cytotoxic payloads directly to tumor cells. The immune checkpoint molecule B7-H3, a member of the B7 family, has become a compelling therapeutic target due to its widespread and significant overexpression across a diverse range of solid tumors, coupled with its minimal expression in healthy tissues. This review critically analyzed the key findings from an early-phase clinical trial evaluating a novel B7-H3-targeting ADC in patients with advanced solid tumors. We delved into the mechanistic rationale behind targeting B7-H3, examining the extensive preclinical data that supported the initiation of this clinical investigation. The review meticulously analyzes the clinical trial's outcomes, including the observed safety profile, efficacy results, and pharmacokinetic characteristics of the ADC. Furthermore, we discuss the potential future implications of this therapeutic strategy within the broader oncology landscape. While the trial highlights the significant promise of B7-H3-directed therapies, it also underscores the substantial complexities inherent in ADC development, particularly regarding optimal patient selection, the crucial role of biomarker identification, and the emergence of potential resistance mechanisms. Ultimately, this article provides a comprehensive evaluation of the therapeutic utility of B7-H3-ADCs, positioning them as a promising and integral component of the evolving paradigm of precision oncology.

Keywords: targeting, antibody–drug conjugate, advanced solid tumors, insights

1. INTRODUCTION

The field of oncology has undergone a significant paradigm shift from non-specific cytotoxic chemotherapy to highly targeted therapeutic approaches [1]. This evolution has been driven by deeper insights into tumor biology, immune evasion mechanisms, and molecular profiling, which have collectively enabled the development of precision medicine strategies. Among these innovations, antibody-drug conjugates (ADCs) represent a compelling therapeutic modality that bridges the gap between the specificity of monoclonal antibodies and the potent cell-killing capabilities of cytotoxic agents [2]. ADCs are designed to selectively deliver cytotoxic payloads to tumor cells via antigen-specific antibodies, thereby enhancing therapeutic efficacy while minimizing off-target toxicity. Recent advancements in ADC technology have focused on optimizing linker stability, payload potency, and antigen selection to improve clinical outcomes. Notably, B7-H3 (CD276) has emerged as a promising target for ADC development due to its high expression in a broad spectrum of solid tumors—including prostate, lung, breast, and neuroendocrine cancers—and its limited expression in normal tissues, which offers a favorable therapeutic index [3]. B7-H3 is a member of the B7 family of immune checkpoint molecules and plays a multifaceted role in tumor progression, immune evasion, angiogenesis, and chemoresistance. Preclinical studies have demonstrated that B7-H3-targeted ADCs exhibit potent anti-

tumor activity in various cancer models, including glioblastoma, neuroblastoma, and prostate cancer⁹. Several agents, such as MGC018, DS7300a, and DB-1311, have entered clinical trials and shown encouraging preliminary efficacy and manageable safety profiles. These trials underscore the potential of B7-H3-targeted ADCs to address unmet needs in patients with refractory or metastatic disease. A recent phase 1/1b clinical trial investigated a novel B7-H3-targeted ADC in a heavily pretreated patient population with advanced solid tumors [4]. This comprehensive review aims to provide an in-depth analysis of the scientific rationale, clinical development, trial design, and outcomes of this therapeutic approach. We will systematically evaluate the key findings concerning its safety, efficacy, and pharmacokinetics, ultimately discussing its potential impact and positioning within the contemporary oncology landscape.

2. B7-H3 Biology and Its Therapeutic Relevance in Malignancy

B7-H3 (CD276) is a type I transmembrane glycoprotein belonging to the B7 family of immune regulatory ligands. While its precise immunological function remains under investigation, it is increasingly recognized as a critical player in tumor biology. B7-H3 is notably overexpressed in a wide range of solid tumors—including non-small cell lung cancer (NSCLC), prostate cancer, breast cancer, glioblastoma, ovarian cancer, and pancreatic cancer—while its expression in normal adult tissues remains minimal, largely due to post-transcriptional regulation by microRNAs [5]. This differential expression profile makes B7-H3 an attractive and selective target for antibody-based therapies, particularly antibody-drug conjugates (ADCs). Emerging evidence highlights B7-H3's multifaceted role in promoting tumor progression and immune evasion. It contributes to immune suppression by inhibiting the activation of CD4⁺ and CD8⁺ T-cells, thereby fostering a tolerogenic tumor microenvironment that enables cancer cells to escape immune surveillance². Additionally, B7-H3 has been implicated in non-immunological processes essential for cancer development, such as epithelial-to-mesenchymal transition (EMT), angiogenesis, metabolic reprogramming, and metastasis³. These functions are supported by its expression on cancer stem cells, tumor-associated vasculature, and stromal components, further reinforcing its role in therapeutic resistance and poor clinical outcomes¹. Recent pan-cancer analyses have revealed that B7-H3 expression correlates with enrichment of oncogenic signaling pathways, including Wnt, TGF- β , and Notch, and is associated with reduced infiltration of cytotoxic CD8⁺ T-cells and increased presence of M1 macrophages [6]. These findings suggest that B7-H3 not only suppresses immune responses but also actively shapes the tumor microenvironment to favor tumor survival and dissemination. Given its dual role in immune modulation and tumor progression, B7-H3 has become a focal point for next-generation immunotherapies. Several B7-H3-targeted ADCs—such as MGC018 and DS-7300a—are currently undergoing clinical evaluation, showing promising antitumor activity and manageable safety profiles in early-phase trials. These agents offer the potential to directly eliminate tumor cells while simultaneously disrupting the immunosuppressive and pro-metastatic functions of B7-H3 [7].

3. Antibody-Drug Conjugates: The Strategic Design of Biopharmaceutical Components

Antibody-drug conjugates (ADCs) are a rapidly evolving class of targeted cancer therapeutics that combine the specificity of monoclonal antibodies with the cytotoxic potency of chemotherapeutic agents [8]. Structurally, ADCs consist of three critical components: a monoclonal antibody that selectively binds to tumor-associated antigens, a cytotoxic payload capable of inducing cell death, and a chemical linker that ensures payload stability during systemic circulation and controlled release within the tumor microenvironment [9]. The design of ADCs has advanced significantly, with innovations in linker chemistry playing a pivotal role in improving pharmacokinetics and minimizing off-target toxicity. Linkers must strike a delicate balance between stability in plasma and efficient payload release upon internalization into tumor cells. Enzyme-cleavable linkers, such as valine-citrulline (Val-Cit), have been

widely adopted due to their selective cleavage by lysosomal proteases like cathepsin B2 [10]. Novel linker designs, including exo cleavable and hydrophilic linkers, have demonstrated enhanced stability and reduced aggregation, even with hydrophobic payloads. The cytotoxic payloads used in ADCs are typically ultra-potent agents, including microtubule inhibitors (e.g., monomethyl auristatin E, maytansinoids) and DNA-damaging compounds (e.g., calicheamicin, duocarmycins). These payloads are designed to exert lethal effects at picomolar concentrations, enabling effective tumor cell killing even in cases of low antigen density. Emerging payload classes, such as topoisomerase I inhibitors and PROTACs, are expanding the therapeutic landscape by targeting quiescent tumor cells and enhancing bystander effects. Despite their promise, ADCs face several developmental challenges [11]. These include heterogeneous antigen expression, potential immunogenicity, premature payload release, and resistance mechanisms such as antigen downregulation or impaired internalization. Moreover, the tumor microenvironment can influence ADC efficacy by modulating enzymatic activity and altering payload metabolism.

4. Preclinical Development and Validation of the B7-H3-Targeting ADC

Extensive preclinical investigations have solidified the rationale for targeting B7-H3 with antibody-drug conjugates (ADCs). B7-H3 is consistently overexpressed in patient-derived xenograft (PDX) models and cell lines across diverse tumor types, including lung, breast, prostate, and glioblastoma [1]. Importantly, studies have confirmed that B7-H3 exhibits efficient internalization upon antibody binding, a critical requirement for ADC-mediated cytotoxic delivery. This internalization facilitates lysosomal trafficking, enabling the release of the payload within the tumor cell. In vivo efficacy studies have demonstrated that B7-H3-targeted ADCs, such as DB-1311, MGC018, and ITC-6102RO, induce robust tumor growth inhibition and, in several models, complete regression. These effects were observed in both cell line-derived xenografts and patient-derived xenografts, underscoring the translational potential of these agents. Notably, DB-1311 showed superior antitumor activity compared to DS7300a analogs, with dose-dependent cytotoxicity and favorable pharmacokinetics in non-human primates [13]. A pivotal aspect of preclinical development was the optimization of the ADC's linker and payload. Cleavable linkers—such as valine-citrulline (Val-Cit) and Ortho Hydroxy-Protected Aryl Sulfate (OHPAS)—were selected for their stability in circulation and selective cleavage within the tumor microenvironment. These linkers enable precise payload release triggered by lysosomal enzymes or acidic pH, enhancing tumor specificity while minimizing systemic toxicity. These payloads are designed to exert lethal effects at picomolar concentrations, ensuring efficacy even in tumors with heterogeneous antigen expression. Moreover, site-specific conjugation strategies have improved ADC homogeneity and reduced off-target uptake by Fcγ and mannose receptors, mitigating lung toxicity risks. Together, these preclinical findings provide compelling evidence for the clinical advancement of B7-H3-targeted ADCs. Their ability to combine tumor specificity, potent cytotoxicity, and favorable safety profiles positions them as promising candidates in the evolving landscape of precision oncology [14].

5. The Phase 1/1b Clinical Trial: Comprehensive Design and Methodological Framework

The primary objectives of this phase 1/1b clinical trial were to rigorously evaluate the safety and tolerability of the B7-H3-targeted antibody-drug conjugate (ADC), determine the maximum tolerated dose (MTD), and identify dose-limiting toxicities (DLTs) during the initial treatment cycles [15]. Secondary endpoints included pharmacokinetic (PK) profiling, immunogenicity assessment, and preliminary evaluation of anti-tumor activity across a spectrum of advanced solid tumors. The study enrolled patients with histologically confirmed advanced or metastatic solid tumors who had progressed on or were intolerant to standard therapies. Eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, measurable disease per RECIST v1.1, and adequate hematologic, hepatic, and renal function [16]. The trial followed a conventional 3+3 dose

escalation design, beginning with accelerated titration at lower dose levels and progressing to higher doses until the MTD or recommended phase 2 dose (RP2D) was established. Following dose escalation, a dose expansion phase was initiated to further characterize the safety, tolerability, and preliminary efficacy of the ADC at the RP2D. The investigational agent was administered intravenously every three weeks (Q3W), with tumor assessments conducted every 6–12 weeks depending on the study phase². Notably, agents such as DB-1311 and MGC018 demonstrated manageable toxicity profiles and promising anti-tumor activity in early-phase trials, particularly in patients with small cell lung cancer (SCLC), nasopharyngeal carcinoma (NPC), and castration-resistant prostate cancer (CRPC)³. The trial design also incorporated exploratory endpoints, including biomarker analyses and correlation of B7-H3 expression with clinical outcomes. Interestingly, some studies reported no significant association between membrane B7-H3 levels and objective response rates, suggesting that ADC efficacy may extend beyond antigen density alone [17].

6. Safety and Tolerability Profile of the B7-H3-Targeting ADC

The safety profile of B7-H3-targeted ADCs has consistently demonstrated manageable toxicity across multiple early-phase clinical trials [18]. Agents such as MGC018, DB-1311, and 7MW3711 have shown tolerability patterns similar to other ADCs utilizing topoisomerase I inhibitors or duocarmycin-based payloads². Common treatment-related adverse events (TRAEs) include:

- Fatigue, nausea, and infusion-related reactions, typically grade 1–2
- Hematologic toxicities such as neutropenia, anemia, and thrombocytopenia, often transient and reversible
- Peripheral neuropathy, observed in a minority of patients, likely related to payload class

Importantly, grade ≥ 3 TRAEs were infrequent and manageable. For example, in the 7MW3711 trial, grade 3 TRAEs included decreased neutrophil and lymphocyte counts, anemia, and myelosuppression, but no treatment-related deaths were reported. Similarly, DXC014, a bispecific ADC targeting B7-H3 and PSMA, showed excellent tolerability in preclinical models, with no dose-limiting toxicities up to 40 mg/kg in non-human primates.

Dose-limiting toxicities (DLTs) observed in clinical trials primarily involved:

- Transient liver enzyme elevations
- Grade 3 fatigue
- Myelosuppression and cytopenia's at higher dose levels

These findings informed the selection of the recommended phase 2 dose (RP2D), which balanced efficacy with tolerability. In the case of MHB088C, the RP2D was established at 3.0 mg/kg Q3W following DLTs of febrile neutropenia and thrombocytopenia at higher doses. The dose expansion cohorts at RP2D have provided encouraging data on both safety and preliminary efficacy, particularly in tumor types such as small cell lung cancer (SCLC) and squamous NSCLC, where objective response rates exceeded 35% and disease control rates approached 100% [19].

7. Efficacy Outcomes and the Predictive Role of Biomarkers

Among patients with measurable disease, the B7-H3-targeted ADC demonstrated encouraging anti-tumor activity, with a confirmed overall response rate (ORR) of 21% and a disease control rate (DCR) of 59% [20]. Partial responses were observed across multiple tumor types, including:

- Non-small cell lung cancer (NSCLC): 26% ORR
- Prostate cancer: 19% ORR
- Ovarian cancer: 15% ORR

These results are consistent with early-phase data from agents such as MGC018, DB-1311, and 7MW3711, which have shown ORRs ranging from 20–36% and DCRs exceeding 90% in select tumor cohorts [21]. Notably, 7MW3711 achieved an ORR of 36% and DCR of 96% in NSCLC patients treated at ≥ 4.5 mg/kg, while MGC018 demonstrated tumor shrinkage in multiple solid tumors, including prostate and breast cancer. A pivotal translational insight from the trial was the positive correlation between tumor B7-H3 expression and clinical response, suggesting that B7-H3 may serve as a predictive biomarker. This aligns with findings from recent studies showing that tumors with high B7-H3 H-scores exhibited superior response rates, particularly in squamous NSCLC and small cell lung cancer [22].

8. Pharmacokinetics, Pharmacodynamics, and Immunogenicity

Pharmacokinetic (PK) analysis of the B7-H3-targeted ADC revealed dose-proportional kinetics, with systemic exposure increasing linearly across escalating dose levels. The terminal half-life of approximately five days aligns with the expected range for ADCs, which typically exhibit half-lives between 3 and 20 days depending on their molecular design and payload characteristics [23]. This duration supports sustained therapeutic exposure while allowing for manageable dosing intervals. A notable observation was the slower clearance in patients with lower tumor burden, likely due to a diminished antigen sink effect. This phenomenon occurs when high levels of target antigen on tumor cells bind and internalize the ADC, accelerating its clearance from circulation. In patients with fewer tumor cells expressing B7-H3, the ADC remains in systemic circulation longer, potentially enhancing exposure and efficacy. Regarding immunogenicity, the absence of clinically significant anti-drug antibody (ADA) development is a promising indicator of the ADC's biocompatibility and low immunogenic risk [24]. This finding is consistent with data from other ADCs employing humanized monoclonal antibodies and stable linker-payload systems. Across multiple clinical trials, baseline ADA incidence typically ranges from 1–8%, with post-treatment ADA development varying between 0–35% depending on the ADC's structure and patient population. In this study, the lack of ADA-related adverse events or altered PK profiles suggests that the ADC's design effectively mitigates immunogenicity concerns. These pharmacologic and immunologic attributes collectively support the ADC's continued clinical development and potential for broader therapeutic application [25].

9. Discussion of Clinical Relevance and Future Directions

The results of this phase 1/1b trial provide a compelling proof-of-concept for B7-H3-directed antibody-drug conjugate therapy in advanced solid tumors. The documented anti-tumor activity in a highly treatment-resistant and heterogeneous patient population highlights the clinical potential of this targeted approach [26]. These outcomes resonate with mounting evidence supporting B7-H3 as a tumor-associated antigen with broad applicability, given its high expression across numerous malignancies and minimal presence in healthy tissues. Several other B7-H3-targeting ADCs are concurrently undergoing clinical investigation, and although direct cross-trial comparisons are limited by variability in design and patient demographics, the aggregated data suggest consistent therapeutic promise across platforms. Nevertheless, these results should be interpreted with caution [27]. The single-arm, non-randomized nature of the study, coupled with relatively small subgroup sizes and limited long-term data, constrains the strength of conclusions. To establish clinical utility and confirm survival benefits, larger randomized phase 2 and 3 trials will be essential. Integration of biomarker-guided patient selection may further enhance therapeutic precision, especially given the observed

correlation between tumor B7-H3 expression and clinical response. Future directions include combination strategies that may extend efficacy and durability. Pairing B7-H3 ADCs with immune checkpoint inhibitors like PD-1/PD-L1 blockade could provide synergistic benefits, potentially reprogram the tumor microenvironment and overcome resistance [28]. Early studies involving enoblituzumab and pembrolizumab have already demonstrated promising activity, reinforcing the rationale for dual immunomodulatory approaches. The expanding landscape of B7-H3-targeted therapies thus represents a dynamic frontier in precision oncology, poised for continued advancement through translational research and clinical refinement [29].

10. CONCLUSION

The encouraging results from this phase 1/1b trial underscore the therapeutic promise of B7-H3-targeted antibody-drug conjugates (ADCs) in the treatment of advanced solid tumors. The manageable safety profile and demonstrable anti-tumor activity in a heavily pretreated population affirm the viability of B7-H3 as a broadly applicable target. These findings are further supported by emerging data from other investigational agents such as YL201, HS-20093, and MGC018, which have shown robust efficacy in tumor types like extensive-stage small cell lung cancer (ES-SCLC), nasopharyngeal carcinoma (NPC), and prostate cancer. Importantly, the integration of biomarker-driven strategies—such as B7-H3 expression profiling and circulating tumor DNA (ctDNA) monitoring—may enhance patient selection and optimize therapeutic outcomes. Studies have also revealed that B7-H3 expression correlates with poor prognosis and aggressive tumor phenotypes, reinforcing its relevance in precision oncology. Looking ahead, combination approaches are gaining momentum. Preclinical models have demonstrated synergistic anti-tumor effects when B7-H3-targeted ADCs are paired with PARP inhibitors, suggesting that dual targeting of DNA damage and immune evasion pathways may overcome resistance and improve response durability. Additionally, bispecific ADCs targeting both B7-H3 and DLL3 are being explored to address tumor heterogeneity and expand therapeutic reach. In conclusion, B7-H3-directed ADCs represent a transformative modality in oncology. Their continued development—through randomized trials, biomarker refinement, and rational combination regimens—will be pivotal in establishing their role as cornerstone therapies in the era of personalized cancer treatment.

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