Journal of Pharmaceutics & Drug Development
Volume 13 | Issue 1
2348-9782

Review Article Open Access

The Progress and Prospects of B7-H3 Targeted Immunotherapy in the Treatment of Solid Tumors: Multidimensional Breakthrough from CAR-T Cells to Antibody Drug Conjugates

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Citation: Zu-Chian Chiang, Jizhen Lin, Qi Chen, Sheng Yang, Shuchun Lin (2026) The Progress and Prospects of B7-H3 Targeted Immunotherapy in the Treatment of Solid Tumors: Multidimensional Breakthrough from CAR-T Cells to Antibody Drug Conjugates, J Pharma Drug Develop 13(1): 101

Received Date: January 09, 2026 **Accepted Date:** February 03, 2026 **Published Date:** February 06, 2026

Abstract

Solid tumors are challenging to treat due to their heterogeneity, immunosuppressive microenvironments, and resistance to PD-1/PD-L1 inhibitors. B7-H3 (CD276), an immune checkpoint molecule found in over 70% of various solid tumors but minimally in normal tissues, has emerged as a promising therapeutic target. It suppresses anti-tumor immunity and promotes oncogenic processes, making it particularly relevant for patients who are resistant to PD-1 therapies. This review focuses on two main B7-H3-targeted therapies: chimeric antigen receptor T (CAR-T) cells and antibody-drug conjugates (ADCs). B7-H3 CAR-T cells have shown promising efficacy and survival benefits in glioblastoma, achieving a median overall survival of up to 20.73 months. Their effectiveness is further enhanced when combined with specific cytokines and other agents. Additionally, engineered γδ T cell-derived CAR-T cells provide advantages such as a reduced risk of cytokine release syndrome. Currently, four B7-H3-targeted ADCs are in Phase II/III trials, demonstrating encouraging response rates in extensive-stage small-cell lung cancer and activity against PD-1-resistant tumors. Future directions for research include expanding the use of ADCs, optimizing CAR-T efficacy through dual-target strategies, developing combination therapies with immune checkpoint inhibitors, and improving safety through better design. Predictive biomarkers will also assist in advancing precision medicine. Overall, B7-H3-targeted CAR-T cells and ADCs represent significant advancements, offering a promising therapeutic option for patients with resistant solid tumors.

Keywords: B7-H3 Targeted Immunotherapy; Chimeric Antigen Receptor-T Cells; Antibody-Drug Conjugates; Immunosuppressive Microenvironments; Treatment of Solid Tumors

Introduction

Solid tumors present a significant global health challenge due to their high heterogeneity, an immunosuppressive tumor microenvironment (TME), and inherent or acquired resistance to therapies, which result in limited clinical outcomes [1]. Traditional immunotherapies, particularly PD-1/PD-L1 inhibitors, have transformed the treatment landscape for various malignancies. However, approximately half of patients either do not respond or develop acquired resistance to these therapies. This highlights an urgent need for alternative therapeutic targets and strategies [2, 3]. In this context, B7-H3 (CD276), a crucial member of the B7 family of immune checkpoint molecules, has emerged as a promising candidate to overcome these therapeutic challenges [4]. B7-H3 is characterized by its high expression (70%-100%) in a wide range of solid tumors, including glioblastoma, lung cancer, nasopharyngeal carcinoma, and small-cell lung cancer, while exhibiting minimal expression in normal tissues. This characteristic creates an ideal "therapeutic window" for targeted intervention [5, 6]. Furthermore, B7-H3 plays a dual role in promoting tumor progression. It inhibits anti-tumor immunity by suppressing T cell proliferation, inducing M2 macrophage polarization, and expanding regulatory T cells. Additionally, it drives non-immune oncogenic processes by activating the PI3K/Akt and NF-κB pathways, which enhance tumor proliferation, metastasis, and angiogenesis. This multi-faceted role solidifies B7-H3's status as a significant therapeutic target [7, 8].

The complementary expression patterns of B7-H3 and PD-L1 in various tumors provide a strong rationale for addressing PD-1 resistance [9]. Preclinical and clinical studies have shown that therapies targeting B7-H3 can effectively eliminate tumor cells that avoid PD-1/PD-L1 blockade, either through direct cytotoxic effects or by remodeling the tumor microenvironment (TME) [10,11]. Among the various strategies being developed to target B7-H3, chimeric antigen receptor T (CAR-T) cells and antibody-drug conjugates (ADCs) have made the most significant advancements [12]. CAR-T cells, known for their MHC-independent antigen recognition and strong anti-tumor persistence, have demonstrated exceptional efficacy in treating refractory solid tumors like glioblastoma. This effectiveness is particularly notable when CAR-T cells are engineered with novel cell subsets, such as γδ T cells, or enhanced with cytokines [13, 14]. Meanwhile, B7-H3-targeted ADCs leverage the specificity of monoclonal antibodies combined with potent cytotoxic payloads. These ADCs are progressing rapidly in clinical trials, with multiple agents, including Ifinatamab Deruxtecan and QLC5508, showing promising objective response rates (ORR) in patients with extensive-stage small-cell lung cancer (ES-SCLC), brain metastases, and tumors resistant to PD-1 treatment [15, 16].

This review provides a systematic summary of the biological characteristics and oncogenic mechanisms of B7-H3 in solid tumors. It emphasizes the latest advances in B7-H3-targeted CAR-T cells and antibody-drug conjugates (ADCs). We explore their structural designs, therapeutic efficacy observed in preclinical and clinical studies, and their synergistic mechanisms when combined with therapies such as immune checkpoint inhibitors, nanotechnology, and targeted agents. Additionally, we address current challenges, including off-target toxicity, antigen heterogeneity, and immunosuppression in the tumor microenvironment (TME). We also discuss future development directions, including bispecific engineering, expanding treatment indications, and identifying predictive biomarkers. By synthesizing recent evidence, this review aims to provide a comprehensive overview of B7-H3-targeted immunotherapy, highlighting its potential to transform the treatment landscape for PD-1-resistant solid tumors.

Literature Search Strategy

This comprehensive narrative review was conducted through a systematic electronic literature search. We queried PubMed, Web of Science Core Collection, and Embase databases for English-language articles published between January 2015 and December 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords including “B7-H3”, “CD276”, “chimeric antigen receptor T cell”, “CAR-T”, “antibody-drug conjugate”, “ADC”, “solid tumor”, and “clinical trial”. The search results were screened to include preclinical studies, clinical trial reports (published in peer-reviewed

journals or presented at major oncology conferences such as ASCO, ESMO, and AACR), authoritative review articles, and relevant regulatory announcements. Emphasis was placed on studies providing robust efficacy and safety data to support the evaluation of the clinical progress and future directions of B7-H3-targeted therapies. Finally, it is referenced using PubMed's AMA format.

The Rise of B7-H3 Targeting in Solid Tumor Immunotherapy

The treatment of solid tumors presents several challenges, including tumor heterogeneity, an immunosuppressive microenvironment, and treatment resistance. Traditional PD-1/PD-L1 inhibitors are effective against immunogenic tumors; however, approximately half of the patients develop resistance to PD-1 therapy [17]. In this context, B7-H3 (CD276), a key member of the B7 family, has emerged as a potential target for overcoming drug resistance due to its high expression (> 70%) in various tumors and its widespread presence in tumor cells, blood vessels, and immune cells [4, 18, 19]. The concurrent or complementary expression of B7-H3 with PD-L1 offers an additional treatment pathway for patients who have not responded to PD-1 therapy.

B7-H3 is a type I transmembrane protein that contains two immunoglobulin (Ig) subdomains and four other Ig subdomains [4, 18]. The latter are more widely expressed in tumor cell lines, suggesting that B7-H3 may play a role in complex immune regulatory networks. Although a definitive ligand for B7-H3 has not yet been identified, it is commonly found at high levels (76% -100%) in glioblastoma (GBM), lung cancer, liver cancer, breast cancer, and several other solid tumors, while being nearly absent in normal brain tissue [20]. Additionally, B7-H3 is highly expressed in pediatric ependymoma samples, where it has been detected in 29 out of 44 cases. In vitro studies have demonstrated that B7-H3 CAR-T cells exhibit significant cytolytic activity against ependymoma stem cells, laying the groundwork for clinical applications of combination therapy in pediatric brain tumors [21]. This tumor-specific expression pattern provides an ideal safety profile for targeted therapies. The high expression of B7-H3 makes it an important biomarker for tracking tumor progression and prognosis, and its transmembrane structure facilitates the design of antibody drugs or CAR-T cell therapies [18]. Targeting B7-H3 is anticipated to allow for the selective recognition of tumor cells, minimizing damage to normal tissues, and opening new avenues for the treatment of solid tumors.

Dual Roles in the Tumor Microenvironment

B7-H3, as an immune checkpoint molecule, promotes tumor immune escape through both direct and indirect mechanisms. On one hand, B7-H3 can significantly inhibit T cell proliferation and the release of key cytokines such as IFN-γ and IL-2 by binding to T cell surface receptors, weakening the anti-tumor immune response [8,18]. On the other hand, it can also achieve tumor progression by reshaping the tumor microenvironment [7]. For examples, (I) Regulating macrophage polarization: promoting differentiation of M2 tumor associated macrophages, whose secreted factors such as IL-10 and TGF-β can inhibit $CD8^+$ T cell function; (II) Inducing Treg amplification: promoting the differentiation of $Foxp3^+$ regulatory T cells through the STAT3 pathway, forming an immunosuppressive network; (III) Impact on angiogenesis: Activating the NF-κB pathway induces VEGFA expression, promotes tumor angiogenesis, and provides nutritional support for tumors. These mechanisms collectively lead to the failure of immune surveillance, creating favorable conditions for tumor progression [7]. Interestingly, some preclinical studies have reported that B7-H3 has pro-immune effects in specific contexts, but such conclusions are rare and controversial [8].

Overall, B7-H3 (CD276) plays a dual and environment-dependent role in tumor immunity, primarily acting as an immunosuppressive factor to promote tumor progression, while also possessing non-immunomodulatory functions, directly supporting tumor cell survival and metastasis. Table 1 summarizes its mechanism of action in tumor immunity, including the following four dimensions, and elucidates the corresponding biological effects and clinical relevance. As follows: (1) Immunosuppressive Effects: Inhibiting anti-tumor immune responses, including (I) direct inhibition of T cell function, (II) promoting the accumula-

tion of immunosuppressive cells, (III) inhibiting natural killer (NK) cell activity. (2) Non-Immune Regulatory Functions: Directly promoting tumor malignancy, including (I) enhancing tumor cell proliferation and survival, (II) promoting tumor metastasis and angiogenesis, (III) inducing treatment resistance. (3) Tumor-Specific Expression Pattern: A key basis for targeted therapy. (4) Context-Dependent Pro-Immune Effects (Rare and Controversial).

Notable Progress of B7-H3-Targeted CAR-T Cells and ADCs

By 2025, notable progress/substantial advances have been made in CAR-T cell therapy targeting B7-H3, particularly in the treatment of gliomas. Furthermore, ADCs have also yielded more remarkable results, with at least four B7-H3-targeting ADCs currently in Phase II/III clinical trials. Structurally, CARs in CAR-T cells and ADCs are very different yet share some similarities.

CARs consist of four core modular components: (1) an extracellular single-chain variable fragment (scFv) serves as the antigen-recognition moiety, enabling specific binding to target antigens expressed on cancer cells; (2) a hinge region connects the scFv to the transmembrane domain and confers structural flexibility to facilitate antigen binding; (3) a transmembrane domain anchors the entire CAR molecule to the cytoplasmic membrane of T cells, ensuring its stable cell surface expression; (4) an intracellular signaling domain transduces activation signals upon antigen engagement [10]. Specifically, CAR-T cell activation is initiated when the extracellular scFv domain binds to its cognate cancer antigen [22, 23].

ADCs are composed of antibodies, linkers, and small-molecule drugs. Linkers act as a bridge between a combination of antibodies and small molecule drugs at both ends, using chemical reactions to form covalent bonds [24].

Therefore, ADCs can selectively recognize antigens that are preferentially expressed on or near tumor cells [25] and bind to specific epitopes via antibodies whose Fc segment can interact with the FcγR receptor of NK cells, thereby triggering an immune response [26]. ADCs after entering tumor cells can directly kill tumor cells by the drugs released from the conjugates and then exerting their cytotoxic effects through some target mechanisms [27-29]

The similarity between the two lies in their similar structures that can target antigens, such as the scFv domain of CARs and the Fab domain of ADCs; this is also the core of targeted therapy. They use this to identify cancer cells and tumor tissues and then exert subsequent anti-cancer effects. Different Complementarity- Determining Regions (CDRs) sequence designs can target different targets, such as HER2 [30], CD47 [31, 32], B3-H7 [10], etc. This review focuses on B3-H7 because it seems to be new emerging target than HER2, and more advantageous than CD47, making it more suitable as a mainstream target for tumor treatment.

B7-H3-Targeted CAR-T Cells in Significant Breakthroughs

In the field of tumor immunotherapy, CAR-T therapy, with its unique advantages of precise targeting and potent killing, has become one of the key directions for conquering malignant tumors, especially achieving milestone progress in the treatment of hematologic malignancies. However, the heterogeneity of solid tumors, the immunosuppressive properties of the tumor microenvironment, and the scarcity of therapeutic targets have long constrained the breakthrough of CAR-T therapy in the field of solid tumors. Against this backdrop, B7-H3, as an immune checkpoint molecule widely expressed on the surface of various solid tumor cells, has become an ideal target for CAR-T therapy due to its key role in tumor proliferation, stem cell maintenance, and immune escape. In recent years, the research and development of CAR-T targeting B7-H3 has continued to make breakthrough progress, not only demonstrating significant survival benefits in the treatment of refractory solid tumors such as malignant gliomas, but also forming diverse and innovative treatment strategies in targeting tumor stem cells, synergistically enhancing efficacy, and overcoming treatment resistance. This section will systematically review the major breakthroughs of B7-H3-targeted CAR-T in clinical applications, mechanisms of action, and combination therapies, showcasing their enormous potential and application prospects in the treatment of solid tumors.

Table 1: B7H3 In Tumor Microenvironments Exhibits Multiple Functions, Including Immunosuppressive Effects, Non-Immune Regulatory Functions, and Tumor-Specific Expression Or Context-Dependent Pro-Immune Effects (Rare). They Possess Unique Core Mechanisms, Biological Effects, and Clinical Relevance

Category	Core Mechanisms	Biological Effects	Clinical Relevance	Ref.
Immuno-suppressive Effects	1. Binds to unconfirmed receptors (e.g., TIGIT, CD28 homologs) on T cells, triggering inhibitory signaling.	1. Reduced T cell proliferation, cytokine secretion (IFN-γ, TNF-α, IL-2) and CTL cytotoxicity.	Alternativeimmunecheckpoint forPD-1/PD-L1-resistant tumors;potential target toreverse TMEsuppresion.	[8]
	2. Promotes recruitment and expansion of Tregs, MDSCs, M2-TAMs.	2. Enhanced immunosuppressive TME formation.		
	3. Inhibits NK cell cytotoxicity via receptor binding.	3. Impaired innate immune surveillance.		
NonImmune Regulatory Functions	1. Activates PI3K/Akt, MAPK/ERK, NF-κB pathways.	1. Promotes tumor cell proliferation, inhibits apoptosis.	Dual-targeting of immune and non-immune-mechanisms improves therapeutic effcacy; predicts treatment resistance.	[7]
	2. Upregulates MMPs, downregulates E-cadherin (EMT); upregulates VEGF/bFGF (angiogenesis).	2. Enhances tumor invasion, metastasis and angiogenesis.		
	3. Activates ATM/ATR DNA repair pathways.	3. Induces resistance to chemo/ radiotherapy and immunotherapy.		
Tumor-Specific Expression	Low/absent in normal tissues; markedly upregulated in 70%+ solid tumors; correlated with advanced stage/metastasis.	Tumor-specific targeting window; supports selective anti-tumor therapy.	Ideal therapeutic-target; potential-prognostic biomarker for solid tumors.	[19]
Context-Dependent Pro-Immune Effects (Rare)	Promotes $CD8^+$ T cell activation in murine autoimmune disease models/low-immunogenic tumors.	Enhanced anti-tumor immunity in specific preclinical contexts.	Clinical relevance unconfirmed in humans; requires further investigation.	[8]

Remarkable Breakthroughs in Glioblastoma Therapy

Clinical studies on B7-H3 CAR-T cells have shown potent killing of glioblastoma (DIPG), with sustained relief within one year, and toxic side effects (headaches) within 1-2 grades [13]. According to a corporate announcement, In December 2025, T-MAX-IMUM Pharmaceuticals' allogeneic B7-H3-targeted CAR-T therapy MT027 obtained FDA approval to start a Phase II clinical trial for recurrent glioblastoma. Earlier Phase I clinical data showed that for the PPS2 population that received no less than 3 doses of the therapy and completed at least one efficacy evaluation, the median overall survival reached 20.73 months, the 12--month overall survival rate soared to 84.6% (far exceeding the historical data of 14%), and the disease control rate was as high as 80% [33]. In clinic trials, a first-in-human phase I clinical trial (NCT04483778) was systemically administered B7H3-CAR-T cells for young patients with relapsed or refractory solid tumors [34, 35]. In patients with recurrent glioblastoma, B7-H3 CAR-T cell treatment extended the median survival from the conventional 6-9 months to 20.3 months (NCT05474378). In a completed first-in-human trial, for all treated patients (n = 21), the median survival from their initial CAR-T cell infusion was 10.7 months and the median survival from diagnosis was 19.8 months with 3 patients still alive at 44, 45 and 52 months from diagnosis [36]. In addition, a preclinical study published in *Journal for ImmunoTherapy of Cancer* developed a new type of B7-H3 CAR-T cell derived from the monoclonal antibody clone A2H4. In a xenograft mouse model of glioblastoma, it not only eradicated the primary tumor but also effectively controlled recurrent tumors, significantly prolonging the survival time of the mice [13].

Efficient Targeting of Tumor Stem Cells

B7-H3 enhances tumor cell proliferation and stemness by activating signaling pathways such as JAK2/STAT3 [12, 37]. Knocking down B7-H3 can induce tumor stem cell differentiation and enhance sensitivity to chemotherapy. Preclinical studies have confirmed that B7-H3 CAR-T cells exhibit significant cytotoxic activity against glioma neurospheres derived from patients [38]. Glioma neurospheres, as an in vitro model rich in tumor stem cells, are much more difficult to treat than ordinary tumor cells. Experiments have shown that B7-H3 CAR-T cells specifically recognizes the highly expressed B7H3 antigen on the surface of neural spheres, triggering cytotoxic reactions that lead to the breakdown of neural sphere structures and cell death [39]. This potent killing effect stems from the direct clearance ability of CAR-T cells towards tumor stem cells, which are considered a key factor in glioma recurrence and drug resistance. The study provides important preclinical evidence for the treatment of glioma with B7-H3 CAR-T cells, especially offering new hope for recurrent or refractory patients. Further exploration of its long-term therapeutic effects in the intracranial microenvironment is needed in the future.

Synergistic Treatment Enhances Efficacy Against Multiple Solid Tumors

David, et al [40] discovered that there is a strong synergistic effect between the histone deacetylase inhibitor Vorinostat (SAHA) and B7-H3 CAR-T cells. SAHA can up-regulate the expression of B7-H3 in tumor cells and B7-H3 CAR in CAR-T cells, and down-regulate the expression of immunosuppressive molecules in CAR-T cells. In vitro and in vivo experiments have confirmed that this combined therapy can significantly enhance the killing effect of B7-H3 CAR-T cells on various solid tumors such as head and neck squamous cell carcinoma, triple-negative breast cancer, and non-small cell lung cancer [40].

The combination of B7H3-CART cells with IL-7/CCL19 can significantly enhance anti-tumor toxicity, and its core mechanism lies in the synergistic activation of immune effects through multiple pathways [41-43]. In B7-H3 CART cells armed with IL-2 mutein, CART cells activates the p-STAT5 pathway, promotes CAR-T cell proliferation, upregulates the expression of $CD44^+$ and $CD62^+$, prolongs cell survival time, and enhances the release ability of granzyme B, directly killing tumor cells [44]. In treating diffuse intrinsic pontine glioma (DIPG), CXCR3-A-modified CART cells migrate more efficiently toward CXCR3 ligands in vitro, compared to unmodified B7-H3 CAR T cells, and when delivered intracerebroventricularly in orthotopic DIPG mouse models, CXCR3-A-modified CAR-T cells show enhanced trafficking into the tumor and improved therapeutic efficacy [45]. Re-

cently, the IL-7/IL-15/CCL19 triple strategy further amplifies the effect [10]. IL-15 enhances CAR-T cell metabolic activity through the STAT5 pathway, IL-7 promotes memory T cell differentiation, and CCL19 guides immune cell enrichment through chemotaxis.

Overcoming PD-1 Resistance

The complementary expression pattern of PD-1/PD-L1 and B7-H3 provides a new approach for the treatment of solid tumors. Research has shown that in tumors with low expression of PD-L1 or resistance to PD-1 inhibitors, B7-H3 often exhibits high expression, forming a way of immune escape. This feature makes B7-H3 targeted therapy a supplementary option for PD-1 treatment failure. For example, in non-small cell lung cancer, B7-H3 CAR-T cells still maintain potent killing against PD-L1 negative tumors, while B7-H3 ADCs show objective remission in PD-1 resistant patients [46]. This complementarity arises from the independent pathways through which B7-H3 exerts its effects, such as inhibiting T cell function and promoting the immunosuppressive microenvironment. In the future, by detecting the combined expression profile of PD-L1 and B7-H3, the target population can be accurately screened, providing new options for immunotherapy resistant patients.

Additionally, B7-H3 CAR-T cells in the U87MG Luc xenograft model exhibited potent clearance ability against drug-resistant tumors, significantly increasing the complete remission rate to 61%. This model monitors tumor growth in real-time through luciferase labeling, confirming that B7-H3 CAR-T cells can accurately target and kill tumor cells, overcoming the resistance challenges of traditional treatments. This breakthrough provides a new strategy for solid tumors such as glioblastoma, especially for patients who are ineffective with PD-1 inhibitors. Further validation of its clinical applicability is needed in the future and exploration of combination therapies to optimize efficacy.

Key Challenges and Unresolved Issues for B7-H3 CAR-T Therapy

Despite the promising early efficacy, substantial challenges hinder the broad application of B7-H3 CAR-T cells in solid tumors. First, the potential for on-target/off-tumor toxicity remains a critical safety concern, as low-level expression of B7-H3 in healthy tissues, such as the placenta and lung epithelia, cannot be entirely ruled out. Second, antigen heterogeneity and loss can lead to immune escape and treatment failure, a phenomenon observed in other solid tumor CAR-T trials. Third, the immunosuppressive tumor microenvironment (TME) actively suppresses CAR-T cell function and persistence through mechanisms involving regulatory T cells, myeloid-derived suppressor cells, and inhibitory cytokines. Fourth, poor tumor infiltration limits the delivery of CAR-T cells to the tumor core. Addressing these hurdles requires innovative strategies such as the development of dual-target CARs, combination with TME-modulating agents, and optimized local delivery routes.

B7-H3-Targeted Adcs in Rapid Progress of Clinical Trials

B7-H3, a target widely expressed on the surface of various solid tumors, provides an important direction for anti-tumor drug development. ADCs, with their unique advantages of "specific targeting and high-efficiency killing," have become a core research area for B7-H3 targeted therapy. In recent years, several B7-H3-targeted ADC drugs have achieved remarkable results in clinical trials, demonstrating significant efficacy not only in major indications, such as small-cell lung cancer, but also making breakthroughs in the treatment of brain metastases, drug resistance reversal, and bringing new hope to patients with advanced cancer. This section mainly focuses on representative B7-H3-targeted ADC drugs for ES-SCLC, which are in the rapid clinical development stage, detailing their trial data and research progress (Table 2).

Ifinatamab Deruxtecan (I-DXd)

Ifinatamab Deruxtecan (I-DXd), co-developed by Daiichi Sankyo and Merck, has achieved remarkable results in early-phase trials for multiple solid tumors while facing twists in phase III research for small-cell lung cancer.

Interim results from the phase II IDeate-Lung01 trial, presented at the 2025 World Conference on Lung Cancer (WCLC), indicated that among 137 previously treated ES-SCLC patients who received 12 mg/kg of I-DXd, the confirmed objective response rate (ORR) reached 48.2%, including 3 complete responses and 63 partial responses. The median duration of response (DOR) was 5.3 months, the disease control rate (DCR) was 87.6%, the median progression-free survival (PFS) was 4.9 months, and the median overall survival (OS) was 10.3 months. Notably, the ORR reached 56.3% in the subset of 32 patients who received it as second-line therapy. Based on this promising data, the US FDA granted I-DXd a breakthrough therapy designation for ES-SCLC patients with disease progression after platinum-based chemotherapy in August 2025. At the 2025 ESMO Congress, supplementary data of this trial showed that in 65 ES-SCLC patients with baseline brain metastases, the intracranial confirmed ORR was 46.2% and the DCR was 90.8%. For the 26 patients without prior brain radiotherapy, the intracranial ORR was as high as 57.7%.

QLC5508 (MHB088C)

QLC5508, also known as MHB088C, is a novel treatment developed by Qilu Pharmaceutical from Minghui Medicine. It has demonstrated impressive efficacy and safety in Phase I clinical trials for ES-SCLC and has progressed to Phase III trials. Furthermore, its potential is being explored for various tumor types and in combination therapies.

The Phase I trial of QLC5508 aimed to evaluate its efficacy and safety in patients with ES-SCLC who had previously received treatment. The results were presented at prominent international academic conferences, showcasing the drug's remarkable therapeutic potential. The following outlines both the initial and updated data on efficacy and safety: (1) Initial data were presented as an oral report at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting in June 2025. Updated results were subsequently selected for a Late-Breaking Abstract (LBA) oral presentation at the 2025 World Conference on Lung Cancer (WCLC). As of June 13, 2025, a total of 106 small cell lung cancer (SCLC) patients participated in the study across three dosage groups: 1.6 mg/kg every two weeks (Q2W), 2.0 mg/kg Q2W, and 2.4 mg/kg every three weeks (Q3W). Among these patients, 47.2% had received second-line or later treatment, and 58.5% had undergone prior immunotherapy. (2) The confirmed objective response rates (ORR) for the three dosage groups were 21.4%, 42.2%, and 43.3%, respectively. The disease control rates (DCR) were 89.3%, 84.4%, and 100%, respectively. The median progression-free survival (mPFS) for the groups was 5.55 months, 5.95 months, and 5.52 months, respectively, while the median overall survival (mOS) for all groups was approximately 11.5 to 11.73 months. (3) The most common grade ≥ 3 treatment-related adverse events (TRAEs) were neutropenia (17.0%) and leukopenia (10.4%), indicating a favorable safety and tolerability profile. Based on these findings, the 2.0 mg/kg Q2W dosage was selected as the recommended dose for future studies.

Furthermore, on December 22, 2025, the Phase III clinical trial of QLC5508 (Protocol No.: QLC5508 - 301) for recurrent small cell Lung cancer (RSCLC) was officially launched at the Shandong Provincial Public Health Clinical Center. This is a multicenter, randomized, open-label, controlled study that compares the efficacy and safety of QLC5508 with physician-chosen standard chemotherapy (topotecan) in patients with RSCLC who failed first-line/second-line treatment. Currently, the trial is in the subject recruitment phase, aiming to confirm the therapeutic advantage of QLC5508 over conventional chemotherapy in patients with RSCLC.

YL201

Findings from the Phase I clinical study of YL201, published in the peer-reviewed journal Nature Medicine, demonstrated its promising efficacy and safety profile in advanced solid tumors [16]. This global multi-center study included 312 patients. Among the 287 patients with evaluable efficacy, 40.8% achieved an objective response, and the disease control rate was as high as 83.6%. Specifically, in extensive-stage small-cell lung cancer patients, the objective response rate reached 63.9% and the disease control rate 91.7%, which were significantly better than existing second-line treatment plans. For nasopharyngeal cancer

patients, the objective response rate was 48.6%. It also filled the gap in the later-line treatment data of lymphoepithelial-like carcinoma and became the first reported later-line treatment drug for this type of tumor. At present, the Phase III clinical study of YL201 for recurrent or metastatic nasopharyngeal carcinoma is underway, and its combined therapy is also advancing steadily. YL201 combined with the PD-1/VEGF bispecific antibody Ivosizumab has entered Phase I/II clinical trials to explore a better treatment effect for advanced solid tumors.

HS-20093 (Risvutatug rezetecan)

On December 10, 2025, GSK announced that its B7-H3-targeted ADC called risvutatug rezetecan received orphan drug designation from the US FDA for the treatment of small-cell lung cancer. Before this designation, the drug had already obtained breakthrough therapy designations from the FDA for relapsed or refractory extensive-stage small-cell lung cancer and osteosarcoma, as well as priority drug designation from the European Medicines Agency. This drug combines a fully human anti-B7-H3 monoclonal antibody with a topoisomerase inhibitor payload. Early clinical data indicate that it has durable therapeutic effects in extensive-stage small-cell lung cancer, and it is also being developed for the treatment of various solid tumors, including lung, prostate, and colorectal cancers.

ADC's Potential for Drug Resistance Reversal

B7-H3-ADCs demonstrate strong cytotoxic effects against tumor cells expressing low levels of B7-H3 through antibody-drug conjugate technology. The mechanism involves the antibody specifically binding to low-abundance B7-H3 molecules, allowing the release of conjugated cytotoxic drugs (such as topoisomerase inhibitors) directly within the target cells, leading to precise destruction of the tumor cells. This distinctive characteristic addresses the limitations of conventional ADCs, which typically depend on high antigen expression levels, thereby presenting a novel therapeutic option for heterogeneous B7-H3 tumors, including certain gliomas and lung cancers. Notably, B7-H3-ADC drugs, such as I-DXd, achieved an objective response rate of 73.7% in patients with PD-1 resistant small cell lung cancer [11].

In tumors that are resistant to PD-1 inhibitors, two primary traits contribute to treatment failure: (1) Downregulation of tumor-associated antigens (TAAs) or MHC molecules, which hinders the recognition and elimination of tumor cells by endogenous αβ T cells; and (2) Overexpression of immune checkpoint molecules (such as PD-L1 and B7-H3) alongside the recruitment of immunosuppressive cells (like Tregs and M2 macrophages) within the TME, leading to T cell exhaustion and functional paralysis. B7-H3-ADCs exert their anti-tumor effects through a dual mechanism: (I) Direct killing of tumor cells and (II) remodeling the immunosuppressive TME to counteract PD-1 resistance. Specifically: Firstly, The antibody component of B7-H3-ADCs binds to B7-H3 molecules on the surfaces of drug-resistant tumor cells, triggering the endocytosis of the ADC-tumor cell complex. The released cytotoxic drugs, such as topoisomerase inhibitors, induce DNA damage and apoptosis in these resistant tumor cells. Secondarily, the lysis of tumor cells are mediated by B7-H3-ADCs releases tumor-associated antigens and damage-associated molecular patterns (DAMPs). This activates dendritic cells (DCs) and enhances antigen presentation. At the same time, the reduction of B7-H3-positive tumor cells and immunosuppressive cytokines (e.g., TGF-β, IL-10) in the TME alleviates the inhibitory signals affecting T cells. This restoration of T cell function enhances the sensitivity of tumors to PD-1 inhibitors. Moreover, combining B7-H3-ADCs with PD-1 inhibitors can create a positive feedback loop, leading to a synergistic effect. B7-H3-ADCs eliminate drug-resistant tumor cells and remodel the TME to restore T cell function, while PD-1 inhibitors further disrupt the PD-1/PD-L1 pathway, amplifying T cell-mediated anti-tumor immunity. Ultimately, this strategy improves the objective response rate and disease control rate in drug-resistant patients. Preclinical studies indicate that this approach can significantly inhibit tumor growth and has manageable safety profiles, paving the way for new treatments for solid tumors.

Table 2: Four B7-H3 Targeted Adcs Have Entered Phase III Clinical Trials: Ifinatamab Deruxtecan (I-Dxd), QLC5508 (MH-B088C), YL201, and HS-20093. These Adcs Have Demonstrated Good Efficacy and Safety in Early And Phase II Studies.

Drug Name	Developer(s)	Key Indications (focus)	Critical Trial Stage (as of 2025)	Core Efficacy Data (from Early/Phase II Studies)	Ref.
Ifinatamab Deruxtecan (I-DXd)	Daiichi Sankyo / Merck	Extensive-stage small cell lung cancer (ES-SCLC)	**Phase III ongoing**	In Phase II IDeate-Lung 01 study: Overall cORR = 48.2%, mOS = 10.3 months; Second-line treatment subgroup cORR = 56.3%, mOS = 12.0 months. Intracranial efficacy: CNS cORR = 46.2% (30.8% CR rate) in patients with brain metastases. Granted Breakthrough Therapy Designation (BTD) by FDA and NMPA-CDE.	[15,47,48]
QLC5508 (MHB088C)	Qilu Pharmaceutical (licensed from Minghui Pharma)	ES-SCLC, lung cancer, prostate cancer, esophageal cancer	**Phase II/III ongoing**	In Phase I study (2.0 mg/kg Q2W dose): cORR = 42.2%, DCR = 84.4%, mPFS = 5.95 months, mOS = 11.73 months. Low rate of ≥ grade 3 TRAEs (neutropenia: 17.0%, leukopenia: 10.4%).	[49,50]
YL201	Chinese Original R&D (led by Sun Yat-sen University Cancer Center)	ES-SCLC, nasopharyngeal carcinoma (NPC), lung lympho-epithelioma-like carcinoma (LELC)	**Phase III ongoing**	In Phase I study (ES-SCLC cohort): cORR = 63.9%, DCR = 91.7%, mPFS = 6.3 months (superior to standard chemotherapy: ORR ~24-35%). First global data for LELC: cORR = 54.2% (fills gap in LELC treatment).	[16]
HS-20093	Hansoh Pharmaceutical	ES-SCLC	**Phase III ongoing**	In Phase I ARTEMIS-001 study (8.0 mg/kg dose): ORR = 61.3%, DCR = 80.6%. Low toxicity: ≥ grade 3 TRAEs = 28.9% (lower than chemotherapy).	[51,52]

Safety Considerations and Current Limitations

While B7-H3-targeted ADCs have demonstrated encouraging activity, their safety and toxicity profiles require careful attention. Dose-limiting toxicities, particularly hematologic adverse events (neutropenia, leukopenia) and drug-related interstitial lung disease (ILD)/pneumonitis, are commonly reported, especially with topoisomerase I inhibitor payloads, and mandate vigilant monitoring. Additionally, despite high objective response rates in selected indications, the duration of response is often modest, suggesting the need for improved efficacy. The efficacy in patients with very low or heterogeneous B7-H3 expression is not well-established. Future research must focus on optimizing ADC design, establishing predictive biomarkers for patient selection, and systematically managing adverse events to improve the therapeutic window.

Future Prospect of B7-H3-targeted CAR-T cells and ADCs

Prospect of B7-H3-Targeted CAR-T Cells in Tumor Therapy

Chimeric antigen receptor (CAR)-T cell therapy has revolutionized the landscape of cancer immunotherapy, achieving remarkable breakthroughs in the treatment of hematological malignancies; however, its efficacy in solid tumors is still hindered by multiple challenges, such as insufficient tumor infiltration, MHC-restricted antigen recognition, immunosuppressive tumor microenvironment (TME), and the risk of recurrence due to antigen loss [3, 53, 54]. As a highly conserved TAA overexpressed on the surface of various solid tumors (including gliomas, lung cancer, and gastrointestinal tumors) but minimally expressed in normal tissues, B7-H3 has emerged as a promising target for CAR-T cell engineering [5, 6, 55]. Recent studies have demonstrated that B7-H3-targeted CAR-T cells, especially when combined with novel cell subsets (e.g., γδ T cells) or multi-modal therapeutic strategies (nanotechnology, immune checkpoint inhibitors, etc.), exhibit enhanced anti-tumor activity and improved safety profiles, providing new avenues to overcome the limitations of traditional CAR-T therapy in solid tumor treatment [9, 14, 37, 56, 57].

This section will focus on the application prospects of B7-H3-targeted CAR-T cells in solid tumor immunotherapy, with an emphasis on engineered γδ T cell platforms and combination therapeutic strategies.

B7-H3 CAR-Engineered γδT Cells for Solid Tumor Immunotherapy

T cells, as core effector cells of adaptive immunity, offer novel strategies for solid tumor immunotherapy, especially when engineered with CARs. The advantages of CAR-modified T cells are mainly reflected in the following aspects: Firstly, CAR-mediated antigen recognition is independent of MHC molecules, which circumvents the immune escape mechanism of solid tumors characterized by downregulated MHC expression that is a critical limitation of traditional αβ T cell therapy.

This feature enables CAR-T cells to directly target TAAs regardless of antigen presentation pathways. Secondly, γδ T cells exhibit superior infiltration capacity in solid tumor tissues compared with αβ T cells, as they are inherently enriched in mucosal epithelial tissues (e.g., lung, gastrointestinal tract) where most solid tumors originate. When engineered with CARs, γδ T cells combine the advantages of MHC-independent recognition, efficient tumor infiltration and low toxicity, making them more suitable for solid tumor treatment. In addition, γδ T cell-derived CAR-T therapy has a lower risk of cytokine release syndrome (CRS) and more controllable side effects than conventional αβ T cell CAR-T products. This is attributed to the milder cytokine secretion profile of γδ T cells and their activation mode that does not rely on strong co-stimulatory signals. These advantages highlight the potential of CAR-engineered T cells, especially CAR-γδ T cells, in conquering solid tumors. Furthermore, combination therapies with CAR-T cells and bispecific T cell engagers (BiTEs) have shown broad application prospects [14].

Furthermore, dual-targeted CAR-T cells based on B7-H3 exhibit enhanced anti-tumor activity by simultaneously recognizing

tumor-associated antigens (such as B7-H3) and tumor-specific antigens. For example, the B7-H3 CAR structure can specifically bind to B7-H3 molecules on the surface of tumor cells, triggering T cell activation and tumor killing. This design can overcome the risk of recurrence caused by antigen loss in single-target therapy. In preclinical studies, dual-targeted CAR-T cells showed stronger cytotoxicity towards solid tumors with high B7-H3 expression, such as gliomas and lung cancer. In the future, by optimizing dual target selection and combining cytokine strategies, this technology is expected to provide more durable treatment options for PD-1-resistant patients while further evaluating its safety and clinical applicability.

B7-H3 CAR-T Cell by Combination Therapy for Solid Tumors

Recently, the integration of B7-H3-CAR-T cell therapy with nanotechnology, targeted agents, and immune checkpoint inhibitors has opened up a new paradigm for the precision treatment of B7-H3-positive solid tumors, addressing the core challenges of traditional CAR-T therapy in solid tumor treatment, such as insufficient tumor infiltration, off-target toxicity, and drug resistance.

Firstly, the combination of B7-H3 CAR-T cells with the B7-H3-targeted gold nanocage doxorubicin delivery system (B7H3-GNC-DOX) achieves a synergistic effect of targeting, response, and amplification. B7-H3-GNC-DOX can increase the accumulation of chemotherapeutic drugs at the tumor site by 4-5 times through its active targeting ability, and its tumor microenvironment-responsive release mechanism can reduce the damage to normal tissues with low B7-H3 expression [56]. More importantly, the local release of doxorubicin can remodel the immunosuppressive TME by reducing the proportion of Tregs and M2--type macrophages, thereby enhancing the infiltration and killing activity of B7-H3 CAR-T cells in solid tumor tissues.

Secondly, B7-H3 CAR-T cell therapy exhibits unique advantages in eradicating tumor stem cells (CSCs), which are the root cause of tumor recurrence and metastasis [39]. In the glioma neurosphere model, B7-H3 CAR-T cells show significantly improved killing efficiency against CSCs [37]; when combined with B7-H3-targeted nanocarriers modified gold nanocages (GNCs), this combination strategy can further penetrate the blood-brain barrier and precisely target intracranial metastatic CSCs [57], providing a promising solution for the treatment of glioma and other tumors with high risk of intracranial metastasis.

Thirdly, the combination of B7-H3 CAR-T cells with PD-1 inhibitors presents a powerful strategy to reverse PD-1 resistance. Preclinical and clinical data have shown that the combination of B7-H3-targeted agents and PD-1 inhibitors can increase the disease control rate to 85% in PD-1-resistant patients [9]. The synergistic mechanism lies in the dual regulation of TME: B7-H3 CAR-T cells directly kill B7-H3-positive tumor cells, while PD-1 inhibitors relieve the exhaustion of CAR-T cells and endogenous αβT cells; conversely, the activation of CAR-T cells can upregulate the expression of PD-L1 on tumor cells, thereby enhancing the sensitivity of tumors to PD-1 inhibitors.

These advances highlight the great potential of B7-H3 CAR-T cell combination therapy in overcoming the key challenges of solid tumor treatment. Future research should focus on optimizing the safety of combination regimens, exploring the optimal sequencing of multi-modal therapies, and expanding the clinical beneficiary population through personalized treatment strategies based on B7-H3 expression levels and TME characteristics.

Prospect of B7-H3-Targeted ADCs In Tumor Therapy

The rapid advancement of B7-H3-targeted ADCs in clinical trials has opened a new era of precision therapy for solid tumors. As a class of agents integrating specific targeting and efficient cytotoxicity, these drugs have demonstrated remarkable efficacy in ES-SCLC, brain metastases, and drug-resistant tumors, while also showing broad application potential in multiple tumor types and combination therapy strategies [15,16,49]. Looking ahead, the development of B7-H3-targeted ADCs will focus on the following key directions, aiming to further improve therapeutic outcomes and benefit more cancer patients.

Expansion of Indications to Diversified Solid Tumors

B7-H3 is commonly overexpressed on the surface of various solid tumors, including esophageal squamous cell carcinoma, metastatic castration-resistant prostate cancer, nasopharyngeal carcinoma, osteosarcoma, colorectal cancer, and glioma. This overexpression provides a strong biological basis for expanding the use of B7-H3-targeted ADCs [51, 54, 56]. Currently, drugs such as I-DXd have shown promising early-phase results in pan-tumor trials. The IDeate-Pantumor01 trial has established a foundation for its application in treating esophageal squamous cell carcinoma and metastatic castration-resistant prostate cancer [48]. Additionally, QLC5508, which has a potent payload called SuperTopoi™ (5-10 times more potent than DXd), is progressing through Phase II and III clinical trials for prostate cancer and esophageal cancer. This drug leverages its high-affinity binding to B7-H3 and facilitates efficient lysosomal payload release [50].

YL201 has demonstrated significant efficacy in nasopharyngeal carcinoma, with an ORR of 48.6%, and in lymphoepithelial-like carcinoma (LELC), with an ORR of 54.2%. This fills an important gap in later-line treatment data for LELC [16]. In the future, as more clinical evidence accumulates, B7-H3-targeted ADCs are expected to become a core treatment option for a variety of B7-H3-positive solid tumors. For tumors with significant unmet medical needs, such as gliomas (characterized by B7-H3 heterogeneity) and osteosarcoma (which has limited treatment options), the precise targeting and bystander killing effects of B7-H3 ADCs may overcome the limitations of traditional therapies [47, 51].

Optimization of Efficacy in Special Populations and Refractory Scenarios

Special patient populations, such as those with brain metastases and drug-resistant tumors, have long posed significant challenges in clinical oncology. B7-H3-targeted ADCs have demonstrated exceptional potential in addressing these difficult cases. Clinical data from the IDeate-Lung01 trial indicate that I-DXd achieves an intracranial confirmed ORR of 46.2% in ES-SCLC patients with baseline brain metastases. This rate increases to 57.7% in patients who have not received prior brain radiotherapy, highlighting its excellent therapeutic activity in the brain [48]. These findings support further exploration of the efficacy of B7-H3-ADCs in other tumors with central nervous system (CNS) metastases, such as breast cancer and melanoma brain metastases. Regarding drug resistance, B7-H3-ADCs can effectively target tumor cells with low B7-H3 expression through bystander killing effects [47].

Additionally, I-DXd has achieved an ORR of 73.7% in PD-1-resistant SCLC patients by remodeling the immunosuppressive TME [11]. Future research aims to optimize the structural design of ADCs by improving payload potency and linker stability, which could enhance efficacy in platinum-resistant, taxane-resistant, and multi-drug-resistant tumors. Additionally, exploring predictive biomarkers will be crucial for accurately identifying patients who would benefit most from these treatments.

Development of Combination Therapy Strategies to Achieve Synergistic Efficacy

Combination therapy is an important trend in anti-tumor drug development, as it can overcome single-agent limitations and achieve synergistic therapeutic effects. B7-H3-targeted ADCs have inherent advantages in combination with other anti-tumor therapies due to their ability to lyse tumors to release antigens and remodel the TME [52]. Currently, YL201 combined with the PD-1/VEGF bispecific antibody Ivosizumab is also being explored in Phase I/II trials for advanced solid tumors [16]. In the future, more combination strategies will be developed:

Combination with immune checkpoint inhibitors (ICIs): B7-H3-ADCs remodel the TME to restore T cell function, while ICIs further block inhibitory pathways. For example, QLC5508 combined with PD-1 inhibitors has shown preliminary efficacy in ES-SCLC Phase Ib trials [6], and risvutatug rezetecan induces antibody-dependent cellular cytotoxicity (ADCC) which can synergize with ICIs [52].

Combination with targeted therapies: For tumors with specific driver mutations, the combination of B7-H3-ADCs with corresponding targeted drugs may overcome resistance, building on the mechanism of YL201's enhanced internalization to overcome B7-H3 heterogeneity.

Combination with radiotherapy: Radiotherapy can upregulate B7-H3 expression, potentially improving ADC targeting, as supported by the bystander killing mechanism of DXd-containing ADCs [47].

Improvement of Drug Safety and Tolerability

Although B7-H3-targeted ADCs have demonstrated favorable safety profiles in clinical trials, QLC5508 has reported a low incidence of grade ≥3 treatment-related adverse events (TRAEs). The main toxicities associated with QLC5508 are neutropenia (17.0%) and leukopenia (10.4%) [49]. Similarly, HS-20093 also shows low toxicity, with grade ≥3 TRAEs occurring in 28.9% of cases [10]. Nevertheless, optimizing safety remains a key priority. Future efforts will include:

Structural optimization: Developing more stable linkers to reduce premature payload release and selecting payloads with higher tumor specificity, as demonstrated in QLC5508's lysosomal payload release design [50].

Individualized dosage adjustment: Based on patient characteristics and pharmacokinetic data, as explored in the Phase I trials of I-DXd and QLC5508 [15, 49].

Standardized adverse event management: Establishing guidelines to handle toxicities promptly, ensuring patient compliance [49, 51].

Exploration of Predictive Biomarkers and Precision Medicine

The effectiveness of B7-H3-targeted antibody-drug conjugates (ADCs) varies among patients, which underscores the need for predictive biomarkers. Currently, B7-H3 expression shows promise as a potential marker, but its detection methods require standardization. Future research will focus on the following three areas:

Optimizing detection methods: Developing sensitive technologies such as immunohistochemistry and liquid biopsies to assess B7-H3 expression.

Exploring combined biomarkers: Combining B7-H3 with TMB, PD-L1 expression, or TME immune cell infiltration to establish predictive models.

Dynamic monitoring: Using liquid biopsies to track biomarker changes during treatment, guiding adjustments.

Discussion

B7-H3 targeted therapy, as an important breakthrough in the field of solid tumor treatment, provides new hope for PD-1 resistant patients. Its core mechanisms include cytokine stacking effects and antigen independent killing, overcoming the limitations of traditional immunotherapy through multi-target synergistic effects. At present, CAR-T therapy and ADC constitute the major technological pillars, demonstrating differentiation advantages.

In terms of CAR-T therapy, the experimental data of B7H3-CART armed with IL-2 is particularly impressive. The cytokine stacking effect of IL-2 mutein significantly enhances the cytotoxicity of Granzyme B^+ $CD8^+$ T cells [44]. This synergistic mechanism provides new ideas for the treatment of solid tumors, but safety issues such as cytokine storms should be taken into account. In the future, bispecific antibody design can be used to simultaneously target B7-H3 and PD-1, further enhancing thera-

peutic specificity.

ADC technology achieves precise killing through coupling antibodies with cytotoxic drugs. The objective remission rate of B7-H3 ADCs in PD-1 resistant patients exceeds 60% [46, 58] and its advantages lie in tumor specific delivery and bystander effect. However, hepatopulmonary toxicity remains the main challenge. Optimizing linker stability and drug loading selection, such as using topoisomerase inhibitors instead of traditional chemotherapy drugs, can significantly improve safety.

Combination strategy with GNC technology achieves precise targeting of intracranial lesions through nanocarriers, solving the problem of blood-brain barrier delivery. Loading B7H3-GNC with doxorubicin increases drug aggregation in tumor tissue by 4-5 times, significantly enhancing targeted killing [56]. This "intelligent delivery" mode provides a new paradigm for the treatment of brain metastases, but further optimization of the biocompatibility of nanocarriers is needed.

Future development directions include: [1] developing bispecific antibodies to enhance targeting specificity; [2] Exploring the synergistic therapy of CART loaded TCE (bispecific antibody) [59, 3] Expand the beneficiary population through the combination of immune checkpoint inhibitors. These strategies are expected to form a combination therapy model of "targeted + immune", ultimately reshaping the treatment pattern of solid tumors. With technological iteration and clinical validation, B7-H3 targeted therapy will bring more long-term survival hope to drug-resistant patients.

However, this review is not without limitations. The conclutions drawn are primarily based on preclinical and early-phase clinical data. The long-term survival benefit and optimal combination strategies await validation in large-scale, randomized Phase III trials. Addtionally, there is a lack of standardized assays and thersholds for defining B7-H3 positivity across different studies, complicating cross-trial comparisons and patient selection. While we have highlighted preliminary safety data, a more in-depth discussion of the management of CAR-T-related toxicities (e.g., CRS, ICANS) and ADC-specific adverse event spectra (e.g., ocular toxicity, hepatotoxicity) is warranted in future updates. It is also important to note that not all B7-H3-targeted approaches have succeeded; some earlier antibody-based therapies yielded inconclusive results [46], underscoring the need for continuous optimization.

Conclusion

B7-H3 targeted CAR-T and ADC therapy provides a breakthrough option for PD-1 resistant solid tumor patients, significantly improving efficacy through mechanisms, such as cytokine stacking and antigen independent killing. Clinical data shows that the combination of B7-H3 CAR-T with IL-2 mutein, and B7-H3 ADCs have achieved outstanding results in complete response rate, objective response rate, and precise targeting, respectively. Additionally, GNC technology enhances drug aggregation and targeted killing through nanocarriers. However, safety issues such as liver and lung toxicity still need to be optimized. In the future, strategies such as developing bispecific antibodies, exploring CAR-T loaded TCE synergistic therapy, and combining immune checkpoint inhibitors can further enhance efficacy, reshape the treatment pattern of solid tumors, and bring long-term survival hope to drug-resistant patients.

Funding

Supported by Natural Science Foundation of Fujian Province (grant number: 2022J01246).

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