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REVIEW

B7-H3/CD276: Novel Immune Checkpoint and Jack of All Trades

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Abstract: Immunotherapy has transformed cancer treatment and outcomes, although resistance mechanisms remain challenging, prompting exploration of additional immune targets, including B7-H3/CD276. Indeed, B7-H3/CD276's complex and contrasting functions mark it as a jack of all trades, challenging conventional classifications of immune markers. B7-H3/CD276 is a protein belonging to the B7 family of immune regulatory molecules. It participates in immune response modulation and has been implicated in both immune activation and suppression, depending on the context though its precise immune function remains incompletely defined. B7-H3/CD276 expression is observed in various cancers and inflammatory conditions. In regard to cancer, there appears to be variability in expression both between and within malignancy types. B7-H3/CD276 targeting therapies have shown promising evidence of activity, particularly in patients over-expressing the B7-H3/CD276 protein based on immunohistochemistry. Here, we detail B7-H3/CD276's proposed immunologic and metabolic roles in the pathogenesis and progression of cancer, describe its heterogeneous patterns of RNA expression in a pan-cancer cohort, and summarize early clinical trial outcomes data.

Keywords: cancer immunotherapy, tumor microenvironment, immune modulation, Targeted therapy, tumor heterogeneity, precision oncology

Introduction

The advent of immunotherapy has stimulated dramatic advancements in cancer therapeutics over the last decade. In particular, immune checkpoint blockade targeting programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) has significantly enhanced clinical outcomes across several cancer types.[1] Still, resistance to anti-PD-1/PD-L1 inhibitors has persisted, with many patients exhibiting brief responses or early disease relapse. Resistance to immune checkpoint blockade thus constitutes a significant hurdle in achieving robust, durable antitumor immune responses and the identification of additional co-targets that can normalize the immunosuppressive microenvironments contributing to treatment resistance is under investigation. One such target is B7 homolog 3 (B7-H3), also known as CD276. This type 1 transmembrane protein belongs to a family of ligands that act as signals for both the innate and adaptive immune system.[2] Notably, it exhibits a propensity for aberrant expression on malignant cells, sparing healthy ones.[2] Moreover, high B7-H3/CD276 RNA expression has been associated with unfavorable prognostic indicators including advanced stage, increased recurrence rate, and poor survival.[3]

In this review, we synthesize the current understanding of B7-H3/CD276's dual roles in immune modulation and tumorigenesis, emphasizing its heterogeneous expression across cancer types and in subcellular compartments. We discuss how these factors inform the mechanisms and therapeutic potential of emerging B7-H3/CD276-targeted therapies.

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B7-H3/CD276 and the Tumor Microenvironment

B7-H3/CD276 has emerged as a key modulator of the tumor microenvironment (TME) with roles extending beyond traditional immune checkpoint signaling and may promote tumorigenesis via non-immune processes (Figure 1A). Specifically, B7-H3/CD276 is expressed on both tumor and antigen-presenting cells (APC), with the potential for further interactions via unidentified receptors on T cells and natural killer (NK) cells. This widespread expression places B7-H3/CD276 in a unique position to influence tumor immunity through a variety of mechanisms that are not yet well understood.[4] Indeed, this molecule does not fit cleanly into a binary classification of most immune checkpoints as it appears to exhibit both co-stimulatory and co-inhibitory functions within the immune system.[5] This dual functionality is increasingly recognized as context-dependent, with growing evidence that this duality may arise from B7-H3/CD276's ability to modulate antigen-specific T-cell receptor signaling cascades by altering the strength and quality of interactions between TCR complex and MHC-peptide and APCs depending on tumor type, immune milieu, and local signaling pathways.[6,7]

The functional output of B7-H3/CD276 also appears to be tightly linked to its location of expression in cellular compartments, which varies across tumor types and TMEs. For instance, it is predominantly localized to the tumor cell membrane and cytoplasm in non-small cell lung cancer, supporting its role in immune modulatory interactions at the cell surface.[10] This is in contrast to the nuclear and tumor-associated vascular expression observed in colorectal cancer, indicating a role in transcriptional regulation and angiogenesis.[11] In gastric cancer, the molecule is largely restricted to the stromal compartment, raising the possibility that it contributes to immune exclusion and extracellular remodeling.[12] These findings highlight the importance of B7-H3/CD276's spatial context, as its function may vary greatly depending on its localization. A recent systematic review by Getu et al offers a detailed examination of B7-H3/CD276 localization across cancers, further reinforcing the idea that therapeutic strategies should consider the spatial dynamics of this molecule to optimize efficacy.[6]

Although the precise downstream events that underlie B7-H3/CD276's role in cancer progression remain murky, we are beginning to unravel the complex mechanisms that govern its seemingly paradoxical tumorigenic pathways, outlined below.

Co-Stimulatory Role

When first described by Chapoval and colleagues' landmark study in 2001, B7-H3/CD276 was thought to be a T cell activator, inducing the proliferation of CD4+ and CD8+ T cells and increasing interferon-gamma (IFN-γ) production.[13] This co-stimulation is thought to occur through enhancement of MHC-TCR signal strength, providing a secondary activation cue to T cells. This theory was corroborated by findings in organ transplant models, where over-expression of B7-H3/CD276 was associated with a higher incidence of acute and chronic allograft rejection, consistent with heightened immune activation.[14] More recently, selective co-stimulatory roles have been described in specific tumor contexts. For example, high B7-H3/CD276 expression has been associated with improved immune surveillance and outcomes in cancers such as diffuse large B cell lymphoma, glioblastoma, and pancreatic neoplasms.[15] It is possible these observations support a model where co-stimulatory B7-H3/CD276 signaling is favored in immune-permissive or inflamed microenvironments, potentially when membrane localization dominates and where effector T cells are actively engaged with APCs.

Co-Inhibitory Role

Despite its initial classification as a co-stimulatory immune modulator, robust preclinical and clinical evidence now point to a predominantly co-inhibitory role for B7-H3/CD276 in many cancer settings. Mechanistically, it has been shown to downregulate T cell proliferation, IL-2 and IFN-γ production, and reduce granzyme B expression, which blunt adaptive immune responses and promote immune evasion.[16] This suppression may be further reinforced by the tumor microenvironment, which promotes B7-H3/CD276 upregulation in response to cytokines like IFN-γ, contributing to a feedback loop of immune evasion.

In vivo, blockade of B7-H3/CD276 has resulted in enhanced CD8+ T cell-mediated antitumor immunity and depletion of cancer stem cell populations, particularly in solid tumors such as breast and colon cancer.[9] There is also preclinical evidence suggesting B7-H3/CD276 potently inhibits natural killer (NK) cell activity, which distinguishes it from PD-1, which is minimally expressed on NK populations.[4] This has important therapeutic implications, as B7-H3/CD276 inhibition may offer a complementary or synergistic effect when combined with PD-1/PD-L1 blockade.[7,17]

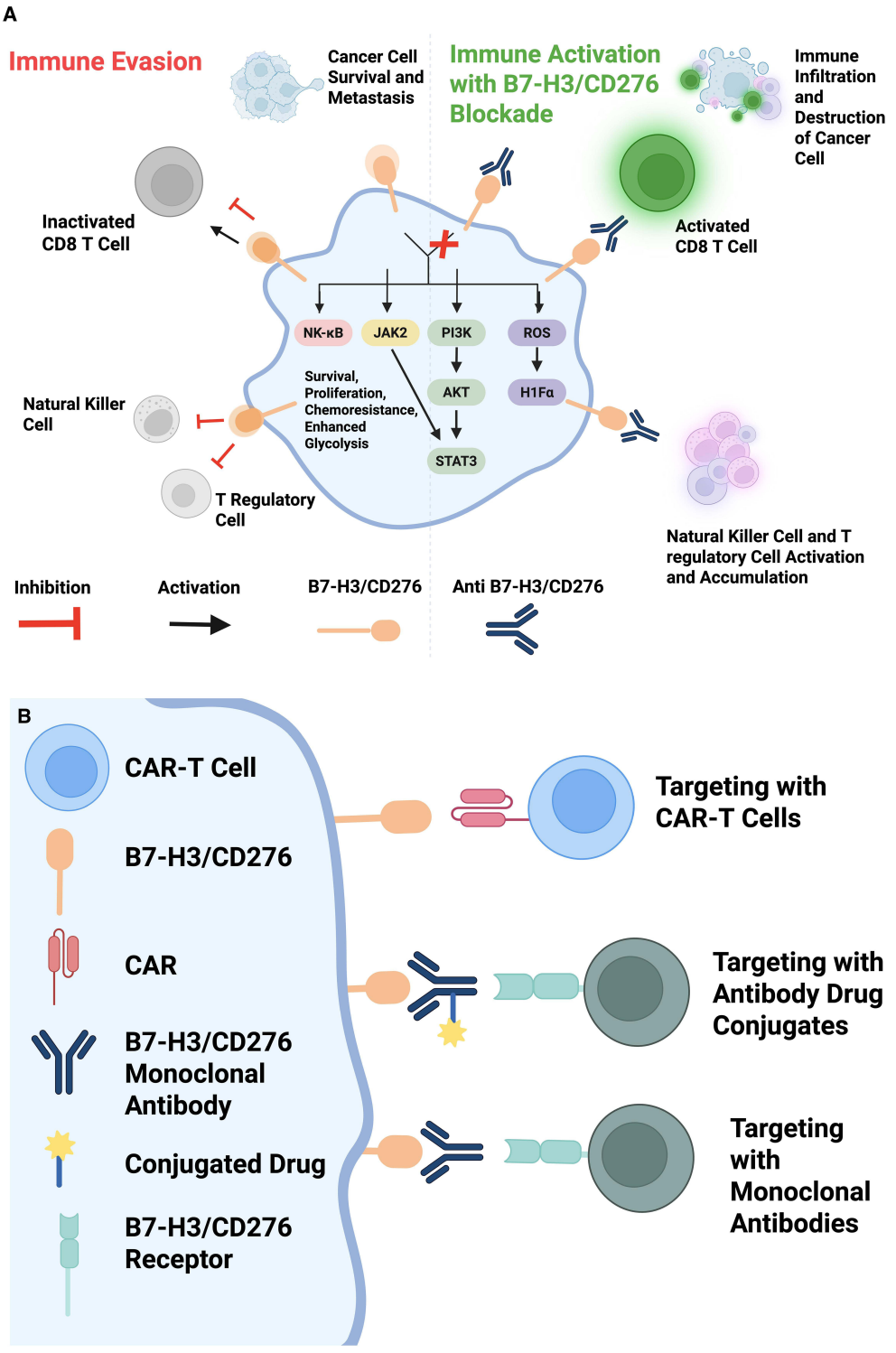

Figure 1 Immune and non-immune roles of B7-H3/CD276, the effects of blockade, and methods of targeting it. (**A**) The below figure illustrates the co-stimulatory and co-inhibitory immune and non-immune effects of B7-H3/CD276 signaling that lead to immune evasion of tumor cells (left) and the proposed antitumor effects of B7-H3/CD276 blockade (right). Although TLT-2 (myeloid cell-like transcript 2) has been identified as a likely co-stimulatory receptor, leading to activation of inactive CD8+ T cells, robust pre-clinical and clinical evidence of B7-H3/CD276's role in immune evasion of cancer cells suggests the presence of additional co-inhibitory receptors.[8] As shown on the right side of the figure, Wang et al found that blockade of B7-H3/CD276 inhibited tumor growth and eliminated cancer stem cells via enhancement of CD8+ T cell antitumor immunity as well as natural killer (NK) cell and T regulatory cell accumulation.[9] As depicted within the cancer cell, B7-H3/CD276 may also exert protumorigenic effects such as cell survival, proliferation, chemoresistance, and enhanced glycolysis via non-immune mechanisms. Created in BioRender. Larkin, B (2025) https://BioRender.com/d41u645. (**B**) Examples are illustrated of the mechanisms employed to target B7-H3/CD276 on tumor cells including CAR-T cell therapy, antibody drug conjugates, and monoclonal antibodies. Created in BioRender. Larkin, B (2025) https://BioRender.com/pbsgx9v.

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Furthermore, in tumors where B7-H3/CD276 localizes to the stroma or endothelium, such as gastric and colon cancer, it may act as a physical and functional barrier, promoting immune exclusion and reducing immune cell infiltration.[11,12]

Non-Immunologic Functions

B7-H3/CD276 is further distinguished from other immune checkpoints by its unique non-immunological promotion of tumorigenesis, treatment resistance, and metabolic adaptation illustrated in Figure 1A. One of the key pathways associated with B7-H3/CD276-mediated therapy resistance is the JAK2/STAT3 axis, which is increasingly phosphorylated by the molecule. In breast cancer models, silencing of B7-H3/CD276 downregulated this pathway, leading to increased sensitivity to paclitaxel.[18] It has also been linked to activation of PI3K/AKT and MAPK signaling, which are central to survival and proliferation in multiple malignancies.

B7-H3/CD276 additionally contributes to tumor metabolic reprogramming, a hallmark of aggressive tumors. It has been shown to do this by stabilizing HIF-1α under oxidative stress, promoting enhanced glycolysis, and facilitating adaptation to hypoxic environments in tumor tissue.[19] Recent mechanistic reviews further delineate how B7-H3/CD276 engages metabolic and angiogenic pathways, including upregulation of glycolysis and ROS-mediated HIF-1α stabilization in both tumor cells and associated vasculature. In colorectal cancer, B7-H3/CD276 supports angiogenesis through the NF-κB pathway via upregulation of VEGF and IL-8.[14] Beyond JAK2/STAT3 and HIF-1α stabilization, recent reports demonstrate that B7-H3/CD276 supports cancer stemness, epithelial-to-mesenchymal transition, and resistance to DNA-damaging agents, thus contributing to therapeutic failure and immune escape in various solid tumors.[7]

Collectively, these findings position B7-H3/CD276 as a multifunctional oncogenic driver, whose immunologic and non-immunologic functions are intertwined and modulated by both tumor type and its localization within the tumor architecture.

B7-H3/CD276 Beyond Cancer

Although B7-H3/CD276 has garnered most attention in oncology, evidence also suggests a prominent role in non-malignant immunologic and metabolic conditions. Its expression and functional activity in non-cancer settings highlights its broader relevance in immune regulation and tissue homeostasis.

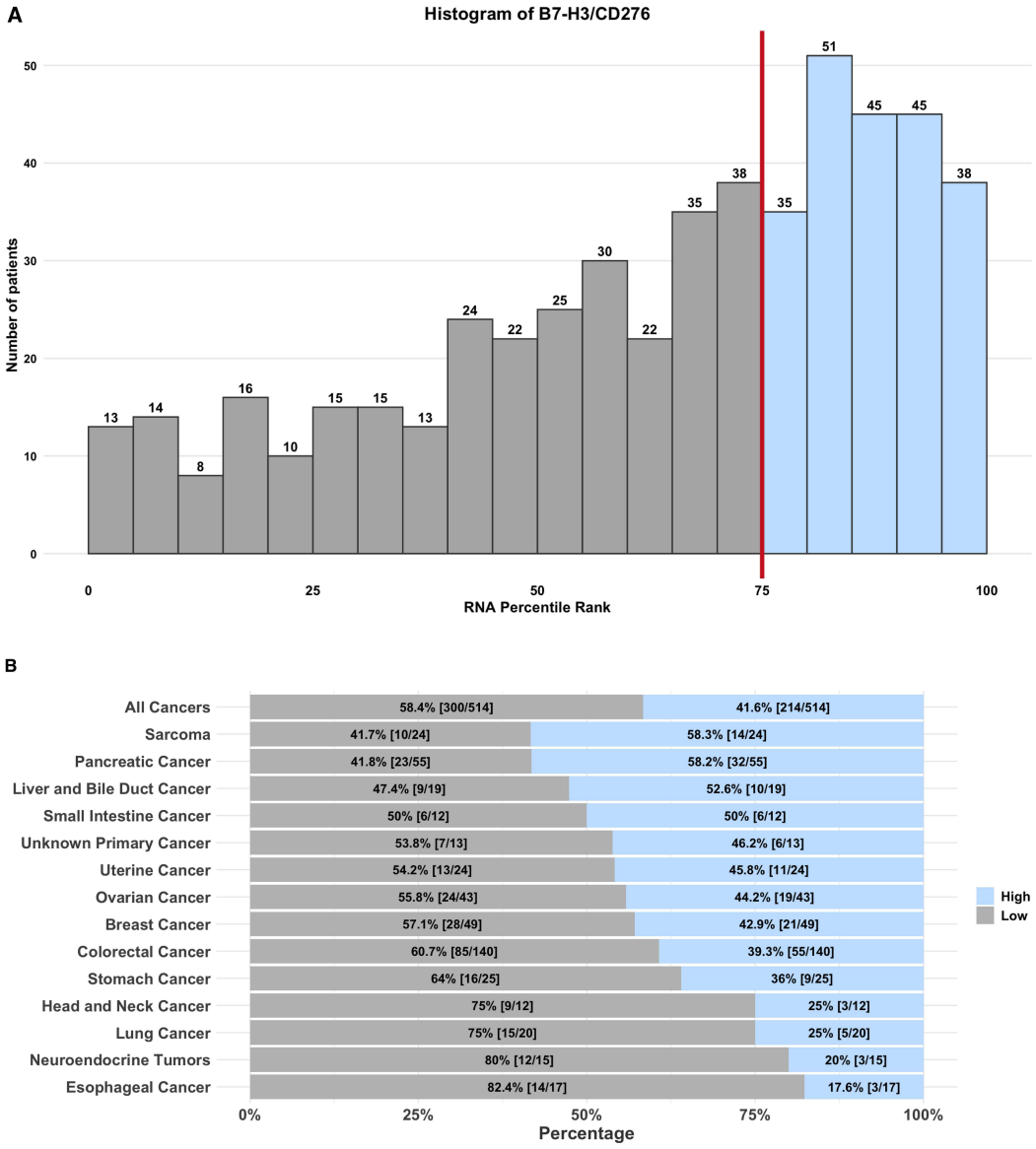
In the transplantation setting, elevated B7-H3/CD276 expression has been associated with heightened immune activation. Notably, Yu and colleagues identified an association between high expression of B7-H3/CD276 in liver transplant recipients and increased risk of acute allograft rejection, implicating this molecule in the modulation of alloimmune responses.[20] Additionally, selective depletion of B7-H3/CD276-alloreactive T cells from recipients of hematopoietic stem cell transplants has been found to significantly reduce the incidence of graft-versus-host-disease.[21] This immunomodulatory role makes B7-H3/CD276 a potential therapeutic target not only in cancer but also in transplant immunology, where balancing activation and tolerance is supremely important.

In metabolic disease, B7-H3/CD276 appears to have novel roles in regulating adipocyte differentiation and systemic metabolism. A study examining human adipocyte progenitor cells found high expression of B7-H3/CD276, and knock-down experiments revealed that the loss of its activity resulted in impaired metabolism with high lipid accumulation. On further investigation, these B7-H3/CD276 knock-out mice developed spontaneous obesity and inflammation of adipose tissue, suggesting that this molecule is prominently involved in maintaining adipose homeostasis and energy balance.[22] These effects may arise from local inflammatory signaling disruptions and impaired adipocyte maturation.

Together, these findings reveal B7-H3/CD276 is a polyfunctional immune checkpoint whose activity extends well beyond tumor immune evasion. Its dynamic, context-dependent signaling has implications for autoimmunity, inflammation, and metabolic disease, making it relevant as a target for a broad spectrum of therapeutic interventions.

Expression of B7-H3/CD276 Across Cancers

In order to better understand B7-H3/CD276 expression in the pan-cancer setting, we conducted a comprehensive analysis of B7-H3/CD276 RNA expression in tumor samples from 514 patients diagnosed with advanced cancer at the University of California San Diego Moores Cancer Center. All patients were consented to Study of Personalized Cancer Therapy to Determine Response and Toxicity, UCSD_PREDICT, NCT0247831. The distribution of B7-H3/CD276 expression is shown in Figure 2A, with RNA expression level defined as either "high" ($\geq 75^{th}$ percentile rank) or "low",($< 75^{th}$



	Present Study#	Zhang et al. Study[22] †		
	High	**High**	**Moderate**	**Low**
Tumor Type				
All Cancers	41.6% [214/514]	27% [56/209]	21% [44/209]	18% [38/209]
Pancreatic Cancer	58.2% [32/55]	31% [7/23]	13% [3/23]	17% [4/23]
Liver and Bile Duct Cancer	52.6% [10/19]	27% [4/15]	40% [6/15]	13% [2/15]
Ovarian Cancer	44.2% [19/43]	19% [2/11]	18% [2/11]	27% [3/11]
Breast Cancer	42.9% [21/49]	30% [3/10]	20% [2/10]	10% [1/10]
Colorectal Cancer	39.3% [55/140]	13% [2/16]	19% [3/16]	12% [2/16]
Stomach Cancer	36% [9/25]	25% [2/8]	25% [2/8]	13% [1/8]
Lung Cancer	25% [5/20]	29% [6/21]	29% [6/21]	18% [4/21]
Esophageal Cancer	17.6% [3/17]	67% [6/9]	11% [1/9]	11% [1/9]

By transcriptomic analysis: High expression defined as ≥75% of RNA percentile rank expression
† By IHC analysis: High expression defined as >50% positive cells, Moderate expression defined as 20-50% positive cells, Low expression defined as < 20% positive cells

Figure 2 Proportion of patients exhibiting high B7-H3/CD276 expression. (**A**) Distribution of B7-H3/CD276 expression (n = 514). Above each column is listed the number of patients falling within each percentile rank. Of the 514 total patients, 214 (41.6%) demonstrated "high" expression of B7-H3/CD276 defined as RNA expression ≥75th percentile rank. (**B**) Proportion of patients with high (≥ 75th percentile rank) and low (< 75th percentile rank) B7-H3/CD276 expression across cancer types. The patterns of B7-H3/CD276 expression across cancer types are shown below (n = 514). Among the various cancer types assessed, elevated RNA expression of B7-H3/CD276 was most frequently observed in patients with sarcoma (58.30%, 14/24), pancreatic cancer (58.20%, 32/55), and liver and bile duct cancer (52.60%, 10/19). Immunohistochemical analysis data from Zhang et al is listed below the figure for comparison between our studies.[23] Patterns of B7-H3/CD276 expression in cancer types with sample sizes <10 are included in Supplementary Figure 1.
Abbreviation: RNA, Ribonucleic acid.

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percentile rank). Of note, while this dichotomization provides a practical framework for analysis, it is not based on established biological thresholds in the absence of field-wide consensus. We adopted this cutoff for consistency with prior work using this dataset. A standardized, biologically or clinically validated cutoff has yet to be determined for B7-H3 /CD276 expression, though such a benchmark would improve cross-study comparability and translational relevance.

Of the 514 tumors evaluated, 214 patients (41.6%) demonstrated high levels of B7-H3/CD276 expression and 300 (58.4%) had low expression. Figure 2B and Supplementary Figure 1 summarize high B7-H3/CD276 expression stratified by cancer type. High B7-H3/CD276 expression was most prevalent in patients with sarcoma (58.30%, 14/24), followed by pancreatic cancer (58.20%, 32/55) and liver and bile duct cancer (52.60%, 10/19). Notably, high expression was demonstrated in at least 20% of the examined tumor samples in the cohort's 11 most common tumor types (uterine, neuroendocrine, stomach, head and neck, small intestine, colorectal, ovarian, and lung). Conversely, the lowest frequencies of high B7-H3/CD276 expression were observed in cervical cancer, kidney and renal pelvis cancer, mesothelioma, ocular melanoma, primary peritoneal carcinoma, and thymic cancers (all 0%) (Supplementary Figure 1). These findings should be interpreted cautiously given the small sample sizes for these cancers (N = 1 for all).

Overall, we observed variability in the level of B7-H3/CD276 expression between and within tumor subtypes, corroborating findings from an analysis by Zhang et al.[23] In their study of 209 tumor samples analyzed by immunohistochemical staining, they found 56 patients (27%, 56/209) with high levels of B7-H3/CD276 protein expression (defined as > 50% positive cells). Figure 1B provides a comparative visualization of the two studies' results stratified by cancer type. While we generally saw higher rates of high expression in our RNA-based dataset, several differences in methodology and sample distribution likely contribute to discrepancies and make direct comparisons difficult. First, our study quantified RNA expression via RNA sequencing, whereas the Zhang study assessed protein levels via IHC, which is subject to differences in antibody specificity, staining protocols, and scoring criteria. It's important to note that protein and RNA levels do not always correlate directly, particularly for checkpoint molecules, which may be regulated post-transcriptionally. Additionally, differences in tumor heterogeneity, including sampling site, stromal content, and immune cell infiltration, can influence both transcriptomic and proteomic measurements and may vary between cohorts.

To further contextualize our findings, compared our results to a recent pan-cancer interrogation by Miller et al, which also used RNA sequencing on real-world tumor samples from the Caris Life Sciences database.[24] In that study, sarcoma and prostate cancers exhibited the highest rates of high B7-H3/CD276 expression at 52.5% and 48.8%, respectively, using top and bottom quartiles within each cancer type to define "high" and "low" expression. This alignment with our own results reinforces the utility of quartile-based approaches while highlighting the ongoing need for standardized expression thresholds and harmonized detection methods.

Targeting B7-H3/CD276

B7-H3/CD276's dynamic pro-tumorigenic effects, paired with its lack of expression in normal tissues and elevated expression across many tumor types, marks it as a particularly appealing candidate in the development of next-generation immune checkpoint inhibitors.[5,15] However, the identity of B7-H3/CD276's receptor continues to elude scientists, making drug development slow and challenging. Still, numerous anti-B7-H3/CD276 agents are in the pipeline, including monoclonal antibodies, antibody-drug conjugates, and chimeric antigen receptor (CAR-T) cell therapies, whose actions are illustrated in Figure 1B.

Monoclonal Antibodies

Monoclonal antibodies aim to block B7-H3/CD276-mediated immune evasion or elicit antibody-dependent cellular cytotoxicity. Enoblituzumab is a humanized anti-B7-H3/CD276 monoclonal antibody that elicits robust antibody-dependent cellular cytotoxicity by binding the Fc portion of B7-H3/CD276 and is the most advanced candidate in this class.[25] It has shown activity both as monotherapy and in combination with PD-1 and CTLA4 inhibitors in Phase I trials.[26] Its mechanism exploits B7-H3/CD276's preferentially elevated expression in malignant cells rather than healthy ones. Moreover, its clinical efficacy appears to correlate with tumor B7-H3/CD276 expression, and studies suggest that antibody-dependent cellular cytotoxicity mechanisms may be most effective when expression is localized at the cell membrane.[10] This highlights the importance of B7-H3/CD276 expression localization in predicting the therapeutic efficacy of monoclonal antibodies.

Antibody Drug Conjugates

Antibody drug conjugates (ADC) deliver cytotoxic agents specifically to B7-H3/CD276-expressing cells. Ifinatamab deruxtecan is a first-in-class antibody-drug conjugate directed against B7-H3/CD276 that has shown promising clinical activity in treating small cell lung cancer.[27] Additional antibody-drug conjugates are also in development, including vobramitamab duocarmazine, which utilizes a duocarmycin-based payload and has demonstrated anti-tumor activity in preclinical neuroblastoma models and early-phase clinical trials in patients with advanced solid tumors.[28,29]

The rapid innovation in the ADC space cannot be overstated. Recent dual-payload ADCs targeting B7-H3/CD276 have demonstrated not only cytotoxicity, but also enhanced immune activation in models of triple negative breast cancer.[30] Additional agents such as ITC-6102RO and YL201, which introduce novel linker chemistry and payloads also show potent in vitro and vivo efficacy and favorable safety profiles.[31,32]

CAR-T

CAR-T therapy has historically been limited in solid malignancies due to the dearth of surface targets that are truly tumor specific. However, B7-H3/CD276's selective expression pattern makes it a strong candidate. B7-H3/CD276-directed CAR-T therapies are now being investigated in numerous early-phase clinical trials and have demonstrated robust clinical activity in pediatric solid tumors including glioma, osteosarcoma, and medulloblastoma.[33] Several designs are under evaluation, including second generation CARs and regional administration strategies such as intratumoral or intraventricular infusion for CNS tumors.

Although results are promising, challenges remain as variability in expression levels and cellular localization may influence CAR-T efficacy and toxicity. For example, nuclear or stromal B7-H3/CD276 expression, as previously described in colorectal and gastric cancers, may evade CAR-T cell recognition. Future design iterations may use multi-antigen targeting strategies to enhance selectivity and reduce off-target effects.

Current Status of B7-H3/CD276 Inhibitor Performance in Early Clinical Trials

Efficacy

Multiple early-phase clinical trials are underway assessing the safety and efficacy of novel B7-H3/CD276 antagonists. The results of those with preliminary overall response rate (ORR) data are reported in Supplementary Table 1. Thus far, B7-H3/CD276 blockade has shown favorable activity across solid tumor types, with the best ORR ranging from 15.4% (2/13) to 35.7% (5/14).[26,27,29,33,34] The variability in ORR across studies may be influenced by several factors, including tumor type, previous treatments, and B7-H3/CD276 expression levels. For example, the study of enoblituzumab (B7-H3/CD276 antagonist) given in combination with pembrolizumab in refractory cancers found that all head and neck cancer patients who had an objective responses overexpressed B7-H3/CD276 on retrospective analysis.[26] This supports that tumor-specific expression may be crucial for predicting efficacy. Conversely, response in solid tumors, like small cell lung cancer varied, reflecting the heterogeneity in tumor biology and the need for more personalized therapeutic strategies. Encouragingly, 19 of the 33 ongoing or completed clinical trials of novel drugs targeting B7-H3/CD276 are selecting for B7-H3/CD276 over-expression. Even in studies that did not, retrospective analysis of B7-H3/CD276 over-expression demonstrated that selecting for it may have had utility. Though early results have been promising, no B7-H3/CD276 targeting agents have received FDA approval as of August, 2025.

Safety

As with any novel therapeutic regimen, safety and toxicity are of paramount importance and concern. We evaluated the toxicity profiles observed in clinical trials that have published preliminary antitumor activity (Supplementary Table 1). NCT04483778 (B7-H3/CD276 CAR T-cell therapy) reported that the most common toxicity observed was cytokine release syndrome (4/11 subjects). All subjects on the study developed B cell aplasia, and one experienced a dose-limiting toxicity.[33] NCT05241392 (B7-H3/CD276 CAR T-cell therapy) reported three grade 3 treatment-related adverse events including increased intracranial pressure, epilepsy, and decreased level of consciousness.[34] Treatment-related adverse

events occurred in 43/49 (87.7%) of the patients enrolled in NCT03729596 (anti-B7-H3/CD276 antibody drug conjugate alone or in combination with an anti-PD-1 antibody), the most common event being neutropenia.[29] Similar trends in the frequency of treatment-related adverse events were reported in NCT04145622 (anti-B7-H3/CD276 antibody drug conjugate), with rates of 98% (124/127).[27] In NCT02475213, (enoblituzumab (anti- B7-H3/CD276 antibody) given in combination with pembrolizumab (anti-PD-1 antibody)), 87.2% (101/116) of the participants experienced a treatment-related adverse event of which 26.8% were ≥ grade 3.[26] Notably, pneumonitis leading to a treatment-related death occurred on this study. This combination of enoblituzumab and pembrolizumab has been the subject of particular concern. In July 2022, MacroGenics, Inc. announced the closure of a study of enoblituzumab given in combination with an anti-PD-1 monoclonal antibody or tebotelimab (PD-1 × LAG-3 bispecific DART®) molecule for patients with squamous cell carcinoma of the head and neck citing deaths potentially associated with hemorrhagic events in 7 of the 62 patients treated.[35] Such toxicity has not been observed in other clinical trials involving enoblituzumab but investigation of these events is ongoing. Though the safety and tolerability profiles of B7-H3/CD276 targeting therapies have been reported as acceptable, it is apparent that careful monitoring of toxicity is warranted as trials continue.

Conclusions and Future Directions

B7-H3/CD276 is a promising immune-oncology target with both immune and tumor-intrinsic functions. The context-dependent activity and heterogeneous expression between and within patients even within the same malignancies observed in our analysis is in accordance with what has been observed in other large-scale pan-cancer studies and underscores the need for biomarker-guided therapy.[36–40] More specifically, this suggests the need for individual tumor immunomic profiling and biomarker selection of patients for specific immune targeted therapies as part of the precision immunotherapy strategy. Investigators are already observing promising synergy when B7-H3/CD276 antagonists have been co-administered with other immune checkpoint inhibitors such as pembrolizumab. Interestingly, however, few ongoing clinical trials of novel drugs targeting B7-H3/CD276 utilize multiple agents (Supplementary Table 1). As novel agents progress through clinical trials, elucidating B7-H3/CD276's receptor and refining its functional characterization will be critical. Moreover, understanding the dual roles and regulatory mechanisms may unlock its full therapeutic potential across cancer types.

While several recent reviews have discussed B7-H3/CD276's immunological roles and therapeutic potential, our work is distinct in that it offers a novel synthesis of B7-H3/CD276's mechanistic ambiguity, context-dependent duality, expression heterogeneity, and multifaceted roles across tumor microenvironments. Efforts to deepen our understanding of B7-H3/CD276's role in tumor immunity, the identity of its receptor, and its interplay with co-expressed markers will be imperative to developing novel drug combinations that mirror the uniqueness of each patient's tumor microenvironment to maximize their efficacy. We further propose that the spatial compartmentalization of B7-H3/CD276 should be integrated into biomarker analysis and clinical prognostication. By shifting focus from simple presence or absence to localization-based stratification, this framework may explain discordant findings in the literature and guide future directions for both research and drug development.

Abbreviations

APC, Antigen presenting cells; ADC, Antibody drug conjugate; B7-H3, B7 homolog 3; CAR-T, Chimeric antigen receptor T-cell therapy; HIF-1α, Hypoxia inducible factor 1 alpha; IFN-γ, Interferon-gamma; IHC, Immunohistochemistry; JAK2, Janus kinase 2 gene; MHC, Major histocompatibility complex; NF-κB, Nuclear factor kappa light chain enhancer of activated B cells; ORR, Overall response rate; PD-1, Programmed death 1; PD-L1, Programmed death ligand 1; RNA, Ribonucleic acid; ROS, Reactive oxygen species; STAT3, Signal transducer and activator of transcription 3; TLT-2, Myeloid cell-like transcript 2.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This review article includes data from a previously conducted clinical study. Ethical approval for the original study was obtained from the UC San Diego Institutional Review Board (Study of Personalized Cancer Therapy to Determine Response and Toxicity, UCSD_PREDICT, NCT02478931). This study was conducted in accordance with the principles of the Declaration of Helsinki. All data included in this review were de-identified, and no additional patient consent was required.

Consent for Publication

Consent for publication was not required for this review article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, Phase 3 trial. *Lancet Oncol*. 2015;16(4):375–384. doi:10.1016/S1470-2045(15)70076-8
2. Collins M, Ling V, Carreno BM. The B7 family of immune-regulatory ligands. *Genome Biol*. 2005;6(6):223. doi:10.1186/gb-2005-6-6-223
3. Lu Z, Zhao Z-X, Cheng P, et al. B7-H3 immune checkpoint expression is a poor prognostic factor in colorectal carcinoma. *Mod Pathol*. 2020;33(11):2330–2340. doi:10.1038/s41379-020-0587-z

4. Lee Y-H, Martin-Orozco N, Zheng P, et al. Inhibition of the B7-H3 immune checkpoint limits tumor growth by enhancing cytotoxic lymphocyte function. *Cell Res*. 2017;27(8):1034–1045. doi:10.1038/cr.2017.90
5. Li G, Quan Y, Che F, Wang L. B7-H3 in tumors: friend or foe for tumor immunity? *Cancer Chemother Pharmacol*. 2018;81(2):245–253. doi:10.1007/s00280-017-3508-1
6. Getu AA, Tigabu A, Zhou M, Lu J, Fodstad Ø, Tan M. New frontiers in immune checkpoint B7-H3 (CD276) research and drug development. *Mol Cancer*. 2023;22(1):43. doi:10.1186/s12943-023-01751-9
7. Zhao S, Zhang H, Shang G. Research progress of B7-H3 in malignant tumors. *Front Immunol*. 2025;16. doi:10.3389/fimmu.2025.1586759
8. Hashiguchi M, Kobori H, Ritprajak P, Kamimura Y, Kozono H, Azuma M. Triggering receptor expressed on myeloid cell-like transcript 2 (TLT-2) is a counter-receptor for B7-H3 and enhances T cell responses. *Proc Natl Acad Sci USA*. 2008;105(30):10495–10500. doi:10.1073/pnas.0802423105
9. Wang C, Li Y, Jia L, et al. CD276 expression enables squamous cell carcinoma stem cells to evade immune surveillance. *Cell Stem Cell*. 2021;28(9):1597–1613.e7. doi:10.1016/j.stem.2021.04.011
10. Sun Y, Wang Y, Zhao J, et al. B7-H3 and B7-H4 expression in non-small-cell lung cancer. *Lung Cancer*. 2006;53(2):143–151. doi:10.1016/j.lungcan.2006.05.012
11. Ingebrigtsen VA, Boye K, Tekle C, Nesland JM, Flatmark K, Fodstad Ø. B7-H3 expression in colorectal cancer: nuclear localization strongly predicts poor outcome in colon cancer. *Int J Cancer*. 2012;131(11):2528–2536. doi:10.1002/ijc.27566
12. Ulase D, Behrens H-M, Krüger S, Zeissig S, Röcken C. Gastric carcinomas with stromal B7-H3 expression have lower intratumoural CD8+ T cell density. *Int J Mol Sci*. 2021;22(4):2129. doi:10.3390/ijms22042129.
13. Chapoval AI, Ni J, Lau JS, et al. B7-H3: a costimulatory molecule for T cell activation and IFN-gamma production. *Nat Immunol*. 2001;2(3):269–274. doi:10.1038/85339
14. Wang R, Ma Y, Zhan S, et al. B7-H3 promotes colorectal cancer angiogenesis through activating the NF-κB pathway to induce VEGFA expression. *Cell Death Dis*. 2020;11(1):55. doi:10.1038/s41419-020-2252-3
15. Dai L, Guo X, Xing Z, et al. Multi-omics analyses of CD276 in pan-cancer reveals its clinical prognostic value in glioblastoma and other major cancer types. *BMC Cancer*. 2023;23(1):102. doi:10.1186/s12885-023-10575-1
16. Suh W-K, Gajewska BU, Okada H, et al. The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses. *Nat Immunol*. 2003;4(9):899–906. doi:10.1038/ni967
17. Wu S, Hu C, Hui K, Jiang X. Non-immune functions of B7-H3: bridging tumor cells and the tumor vasculature. *Front Oncol*. 2024;14:1408051. doi:10.3389/fonc.2024.1408051
18. Liu H, Tekle C, Chen Y-W, et al. B7-H3 silencing increases paclitaxel sensitivity by abrogating Jak2/Stat3 phosphorylation. *Mol Cancer Ther*. 2011;10(6):960–971. doi:10.1158/1535-7163.MCT-11-0072
19. Lim S, Liu H, Madeira da Silva L, et al. Immunoregulatory protein B7-h3 reprograms glucose metabolism in cancer cells by ROS-mediated stabilization of HIF1α. *Cancer Res*. 2016;76(8):2231–2242. doi:10.1158/0008-5472.CAN-15-1538
20. Yu X, Wei B, Su R, et al. A risk assessment model of acute liver allograft rejection by genetic polymorphism of CD276. *Mol Genetics Genomic Med*. 2019;7(6):e689. doi:10.1002/mgg3.689
21. Hashimoto H, Kasteleiner P, Kressin J, et al. Removal of CD276+ cells from haploidentical memory T-cell grafts significantly lowers the risk of GVHD. *Bone Marrow Transplant*. 2021;56(10):2336–2354. doi:10.1038/s41409-021-01307-9.
22. Picarda E, Galbo PM, Zong H, et al. The immune checkpoint B7-H3 (CD276) regulates adipocyte progenitor metabolism and obesity development. *Sci Adv*. 2022;8(17):eabm7012. doi:10.1126/sciadv.abm7012
23. Zhang Z, Jiang C, Liu Z, et al. B7-H3-targeted CAR-T cells exhibit potent antitumor effects on hematologic and solid tumors. *Mol Therap Oncoly*. 2020;17:180–189. doi:10.1016/j.omto.2020.03.019
24. Miller CD, Lozada JR, Zorko NA, et al. Pan-cancer interrogation of B7-H3 (CD276) as an actionable therapeutic target across human malignancies. *Canc Res Commun*. 2024;4(5):1369–1379. doi:10.1158/2767-9764.CRC-23-0546
25. Loo D, Alderson RF, Chen FZ, et al. Development of an Fc-enhanced anti-B7-H3 monoclonal antibody with potent antitumor activity. *Clin Cancer Res*. 2012;18(14):3834–3845. doi:10.1158/1078-0432.CCR-12-0715
26. Aggarwal C, Prawira A, Antonia S, et al. Dual checkpoint targeting of B7-H3 and PD-1 with enoblituzumab and pembrolizumab in advanced solid tumors: interim results from a multicenter phase I/II trial. *J ImmunoTherap Cancer*. 2022;10(4):e004424. doi:10.1136/jitc-2021-004424
27. Doi T, Patel M, Falchook GS, et al. 453O DS-7300 (B7-H3 DXd antibody-drug conjugate [ADC]) shows durable antitumor activity in advanced solid tumors: extended follow-up of a phase I/II study. *Ann Oncol*. 2022;33:S744–S745. doi:10.1016/j.annonc.2022.07.582
28. Brignole C, Calarco E, Bensa V, et al. Antitumor activity of the investigational B7-H3 antibody-drug conjugate, vobramitamab duocarmazine, in preclinical models of neuroblastoma. *J ImmunoTherap Cancer*. 2023;11(9):e007174. doi:10.1136/jitc-2023-007174
29. Shenderov E, Mallesara GHG, Wysocki PJ, et al. 620P MGC018, an anti-B7-H3 antibody-drug conjugate (ADC), in patients with advanced solid tumors: preliminary results of phase I cohort expansion. *Ann Oncol*. 2021;32:S657–S659. doi:10.1016/j.annonc.2021.08.1133
30. Zhou ZZ, Si Y, Zhang J, et al. A dual-payload antibody-drug conjugate targeting CD276/B7-H3 elicits cytotoxicity and immune activation in triple-negative breast cancer. *Cancer Res*. 2024;84(22):3848–3863. doi:10.1158/0008-5472.CAN-23-4099
31. Shin SH, Ju EJ, Park J, et al. ITC-6102RO, a novel B7-H3 antibody-drug conjugate, exhibits potent therapeutic effects against B7-H3 expressing solid tumors. *Can Cell Inter*. 2023;23(1):172. doi:10.1186/s12935-023-02991-x
32. Ma Y, Yang Y, Huang Y, et al. A B7H3-targeting antibody-drug conjugate in advanced solid tumors: a phase 1/1b trial. *Nature Med*. 2025;31(6):1949–1957. doi:10.1038/s41591-025-03600-2
33. Pinto NR, Albert CM, Taylor M, et al. Effect of bispecific B7H3 x CD19 CAR T cells on host CD19 expression and CAR T cell engraftment. *J Clin Oncol*. 2023;41(16_suppl):10043. doi:10.1200/JCO.2023.41.16_suppl.10043
34. Zhang Y, Feng R, Chi X, et al. Safety and efficacy of B7-H3 targeting CAR-T cell therapy for patients with recurrent GBM. *J Clin Oncol*. 2024;42(16_suppl):2062. doi:10.1200/JCO.2024.42.16_suppl.2062
35. MacroGenics Announces Closure of CP-MGA271-06 Study Evaluating Enoblituzumab plus Checkpoint Inhibition in Head and Neck Cancer. MacroGenics, Inc. Available from: http://ir.macrogenics.com/news-releases/news-release-details/macrogenics-announces-closure-cp-mga271-06-study-evaluating. Accessed August 20, 2025.

36. Krishnamurthy N, Nishizaki D, Lippman SM, et al. High CTLA-4 transcriptomic expression correlates with high expression of other checkpoints and with immunotherapy outcome. *Therapeut Adv Med Oncol*. 2024;16:17588359231220510. doi:10.1177/17588359231220510
37. Adashek JJ, Goloubev A, Kato S, Kurzrock R. Missing the target in cancer therapy. *Nat Cancer*. 2021;2(4):369–371. doi:10.1038/s43018-021-00204-w
38. Adashek JJ, Kato S, Nishizaki D, et al. LAG -3 transcriptomic expression patterns across malignancies: implications for precision immunotherapeutics. *Cancer Med*. 2023;12(12):13155–13166. doi:10.1002/cam4.6000
39. Nishizaki D, Kurzrock R, Miyashita H, et al. Viewing the immune checkpoint Vista: landscape and outcomes across cancers. *ESMO Open*. 2024;9(4):102942. doi:10.1016/j.esmoop.2024.102942
40. Fujiwara Y, Kato S, Nesline MK, et al. Indoleamine 2,3-dioxygenase (IDO) inhibitors and cancer immunotherapy. *Cancer Treat Rev*. 2022;110:102461. doi:10.1016/j.ctrv.2022.102461
41. Larkin B, Nishizaki D, Miyashita H, et al. Diversity in B7-H3/CD276 expression across cancer types: exploring a dynamic novel immune checkpoint. *J Clin Oncol*. 2024;42(16_suppl):3133. doi:10.1200/JCO.2024.42.16_suppl.3133