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Review Article

B7-H3 Inhibitors in Oncology Clinical Trials: A Review

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ABSTRACT

B7-H3 is a transmembrane receptor highly prevalent on malignant cells and plays an important role in adaptive immunity that is not fully elucidated. Targeted B7-H3 inhibitors, including antibody-drug conjugates, radioimmunotherapy, and monoclonal antibodies, are a new class of antineoplastic agents showing promising preliminary clinical efficacy, observed with several of these agents against multiple tumor types. Particularly promising treatments are enoblituzumab for prostate cancer, ^{131}I-omburtamab for central nervous system malignancies, and HS-20093 for small-cell lung cancer but further studies are warranted. There are clinical trials on the horizon that have not yet enrolled patients examining chimeric antigen receptor T-cell therapies, bi- and tri-specific killer engagers, and dual-affinity retargeting proteins. These data will be telling of the efficacy of B7-H3 inhibitors in both hematologic and solid malignancies. This study aimed to compile available results of B7-H3 inhibitors in oncology clinical trials.

Keywords: B7-H3, CD276, cancer, clinical trial, review

INTRODUCTION

B7-H3, also known as CD276 and B7RP-2, is a type 1 transmembrane glycoprotein with two isoforms comprised of an extracellular V- and C-like Ig domain.[1] Immunocytes, dendritic cells of all maturations, monocyte-derived dendritic cells, and malignant cells primarily express the 4IgB7-H3 isoform, whereas benign and malignant hepatocytes preferentially express the 2IgB7-H3 isoform.[2] Both isoforms downregulate interleukin (IL)-2, interferon-γ (IFNγ), perforin, granzyme B production, inhibit T-cell proliferation, and downregulate activity of CD4+ T cells, CD8+ T cells, CD3+ T cells, γδT cells, Th17 cells, natural killer (NK) cells, macrophages, dendritic cells, and neutrophils (Fig. 1).[3] In addition, microenvironment immunosuppressive FOXP3+ regulatory T cells are positively associated with B7-H3 expression.[3] Further supporting its role in immunosuppression, B7-H3 is associated with increased production of transforming growth factor–β1 and IL-10.[3] In macrophages, B7-H3 has been shown to promote M1 to M2 phenotype transition and polarization of

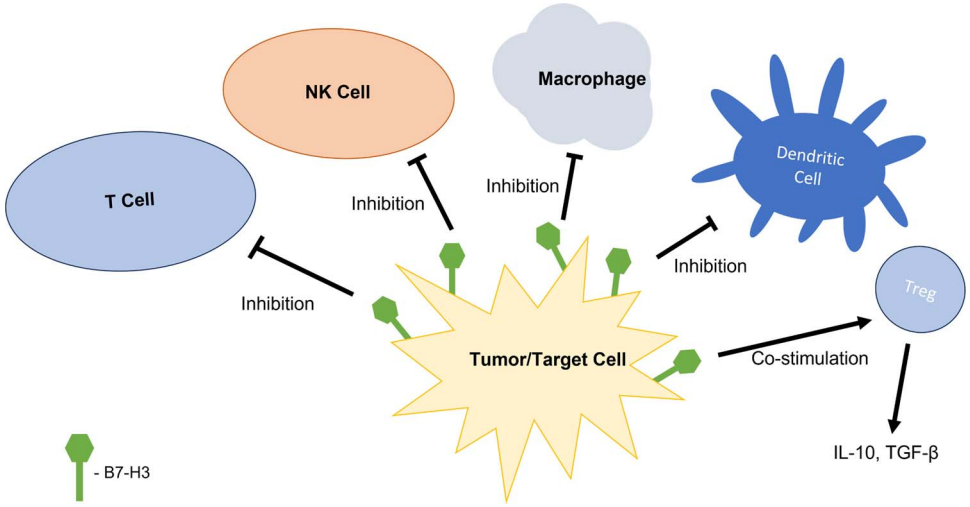

Figure 1. Immune cell interactions with B7-H3. B7-H3 interacts with multiple immune cells and influences various cellular processes, as it is expressed on both tumor cells and antigen-presenting cells. Although the specific receptor to which it binds remains uncertain, B7-H3 inhibits CD4 and CD8+ T cells, natural killer (NK) cells, macrophages, and dendritic cells and interferes with regulatory immunologic processes. It also upregulates cytokines, such as interleukin (IL)-10, further creating an anti-inflammatory environment for various cancer types to proliferate.

type 2 macrophages.[3] B7-H3–directed macrophage immunosuppression is also achieved by CCL2-CCR2-M2 axis-modification. Neutrophil B7-H3 expression is induced by tumor-derived granulocyte macrophage colony-stimulating factor via the JAK-STAT3 pathway.[3]

B7-H3 is important for adaptive immunity inhibition, exhibiting increased CD4, CD8, NK, and NK T-cell binding with T-cell activation. B7-H3 can inhibit NK cell activation via toll-like receptor-2 and -4 signaling. Increased B7-H3 expression on antigen-presenting cells reduces CD4 and CD8 T-cell activation and effector cytokine release.[4] In nonmalignant cells, the function of B7-H3 is both inhibitory, suppressing T-cell activation, as well as stimulatory, enhancing the activity of the major histocompatibility complex–T-cell receptor signal between antigen-presenting cells and T cells.[4,5] Of note, B7-H3 is not expressed on resting T cells, indicating that B7-H3 may not be involved in T-cell priming but rather T-cell expansion, as opposed to other related immunomodulating glycoproteins, CTLA-4, CD28, and PD-1.[6]

Preclinical Studies of B7-H3 in Cellular and Animal Models

B7-H3 is multifaceted in promoting cancer survival via interaction with multiple pathways, including nuclear factor erythroid 2–related factor 2, hypoxia-inducible factor-1α, enolase 1, c-Myc-lactate dehydrogenase-A axis, and PI3K/Akt/mTOR (mechanistic target of rapamycin kinase), as well as promoting glycolysis in various tumor cell types.[7–11] B7-H3 is upregulated and overexpressed in non–small cell lung cancer (NSCLC), prostate cancer, clear-cell renal cell carcinoma (RCC), urothelial carcinoma, ovarian cancer, glioblastoma (GBM), osteosarcoma, pancreatic cancer, and neuroblastoma.[12,13] Soluble B7-H3 is associated with a worse prognosis in gastric adenocarcinoma and ovarian cancer.[14,15] B7-H3 is an attractive therapeutic target because it is highly expressed homogenously within differentiated tumor cells, is expressed on tumor-associated vasculature and stroma, and is restricted in normal tissue distribution.[4]

The tumor suppressor miR-124 regulates B7-H3 through the SIRT1/NFκB/B7-H3/TNF-α (tumor necrosis factor) axis, as seen in patients with osteosarcoma expressing decreased levels of miR-124 and increased levels of B7-H3, which was positively correlated with clinical staging.[3,16] B7-H3 has been shown to upregulate vascular endothelial growth factor (VEGF)-A expression and increase tumor angiogenesis via the nuclear factor–κB (NF-κB) pathway in colorectal cancer (CRC).[17] B7-H3 binds with major vault protein and activates MEK, increasing cancer stem cell proliferation and impairing cell polarity, supporting invasion in breast cancer cell lines.[18] In immortalized breast cancer cells, B7-H3 increases glucose uptake and metabolism by stabilizing hypoxia-inducible factor-1α. In a triple-negative breast cancer (TNBC) xenograft murine model, B7-H3 promoted glucose uptake and aerobic glycolysis.[19]

In a murine mastocytoma model, B7-H3 enhanced immunogenicity via increased CD8+ cytotoxic T-cell growth, division, and tumor-directed cytolytic activity.[20] Similarly, a study of NSCLC showed a positive correlation between B7-H3 tumor expression and tumor-infiltrating NK cells, plasmacytoid dendritic cells, CD45+, CD8+, and CD8:CD3+ T tumor-infiltrating T-lymphocytes (TILs).[21] A subsequent study found that immunoglobulin-like transcript increases B7-H3 coexpression, demonstrating worse prognosis and decreased TILs in NSCLC.[22]

B7-H3–targeted agents have demonstrated efficacy in many preclinical murine models, as mouse B7-H3 protein has a 93% amino acid similarity with the human molecule.[23] One preclinical study used a monoclonal antibody (mAb), 376.96, radiolabeled with ^{212}Pb to target a B7-H3 antigen in ovarian cancer xenograft mice, both alone and in combination with carboplatin, which resulted in 2- to 3-fold increased longevity as compared to untreated controls.[24] Another study silenced B7-H3 via small hairpin RNA, which led to increased sensitivity to paclitaxel.[25] B7-H3 was overexpressed in murine models with acute myeloid leukemia (AML) but was not significantly expressed in regular bone marrow progenitor cells, suggesting that this target could be used for AML-specific chimeric antigen receptor T-cell (CAR-T) therapy.[26] In xenograft models of B7-H3–expressing pediatric solid tumor cancers, including Ewing sarcoma, osteosarcoma, and medulloblastoma, regressions were achieved with B7-H3–directed CAR-T therapy *in vivo*.[27] In addition, B7-H3–directed CAR-T therapy inhibited NSCLC tumorigenesis, and a B7-H3/C16 bispecific killer cell engager increased NK cell activation, resulting in an 80% reduction in tumor volume area under the curve (AUC) without significant adverse effects in a lung adenocarcinoma mouse xenograft model.[28]

Owing to the promising efficacy demonstrated in preclinical studies, clinical trials have been initiated to determine the safety and efficacy of B7-H3 inhibitors in multiple cancer types. This clinical review aimed to provide a concise compilation of the currently available results of clinical trials of B7-H3 inhibitors currently in development (Table 1). The information in this review was collected from publicly available abstracts presented at oncology conferences, published manuscripts, and clinical trials registered on clinicaltrials.gov.

B7-H3 INHIBITORS CLINICAL TRIALS IN SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES MONOCLONCAL ANTIBODY STRATEGIES TO TARGET B7-H3

Enoblituzumab (previously MGA271)

Enoblituzumab (MacroGenics, Inc., Rockville, MD, USA) is a humanized IgG1 mAb that targets B7-H3 (see Table 1 and Fig. 2). The manufacturing goal of this agent was to engineer an Fc that enhanced binding to fragment crystallizable (FC) FcγR (CD16A) and decreased binding to FcγR (CD32B) to augment activation and inhibition, respectively, of antibody-dependent cellular cytotoxicity (ADCC).[29] The first human phase I trial of enoblituzumab used a standard 3 + 3–dose escalation design and treated 171 patients at intravenous (IV) doses of 0.01 to 15 mg/kg, weekly on a schedule of 4 weeks on and 4 weeks off for cycle 1, then weekly on a schedule of 3 weeks on and 1 week off for subsequent cycles. The trial enrolled patients with melanoma status post checkpoint inhibitor, head and neck squamous cell carcinoma (HNSCC), clear cell RCC, TNBC, and high B7-H3–expressing cancers, including bladder and lung carcinoma not otherwise specified. Patients completed a median of 3 (range, 0–8) prior chemotherapies or immunotherapies. No dose-limiting toxicities (DLTs) were observed at doses up to 15 mg/kg, and no maximum tolerated dose was identified. Of patients, 83.7% experienced a treatment-related adverse effect (TrAE), and only 5% experienced grade 3 or 4 (G3/4) TrAEs, which included infusion-related reaction or cytokine release syndrome in 1.6%. The most common G1/2 TrAEs included infusion reaction in 42%, fatigue in 33%, and nausea in 24.5%. Pharmacokinetics were linear. Decreases in tumor size were observed and ranged from 2% to 69% across several tumor types. Objective responses were observed in melanoma, prostate, and bladder cancers. Minor decreases in tumor size (ie, $< 30\%$) were observed in patients with breast cancer, clear cell RCC, NSCLC, and HNSCC.[29]

In a single-arm phase II trial of operable intermediate-to-high risk localized prostate cancer, at least Gleason 7 (4 + 3), 32 males were treated with neoadjuvant enoblituzumab 15 mg/kg IV weekly for 6 weeks, followed by a drug holiday for 2 weeks before prostatectomy. Of patients, 50% ($n = 16$) achieved a prostate-specific antigen (PSA) decline, median −13.5 (range, −31.5 to −1.77) at 50 days postprostatectomy. Among the remaining 16 patients who did not have a PSA decline, the median change was 8.49 (range, 1.63–54.5). One year after prostatectomy, PSA had decreased to undetectable levels in 66% (95% CI, 47%–81%) of patients. At the time of prostatectomy, Gleason was higher in 4 patients, lower in 16, and unchanged in 12 patients. No G4 TrAEs were reported. G3 TrAEs included one person each experiencing an infusion-related reaction, amylase/lipase increase, maculopapular rash, myocarditis/pericarditis, and pericardial effusion. G1 TrAEs were observed in 31 and G2 were observed in 12 patients, primarily fatigue ($n = 23$), headache or dizziness ($n = 14$), flu-like symptoms ($n = 13$), gastrointestinal distress ($n = 12$), and upper respiratory symptoms ($n = 12$). There were no surgical delays or complications, meeting the study investigators' primary safety endpoint. The observed half-life was 25 days.[30] Circulating cytokines, chemokines, and soluble protein levels were monitored and revealed significant increases in circulating s41-BB, IL-17/IL-17A, IL-36b, and IL-2. Significant decreases were identified in IL-6 and IL-15 in pre- versus post-treatment analysis. These immunomodulation parameters support the activation of granzyme B, interferon signaling, and myeloid inflammation.[31]

Enoblituzumab and pembrolizumab

There were 133 patients with NSCLC, HNSCC, urothelial carcinoma, and melanoma enrolled in phase I and II studies of pembrolizumab with enoblituzumab. The maximum tolerated dose of enoblituzumab with pembrolizumab was not reached. Phase II participants were treated with enoblituzumab 15 mg/kg every 3 weeks and

Table 1. B7-H3 inhibitor trials[29–35,37,38,40–46]

Drug Name	Trial Phase	Tumor Type	Mechanism	MTD/RP2D	Dose-Limiting Toxicities	Most Common Toxicities	Terminal Half-Life	N	Antitumor Activity	Biomarkers Examined
Enoblituzumab (MGA271)	I - dose escalation	Bladder, HNSCC, Melanoma, NSCLC, RCC, TNBC	IgG1 mAb against B7-H3	15 mg/kg	None	Infusion-related reaction (42%) Fatigue (33%)	NA	171	PR: melanoma, prostate, bladder SD: TNBC, RCC, NSCLC, HNSCC	NA
Enoblituzumab (MGA271) – neoadjuvant	II - single arm	Prostate cancer, ≥ Gleason 7 (4 + 3)	IgG1 mAb against B7-H3	15 mg/kg	25 d	Fatigue (72%) headache (44%)	NA	32	PR: $n = 16$ SD: $n = 12$ PD: $n = 4$	IL-2, IL-6, IL-15, IL-17, IL-17A, IL36b, PSA, s41-BB
Enoblituzumab (MGA271) + Pembrolizumab	I + II	HNSCC, Melanoma, NSCLC, Urothelial carcinoma	IgG1 mAb against B7-H3 + IgG4 against PD-1	15 mg/kg	G5 pneumonitis	Infusion-related reaction (47.4%) Fatigue (25.6%)	Cycle 1: 141.7 h cycle 2: 275.6 h	133	CR: 1 patient HNSCC PR: 18% of patients, including; HNSCC, NSCLS, urothelial, melanoma	NA
Enoblituzumab (MGA271) + Retifanlimab or Tobotelimab	I	HNSCC	IgG1 mAb against B7-H3 + IgG4k against PD-1 or + DART against PD-1	15 mg/kg	G5 hemorrhage	NA	NA	62	NA, early termination	NA
Omburtamab (^{131}I-8H9)	I + II	B7-H3–positive desmoplastic Small round cell, medulloblastoma, neuroblastoma, retinoblastoma, rhabdomyosarcoma	radiolabeled mAb targeting B7-H3	< 1 y: 25 mCi 1–3 y: 33.5mCi ≥ 3 y: 50 mCi	myelosupression, chemical meningitis	Lymphopenia (64%) thrombocytopenia (55%) leukopenia (47%)	2 h	109	3 y OS: 57%, median 51 mo PFS: with CNS/LM 45.8% at 12 mo	NA
Omburtamab (^{131}I-8H9)	II	Neuroblastoma with CNS/LM	radiolabeled mAb targeting B7-H4	<1 y: 25 mCi 1–3 y: 33.5mCi ≥ 3 y: 50 mCi	Myelosupression, chemical meningitis. G5 thrombocytopenia	Thrombocytopenia (32%) lymphopenia (28%) nausea/vomiting (28%)	2 h	50 (20 measurable disease)	CR: $n = 5$ PR: $n = 2$ SD: $n = 7$ PD: $n = 5$	MYCN amplification
Vobramitamab Duocarmazine	I	Advanced solid tumors, melanoma	ADC - duocarmycin payload	3 mg/kg	neutropenia, fatigue	Anemia neutropenia fatigue*	NA	29	PR: melanoma (n =3)	NA
Vobramitamab Duocarmazine	I - cohort expansion	HNSCC, mCRPC, Melanoma, NSCLC, TNBC	ADC - duocarmycin payload	3 mg/kg	Neutropenia, fatigue	Neutropenia fatigue erythrodysesthesia*	NA	49	PR: mCRPC ($n = 2$), melanoma ($n = 1$)	PSA: 11/22 with 50% reduction

Table 1 continues on next page

Table 1. Continued

Drug Name	Trial Phase	Tumor Type	Mechanism	MTD/RP2D	Dose-Limiting Toxicities	Most Common Toxicities	Terminal Half-Life	*N*	Antitumor Activity	Biomarkers Examined
Ifinatamab Deruxtecan	I	CRPC, esophageal SCC, sqNSCLC, SCLC	IgG1 mAb against B7-H3 with exatecan payload	12 mg/kg	G5 ILD	Nausea/vomiting (61%) infusion-related reaction (35%)	NA	127	PR: 24 patients with SCLC, sqNSCLC, mCRPC SD: 5 patients with SCLC, mCRPC	NA
Ifinatamab deruxtecan	I/II - dose escalation	Advanced solid tumors	IgG1 mAb against B7-H3 with exatecan payload	12 mg/kg	none	Nausea/vomiting (65.5%) infusion-related reaction (34.5%) fatigue (34.5%)	NA	29	PR: $n = 6$ SD: $n = 15$	NA
HS-20093	I	Advanced solid tumors, NSCLC, sarcoama, SCLC	Fully humanized IgG1 targeting B7-H3, with DAR 4 targeted payload	12 mg/kg	1 at 12 mg/kg 2 at 16 mg/kg NA	Leukopenia neutropenia anemia*	NA	53	PR: $n = 14$, SCLC (7 of 9) Disease Control: $n = 34$	B7-H3 expression

*Further data not reported.

ADC: antibody-drug conjugate; CNS: central nervous system; CR: complete response; DART: dual-affinity retargeting proteins; DLTs: dose-limiting toxicities; G5: grade 5; HNSCC: head and neck squamous cell carcinoma; IL: interleukin; ILD: interstitial lung disease; IgG: immunoglobulin G; LM: leptomeningeal metastases; mAb: monoclonal antibody; mCRPC: metastatic castration-resistant prostate cancer; MTD: maximum tolerated dose; NA: not available; NSCLC: non–small cell lung cancer; OS: overall survival, PFS: progression free survival; PR: partial response; PSA: prostate-specific antigen; RCC: clear-cell renal cell carcinoma, RP2D: recommended phase II dose; SCLC: small-cell lung carcinoma; SD: stable disease; sqNSCLC: squamous non–small cell lung cancer; TNBC: triple-negative breast cancer.

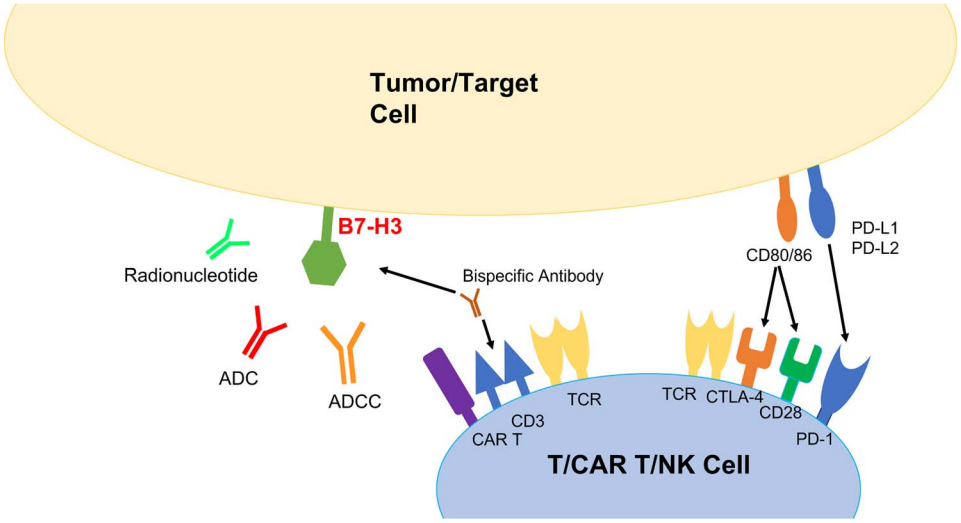

Figure 2. Mechanism of current and future immunotherapies against B7-H3. Clinical therapies against B7-H3 include monoclonal antibodies, B7-H3–specific antibody-dependent cell-mediated cytotoxicity (ADCC), B7-H3-specific antibody-drug conjugates (ADC), radioimmunotherapy via radionucleotides, engineered chimeric antigen receptor T (CAR-T) cells, and B7-H3 and CD3 directed bispecific antibodies. On the right, is a contrast depiction of select current immune-directed therapies, including PD-L1, PD-L2, and CTLA-4 therapies. Adapted from Zhao et al[71] with permission under the Creative Commons Attribution 4.0 International License

pembrolizumab 2 mg/kg every 3 weeks. TrAEs occurred in 87% of patients. The most prevalent G1/2 TrAEs were infusion-related reactions (47.4%), fatigue (25.6%), rash (9.8%), and nausea (9.8%). The most prevalent G1/2 immune-related adverse effects (AEs) were rash (9.8%), thyroid dysregulation (7.5%), arthralgias (6.8%), and hepatic injury (6%). Of patients, 28.6% experienced G3/4 TrAEs, including infusion-related reaction (6.8%), lipase increase (6%), lymphocyte count decrease (4.5%), fatigue (2.3%), rash (1.5%), decreased appetite (1.5%), anemia (0.8%), and diarrhea (0.8%). G3/4 immune-related AEs included lymphopenia (4.5%), pneumonitis (2.3%), and rash (1.5%), and one person each (0.8%) experienced diarrhea, anemia, adrenal insufficiency, or myocarditis. One treatment-related death occurred secondary to pneumonitis. Pharmacokinetic analysis after the first dose demonstrated peak serum concentration (Cmax) was 420 μg/mL (40% coefficient of variation), time to peak drug concentration (*t*max) was 3 hours, AUCτ = 36,889 μg·hr/mL, half-life ($t_{½}$) 141.7 hours, and steady-state volume of distribution (V_{ss}) was 46.9 mL/kg. Pharmacokinetic analysis after cycle 2/day 1 treatment demonstrated Cmax = 797 μg/mL, *t*max = 3 hours, AUCτ = 93,590 μg·hour/mL, $t_{½}$ 275.6 hours, and V_{ss} = 62.1 mL/kg. Pharmacokinetics were linear. Complete response was achieved in one patient with PD-1/PD-L1 inhibitor naïve HNSCC. Objective responses were achieved in 6 of 18 patients with checkpoint inhibitor naïve HNSCC, 5 of 14 patients with checkpoint inhibitor naïve NSCLC, 2 of 21 patients with NSCLC status-post prior PD-1/PD-Ll inhibitor, 1 of 17 patients with urothelial cancer, and 1 of 13 patients with melanoma.[32]

Enoblituzumab ± retifanlimab or tobotelimab

Enoblituzumab was studied in combination with retifanlimab (previously named MGA012, INCMGAA00012; MacroGenics, Inc., Rockville, MD, USA), a humanized, hinge-stabilized IgG4k anti–PD-1 mAb and in combination with tobotelimab (previously MGD013) (MacroGenics, Inc., Rockville, MD, USA) a humanized, Fc-bearing, bispecific, tetravalent dual-affinity re-targeting proteins (DART) molecule that binds PD-1 and lymphocyte-activation gene 3 to inhibit interaction with PD-L1, PD-L2, and MCH II as the first-line treatment for patients with recurrent or metastatic HNSCC. Patients were administered enoblituzumab 15 mg/kg plus retifanlimab 375 mg or enoblituzumab 15 mg/kg plus tobotelimab 600 mg IV every 3 weeks.[35] The trial was terminated after an initial review of safety data revealed seven fatalities in the 62 patients treated. Six of seven fatalities were assessed to be attributed to disease progression or unrelated to the study, but one death was possibly related to the study therapies.[34] Deaths occurred primarily because of hemorrhage but at a higher rate than reported previously (1%–3.6%), prompting the Food and Drug Administration to close the study.[34,35]

RADIOIMMUNOTHERAPY STRATEGIES TO TARGET B7-H3

Omburtamab (Previously ^{131}I-8H9)

Omburtamab (Y-mAbs-Therapeutics, INC., New York, NY, USA) is a radiolabeled mAb 8H9 targeting B7-H3 and emits beta particles and gamma rays with a specific activity of 100 mCi/mg (see Table 1 and Fig. 2). ^{131}I-omburtamab binds the FG loop of the IgV domain of B7-H3, a sequence critical to T-cell inhibition by B7-H3.[13,36] Metastatic neuroblastoma is an especially attractive B7-H3 target as B7-H3 is upregulated almost universally in brain-metastatic disease due to the

downregulation of miR-29, theoretically increasing susceptibility to B7-H3 inhibition.[13]

To date, two trials of omburtamab have resulted. The first trial evaluated intrathecal ^{131}I-omburtamab in 109 patients with B7-H3–positive neuroblastoma, medulloblastoma, retinoblastoma, rhabdomyosarcoma, and desmoplastic small round cell tumor. Part 1 was an open-label 3 + 3–dose escalation from 10 mCi to 100 mCi. The recommended intrathecal doses were by age group, including 25 mCi for ages younger than 1 year, 33.5 mCi for ages 1 to 3 years, and 50 mCi for 3 years or older, intraventricularly infused as two doses, four weeks apart via an Ommaya reservoir.[37] In part 2, patients received a dosimetry dose of 2 mCi on week one, followed by 50 mCi on week two. If tolerated, patients received a second identical cycle beginning 4 weeks after the second dose of 50 mCi. Most patients received previous treatments, including chemotherapy (95.3%) and external beam radiation therapy (91.6%), and 77.6% were status postsurgical intervention.[37] Of patients, 94% experienced any grade TrAE, and 85.3% of patients experienced a grade $\geq$ 3 TrAE. All hematologic TrAEs were grade $\geq$3, including lymphopenia (64%), thrombocytopenia (55%), leukopenia (47%), neutropenia (43%), and anemia (30%). Other G3/4 TrAEs included vomiting (2.8%), cough (0.9%), and diarrhea (0.9%).[37] The most frequent G1/2 TrAEs were vomiting (31%), cough (26%), and headache (24%). Of patients, 19% discontinued treatment due to myelosuppression, and 3% discontinued due to chemical meningitis.[38] Secondary malignancy, myelodysplastic syndrome, and AML were noted in two patients.[38] The primary efficacy endpoint was overall survival (OS) at 3 years, and secondary efficacy endpoints were central nervous system (CNS)/leptomeningeal metastases (LM), progression-free survival (PFS) at 12 months, and duration of follow-up. The 3-year OS was 57%, and the median survival was estimated at 51 months (95% CI, 31–not estimable) after a median follow-up of 76 months (range, 1.6–176). In patients with CNS/LM, PFS was 45.8% at 12 months.[37]

A phase 2 trial of ^{131}I-omburtamab monotherapy enrolled 50 patients with CNS/LM metastases from neuroblastoma. Patients were administered 25 to 50 mCi, with age-based dosing, intrathecally once during week one, followed by a 3-week observation period, and a second injection was delivered as 50 mCi during week five unless presenting with a grade 4 toxicity. Twenty patients had measurable disease at baseline, 6 with LM, 5 with parenchymal metastases (PM), and 9 with both LM and PM, 41 were International Neuroblastoma Staging System stage 4 disease at enrollment. Twenty-one patients had tumors with MYCN amplification. Twenty-three had tumors with neither MYCN gain nor amplification. Forty-nine patients received prior treatments, including 46 who had received CNS-directed radiation therapy, 28 of whom had received craniospinal irradiation, 46 who had received chemotherapy, and 37 who had undergone prior surgical intervention, notably 26 of whom were reported as potentially curative surgery and 2 palliative.[37] Forty-nine patients experienced a TrAE, with 33 being grade 3 or higher TrAE. The most common G1/2 TrAEs were nausea or vomiting (n = 14), headache (n = 12), and anemia (n = 10). G3/4 TrAEs included thrombocytopenia (n = 16), lymphopenia (n = 14), leukopenia (n = 12), neutropenia (n = 12), anemia (n = 2), vomiting (n = 1), and alanine transaminase elevation (n = 1).[37] Fourteen patients discontinued therapy because of myelosuppression, and one discontinued because of chemical meningitis. One death occurred because of G4 thrombocytopenia and subsequent intracranial hemorrhage.[38] A secondary malignancy, papillary thyroid cancer, was reported in one patient.[38] The primary efficacy endpoint was PFS at 6 months, and secondary efficacy endpoints were OS at 12 months and overall response rate (ORR) at 6 months. PFS at 6 months was 75%, and at the median follow-up time of 23 months, 26 were alive without progression. At 6 months, ORR was 35% of 20 patients with measurable disease; 5 had CR, and 2 had a partial response (PR). Seven had stable disease (SD), and five had progressive disease (PD). One patient was not evaluable.[37]

Pharmacokinetic analysis from intrathecal omburtamab was completed on both cerebrospinal fluid (CSF) and serum. In serum, Tmax = 24 hours, Cmax = 2683 Bq/mL, $T\frac{1}{2}$ = 47.7 hours. In CSF following CSF administration, Tmax = 0.5 hours, Cmax = 1308195 Bq/mL, volume of distribution (Vd) = 27.1, clearance half-life = 2 hours.[37]

Y-mAbs-Therapeutics, Inc. applied for Food and Drug Administration approval of omburtamab in September 2022 but was denied because the observed responses could not unequivocally be attributed to omburtamab and because of safety concerns related to the delivery method and the observed serious AEs of myelosuppression.[38]

A trial of ^{177}Lu-DTPA-omburtamab was terminated early after administration to two patients with medulloblastoma without further disclosure from Y-mAbs-Therapeutics.[39]

ANTIBODY DRUG CONJUGATE STRATEGIES TO TARGET B7-H3

HS-20093

HS-20093 (Jiangsu Hansoh Pharma, Jiangsu, China) is an IV B7-H3 ADC (see Table 1 and Fig. 2). In a 3 + 3–dose escalation study investigating doses of 1.0 to 16 mg/kg, 53 patients with NSCLC (n = 29), SCLC (n = 11), sarcoma (n = 9), and other advanced solid tumors (n = 4) were enrolled. Mean prior lines of therapy was 3.2 (range, 1–12), and 25 patients received at least 3 prior therapies. DLTs (n = 3) were observed in 1 patient receiving 12 mg/kg and 2 patients receiving 16 mg/kg of HS-20093. The maximum tolerated dose was 12 mg/kg. Of patients, 100% experienced a TrAE, most commonly leukopenia, neutropenia, anemia, pyrexia, nausea, thrombocytopenia, hypoalbuminemia, vomiting,

lymphopenia, infusion-related reaction, and fatigue. Of 40 evaluable patients, irrespective of the pretreatment B7-H3 expression, 14 achieved PR; disease control was achieved in 85% (95% CI, 70.2–94.3). Seven of nine SCLC patients with measurable disease achieved PR, noted at first response assessment for all, showing a median response time of 6 weeks, including patients that progressed on prior derivative of camptothecin treatment.[40]

Ifinatamab Deruxtecan (Previously DS-7300a)

Ifinatamab Deruxtecan (Daiichi Sankyo, Inc., Tokyo, Japan) is an anti–B7-H3 IgG1 mAb with a conjugated exatecan derivative payload (see Table 1 and Fig. 2). In a phase I dose-escalation study, 127 patients with metastatic castration-resistant prostate cancer (mCRPC), esophageal squamous cell carcinoma, squamous cell NSCLC, and SCLC were enrolled. Doses ranged from 0.8 to 16 mg/kg IV every 3 weeks.[41] TrAEs occurred in 124 patients (98%), with nausea (61%), infusion-related reaction (35%), and vomiting (31%) being the most common. G3/4 TrAEs included anemia (11%) and lymphopenia (2.8%).[41,42] One patient experienced a G5 TrAE of interstitial lung disease at 16 mg/kg. The recommended phase II dose was determined to be 12 mg/kg every 3 weeks.[42] The ORR was 33% (30/91) among patients with measurable disease. Responses were noted in 78% (7/9) of SCLC, 40% (2/5) of squamous cell NSCLC, and 38% (16/42) mCRPC. The total disease control rate (PR + SD) was 71.4% across all tumor types.[41]

In a subgroup analysis of the phase I/II dose-escalation study for advanced solid tumors, 29 patients with mCRPC were enrolled in part 1, where they received 0.8 to 16 mg/kg IV every 3 weeks. The median duration of treatment was 13.9 weeks with a range of 3 to 40 weeks. In part 2 of the study, 5 patients received 12 mg/kg IV every 3 weeks. Patients in part 1 and 2 were heavily pretreated, having failed a median of 6 (range, 2–10) and 5 (range, 3–10) prior lines of therapy, respectively. All 29 patients experienced adverse reactions to treatment, 7 required dose reduction, and there were no discontinuations. Most prevalent TrAEs were nausea (65.5%), infusion reactions (34.5%), and fatigue (34.5%). G3/4 TrAEs occurred in 10 patients (34.5%), most commonly anemia (17.2%). There were no DLTs. At a range of 6.4 to 16 mg/kg, PR was noted in 6 patients and SD in 15.[43]

Vobramitamab Duocarmazine (Previously MGC018)

Vobramitamab duocarmazine (MacroGenics, Inc., Rockville, MD, USA) is an ADC with a duocarmycin payload that targets B7-H3 (see Table 1 and Fig. 2). In a 3 + 3 + 3–dose escalation study, 29 patients were given 0.5 to 4 mg/kg IV every 3 weeks. Eligible patients had advanced solid tumors. Common adverse events (>25%) included anemia, neutropenia, fatigue, hyperpigmentation, infusion site reactions, nausea, and palmar-plantar erythrodysesthesia. DLTs were observed in two patients, including a G4 neutropenia at 2 mg/kg and a G3 fatigue at 4 mg/kg. All three melanoma patients treated achieved measurable reductions in target lesion size, including decreases of 24.4%, 27.5%, and 35%, respectively, at the time of data cutoff. [44]

Vobramitamab duocarmazine was then investigated in a phase I cohort expansion with 49 patients, including NSCLC, mCRPC, TNBC, HNSCC, and melanoma. Patients were treated with 3 mg/kg IV every 3 weeks. Of seven patients with measurable mCRPC who had reached the first restaging scans, four achieved reductions in target lesions, including reductions of 13%, 21%, 27%, and 35%. Of 22 evaluable mCRPC patients, 11 had 50% or greater PSA reduction. One patient with melanoma achieved a confirmed PR. At least one G1/2 adverse event occurred in 43 patients, most commonly including neutropenia, fatigue, palmar-plantar erythrodysesthesia, and headache. DLTs observed included one G4 neutropenia and one G3 fatigue.[45]

In a phase I/Ib dose-escalation and cohort-expansion study, vobramitamab duocarmazine was combined with lorigerlimab (a PD-1/CTLA-4 expressing the DART molecule). In a 3 + 3 design escalating from 1.0 to 3.0 mg/kg IV every 3 weeks and lorigerlimab at 6 mg/kg, a total of 32 patients with NSCLC and mCRPC were treated. This trial is currently still in progress.[46]

DISCUSSION

Various agents are in development against B7-H3, including radioimmunoligands, ADCs, mAb, CAR T-cell therapies, and DART. Antitumor efficacy has been observed with several of these agents against multiple tumor types, including clear-cell RCC, desmoplastic small round cell tumor, esophageal squamous cell carcinoma, HNSCC, medulloblastoma, melanoma, neuroblastoma, NSCLC, prostate cancer, retinoblastoma, rhabdomyosarcoma, SCLC, TNBC, and urothelial carcinoma. Although the radiolabeled mAb ^{131}I-omburtamab has demonstrated efficacy against neuroblastoma, significant toxicity has prevented further development of this agent.[38] However, other strategies to target B7-H3 remain under investigation.

B7-H3 mAb treatment as monotherapy or combined with PD-1 inhibitors was generally safe and well tolerated. No DLTs were observed with enoblituzumab either alone or in combination with pembrolizumab, up to a dose of 15 mg/kg. No maximum tolerated dose was identified. Combination treatment with enoblituzumab and pembrolizumab resulted in one treatment-related death secondary to pneumonitis. The most common enoblituzumab G3/4 TrAEs were infusion reactions followed by lipase/amylase increase.

In contrast, intrathecal B7-H3 radioligand treatment with ^{131}I-omburtamab resulted in much more significant

Table 2. B7-H3 inhibitor ongoing clinical trials[72–92]

Treatment Type	Drug Name	Trial Phase	Tumor Type	Mechanism	Delivery Method	Trial Number
BiTE	XmAb808	I	HNSCC melanoma excluding uveal melanoma NSCLC urothelial carcinoma RCC, clear-cell CRPC ovarian cancer, epithelial TNBC colorectal cancer	Bispecific antibody B7-H3 and CD28	Intravenous in combination with pembrolizumab	NCT05585034
DART	Obrindatamab (MGD009)	I	Relapsed or refractory B7-H3 expressing tumors	B7-H3 × CD3 DART protein	Intravenous in combination with retifanlimab (MGD012)	NCT03406949
CAR T Cell	UTAA06	I	Relapsed or refractory acute myeloid leukemia	B7H3 CAR T Cell	Intravenous	NCT05731219
	B7H3 CAR T cell	I	Diffuse intrinsic pontine glioma/diffuse midline glioma and recurrent or refractory pediatric CNS tumors	B7H3 CAR T Cell	Intracerebroventricular or into tumor resection cavity	NCT04185038
	B7H3 CAR T cell - in between temozolomide cycles	I/II - parallel arm	Recurrent or refractory GBM	B7H3 CAR T Cell	Intratumoral or intracerebroventricular injection	NCT04077866
	B7H3 CAR T Cell	I	Recurrent or refractory GBM	B7H3 CAR T Cell	Intratumoral or intracerebroventricular injection	NCT04385173
	T-cell injection targeting TAA06 chimeric antigen receptor	I	B7-H3–positive relapsed/ refractory neuroblastoma	B7H3 CAR T Cell	Intravenous	NCT05562024
	fhB7H3.CAR-TsFludarabine Cyclophosphamide	I/II	Hepatocellular Carcinoma	B7H3 CAR T cell	Intravenous	NCT05323201
	B7H3 CAR T cell	I	Recurrent GBM, IDH wild-type	B7H3 CAR T cell	Intracerebroventricular with or without intratumor injection	NCT05474378
	B7H3 CAR T cell	I/II	CD276 (B7-H3) Positive refractory and recurrent solid tumors	B7H3 CAR T Cell	Intravenous	NCT04432649
	IL-13 Rα2 or B7-H3 UCAR-T	I	Advanced glioma	B7H3 CAR T cell	Intracranial or intravertebral injection after resection	NCT05752877
	B7H3 CAR T cell	I	Recurrent or refractory GBM	B7H3 CAR T cell	Intracranial or intravertebral injection in between temozolomide cycles	NCT04385173
	B7H3 CAR T cell	I	Recurrent or refractory GBM	B7H3 CAR T cell	Intracerebroventricular	NCT05366179

BiTE: bispecific T-cell engage; CAR-T: chimeric antigen receptor T-cells; CNS: central nervous system; CRPC: castration-resistant prostate cancer; DART: dual-affinity retargeting proteins; GBM: glioblastoma multiforme; HNSCC: head and neck squamous cell carcinoma; IL-13: interleukin-13; NSCLC: non–small cell lung cancer; RCC: renal cell carcinoma, SCFV: single-chain variable fragments; TGFβ: transforming growth factor-β; TNBC: triple-negative breast cancer.

Table 2 continues on next page

Table 2. Continued

Treatment Type	Drug Name	Trial Phase	Tumor Type	Mechanism	Delivery Method	Trial Number
	B7H3 CAR T cell	I	Recurrent epithelial ovarian cancer	B7H3 CAR T cell	Intraperitoneal infusion	NCT04670068
	B7H3 CAR T cell	I	Recurrent GBM	B7H3 CAR T cell	Intracerebroventricular or into tumor resection cavity	NCT05241392
	B7H3 CAR T cell	I	B7-H3–positive solid tumors	B7H3 CAR T cell	Intravenous	NCT05515185
	B7H3 CAR T cell	I	Ovarian cancer	fully human B7H3 CAR T cell	Intraperitoneal infusion	NCT05211557
	B7H3 CAR T cell	I	Pediatric patients with B7H3+ solid tumors	B7H3 CAR T cell	Intravenous	NCT04897321
	B7-H3, EGFR806, HER2, and IL13-Zetakine (Quad) CAR T cell locoregional immunotherapy	I	Pediatric diffuse intrinsic pontine glioma, diffuse midline glioma, and recurrent or refractory central nervous system tumors	Combinations of B7-H3, EGFR806, HER2, and IL13-zetakine CAR-T cells	Intracerebroventricular	NCT05768880
	B7H3 CAR T cell +, CD19, or + EGFRt, or + HER2tG	I	Pediatric solid tumor germ cell tumor retinoblastoma hepatoblastoma Wilms tumor rhabdoid tumor osteosarcoma Ewing sarcoma rhabdomyosarcoma synovial sarcoma clear-cell sarcoma malignant peripheral nerve sheath tumors desmoplastic small round cell tumor soft tissue sarcoma neuroblastoma melanoma	B7H3 CAR T cell or B7H3 +CD19, or + EGFR, or +HER2tG co-expressing CAR T cell	Intravenous	NCT04483778
	B7H3 CAR T cell with CD4+ secretory CAR T cells	I	Advance cancer that expresses B7H3	B7H3 CAR T cell with CD4+ CAR T expressing TGF-β−CAR and secreting IL7/ CCL19 and/or SCFVs against PD1/CTLA4/Tigit	Intravenous	NCT03198052
	B7-H3–specific CAR T cell locoregional immunotherapy	I	Diffuse intrinsic pontine glioma/diffuse midline glioma and recurrent or refractory pediatric CNS tumors	B7H3 and EGFR co-expressing CAR T cell	Intracerebroventricular or into tumor resection cavity	NCT04185038
	B7H3 + EGFR CAR T cell	I	EGFR/ B7H3-positive advanced lung cancer, EGFR/B7H3-positive advanced TNBC	B7H3 and EGFR co-expressing CAR T cell	Intravenous	NCT05341492

BiTE: bispecific T-cell engage; CAR-T: chimeric antigen receptor T-cells; CNS: central nervous system; CRPC: castration-resistant prostate cancer; DART: dual-affinity retargeting proteins; GBM: glioblastoma multiforme; HNSCC: head and neck squamous cell carcinoma; IL-13: interleukin-13; NSCLC: non–small cell lung cancer; RCC: renal cell carcinoma, SCFV: single-chain variable fragments; TGFβ: transforming growth factor-β; TNBC: triple-negative breast cancer.

toxicity, including DLTs, and required frequent treatment cessation due to myelosuppression and chemical meningitis. The most common G3/4 TrAEs were pancytopenias, the most common of which were thrombocytopenia and lymphopenia, likely related to the systemic gamma radiation effects even when administered intraventricularly.

B7-H3–directed ADCs, vobramitamab duocarmazine and ifinatamab deruxtecan, caused dose-limiting neutropenia and fatigue, but no DLTs were observed with HS-20093. Ifinatamab deruxtecan administered at 16 mg/kg resulted in one death due to interstitial lung disease, likely related to cathepsin B expression in pulmonary macrophages, the enzyme responsible for ifinatamab deruxtecan linker cleavage, as observed in another ADC from Daiichi Sankyo, trastuzumab deruxtecan.[47]

Beyond the B7-H3 strategies discussed above, immune effector cell agents are also in development. As an example, FT573 (Fate Therapeutics, San Diego, CA) is a chimeric antigen receptor NK cell derived from induced pluripotent stem cells. Preclinical studies indicated that FT573 was more effective than CAR-T against B7-H3 in vitro and in Nalm6 tumor-bearing mice in reducing disease burden. Flow cytometry analysis of in vitro cells showed increased CD107a and IFNγ, suggesting increased degranulation and inflammatory cytokine production with FT573 treatments.[48] CAR-T cells targeting B7-H3 have been initiated as IV administration and intracerebroventricular and intraperitoneal administration in both solid tumor and hematologic cancers (Table 2).

Trispecific killer engagers with B7-H3 fragment linked to CD16 by IL15 are also under development and have shown preclinical efficacy against multiple myeloma, prostate cancer, and pancreatic adenocarcinoma.[49–51] Additional analysis showed increased tumor-targeted NK cell activity by increased degranulation, as evidenced by increased CD107a and cytokine production, demonstrated by increased IFNγ, compared with controls in prostate cancer cell lines.[49] GT Biopharma is developing a B7-H3–directed trispecific killer engager, GTB-5550, to target solid tumors.[52]

Additional clinical trials of ADCs, BiTEs, DARTs, and CAR-T targeting B7-H3 are currently open and enrolling, as summarized in Table 2.

The future development of B7-H3–directed radioligands is unclear. Y-mAbs-Therapeutics created a lutetium labeled omburtamab, which entered a clinical trial for medulloblastoma in 2019, but the study was terminated without explanation.[39] Another beta-emitting radioimmunotherapy, yttrium-90-labeled MIL33b, named ^{90}Y-DOTA-MIL33B, has shown high affinity to 4Ig-B7-H3. ^{90}Y-DOTA-MIL33B administration induced complete tumor regression and long-term survival in more than half of murine models harboring radioresistant colorectal CT26 tumors. Post-hoc evaluation of CD8b+ cells indicates that ^{90}Y-DOTA-MIL33B could have a role as an immune-priming agent in 4Ig-B7-H3–expressing solid tumors.[53]

Strategies that combine B7-H3 inhibitors with other agents are promising and backed by preclinical rationale. In ovarian cancer cell lines, B7-H3xCD3 BiTE, in combination with tyrosine kinase inhibitor sorafenib, showed synergistic antitumor effects, including upregulation of B7-H3 and augmented tumor cell death both in vivo and in vitro.[54] A bispecific fusion protein to B7-H3 and PD-L1 that simultaneously engages B7-H3 and PD-L1 on tumor cells has shown promising in vitro effects with 10,000-fold affinity to B7-H3 receptors on B7-H3–expressing tumor cells and increased potency of ADCC via the PD-1/PD-L1 pathway. IL-2 production was also enhanced, stimulating CD8+ T cells and improving activation of CD16a by Fc modification, resulting in increased selective cytotoxicity of tumor cells.[54] Similarly, in a study of NSCLC in a murine model with nonresponsiveness to anti–PD-L1 inhibition, co-blockade of B7-H3 and PD-L1 significantly increased CD8+ TIL, of note as B7-H3 expressing NSCLC tumors housed fewer CD8+ TIL than those without B7-H3 expression.[56] Co-administration of enoblituzumab and pembrolizumab support these synchronous B7-H3 and PD-1 inhibition analyses, resulting in synergistic antitumor activity, especially in HNSCC and NSCLC. An analysis of tumor tissue in 634 patients with NSCLC revealed that 80.4% of cases expressed B7-H3 predominantly in the cytoplasm and membrane, with co-expression of PD-L1 and B7-H3 in 17.6% of cases. B7-H3 expression was not associated with CD3-, CD8-, and CD20-positive TILs.[57] In patients with SCLC, B7-H3 is more highly expressed than B7-H4 or PD-L1, and B7-H3 exhibited low association with PD-L1 expression, possibly suggesting that combination B7-H3 and PD-L1 inhibition in SCLC might be a less effective approach than in NSCLC.[58]

The relationship between B7-H3 and tumor angiogenesis is also under evaluation. Pathologic angiogenesis via B7-H3 signaling has been demonstrated in kidney, colon, lung, and breast cancer models.[59,60] Of note, B7-H3 signaling has not been shown to support native angiogenesis. Soluble B7-H3 in pancreatic cancer model supernatant is associated with an increase in migration and invasion properties related to increased NF-κB activity via a toll-like receptor-4–dependent mechanism, resulting in increased VEGF and IL-8 expression.[61] Both IL-8 and VEGF are stimulators of tumor angiogenesis.[62] A similar analysis in colorectal cancer revealed modulation of angiogenesis by B7-H3 upregulation of VEGFa expression in CRC cells via NF-κB signaling.[63] In B7-H3 knockdown CRC cells, Wang et al observed significantly inhibited migration, invasion, and tube formation of human umbilical vein endothelial cells.[63] Further elucidation of the potential role of B7-H3 in tumor angiogenesis may yield additional rationale for combination strategies, particularly in combination with ICI or other antiangiogenic therapies as reviewed in varied combinations for NSCLC, hepatocellular carcinoma, and RCC.[64–66]

Correlation of B7-H3 with other potential therapeutic targets is in progress. B7-H3 expression is highly correlated with HER2 expression, and a combination of trastuzumab with 3E8, a B7-H3 antibody used in preclinical studies, was superior to either agent alone in gastric cancer xenograft mouse models.[67] Angio-associated migratory cell protein (AAMP) has recently been identified as a synergistic binding partner, increasing the proliferation of Jurkat leukemia-modeling cells supporting cancer cell proliferation. The same study identified B7-H3 coexpression in GBM cells and was highest in vimentin-positive mesenchymal GBM cells. However, no further data were reported on functional analysis of coexpression.[68] AAMP has also been identified to promote colorectal cancer and NSCLC cell migration and invasion, further raising interest as a potential therapeutic target.[69,70] Because B7-H3 is also noted to play an important role in these cancer types, a combination approach targeting both B7-H3 and AAMP could be promising in NSCLC, CRC, and GBM.

CONCLUSION

This clinical review outlines current clinical trials of B7-H3 inhibitors and potential future B7-H3–directed strategies. B7-H3 inhibitors have shown early promising results in solid tumor malignancies. Ongoing studies will further investigate the efficacy and safety of B7-H3 inhibitors in various cancer types and in combination with other agents.

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