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Review Article

4-1BB Antibodies in Oncology Clinical Trials: A Review

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ABSTRACT

4-1BB is a transmembrane glycoprotein found on T lymphocytes, and signaling through 4-1BB activates and differentiates CD3+ and CD8+ T cells. The ability of 4-1BB to stimulate cytotoxic T-cell responses makes it a promising target for therapeutic cancer immunotherapy development. 4-1BB antibodies have shown promising antitumor activity in preclinical studies and clinical trials. Common side effects include transaminase elevation, cytopenias, fatigue, and nausea. This clinical review summarizes past and current 4-1BB antibodies in oncology clinical trials.

Keywords: 4-1BB, CD137, clinical trial, immunotherapy

INTRODUCTION

4-1BB, also known as CD137, is a transmembrane glycoprotein and a member of the TNF-receptor superfamily 9. The only ligand of 4-1BB is 4-1BBL, a member of the TNF ligand superfamily, which is induced and found on activated antigen-presenting cells. Binding of 4-1BBL and 4-1BB results in a bidirectional signaling pathway.[1] The 4-1BB receptor relays a costimulatory signal, which activates and differentiates CD4+ and CD8+ T cells.[2] Bcl-2-related protein A1 (Bfl-1) and B-cell lymphoma-extra large (Bcl-xL) are induced by the 4-1BB signal, inducing their expression. Nuclear factor–kB mediates Bfl-1 and Bcl-xL in CD8+ T cells, increasing cell survival (Fig. 1).[3,4]

4-1BB–mediated anti-cancer effects include the ability to induce activation of cytotoxic T lymphocytes and high amounts of interferon-gamma (IFN-γ).[5] The agonistic antibodies bind to 4-1BB and stimulate CD8+ T cells.[4] This stimulation promotes proliferation, survival, and cytolytic activity, including increased IFN-γ production, leading to tumor regression.[4] Across multiple cancer types, patients with high expression of 4-1BB and low expression of CD8 T cells have worse survival.[6] Leukemic cells with 4-1BB overexpression significantly correlate with poor prognosis.[7] The ability of 4-1BB to stimulate cytotoxic T-cell responses makes it a promising target for therapeutic cancer immunotherapy development. 4-1BB–directed agents showed promising results in preclinical studies. After administering an anti-4-1BB monoclonal antibody, antitumor efficacy was observed in murine studies.[8] In one mouse model, anti-4-1BB antibodies demonstrated in vivo activity against lymphoma, and another study demonstrated that the antitumor activity is mediated by T lymphocytes and natural killer (NK) cells. [9]

This clinical review aimed to provide a concise compilation of the currently available results of clinical trials of 4-1BB–directed agents 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. Search terms on ClinicalTrials.gov included "4-1BB" and "CD137." The filter term used was

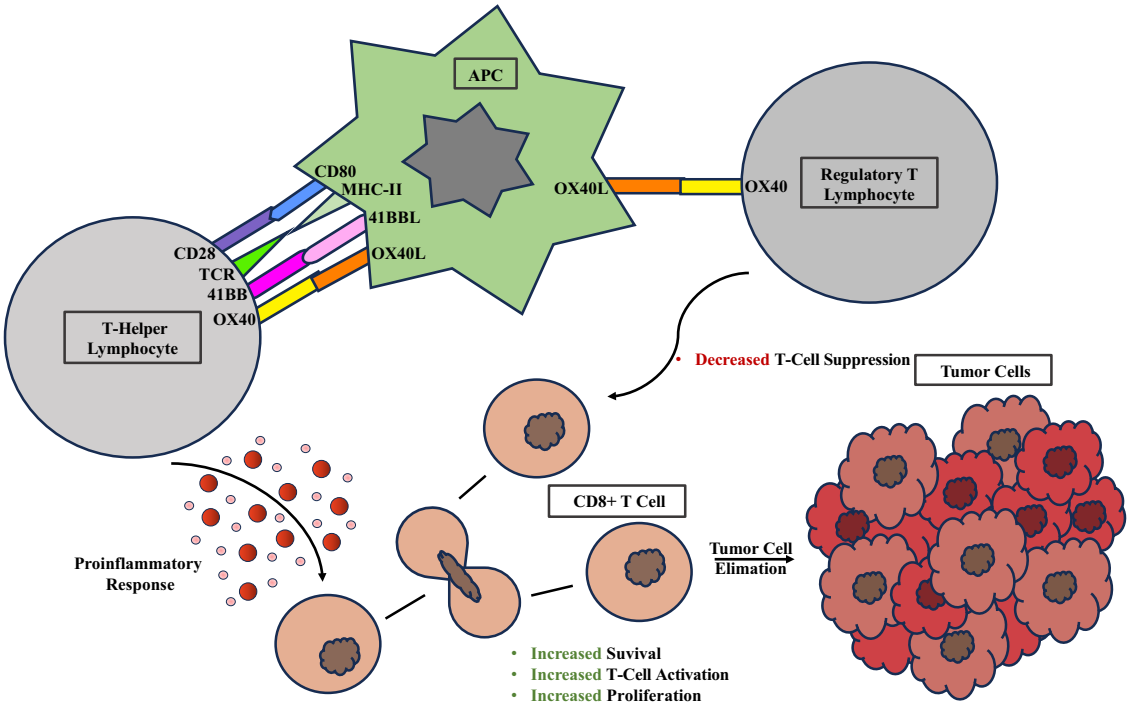

Figure 1. Depiction of 4-1BB roles and effects on antitumor T-cell immunity. 4-1BB binds to ligand 4-1BBL, resulting in a proinflammatory response. This increases survival, T-cell activation, and proliferation of CD8+ T cells. Simultaneously, OX40 binds to OX40L, decreasing T-cell suppression. Both diminish tumor immunosuppression and boost the antitumor immune response. The 4-1BB signaling cascade triggers cytokine activation, while the OX40 signaling cascade induces transcriptional changes to attune the immune response. Adapted based on Mascarelli et al[3] under the terms of a Commons CC-BY license.

"interventional." For trials that were completed, additional searches for associated articles were performed with Google to find published data, if available. This search was completed on February 13, 2024.

CLINICAL TRIALS OF 4-1BB ANTIBODIES WITH PUBLISHED RESULTS

ADG106

ADG106 (Adagene, China) is a human agonistic monoclonal IgG4 antibody that targets 4-1BB to mediate antitumor activity.[10] As of January 2020, 15 patients with various cancers in an unspecified cancer phase (adenoid cystic carcinoma, non–small cell lung carcinoma [NSCLC], nasopharyngeal carcinoma, pleural mesothelioma, and follicular lymphoma) were enrolled in the phase 1 dose-escalation study. Dose escalation was designed with accelerated titration at the initial dose level, followed by traditional Fibonacci 3 + 3. Patients received doses of 0.1 to 10.0 mg/kg intravenously (IV) every 3 weeks (Q3W). A disease control rate of 57% was observed, with stable disease (SD) in eight patients and tumor shrinkage in three patients (two with adenoid cystic carcinoma and one with NSCLC). Of enrolled patients, 46% had treatment-related adverse events (TRAEs), all of which were grade 1, including elevated lactate dehydrogenase, chest discomfort, mouth ulceration, hemoptysis, pyrexia, rash, pruritis, nausea, and vomiting. No dose-limiting toxicities were observed. The study concluded that ADG106 is tolerable up to doses of 5 mg/kg in non-Hodgkin lymphoma and solid tumors. The tools for toxicity evaluation and response assessment were not specified.[10] A retrospective analysis of 28 pretreatment formalin-fixed and paraffin-embedded blood and plasma specimens was performed in a second abstract with updated trial results. The study identified an undisclosed predictive biomarker that correlated with tumor shrinkage after ADG106 treatment. Four patients in the phase 1 study were positive for this biomarker, three of which achieved greater than 30% tumor shrinkage and were treated at the 3- or 5-mg/kg dose levels. In the dose expansion cohorts, patients will be treated at either 3 or 5 mg/kg, with a focus on this predictive biomarker.[11]

AGEN2373

AGEN2373 (Agenus, Lexington, MA) is a conditionally active 4-1BB agonist antibody designed to selectively enhance tumor immunity while mitigating side effects associated with systemic activation of 4-1BB.[12] As of January 2021, 19 patients (median age 54.4 years, range 33–74; 11 men, 8 women; 7 with prior immunotherapy) with advanced solid tumors were enrolled in the study across five cohorts. Each patient received AGEN2373 on day 1 of a 28-day cycle (every 4 weeks [Q4W] dosing). A standard 3 + 3 scheme was followed using doses ranging from 0.03–10 mg/kg. TRAEs were observed in 57%, with none being grade 3 or higher. The most common events were fatigue and nausea. Dose-limiting toxicities were not observed. Drug-related elevations in liver transaminases

Table 1. 4-1BB Antibody Clinical Trials with Published Results

Drug Name	Trial Phase	Tumor Type	No. of Patients	MTD/ Recommended Phase 2 Dose	Dose-Limiting Toxicities	Adverse Effects	Antitumor Response	Other (PK, PD, Biomarkers)
ADG106[10,11]	I	Adenoid cystic carcinoma, NSCLC, nasopharyngeal carcinoma, malignant pleural mesothelioma, follicular lymphoma	15	3 or 5 mg/kg	n/a	Elevated LDH, chest discomfort, mouth ulceration, hemoptysis, pyrexia, rash, pruritis, nausea, vomiting	30% tumor shrinkage in patients with unspecified predictive biomarker	
AGEN2373[12]	I	Advanced solid tumors	19	3 mg/kg	n/a	Fatigue, nausea, elevated transaminases, elevated bilirubin	5 SD	
ATOR-1017[13]	I	Advanced solid tumors	22		n/a	Fatigue, febrile neutropenia, elevated transaminases, thrombocytopenia, leukopenia	10 SD	Dose-proportional kinetics
GEN1042[14,15]	I	Melanoma, NSCLC, colorectal cancer	50	n/a	200 mg - G4 ALT elevation	Nausea, fatigue, pyrexia, ALT elevation	Biologic and early antitumor activity	
GEN1046[16–18]	I	Colorectal, ovarian, pancreatic and NSCLC	61	n/a	n/a	Fatigue, hypothyroidism, transaminase elevation	Reduction in patients with PD-L1 + tumors	Activated NK cells, increased numbers of CD8+ T cells, peripheral IFN-g and CXCL9/10 were seen starting in cycle 1 and were maintained or increased through cycle 2
	IIa	Colorectal, ovarian, pancreatic and NSCLC	40	n/a	n/a	Fatigue, hypothyroidism, transaminase elevation	Reduction in patients with PD-L1 + tumors	Activated NK cells, increased numbers of CD8+ T cells, peripheral IFN-g and CXCL9/10 were seen starting in cycle 1 and were maintained or increased through cycle 2
LVGN6051[19]	I	Advanced solid tumors	12	n/a		n/a	Tumor reductions by >10% were observed in melanoma and neuroendocrine tumors	
	I pembrozilumb combination	Advanced solid tumors	4	n/a	2 mg/kg + 200 mg pem - DLT	Elevated transaminases, thrombocytopenia, neutropenia, nausea, fatigue	Tumor reductions by >10% were observed in melanoma and neuroendocrine tumors	
PE0116[20]	I	Advanced solid tumors	19	n/a	3 mg/kg - G4 thrombocytopenia	Transaminase elevation, thrombocytopenia, leukopenia, anemia, hypokalemia, hyponatremia, hypoalbuminemia, hypothyroidism, bone pain	1 PR 4 SD	
PRS-343[21]	I	Melanoma, breast, gastric/gastroesophageal junction, gynecological, colorectal, biliary tract, pancreatic, urothelial, and salivary duct cancers	74	n/a	5 mg/kg - G4 infusion-related reaction	Nausea, fatigue, vomiting, infusion-related reaction	13 SD 3 PR 1 CR	
	I atezolizumab combination	Melanoma, breast, gastric/gastroesophageal junction, gynecological, colorectal, biliary tract, pancreatic, urothelial, and salivary duct cancers	41	n/a	8 mg/kg PRS-343 + 1200 mg ATZ - Grade 4 AST elevation, Grade 5 hepatic failure	Nausea, fatigue, vomiting, infusion-related reaction, anemia		

Table 1 continues on next page

Table 1. Continued

Drug Name	Trial Phase	Tumor Type	No. of Patients	MTD/ Recommended Phase 2 Dose	Dose-Limiting Toxicities	Adverse Effects	Antitumor Response	Other (PK, PD, Biomarkers)
RO7122290[22,23]	Ia	NSCLC, colorectal cancer, breast carcinoma, mesothelioma, small cell lung cancer, RCC	65	n/a	45 mg - G3 febrile neutropenia 130 mg - G3 cytokine release syndrome	Pneumonia, AST elevation, asthenia	11 CR or PR, 6 immune checkpoint inhibitor naive	Dose-dependent increase in AUC Large numbers of CD8+Ki67+ T cells in tumor biopsies
	Ib atezolizumab combination	NSCLC, colorectal cancer, breast carcinoma, mesothelioma, small cell lung cancer, RCC	50	n/a	500 mg - G3 pneumonitis	Neutropenia, lymphocytopenia, pneumonia, pneumonitis		Same as phase Ia
Urelumab[24]	I	Solid tumors, B-cell non-Hodgkin lymphoma, colorectal cancer, head and neck cancer	73	0.1 mg.kg	None	Elevated transaminases, fatigue, leukopenia		
Utomilumab (PF-05082566)[25–30]	I	Refractory follicular lymphoma, CD20+ non-Hodgkin lymphomas	55	n/a	None	Pyrexia, fatigue, rash, dizziness, decreased appetite	2 PR	
	I rituximab combination	Refractory follicular lymphoma, CD20+ non-Hodgkin lymphomas	67	n/a	None	ALT elevation, fatigue, diarrhea, neutropenia	4 CR 10 PR	
	I pembrozilumb combination	NSCLC, RCC, head & neck, pancreatic, thyroid, small cell lung cancer, colon, sarcoma, thymoma, and melanoma	23	n/a	None	Pyrexia, fatigue, rash, dizziness, decreased appetite	6 CR or PR	
	I mogamulizumab combination	Head and neck SCC, NSCLC adenocarcinoma NSCLC, colorectal cancer, ovarian cancer	24	At least 2.5 mg/kg	None	Fatigue, rash, diarrhea	9 SD	
	I Ivuxolimab combination	Bladder, gastric, cervical, melanoma, HNSCC, NSCLC	57	20 mg/kg + 0.3 mg/kg Ivuxolimub	None	Rash, pruritis, fatigue, anemia, elevated lipase, decreased appetite	18 SD 2 PR	
	II	Bladder, gastric, cervical, melanoma, HNSCC, NSCLC	30	n/a	None	Rash, fatigue, elevated ALT	14 SD 1 PR	
	I	Immune checkpoint inhibitor refractory melanoma and NSCLC	63	n/a	None	Fatigue, nausea, diarrhea, headache, elevated AST, diarrhea, colitis, hyponatremia, hyperbilirubinemia	20 SD	

AUC: area under the curve; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CR: complete response; HNSCC: head and neck squamous cell carcinoma; IFN-g: interferon gamma; LDH: lactate dehydrogenase, n/a: not available; NK: natural killer; NSCLC: non–small cell lung cancer; PD: pharmacodynamic; PD-L1: programmed cell death ligand 1; PK: pharmacokinetic; PR: partial response, RCC: renal cell carcinoma; SCC: squamous cell carcinoma; SD: stable disease.

(alanine aminotransferase [ALT], aspartate aminotransferase [AST]) or bilirubin beyond 1 grade were also not observed. Toxicity was evaluated using CTCAE v5.0. Prolonged disease stabilization as the best response occurred in 5 patients (26.3%; range, 6–41 weeks), three of which were seen in heavily pretreated patients with metastatic leiomyosarcoma, including one who had progressed on prior combination checkpoint immunotherapy. Antitumor activity was assessed with RECIST v1.1. The 3.0 mg/kg cohort was continuing enrollment.[12] AGEN2373 has been identified as a potential partnering agent for other immunomodulatory agents, including planned expansion in a combination regimen with balstilimab (anti-PD-1).

ATOR-1017

ATOR-1017 (Alligator Bioscience, Sweden) is a human agonist Fcγ-receptor cross-linking–dependent IgG4 antibody targeting the costimulatory receptor 4-1BB.[13] Patients were enrolled in single-patient cohorts for doses up to 40 mg and thereafter in cohorts of 3–6 patients. ATOR-1017 was administered via IV Q3W as monotherapy. Twenty-two patients with a median age of 55 years (ovarian cancer, choroidal melanoma, anal cancer, cholangiocarcinoma, gastrointestinal stromal tumor, breast cancer, pancreatic cancer, adenoid cystic cancer, malignant melanoma, colorectal cancer) were enrolled. Patients were previously treated with a median of 4 (0–6) lines of chemotherapy and/or 2 (0–3) lines of immunotherapy. Nine total dose levels have been evaluated, ranging from 0.38–600 mg, and dose escalation was ongoing. Of 22 patients, 12 reported TRAEs, most commonly including fatigue (13.6%) and neutropenia (13.6%). Five patients experienced grade 3-4 TRAE, which included neutropenia, febrile neutropenia, chest pain, increased liver enzymes, leukopenia, and thrombocytopenia. None of the patients discontinued trial treatment because of TRAEs, no dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. Eighteen patients discontinued treatment because of disease progression, clinical deterioration, withdrawal of consent, or death due to disease progression. The study did not specify the method of toxicity evaluation. Four remained on treatment as of January 18, 2022. Preliminary pharmacokinetic data showed dose-proportional kinetics. A dose-dependent increase in pharmacodynamics (PD) biomarkers demonstrated target-mediated biological activity and proof-of-mechanism.[13] Ten patients showed SD, which was the best response achieved. Antitumor activity was assessed with iRECIST.

GEN1042

GEN1042 (Duobody - CD40x4-1BB; BNT 321; Genmab A/S, Denmark; BioNTech, Germany) is a bispecific antibody that conditionally activates CD40 and 4-1BB on immune cells.[14] In the dose-escalation phase, 50 patients with metastatic or nonresectable non–central nervous system solid tumors, including melanoma, non–small cell lung cancer (NSCLC), and colorectal cancer, received doses of GEN1042 between 0.1 and 400 mg IV Q3W. Notable adverse events (AEs) included nausea ($n = 5$), fatigue ($n = 11$), pyrexia ($n = 8$), and transaminase elevation ($n = 8$), with 3 being grade 3 and higher. Grade 4 transaminase elevation was a dose-limiting toxicity at 200 mg and resolved with corticosteroids. The method of toxicity evaluation was not specified. The maximum tolerated dose was not reached. Of patients, 51% achieved complete/partial response (PR) or SD. Antitumor activity was assessed by RECIST v1.1. The trial demonstrated favorable pharmacokinetics and PD at 100 mg Q3W and was therefore chosen as the expansion dose.[14]

Following the first-in-human phase 1 trial of GEN1042, a clinical trial investigating the combination of GEN1042, pembrolizumab, and standard chemotherapy (nab-paclitaxel + gemcitabine or cis/carboplatin + 5-FU) began in 2019.[15] Twenty patients with various advanced solid malignancies (NSCLC, melanoma, and head/neck squamous cell carcinoma [HNSCC]) received the GEN1042 + pembrolizumab combination, and 17 patients (HNSCC and pancreatic ductal adenocarcinoma) received the GEN1042 + pembrolizumab + chemotherapy combination. Notable AEs observed with the first combination were pruritis in 20%, rash in 20% (grade 3 in 5%), and pyrexia in 15%. Common AEs observed with the second combination included nausea and diarrhea in 17.6%, fatigue in 23.5%, transaminase elevation in 29.4% (grade 3 in 5.9%), and rash in 23.5% (grade 3 in 5.9%). All AEs in both cohorts were manageable, and no dose-limiting toxicities were seen. The method of toxicity evaluation was not specified. Antitumor activity was assessed with RECIST v1.1.

GEN1046

GEN1046 (DuoBody-PD-L1x4-1BB; Genmab A/S; BioNTech) is a bispecific antibody targeting 4-1BB and simultaneously blocking programmed cell death ligand 1 (PD-L1).[16–18] As of 2020, 61 patients with unresectable or metastatic solid tumors, including colorectal, ovarian, pancreatic, and NSCLC, were enrolled in the dose-escalation portion of the first-in-human phase I/IIa trial. Patients received GEN1046 IV Q3W at doses of 25–1200 mg. TRAEs grade 3 and higher included fatigue in 1.6%, hypothyroidism in 1.6%, and transaminase elevation in 9.8%. Common grade 1-2 AEs included fatigue in 11.5%, hypothyroidism in 14.8%, and transaminase elevation in 14.8% of patients. The maximum tolerated dose was not reached, and six patients experienced dose-limiting toxicities, which the authors did not specify. The authors did not specify the method of toxicity evaluation. Disease control (SD or PR) was achieved in 40 of 61 patients, and PRs were observed in patients with ovarian cancer, triple-negative breast cancer, and immune checkpoint inhibitor–pretreated NSCLC.[16,17] Preliminary results from the dose-expansion portion of the study were presented in 2021.[18] By May 2021, 40 patients with PD-L1–negative relapsed

or refractory NSCLC were enrolled in an expansion cohort to analyze PD and immune markers. Patients received 100 mg IV Q3W. Within the first two cycles, pharmacodynamic modulation of immune markers was demonstrated. Activated NK cells, increased numbers of CD8+ T cells, peripheral IFN-γ, and CXCL9/10 were seen starting in cycle 1 and were maintained/increased through cycle 2. Five patients achieved PRs, all of which had greater induction of IFN-γ, CXCL9/10, and activated NK cells. Of 25 patients, 16 that had received prior anti–PD-1 therapy within 8 months before their first GEN1046 doses had higher disease control rates. Twenty-six patients showed some degree of tumor reduction, most of which had PD-L1–positive tumors. Of 16 patients, 12 that showed no degree of tumor reduction had PD-L1–negative tumors.[18] Both studies did not specify the methods to assess for antitumor activity.

LVGN6051

LVGN6051 (Lyvgen Biopharma, Shanghai, China) is a monoclonal antibody against 4-1BB with an engineered Fc capable of selectively binding to the Fcγ receptor IIB.[19] The first-in-human phase 1 trial included an accelerated dose-escalation design for monotherapy up to 2 mg/kg of LVGN6051, followed by a traditional dose-escalation 3 + 3 design for higher doses either alone or in combination with pembrolizumab. Both agents were administered IV Q3W. At the cut-off date on January 18, 2021, 16 subjects had been enrolled, including 12 into the monotherapy cohorts and 4 into the combination cohort. The authors did not specify all of the cancers that the study assessed. In the monotherapy arm, there were no TRAEs and the doses were up to 7 mg/kg. In the combination cohort, TRAEs included increased ALT/AST, thrombocytopenia, neutropenia, nausea, and fatigue. In the combination cohort, one patient with predominant hepatic metastases and a history of intermittent grade 2 hepatic impairment experienced grade 3 increased ALT/AST (dose-limiting toxicity) on cycle 1 day 15 that resolved to baseline without corticosteroids on cycle 1 day 18. The method of toxicity evaluation was not specified. SD was observed in 7 of 10 evaluable patients in the monotherapy cohort, with the longest treatment being 8+ months. In both melanoma and neuroendocrine malignancies, tumor reductions by more than 10% were observed.[19] An immune partial response was observed in one patient who had progressed on an anti–PD-L1-based therapy for 6+ months to the combination arm. The authors did not specify the methods used to assess antitumor activity.

PE0116

PE0116 (Hyamab, Shanghai, China) is a humanized agonist antibody to 4-1BB that promotes and activates T cells. Preliminary results of the first-in-human/phase I trial were presented in 2022. Nineteen patients with solid tumors that have progressed on standard-of-care or experimental therapies were enrolled in the dose-escalation phase. PE0116 was administered via IV (once in the first 28-day cycle, followed by Q3W thereafter) and investigated at six dose levels ranging between 0.03 and 3 mg/kg. One dose-limiting toxicity of grade 4 thrombocytopenia was observed at the 3 mg/kg dose level. Three serious AEs were reported. Grade 1 and 2 AEs included ALT and AST increase, platelet decrease, white blood cell decrease, anemia, hypokalemia, hyponatremia, hypoalbuminemia, hypothyroidism, and bone pain. TRAEs were assessed with CTCAE v5. One ovarian cancer patient with liver metastasis achieved an immune partial response after six cycles of treatment, and four patients achieved immune stable disease. The method to assess antitumor activity was not specified. The recommended phase II had not yet been reached, and dose escalation was ongoing.[20]

PRS-343

PRS-343 (Pieris Pharmaceuticals, Boston, MA) is a bispecific antibody-Anticalin (recombinant human proteins that are based on lipocalins) fusion protein targeting 4-1BB and HER2.[21] Seventy-four patients with various *HER2*+ solid tumors (melanoma, breast, gastric/gastroesophageal junction, gynecological, colorectal, biliary tract, pancreatic, urothelial, and salivary duct cancers) were enrolled in the phase 1 monotherapy dose-escalation study. Patients were treated at doses from 0.0005–8 mg/kg IV Q3W, 8–18 mg/kg every 2 weeks [Q2W], and 8 mg/kg weekly. The minimal active dose was 2.5 mg/kg Q3W. Of 33 patients who were treated at active-dose levels and were evaluated for response, 52% had disease control (40% SD, 9% PRs, and 3% complete response). Patients who had a PR or SD showed confirmed expansion of CD8+ T cells. TRAEs included nausea and fatigue in 9% (1% with grade 3 fatigue), vomiting and chills in 6%, and mild/moderate infusion-related reaction in 19% (2% with grade 3). A grade 4 infusion-related reaction was observed at 5 mg/kg.

Forty-one patients with various *HER2*+ solid tumors (breast, gastric/gastroesophageal junction, gynecological, colorectal, biliary tract, pancreatic, urothelial, NSCLC, and salivary duct cancer) were enrolled in a phase 1 combination dose-escalation study with atezolizumab. Doses investigated included 0.05–8 mg/kg IV of PRS-343 and 1200-mg flat dose of atezolizumab Q3W. Twenty-seven patients were evaluable for response, and 37% had disease control (15% with PR and 22% with SD). TRAEs included fatigue in 8%, vomiting in 28%, nausea in 5%, infusion-related reaction in 26% (grade 3 in 2%), and anemia in 3% (grade 3 in 1%). Grade 4 AST elevation and grade 5 hepatic failure were observed at 8 mg/kg PRS-343 + 1200 mg atezolizumab. The methods to assess toxicity and antitumor activity are not specified.

RO7122290

RO7122290 (Roche, Switzerland) is an antibody-like fusion protein based on a Fab moiety recognizing FAP as well as a trimeric 4-1BB ligand.[22] This dual-binding

results in increased activation of NK cells and T cells at the tumor site. Preliminary results of the first-in-human trial exploring pharmacokinetics, PD, and antitumor activity were presented at ESMO 2020.[22] In part A, 65 patients were treated with a weekly IV infusion at 13 doses ranging from 5–2000 mg. AEs grade 3 or higher in part A included pneumonia in 4% ($n = 3$), AST elevation in 4% ($n = 3$), and asthenia in 6% ($n = 4$). Drug-limiting toxicities in part A included grade 3 febrile neutropenia at 45 mg and grade 3 cytokine release syndrome at 130 mg. In Part B, 50 patients were treated with a weekly IV infusion at 8 doses from 45 mg to 2000 mg, in combination with atezolizumab 1200 mg IV Q3W. AEs grade 3 and higher included neutropenia in 6% ($n = 3$), lymphocytopenia in 6% ($n = 3$), pneumonia in 8% ($n = 4$), and pneumonitis in 8% ($n = 4$). One dose-limiting toxicity of grade 3 pneumonitis was observed in Part B at 500 mg. The authors did not specify what tumors were present in the enrolled patients. Neither part specified the methods for assessing toxicity and antitumor activity. Pharmacokinetics analysis from parts A and B demonstrated a dose-dependent increase in the area under the curve and was suggestive of target-mediated drug disposition. Paired tumor biopsies showed large numbers of CD8+Ki67+ T cells. Part C of the study will investigate the safety and efficacy of specific familial adenomatous polyposis (FAP+) tumors, and results have not yet been published.[23]

Urelumab

Urelumab (BMS-663513) (Bristol Myers-Squibb, New York, NY) is a fully human, non–ligand-blocking agonist antibody. It is an IgG4 engineered with a hinge mutation (S228P) for stability and reduced Fc receptor binding. In preclinical studies, urelumab enhanced T-cell survival, IFN-γ production, and the cytolytic activity of antigen-specific T cells.[24] Clinical development of urelumab started in 2005 and was initially evaluated as a monotherapy in two studies. CA186-001 (-001) was the first in human trial of urelumab, which investigated dosing of 0.3, 1, 3, 6, 10, or 15 mg/kg Q3W. One hundred fifteen patients were enrolled and treated. CA186-006 (-006) was a randomized, multidose, open-label, parallel four-arm, phase II study in patients with stage III/IV melanoma. One hundred fifty-nine patients were enrolled, 158 of which received either a 0.1-, 1-, or 5-mg dose of urelumab Q3W or 1 mg/kg every 6 weeks. Both studies were stopped in December 2008 because of the occurrence of two hepatotoxicity-related deaths. CA186-011 restarted the urelumab clinical development program in February 2012 to evaluate monotherapy doses less than 1 mg/kg, with both a dose escalation and expansion portion,[24] in which a total of 73 patients were treated. The results of these three studies were presented in aggregate ($n = 346$) in one publication.[24]

In the dose-escalation portion (part 1) of the CA186-011 study, successive cohorts of patients received the following treatments: cohort 1 with 0.1 mg/kg Q3W and cohort 2 with 0.3 mg/kg Q3W. In part 2, cohorts 1 and 2 were expanded to 20 patients with advanced solid tumors. In part 3, the study enrolled 10 patients, each with B-cell non-Hodgkin lymphoma, colorectal cancer, and head and neck cancer at the highest tolerated dose of 0.3 mg/kg Q3W.[24]

Across the three studies, doses of urelumab (between 1 and 15 mg/kg) were associated with more frequent TRAEs compared with lower doses (0.1 or 0.3 mg/kg). The most frequent TRAEs for doses at or above 1 mg/kg were increased AST (27%), increased ALT (27%), and fatigue (24%). The most frequent TRAEs for patients at a 0.3 mg/kg-dose level were increased AST and fatigue (both 14%), and at 0.1 mg/kg, fatigue (16%) and nausea (13%) were the most common. Higher urelumab doses (between 1 and 15 mg/kg) were associated with more frequent severe (grade 3 or higher) TRAEs compared with the lower doses (0.1 and 0.3 mg/kg). The rate of patients discontinuing treatment due to side effects increased with higher urelumab doses. At the highest dose (≥1 mg/kg), 16% (37/229 patients) stopped treatment because of AEs, compared with 9% (5/56) at the 0.3 mg/kg dose and 11% (7/61) at the 0.1 mg/kg dose. At 1 and 5 mg/kg, two deaths related to hepatotoxicity were reported. The incidence of transaminitis increased with urelumab doses at or above 1 mg/kg. Urelumab treatment led to decreases in neutrophils, platelets, and leukocytes across all tested doses, with severity ranging from mild (grade 1) to severe (grade 4). The methods to assess toxicity evaluation were not specified.

The half-life of urelumab was estimated to be approximately 18 days. The minimum concentration (C_{min}) at steady state was greater than the pharmacologically active exposure level based on the in vitro human T-cell–binding affinity of 0.1 mg/mL. Every 3 weeks, 0.1 mg/kg of urelulab triggered the production of IFN-induced cytokines and IFN-response genes. In summary, at 0.1 mg/kg Q3W, urelumab demonstrated good tolerability with evidence of immunologic activity.[24] The methods that the authors used to assess antitumor activity were not specified.

Utomilumab

Utomilumab (PF-05082566; Pfizer, New York, NY) is an agonistic monoclonal antibody that targets 4-1BB.[25] Fifty-five patients with advanced solid tumors were enrolled in the first-in-human phase 1 monotherapy dose-escalation study, and the results were published in March 2018. Patients were given 0.006–10 mg/kg IV Q4W. One patient experienced an AE of grade 3 fatigue. Other AEs observed were all less than grade 3 and included pyrexia, fatigue, rash, dizziness, and decreased appetite. No dose-limiting toxicities were observed. The objective response rate across all patients treated was 3.8%. Among 15 patients with Merkel cell carcinoma, the objective response rate was 13.8%.[25] The recommended phase 2 dose was not formally declared. The favorable safety profile and antitumor activity allowed for further evaluation in both monotherapy and combination therapy trials.

The methods to assess for toxicity and antitumor activity were not specified by the authors.

Sixty-seven patients with relapsed or refractory follicular lymphoma and other CD20+ non-Hodgkin lymphomas were enrolled in the phase 1a utomilumab and rituximab combination study published in March 2020.[26] Patients received either 0.03–10.0 mg/kg utomilumab IV Q4W together with 375 mg/m^2 rituximab IV weekly in the dose-escalation cohort or 1.2mg/kg IV Q4W utomilumab plus rituximab IV weekly in the dose-expansion cohort. Most AEs observed were grades 1 or 2, including fatigue in 16.4%. Grade 3 TRAEs were observed in 3.0% of patients, including neutropenia, diarrhea, and ALT elevation. No dose-limiting toxicities were observed. The maximum tolerated dose was not reached. The methods to assess toxicity were not specified by the authors. The objective response rate was 21.2% in patients with non-Hodgkin lymphoma (including 4 complete responses and 10 PRs). The method to assess response was not specified. A formal phase 2 dose was not declared.[26]

A phase Ib trial was performed to assess the combination of utomilumab and pembrozilumab.[27] On day 1 of 21-day cycles, patients ($n = 23$) received a starting dose of PF-2566 0.45 mg/kg with escalation to 0.9, 1.8, 3.6, and 5 mg/kg and pembrolizumab (2 mg/kg) IV. NSCLC ($n = 6$), renal cell carcinoma (n = 5), head and neck ($n = 3$), pancreatic ($n = 2$), thyroid ($n = 2$), and one each of small cell lung cancer, colon, sarcoma, thymoma, and melanoma were the tumor types treated in this study. No dose-limiting toxicities were reported. Six patients remained on treatment at the time of the abstract submission. Treatment-emergent adverse events (TEAE) were mostly Grade 1-2, with no apparent relationship between increasing doses of PF-2566 and the frequency or severity of AEs. No patients discontinued treatment because of TRAEs. There were no substantial changes in inflammatory cytokines or their association with clinical symptoms. The concentrations of PF-2566 were higher than the preclinical predicted efficacious concentration and increased with increasing doses. PD responses (lymphocyte subsets) were observed.[27] Six of 23 treated patients (26%, 95% CI: 10.2, 48.4) had confirmed complete or PRs per RECIST 1.1 as follows: complete response in small cell lung cancer ($n = 1$), PRs in renal cell carcinoma ($n = 2$), NSCLC ($n = 1$), head and neck ($n = 1$), and anaplastic thyroid ($n = 1$).[27] The authors did not specify the methods to assess toxicity and antitumor activity.

A phase Ib trial was performed to assess the combination of utomilumab and mogamulizumab (CCR4 monoclonal antibody). HNSCC ($n = 11$), squamous NSCLC ($n = 7$), adenocarcinoma NSCLC ($n = 3$), colorectal cancer ($n = 2$), and ovarian cancer ($n = 1$) were the solid tumor types assessed in this study. Seven patients with squamous NSCLC, one with adenocarcinoma NSCLC, and seven with SCCHN all were relapsed or refractory to anti–PD-1/PD-L1 checkpoint inhibitor therapy. Eleven patients received 1.2 mg/kg, four patients received 2.4 mg/kg, three patients received 5 mg/kg, and six patients received a 100-mg flat dose of utomilumab Q4W. All patients also received 1 mg/kg of IV mogamulizumab weekly for 4 consecutive weeks and then biweekly onward. No dose-limiting toxicities were reported up to the 5-mg/kg cohort. No serious AEs related to the combination of drugs were reported. AEs included fatigue (45.8%), rash (29.2%), and diarrhea (25.0%), all of which were grade 1 or 2 severities. Eight patients reported all-casualty grade 3 to 4 AEs. Ten patients experienced serious AEs, which were determined to be unrelated to utomilumab or mogamulizumab.[27] The authors did not specify the methods to assess toxicity. The relationship between serum pharmacokinetic parameters and dose could not be determined because of the low number of patients in this study. A transient reduction in circulating T cells was confirmed for patients being treated with a combination of utomilumab and mogamulizumab. Nine patients had the best overall response of SD, including one patient with PD-L1–refractory squamous lung cancer who achieved a PR. Antitumor activity was assessed with RECIST v1.1.[28]

A phase Ib study was performed by combining utomilumab (4-1BB) with ivuxolimab (OX40).[29] In the dose-escalation portion, 57 patients were enrolled, including advanced bladder ($n = 7$), gastric ($n = 9$), cervical ($n = 5$), melanoma ($n = 18$), HNSCC ($n = 12$), or NSCLC ($n = 6$). Ivuxolimab was administered via IV in sequential doses Q2W in combination with 20 or 100 mg of utomilumab Q4W. Patients were enrolled into five dose cohorts as follows: 0.1 mg/kg + 20 mg ($n = 11$), 0.3 mg/kg + 20 mg ($n = 20$), 0.3 mg/kg +100 mg ($n = 12$), 1.0 mg/kg +100 mg ($n = 11$) and 3.0 mg/kg +100 mg ($n = 11$). All-causality grade 1-2 AEs occurred in 23 of 57 patients and grade 3-4 AEs in 28 of 57 patients. Of 57 patients, 6 experienced grade 5 AEs because of disease progression ($n = 5$) and euthanasia ($n = 1$). Of 57 patients, 4 discontinued treatment because of grade 4 colon perforation of unknown causality, treatment-related grade 3 infusion-related reaction, disease-related grade 4 hepatobiliary disorder, or disease-related grade 3 pain in the extremities. No dose-limiting toxicities were reported. The most common TRAEs consisted of pruritis (20%), fatigue (13.3%), anemia (13.3%), decreased appetite (10%), and rash (10%). Grade 3 TRAEs of lymphopenia rash, pustular rash, immune-related rash erythematosus, and maculopapular rash occurred in one patient each. An asymptomatic, grade 4 TRAEs and immune-related AEs of increased lipase levels in cycle five were observed for one melanoma patient. This was resolved, and there was no change in the treatment of the study. Toxicity was evaluated with CTCAE v4.03. Two melanoma patients achieved PR (0.3 mg/kg +20 mg and 0.3 mg/kg+100 mg), and 18 patients achieved SD; 35.1% was the disease control rate across all dose levels.

In the dose-expansion portion of the combination of utomilumab with ivuxolimab, 30 patients were enrolled, including patients with melanoma ($n = 10$) and NSCLC ($n = 20$).[29] Owing to the dose-escalation study results, a

dose of 30 mg (a flat-dose equivalent to 0.3 mg/kg) of ivuxolimab was administered via IV Q2W combined with 20 mg of utomilumab IV Q4W. Grade 1-2 all-causality AEs were reported in 14 of 30 patients. Grade 3-4 all-causality AEs occurred in 11 of 30 patients. Of 30 patients, 5 died because of all-causality AEs, including disease progression ($n = 2$), pulmonary embolism ($n = 1$), myocardial infarction ($n = 1$), or seizure ($n = 1$). No dose-limiting toxicities were reported. Treatment was discontinued because of a grade 2 rash in one patient and a grade 3 diffuse left chest wall pain in one patient. Five patients experienced TRAEs causing treatment interruptions, including grade 3 rash, grade 2 fatigue, and grade 2 ALT elevation. PR was achieved by one NSCLC patient lasting 77 weeks. Seven of 10 melanoma patients and 7 of 20 NSCLC patients achieved SD. Tumor response was assessed with a combination of RECIST v1.1 and iRECIST.

All 87 patients (both escalation and expansion studies) on the combination of ivuxolimab and utomilumab had pharmacokinetics samples collected. Following the combination of IV ivuxolimab and utomilumab, the ivuxolimab area under the concentration-time curve increased in a dose-dependant manner for the 0.3- to 3.0-mg/kg dose range. There was a similar coefficient of variation between the weight-based dosing group (0.3 mg/kg + 100 mg) and the flat-dosing group (30 mg + 20 mg). Based on the concentration-time curve, a range between 1.4 and 1.8 was observed for the accumulation ratio of ivuxolimab.[29]

A study was performed to assess utomilumab in patients with immune checkpoint inhibitor–refractory melanoma ($n = 43$) and NSCLC ($n = 20$).[30] Patients who were previously on an anti–CTLA-4 and/or anti–PD-1/PD-L1-inhibitor and had documented disease progression were included in the study. Utomilumab was administered at either a 0.24 mg/kg ($n = 36$), 1.2 mg/kg ($n = 26$), or 10 mg/kg ($n = 1$) dose as a 1-hour IV infusion Q4W for up to 2 years. TEAEs were reported in 55 (87.3%) patients, and 18 patients (28.6%) reported having serious TEAEs. Five (7.9%) patients stopped the trial because of TEAEs. The most common TRAEs included fatigue (15.9%), nausea (15.9%), diarrhea (9.5%), headache (6.3%), and elevated AST (6.3%). Seventeen patients experienced grade 1 TRAEs and 12 experienced grade 2 TRAEs. Grade 3 TRAEs were reported in two patients, including diarrhea ($n = 1$), colitis ($n = 1$), and hyponatremia ($n = 1$). Grade 1 and grade 4 hyperbilirubinemia were reported in one patient each. There were no treatment-related deaths. Likely due to preexisting host antibodies cross-reacting with utomilumab, eight patients had positive antidrug antibodies against utomilumab. Treatment-induced antidrug antibodies were present in 31 (46.3%) patients, none of which were treatment boosted. Treatment-induced neutralizing antibodies were exhibited in 13 (19.4%) patients. No patients with NSCLC achieved an objective response, while 2.3% of melanoma patients achieved an objective response. Ten patients, each with melanoma and NSCLC, reported SD.[30]

DISCUSSION

A number of 4-1BB–directed agents have entered clinical trials in both monotherapy and combination therapy for patients with a large variety of solid tumors. Eleven such agents have published data at the time of this manuscript's drafting, and others are certain to be published in the following months. The most common solid tumors that were targeted through these trials included NSCLC, melanoma, colorectal cancer, and HNSCC.

Currently, RO7122290, GEN1042, GEN1046, PRS-343, ADG106, PE0116, LVGN6051, PF-05082566, and BMS-663513 have evidence of antitumor activity, including either complete or PRs.[10,14,17,19–22,25,29] ATOR1017 and AGEN2373 demonstrated evidence of SD without any objective responses.[12,13] 4-1BB–directed agents appear promising for melanoma, NSCLC, and a variety of squamous cell carcinomas. PRs or complete responses were observed in patients with melanoma treated with LVG6051, utomilumab monotherapy, and ivuxolimab combination.[19,25,29] Additionally, all of the utomilumab combination therapy trials demonstrated objective responses in patients with NSCLC. Other trials with notable responses include AGEN2373, achieving complete response in a patient with pancreatic squamous cell carcinoma, and ADG106, achieving significant tumor shrinkage in patients with PD-L1+ tumors.[10,12]

Similar to many other cancer treatments, the most common TRAEs noted have included fatigue, neutropenia, transaminase elevation, anemia, and gastrointestinal effects such as nausea and vomiting. The most common dose-limiting toxicities noted for RO7122290, GEN1042, LVGN6051, and PE0116 included transaminase elevation, thrombocytopenia, and neutropenia.[14,19,20,22] Less frequent AEs include rash, pruritis, electrolyte abnormalities, and decreased appetite.

All 4-1BB–directed agents with currently published results are administered via IV and are either agonistic or antagonistic monoclonal antibodies. Pharmacokinetics and PD properties vary between agents, but most of the infusion schedules are similar, given their long half-lives. RO7122290 has a shorter half-life of approximately 78 hours in comparison to an agent such as PF-05082566, which has a half-life between 208 and 349 hours. Reflecting these half-lives, RO7122290 was administered on a weekly infusion schedule, while PF-05082566 was administered Q4W.[22,25]

Analysis of potential selective biomarkers in these trials has been inconsistent. ADG106 and GEN 1046 noted significant tumor shrinkage in patients with PD-L1+ tumors.[10,17] Additionally, the ADG106 trial showed evidence that patients with an "unspecified" biomarker also had significant tumor shrinkage.[11] Successful

development of this drug class may require further investigation of other potential selective biomarkers.

This review has several notable limitations. Overall, there is a lack of consistency in how information is presented in our manuscript, and this reflects the variability of the information reported in the abstracts and publications of each of the clinical trials that we summarize. In addition, some of these trials are still ongoing, and additional results will likely be presented or published in the near future. Furthermore, other clinical trials of 4-1BB–directed agents are ongoing and have not yet presented any preliminary results. Our review aimed to summarize the results of these trials, with the understanding that this field of investigation is ongoing, with incomplete results currently available.

CONCLUSION

Combination strategies with 4-1BB–directed agents are promising, and combination agents that have been investigated to date include atezolizumab, pembrozilumab, rituximab, mogamulizumab, and ivuxolimab. In fact, PF-05082566 is currently undergoing numerous combination therapy trials with all the previously listed agents except atezolizumab. Preliminary results from the PF-05082566 combinations showed multiple patients with SD and objective responses. To date, most of these combinations have been well-tolerated.

In summary, 4-1BB–directed antibodies are a promising class of agents, showing significant antitumor activity in various solid tumor cancers. Additional trials are ongoing to further investigate safety, efficacy, PD, pharmacokinetics, and combinations with other agents.

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