Targeting 4-1BB for tumor immunotherapy from bench to bedside

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Immune dysfunction has been proposed as a factor that may contribute to disease progression. Emerging evidence suggests that immunotherapy aims to abolish cancer progression by modulating the balance of the tumor microenvironment. 4-1BB (also known as CD137 and TNFRS9), a member of tumor necrosis factor receptor superfamily, has been validated as an extremely attractive and promising target for immunotherapy due to the upregulated expression in the tumor environment and its involvement in tumor progression. More importantly, 4-1BB-based immunotherapy approaches have manifested powerful antitumor effects in clinical trials targeting 4-1BB alone or in combination with other immune checkpoints. In this review, we will summarize the structure and expression of 4-1BB and its ligand, discuss the role of 4-1BB in the microenvironment and tumor progression, and update the development of drugs targeting 4-1BB. The purpose of the review is to furnish a comprehensive overview of the potential of 4-1BB as an immunotherapeutic target and to discuss recent advances and prospects for 4-1BB in cancer therapy.

KEYWORDS
4-1BB, immunotherapy, cancer, immune checkpoint inhibitor, clinical trials

Introduction

Tumor immunotherapy exerts antitumor efficacy through the interaction of the host immune system with tumor-associated antigens (1). It can restore or enhance the body’s immune system’s natural defenses against tumors, which typically targets specific biomolecules on the surface of cancer cells, exemplified by tumor-associated antigens (2). Immunotherapy including immune checkpoint inhibitor (ICI) and CAR-T therapy
has made breakthroughs in tumor treatment, but the overall response rate is not high, and many patients cannot benefit from it (3–6). Therefore, the development of new immune checkpoints and biomarkers and expansion of the beneficiary population from immunotherapy are urgent problems to be solved.

Neoantigen epitopes generated by somatic mutations in cancer cells play an important role in T-cell immune responses, which have become an important driver of immune checkpoint discovery in immunotherapy. 4-1BB, also termed 4-1BB and TNFRSF9, was identified in 1989 and originally described as an inducible gene, which was expressed in T lymphocytes (7). 4-1BB exhibited an important effect in various cells and participated in the activation of multiple immune cells, such as CD8 T cells and cytotoxic T lymphocytes (CTL) (8). Emerging evidence has demonstrated that targeting 4-1BB is a uniquely attractive strategy for tumor immunotherapy (9–13). In this review, we discuss the recent advances and prospects of the cancer immunotherapy checkpoint 4-1BB from the aspects of structure, expression, role in tumor microenvironment, development of clinical drugs targeting 4-1BB, and their combination with traditional treatment methods.

Structure of 4-1BB and its ligand

4-1BB, a glycosylated type I membrane protein, contains four cysteine-rich pseudo repeats, which contribute to the formation of a cytoplasmic signaling domain, extracellular domain, and short helical transmembrane domain (7). An elongated structure was generally formed by the extracellular domain of TNFR (variation range: 1 to 4 CRDs). Based on this, antibodies can bind to these molecules through many modalities. Efficient binding of 4-1BB L to 4-1BB results in rapid receptor activation in response to antigenic stimulation. 4-1BBL (TNFSF9), a type II membrane protein of the TNF ligand superfamily, is the binding partner of 4-1BB (14, 15). TNFSF members, typically expressed on the cell membrane, exist in a homotrimeric complex (16–18), which can be divided into three parts: (a) LTA, TNF, RANKL, LIGHT, Apo2L/TRAIL, and CD40L (19, 20); (b) BAFF, APRIL, and EDA; and (c) GITRL, 4-1BBL, and OX40L, among which OX40L and GITRL exhibit a flatter conformation (19, 21). The sequences of 4-1BBL were poorly conserved in human and mouse.

As a member of the tumor necrosis factor superfamily, 4-1BB is mostly expressed on the surface of activated T cells but also on B cells, NK cells, and DC cells (22, 23). 4-1BB is widely distributed on various tumor cells (such as lung tumor cells, and leukemia cells) and has been identified in tissues (such as liver cancer tissue, and tumor vessel walls). Alfaro et al. found that 4-1BB is also expressed in tonsil and lymph node follicular structures. Thence, a comprehensive analysis of its distribution helps uncover potential roles and functions.

Role of 4-1BB in the tumor microenvironment

As shown in Figure 1, both IL-15 and IL-2 can promote the expression of 4-1BB on NK cells, which stimulates the proliferation of NK cells and produces IFN-γ, thus leading to the activation of T cells (24). 4-1BB facilitates the proliferation of CD8+ T cells to produce memory T (Tm) cells (25, 26). Stimulation by 4-1BB will upregulate the expression IL-2 and IFN-γ in CD4+ and CD8+ T cells. However, 4-1BB expresses a controversial effect in T regulatory cells (Treg), which leads to Treg proliferation but alters Treg for cytotoxic or helper effects (27, 28). 4-1BBL inhibits the conversion of CD4+FOXP3+ cells to CD4+FOXP+ (29). 4-1BB is also expressed in monocytes, and it promotes upregulation of IL-8 and TNF-α but downregulation of IL-10. The differentiation of monocytes into dendritic cells can be promoted by 4-1BB, and dendritic cells then secrete IL-6 and IL-12 (30). However, 4-1BB stimulation differentiates monocytes into M2 macrophages and accelerates B-cell apoptosis, which also promotes the expression of TNF-α/β in B cells (31).

4-1BB in cancer progression

Through the PI3K/AKT/mTOR pathway, expression of 4-1BB was induced by EBV protein LMP1 to facilitate immune evasion in Hodgkin and Reed–Sternberg cells (32). Low levels of the soluble form of 4-1BBL in patients with AML were associated with better prognosis, especially longer disease-free survival (33). 4-1BB L and 4-1BB were abnormally expressed in tumor cells in hematopoietic malignancies, and their interaction promotes tumor growth in cutaneous T-cell lymphoma (34). Overexpression of 4-1BB on leukemic cells was significantly related to poor prognosis (35). Antitumor activity was enhanced in 4-1BB-knockout mice (36). Similarly, the tumor growth was seriously blocked in 4-1BB knockout mice subcutaneously injected with CT26 cells (37). The findings further proved the critical role of 4-1BB-4-1BBL in tumor development.

4-1BB-targeted drug development

The efficacy of the 4-1BB antibody in preventing cancer in animals has prompted clinical development. The use of monoclonal antibodies to treat cancer has achieved great success over the past few decades, many of which have been under evaluation in different clinical trials, as shown in Table 1.
Urelumab (BMS-663513), the first 4-1BB-targeted therapy to enter clinical trials developed by Bristol–Myers Squibb, is a human IgG4 human monoclonal antibody, which will not inhibit the interaction between 4-1BB with its ligand (38). Preliminary clinical results in phase 1/2 disclosed in 2008 showed encouraging efficacy, but further development was hindered by liver toxicity (39). Urelumab reentered clinical trials in 2012, which was combined with nivolumab, cetuximab, rituximab, and elotuzumab, respectively (12). However, hepatotoxicity of the antibody emerged shortly thereafter, causing the urelumab development program to be shelved. Currently, urelumab, a potent agonist mAb, is still under different clinical trials (Table 1), and strategies to avoid hepatotoxicity and achieve appropriate drug exposure levels are worth investigating. Utomilumab (PF-05082566) is a 4-1BB-humanized IgG2 monoclonal antibody developed by Pfizer (40). Compared with urelumab, it has a higher safety profile and is currently undergoing multiple clinical trials (41).

To reduce the hepatotoxicity of systemic 4-1BB agonists, the development of bispecific antibodies against 4-1BB has been recognized as a viable strategy, and some bispecific antibodies, including GEN1046 (PD-L1/4-1BB) and PRS343 (HER2/4-1BB), are currently being evaluated in different clinical trials (Table 1) (42, 43). ES101 (INBRX-105), a first-in-class tetravalent bispecific antibody targeting PD-L1/4-1BB, originally developed by Inhibria, was introduced into its Greater China rights by Kewan Pharmaceuticals (44). It contains four domains, and two of them target PD-L1 while the other two target 4-1BB, which can alleviate PD-1/PD-L1-mediated immune checkpoint inhibition. The 4-1BB-binding domain may drive the aggregation of 4-1BB molecules on the surface of T cells, so that 4-1BB-mediated immune activation can be concentrated on T cells near the tumor, effectively reducing the potential off-target toxicity.

In addition to double-antibody drugs, the development of 4-1BB targets has been extended to tertiary and tetraspecific antibodies. NM21-1480 is a monovalent trispecific antibody fragment molecule against PD-L1, 4-1BB, and human serum protein (HSA) (45). NM21-1480 exerts a synergistic effect of 4-1BB agonism and PD-L1 blockade and shows an extended half-life by binding to HSA, thereby reducing the frequency of dosing. GNC-035 is a four-antibody drug targeting PD-L1/CD3/4-1BB/ROR1, while GNC-039 targets PD-L1/4-1BB/CD3/EGFR. In terms of design, both GNC-035 and GNC-039 build symmetrical tetraspecific antibodies based on IgG with three scFvs in series. Among them, PD-L1, 4-1BB, and CD3 are immunoregulatory functions, and the fourth target is tumor antigen. Both drugs are undergoing evaluation in different clinical trials (Table 1).

**Future directions**

Immunotherapy is known as the fourth cancer treatment after surgery, radiotherapy, and chemotherapy, which has changed the treatment patterns of patients with advanced cancer.
| Drug       | Study Title                                                                 | ClinicalTrials   | Phase   | Status               |
|------------|------------------------------------------------------------------------------|------------------|---------|----------------------|
| EU 101     | A Study to Evaluate Safety, Efficacy, and Pharmacokinetics in Participants With Advanced Solid Tumors | NCT04903873     | Phase 1 | Recruiting           |
|            | Expanded Access Program Using I-MM-101 for Patients With Advanced Pancreatic Cancer | NCT04137822     | Unknown | No longer available  |
|            | A Study of Belinostat + Carboplatin or Paclitaxel or Both in Patients With Ovarian Cancer in Need of Relapse Treatment | NCT00421889     | Phase 1 | Completed            |
|            | Study of Lanreotide in Metastatic or Recurrent Grade I-II Hindgut NET        | NCT03083210     | Phase 4 | Completed            |
| Urelumab   | Urelumab (4-1BB mAb) With Rituximab for Relapsed, Refractory or High-risk Untreated Chronic Lymphocytic Leukemia (CLL) Patients | NCT02420938     | Phase 2 | Withdrawn            |
|            | Combination Study of Urelumab and Rituximab in Patients With B-cell Non-Hodgkins Lymphoma | NCT01775631     | Phase 1 | Completed            |
|            | Phase I-II Study of Intratumoral Urelumab Combined With Nivolumab in Patients With Solid Tumors | NCT03792724     | Phase 1 | Not yet recruiting   |
|            | Combination Study of Urelumab and Cetuximab in Patients With Advanced/Metastatic Colorectal Cancer or Advanced/Metastatic Head and Neck Cancer | NCT02110082     | Phase 1 | Completed            |
|            | Neoadjuvant Nivolumab With and Without Urelumab in Cisplatin-Ineligible or Chemotherapy-refusing Patients With Muscle-Invasive Urothelial Carcinoma of the Bladder | NCT02845323     | Phase 2 | Recruiting           |
|            | An Investigational Immuno-therapy Study to Determine the Safety of Urelumab Given in Combination With Nivolumab in Solid Tumors and B-cell Non-Hodgkin’s Lymphoma | NCT02253992     | Phase 1 | Terminated           |
|            | A Phase 1 Open Label Study of the Safety and Tolerability of Elotuzumab (BMS-901608) Administered in Combination With Either Urelumab (BMS-986015) or Urelumab (BMS-663513) in Subjects With Multiple Myeloma | NCT02252263     | Phase 1 | Completed            |
|            | Safety, Tolerability, Pharmacokinetics, and Immunoregulatory Study of Urelumab (BMS-663513) in Subjects With Advanced and/or Metastatic Solid Tumors and Relapsed/Refractory B-cell Non-Hodgkin’s Lymphoma | NCT01471210     | Phase 1 | Completed            |
|            | Study of Urelumab in Subjects With Advanced and/or Metastatic Malignant Tumors | NCT02534506     | Phase 1 | Completed            |
|            | A Study of BMS-663513 Administered in Combination With Chemotherapy to Subjects With Advanced Solid Malignancies | NCT00351325     | Phase 1 | Terminated           |
|            | A Study of BMS-663513 in Combination With Chemoradiation in Subjects With Non Small Cell Lung Carcinoma (NSCLC) | NCT00461110     | Phase 1 | Terminated           |
|            | Study of BMS-663513 in Patients With Advanced Cancer | NCT00309023     | Phase 1 | Terminated           |
|            | Stereotactic Body Radiotherapy (SBRT) Plus Immunotherapy for Cancer | NCT03431948     | Phase 1 | Active, not recruiting |
|            | Anti-LAG-3 Alone and in Combination w/Nivolumab Treating Patients w/Recurrent GBM (Anti-4-1BB Arm Closed 10/16/18) | NCT02658981     | Phase 1 | Active, not recruiting |
|            | Phase II, 2nd Line Melanoma - RAND Monotherapy | NCT00612664     | Phase 2 | Completed            |
|            | Combination of Anti-4-1BB and Ipilimumab in Patients With Melanoma | NCT00803374     | Phase 1 | Withdrawn            |
|            | Platform Study of Neoadjuvant and Adjuvant Immunotherapy for Patients With Resectable Adenocarcinoma of the Pancreas | NCT02451982     | Phase 2 | Recruiting           |
|            | Combining PD-1 Blockade, 4-1BB Agonism and Adoptive Cell Therapy for Metastatic Melanoma | NCT02652455     | Early   | Active, not recruiting |
| Sytalizumab | The Safety and Efficacy of TWP-101 in Patients With Advanced Solid Tumor | NCT04871347     | Phase 1 | Not yet recruiting   |
|            | Safety, Tolerability and Pharmacokinetics of TWP-101 in Patients With Advanced Melanoma and Urothelial Carcinoma | NCT04871334     | Phase 1 | Recruiting           |
| LVGN-6051  | A Study of LVGN6051 Combined With Anlotinib in Patient With Soft Tissue Sarcoma | NCT05301764     | Phase 1 | Recruiting           |
|            | Phase 1 Trial of LVGN6051 as Single Agent and in Combination With Keytruda (MK-3475-A31/KEYNOTE-A31) in Advanced or Metastatic Malignancy | NCT04130542     | Phase 1 | Recruiting           |
|            | Study of LVGN6051 (4-1BB Agonist Antibody) in Advanced or Metastatic Malignancy | NCT04694781     | Phase 1 | Recruiting           |
|            | Study of LVGN616 and LVGN6051 in Combination With Nab-Paclitaxel or Bevacizumab and Cyclophosphamide in Metastatic Solid Tumors | NCT05075993     | Phase 1 | Recruiting           |
|            | Phase 1 Trial of LVGN7409 (CD40 Agonist Antibody) as Single Agent and Combination Therapies in Advanced or Metastatic Malignancy | NCT04635995     | Phase 1 | Recruiting           |

(Continued)
| Drug               | Study Title                                                                 | ClinicalTrials   | Phase | Status             |
|-------------------|-----------------------------------------------------------------------------|------------------|-------|--------------------|
| **YH-004**        | Study of YH004 (4-1BB Agonist Antibody) in Advanced or Metastatic Malignancy | NCT05040932      | Phase 1 | Recruiting         |
| **GEN1046**       | GEN1046 Safety and PK in Subjects With Advanced Solid Malignancies          | NCT04937153      | Phase 1 | Recruiting         |
|                   | Safety and Efficacy Study of GEN1046 as a Single Agent or in Combination With Another Anti-cancer Therapy for Treatment of Recurrent (Non-small Cell) Lung Cancer | NCT05117242      | Phase 2 | Recruiting         |
|                   | GEN1046 Safety Trial in Patients With Malignant Solid Tumors                | NCT03917381      | Phase 1 | Recruiting         |
| **PRS343**        | PRS-343 in HER2-Positive Solid Tumors                                       | NCT03330561      | Phase 1 | Completed          |
|                   | PRS-343 in Combination With Atezolizumab in HER2-Positive Solid Tumors      | NCT03650348      | Phase 1 | Active, not recruiting |
|                   | Cinrebafusp Alfa in Combination With Ramucirumab and Paclitaxel in HER2-High Gastric or GE/Adenocarcinoma and in Combination With Tucatinib in HER2-Low Gastric or GE/Adenocarcinoma | NCT05190445      | Phase 2 | Recruiting         |
| **ES101**         | A Study of ES101 (PD-L1x4-1BB Bispecific Antibody) in Patients With Advanced Malignant Thoracic Tumors | NCT04841538      | Phase 1 | Withdrawn          |
|                   | A Study of ES101 (PD-L1x4-1BB Bispecific Antibody) in Patients With Advanced Solid Tumors | NCT04009460      | Phase 1 | Terminated         |
|                   | Ankle - Brachial Index Measurement in Atrial Fibrillation                   | NCT02986282      | Not applicable | Completed |
| **Cinrebafusp alfa** | Cinrebafusp Alfa in Combination With Ramucirumab and Paclitaxel in HER2-High Gastric or GE/Adenocarcinoma and in Combination With Tucatinib in HER2-Low Gastric or GE/Adenocar | NCT05190445      | Phase 2 | Recruiting         |
| **HLX-35**        | HLX35(EGFR+4-1BB Bispecific) in Patients With Advanced or Metastatic Solid Tumors | NCT05360381      | Phase 1 | Not yet recruiting |
| **IBI319**        | Study of the Efficacy and Safety of IBI319 in Patients With Advanced Malignant Tumors | NCT04708210      | Phase 1 | Recruiting         |
| **TJ-033721**     | Study of TJ033721 in Subjects With Advanced or Metastatic Solid Tumors      | NCT04900818      | Phase 1 | Recruiting         |
| **ATG 101**       | A Study of Evaluating the Safety and Efficacy of ATG-101 in Patients With Metastatic/Advanced Solid Tumors and Mature B-cell Non-Hodgkin Lymphomas | NCT04986865      | Phase 1 | Recruiting         |
|                   | Study of ASC-101 in Patients With Hematologic Malignancies Who Receive Dual-cord Umbilical Cord Blood Transplantation | NCT01983761      | Phase 1 | Recruiting         |
| **Antithymocyte Globulin and Cyclosporine in Preventing Graft-Versus-Host Disease in Patients Undergoing Chemotherapy With or Without Radiation Therapy Followed By Donor Stem Cell Transplant for Acute Lymphoblastic Leukemia** | NCT00093587      | Not Unknown | Applied |
| **Thymoglobulin to Prevent Acute Graft vs. Host Disease (GvHD) in Patients With Acute Lymphocytic Leukemia (ALL) or Acute Myelogenous Leukemia (AML) Receiving a Stem Cell Transplant From a Haploidentical Donor** | NCT0088543 | Not Unknown | Completed |
| **LBL-024**       | A Phase II/II Clinical Study of LBL-024 in Patients With Advanced Malignant Tumors | NCT05170958      | Phase 1 | Recruiting         |
| **MCLA-145**      | A Study of Bispecific Antibody MCLA-145 in Patients With Advanced or Metastatic Malignancies | NCT03922204      | Phase 1 | Recruiting         |
| **ABL-503**       | This is a Study to Evaluate the Safety and Tolerability of ABL503, and to Determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of ABL503 in Subjects With Any Progressive Locally Advanced or Metastatic Solid Tumors | NCT04762664      | Phase 1 | Recruiting         |
| **PM 1032**       | A Study of Ramucirumab (IMC-1121B) and Paclitaxel in Participants With Solid Tumors | NCT01515306      | Phase 2 | Completed          |
| **QLF-31907**     | A Phase Ia Clinical Study of QLF31907 Injection in Patients With Advanced Malignant Tumors | NCT05150405      | Phase 1 | Recruiting         |
| **FS-120**        | FS120 First in Human Study in Patients With Advanced Malignancies           | NCT04648202      | Phase 1 | Recruiting         |
| **RO-7227166**    | A Study to Evaluate the Safety, Pharmacokinetics and Preliminary Anti-Tumor Activity of RO7227166 in Combination With Obinutuzumab and in Combination With Glofitamab Following a Pre-Treatment Dose of Obinutuzumab Administered in Participants With Relapsed/Refractory B-Cell Non-Hodgkin’s Lymphoma | NCT04077723      | Phase 1 | Recruiting         |
| **HBM-7008**      | HBM7008 -Study on Subjects With Advanced Solid Tumors                      | NCT05306444      | Phase 1 | Recruiting         |
| **ND-021**        | A Study of NM21-1480 in Adult Patients With Advanced Solid Tumors           | NCT04442126      | Phase 1 | Recruiting         |
| **GNC-035**       | A Study of GNC-035, a Tetra-specific Antibody, in Participants With Locally Advanced or Metastatic Breast Cancer | NCT05160545      | Phase 1 | Recruiting         |
|                   | A Study of GNC-035, a Tetra-specific Antibody, in Participants With Locally Advanced or Metastatic Solid Tumors | NCT05039931      | Phase 1 | Recruiting         |

(Continued)
| Drug       | Study Title                                                                 | ClinicalTrials | Phase     | Status              |
|------------|------------------------------------------------------------------------------|----------------|-----------|---------------------|
| GNC-035    | A Study of GNC-035, a Tetra-specific Antibody, in Participants With Relapsed/Refractory Hematologic Malignancy | NCT05104775    | Phase 1   | Recruiting          |
|            | A Study of GNC-038, a Tetra-specific Antibody, in Participants With R/R Diffuse Large B-cell Lymphoma (DLBCL) | NCT05192486    | Phase 1   | Recruiting          |
|            | A Study of GNC-038, a Tetra-specific Antibody, in Participants With R/R Non-Hodgkin Lymphoma | NCT04606433    | Phase 1   | Recruiting          |
|            | Mechanism of Resistance to GNC-038 in Relapsed and Refractory Diffuse Large B-cell Lymphoma | NCT05189782    | Unknown   | Recruiting          |
| ADG-106    | A Study to Evaluate the Combination of Nivolumab With ADG106 in Metastatic NSCLC | NCT05236608    | Phase 1   | Recruiting          |
|            | A Study of ADG106 In Combination With PD-1 Antibody In Advanced or Metastatic Solid Tumors and/or Non-Hodgkin Lymphoma | NCT04775680    | Phase 1   | Recruiting          |
|            | A Phase Ib Safety lead-in, Followed by Phase II Trial of ADG106 in Combination With Neoadjuvant Chemotherapy in HER2 Negative Breast Cancer | NCT05275777    | Phase 1   | Recruiting          |
|            | Study of ADG106 With Advanced or Metastatic Solid Tumors and/or Non-Hodgkin Lymphoma | NCT03802955    | Phase 1   | Recruiting          |
|            | Study of 4-1BB Agonist ADG106 With Advanced or Metastatic Solid Tumors and/or Non-Hodgkin Lymphoma | NCT03707093    | Phase 1   | Active, not recruiting |
|            | ADG126, ADG126 in Combination With Anti PDI Antibody, and ADG126 in Combination With ADG106 in Advanced/Metastatic Solid Tumors | NCT04654069    | Phase 1   | Recruiting          |
|            | A Phase Ib Study of ADG116, ADG116 Combined With Anti-PD-1 Antibody or Anti-4-1BB Antibody in Solid Tumors Patients | NCT04501276    | Phase 1   | Recruiting          |
| Utmolumab  | Utmolumab and BA101b Vaccination in Patients With HPV-16-Positive Incurable Oropharyngeal Cancer | NCT03258008    | Phase 2   | Completed           |
|            | T-Cell Infusion, Aldesleukin, and Utmolumab in Treating Patients With Recurrent Ovarian Cancer | NCT03318900    | Phase 1   | Active, not recruiting |
|            | Safety and Efficacy of Arcapitabone Cileoleucel in Combination With Utmolumab in Adults With Refractory Large B-cell Lymphoma | NCT03704298    | Phase 1   | Active, not recruiting |
|            | Avelumab, Utmolumab, Rituximab, Ibrutinib, and Combination Chemotherapy in Treating Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma | NCT03440567    | Phase 1   | Active, not recruiting |
|            | The AVIATOR Study: Trastuzumab and Vinorelbine With Avelumab OR Avelumab and Utmolumab in Advanced HER2+ Breast Cancer | NCT03414658    | Phase 2   | Recruiting          |
|            | 4-1BB Agonist Monoclonal Antibody PF-05082566 With Trastuzumab Emtansine or Trastuzumab in Treating Patients With Advanced HER2-Positive Breast Cancer | NCT03364348    | Phase 1   | Active, not recruiting |
|            | Utmolumab, Cetuximab, and Irinotecan Hydrochloride in Treating Patients With Metastatic Colorectal Cancer | NCT03290937    | Phase 1   | Active, not recruiting |
|            | Avelumab, Utmolumab, Anti-OX40 Antibody PF-04518600, and Radiation Therapy in Treating Patients With Advanced Malignancies | NCT03217747    | Phase 2   | Active, not recruiting |
| RITUXIMAB  | RITUXIMAB + IMMUNOTHERAPY IN FOLLICULAR LYMPHOMA                              | NCT03636503    | Phase 1   | Active, not recruiting |
|            | A Study Of Avelumab In Combination With Other Cancer Immunotherapies In Advanced Malignancies (JAVELIN Medley) | NCT02554812    | Phase 2   | Active, not recruiting |
|            | Avelumab In Combination Regimens That Include An Immune Agonist, Epigenetic Modulator, CD20 Antagonist and/or Conventional Chemotherapy in Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (R/R DLBCL) | NCT02951156    | Phase 3   | Terminated          |
|            | Avelumab With Binimetinib, Sunitizumab Govitecan, or Liposomal Doxorubicin in Treating Patients With Stage IV or Unresectable, Recurrent Triple Negative Breast Cancer | NCT03971409    | Phase 2   | Recruiting          |
|            | Continued Access Study for Participants Deriving Benefit in Pfizer-Sponsored Avelumab Parent Studies That Are Closing | NCT03059522    | Phase 3   | Recruiting          |
|            | Study Of OX40 Agonist PF-04518600 Alone And In Combination With 4-1BB Agonist PF-05082566 | NCT02315066    | Phase 1   | Completed           |

(Continued)
However, only a minority of cancer patients can benefit from it. Treatment methods such as surgery, chemotherapy, radiotherapy, and targeted therapy can synergize with immunotherapy to enhance the curative effect. Guillerey et al. found that anti-4-1BB mAb combined with chemotherapy could prevent MM relapse and prolong survival in MM mice (47). A study undertaken by Newcomb et al. demonstrated that radiation could synergistically enhance the antitumor effect of anti-4-1BB therapy in a mouse glioma model (48). Moreover, anti-4-1BB mAbs could enhance the efficacy of other antitumor Abs (such as cetuximab, rituximab, and trastuzumab) and exert synergistic effects. Taken together, combination therapy for tumors may also be the future direction of tumor therapy.

TABLE 1 Continued

| Drug | Study Title | ClinicalTrials | Phase | Status |
|------|-------------|----------------|-------|--------|
| ATOR-1017 | ATOR-1017 First-in-human Study | NCT04144842 | Phase 1 | Recruiting |
| AGEN-2373 | Anti-4-1BB and Anti-CTLA-4 Monoclonal Antibody in Patient With Advanced Cancer | NCT04121676 | Phase 1 | Recruiting |
| CTX-471 | Study of CTX-471 in Patients Post PD-1/PD-L1 Inhibitors in Metastatic or Locally Advanced Malignancies | NCT03881488 | Phase 1 | Recruiting |
| PRS-344 | A Study of PRS-344/S095012 (PD-1x4-1BB Bispecific Antibody-Anticalin Fusion) in Patients With Solid Tumors | NCT03519388 | Phase 1 | Recruiting |
| RO-7122290 | Study To Evaluate Safety, Pharmacokinetics, Pharmacodynamics, And Preliminary Anti-Tumor Activity Of RO7122290 In Combination With Chisatamab With Obinutuzumab Pre-Treatment | NCT04826003 | Phase 1 | Recruiting |
| Anti BCMA CART cell therapy | Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatments and Combinations in Patients With Urothelial Carcinoma (MORPHEUS-UC) | NCT03767725 | Phase 1 | Unknown |
| BCMA Chimeric Antigen Receptor Expressing T Cells Therapy for Relapsed/Refractory Multiple Myeloma | Master Protocol for the Phase 1 Study of Cell Therapies in Multiple Myeloma | NCT03943472 | Early Phase 1 | Recruiting |
| Study of T Cells Targeting CD19/BCMA (CART-19/BCMA) for High Risk Multiple Myeloma Followed With Auto-HSCT | NCT03455972 | Phase 1 | Recruiting |
| A Study of BCMA-directed CAR-T Cells Treatment in Subjects With r/r Multiple Myeloma | NCT03751293 | Phase 1 | Unknown |
| Clinical Trial Using Humanized CART Directed Against BCMA (AR10002h) in Patients With Relapsed/Refractory Multiple Myeloma to Proteasome Inhibitors, Immunomodulators and Anti-CD38 Antibody | NCT04309981 | Phase 1 | Recruiting |
| A Study of BCMA-directed CAR-T Cells Treatment in Subjects With r/r Multiple Myeloma | NCT04322292 | Phase 1 | Unknown |
| BCMA-directed CAR-T Cell Therapy in Adult Patients With Relapsed and/or Refractory Multiple Myeloma | NCT04318327 | Phase 1 | Recruiting |
| Humanized CD8+ T-cells Expressing an Anti-BCMA CAR in Patients With Myeloma | NCT03448978 | Phase 1 | Completed |
| CART-BCMA Cells for Multiple Myeloma | NCT02546167 | Phase 1 | Completed |
| Humanized CAR-T Cells of Anti-BCAM and Anti-CD19 Against Relapsed and Refractory Multiple Myeloma | NCT04194931 | Phase 1 | Unknown |
| BCMA Chimeric Antigen Receptor Expressing T Cells in Multiple Myeloma Safety and Efficacy Evaluation of BCMA-CART for Treating Multiple Myeloma | NCT03093168 | Phase 1 | Unknown |
| NCT03492268 | Not applicable Withdrawn |
| Efficacy and Safety Evaluation of BCMA-UCART | NCT03752541 | Not applicable Suspended |
| HOT-1030 | A Study of HOT1030 in Patients With Advanced Solid Tumors | NCT05060263 | Phase 1 | Recruiting |
| Delolimogene mupadenorepvec | A Phase I/II Trial Investigating LOAd703 in Combination With Atezolizumab in Malignant Melanoma | NCT04123470 | Phase 1 | Recruiting |
| A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Metastatic Colorectal Cancer (Morpheus-CRC) | NCT03555149 | Phase 1 | Recruiting |
| LOAd703 Oncolytic Virus Therapy for Pancreatic Cancer | NCT02075196 | Phase 1 | Recruiting |
| BT 7480 | Study BT7480-100 in Patients With Advanced Malignancies Associated With Nectin-4 Expression | NCT05163041 | Phase 1 | Recruiting |

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Conclusion

To summarize, existing studies support immunotherapies targeting the 4-1BB pathway for the treatment of cancer. In the study, we have summarized the structure of 4-1BB and its ligand as well as the expression in various immune cells and tumor cells. More importantly, we discuss the role of 4-1BB in the microenvironment and tumor progression. Furthermore, the development of drug-targeted 4-1BB was summarized and updated, which exhibited tremendous potential in clinical trials. Although the anti-4-1BB therapy provides hope for cancer treatment, the effectiveness of drugs targeting 4-1BB in clinical antitumor therapy alone or in combination with other antitumor therapies still needs to be investigated in the future.

Author contributions

Y-TW, K-FC and Q-BL conceived the review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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