Review Article

The BiTE (Bispecific T-Cell Engager) Platform: Development and Future Potential of a Targeted Immuno-Oncology Therapy Across Tumor Types

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Immuno-oncology therapies engage the immune system to treat cancer. BiTE (bispecific T-cell engager) technology is a targeted immuno-oncology platform that connects patients' own T cells to malignant cells. The modular nature of BiTE technology facilitates the generation of molecules against tumor-specific antigens, allowing off-the-shelf immuno-oncotherapy. Blinatumomab was the first approved canonical BiTE molecule and targets CD19 surface antigens on B cells, making blinatumomab largely independent of genetic alterations or intracellular escape mechanisms. Additional BiTE molecules in development target other hematologic malignancies (eg, multiple myeloma, acute myeloid leukemia, and B-cell non-Hodgkin lymphoma) and solid tumors (eg, prostate cancer, glioblastoma, gastric cancer, and small-cell lung cancer). BiTE molecules with an extended half-life relative to the canonical BiTE molecules are also being developed. Advances in immuno-oncology made with BiTE technology could substantially improve the treatment of hematologic and solid tumors and offer enhanced activity in combination with other treatments. ***Cancer* 2020;126:3192-3201**.

KEYWORDS: B cell, blinatumomab, hematologic malignancies, T cell, tumor-specific antigen.

INTRODUCTION

Immuno-oncology therapies are clinically validated methods of treating various blood cancers and solid tumors.[1,2] Hematologic cancers are particularly well suited for immune-targeting therapies, as malignant blood cells circulate with immune cells.[2] Several immuno-oncology therapies are in development.

Monoclonal antibody checkpoint inhibitors that block binding of checkpoint proteins (eg, programmed cell death protein 1 [PD-1] and cytotoxic T-lymphocyte–associated protein 4 [CTLA-4]) are effective in many types of cancer. They demonstrate good efficacy and safety in several solid tumors, particularly when targeting PD-1, with successful treatment in non–small-cell lung, kidney, and bladder cancers.[3-5] However, many patients do not respond to, or relapse after, treatment with checkpoint inhibitors. Except in non-Hodgkin lymphoma, data from hematologic malignancies have been mostly disappointing, particularly in myeloma and leukemia,[5-7] with overall response rates of 12.0% to 48.5% in approved indications.[8-15]

By comparison, response rates are higher with other immuno-oncology therapies. Chimeric antigen-receptor (CAR) T-cell therapies reprogram a patient's T cells to attack a specific cellular antigen, such as CD19 in the treatment of B-cell malignancies and B-cell maturation antigen (BCMA) in multiple myeloma (MM). CAR T-cell therapies have demonstrated promising efficacy in treating hematologic cancers; although their use in solid tumors has not been as successful, there have been some positive results in neuroblastoma, human epidermal growth factor receptor 2 tumors, and non–small-cell lung cancer.[16-19] The genetic modification and in vitro proliferation of T cells require a lengthy, complex manufacturing process, which is a drawback of this therapy, limiting broad and timely availability for patients. Another disadvantage is the current requirement for lymphodepletion by prior conditioning chemotherapy as a prerequisite for enhanced efficacy.[20]

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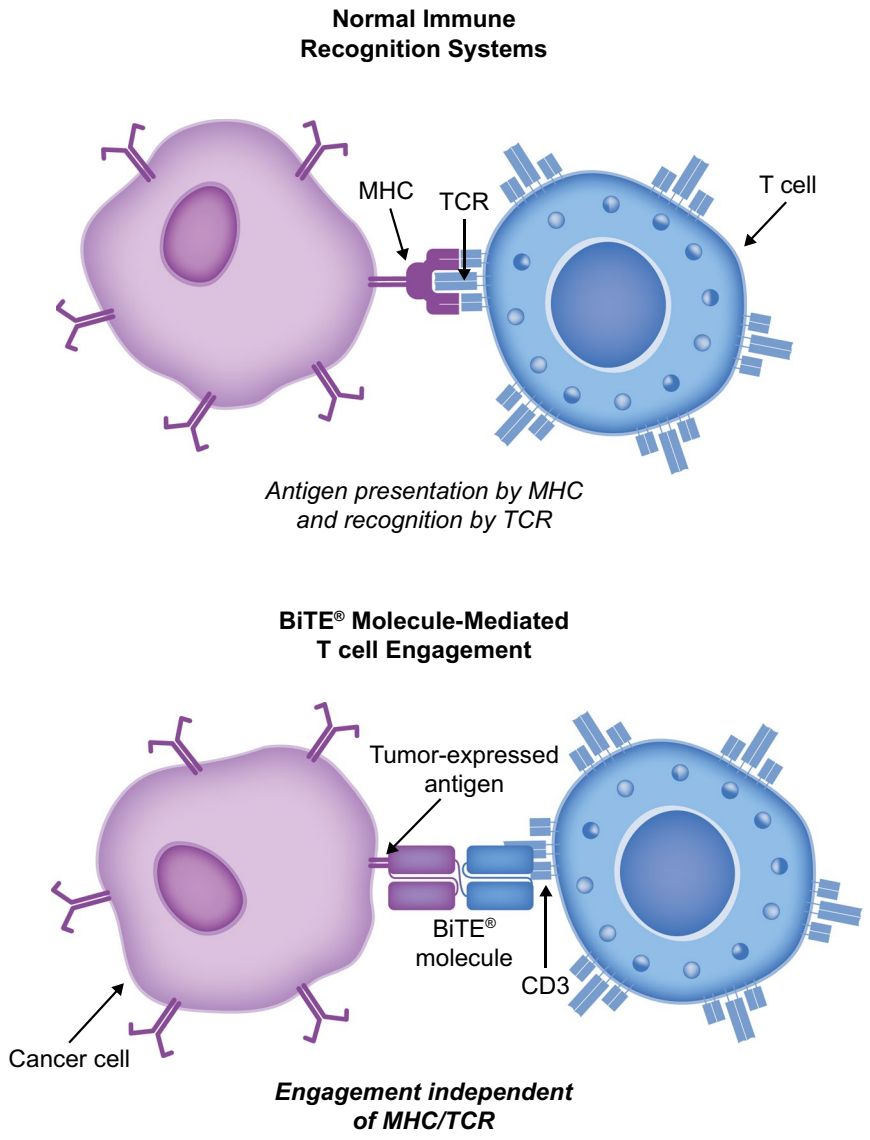

FIGURE 1. The mechanism of action for bispecific T-cell engager (BiTE) is illustrated. CD indicates cluster of differentiation; MHC, major histocompatibility complex; TCR, T-cell receptor.

BiTE (bispecific T-cell engager) therapies link endogenous T cells to tumor-expressed antigens, activating the cytotoxic potential of a patient's own T cells to eliminate cancer without genetic alteration of the T cells or need for ex vivo expansion/manipulation.[21,22] BiTE molecules can be used as monotherapies and offer enhanced activity in combination with other treatments.

BITE MECHANISM OF ACTION AND NOVEL CONSTRUCTS AIMED AT NEW TUMOR-EXPRESSED ANTIGENS

BiTE molecules are antibody constructs with 2 binding domains: 1 recognizing tumor-expressed antigens (eg, BCMA, CD19, δ-like protein 3 [DLL3]), and another, CD3, recognizing T cells (Fig. 1). The binding domains are 2 single-chain variable fragment (scFv) regions from monoclonal antibodies, joined by a flexible peptide linker. The first scFv binding domain can be modified to target any surface antigen, providing off-the-shelf, immediate therapies against various tumors and allowing retreatment. The second scFv binding domain is always specific for CD3, the invariable part of the T-cell receptor complex. When a BiTE molecule engages both a cytotoxic T cell and a tumor cell, the T cells start to proliferate, increasing overall numbers of effector cells and strengthening the potency of BiTE therapy.[23] Malignant

cell lysis is then triggered. Because this happens without the need for co-stimulation or typical major histocompatibility complex mechanisms, BiTE molecules can engage any T cells.[24,25]

Blinatumomab, the first and currently only approved BiTE therapy, targets the CD19 receptor on both normal and malignant B cells, and is a highly potent molecule with cytotoxic effects observed at low exposures (10-100 pg/mL)[26]; in its presence, T cells can perform serial-target lysis, rapidly binding and killing many cells.[27] This mechanism of action is the hallmark of BiTE therapies and is observed in other BiTE molecules under development.[24] The efficacy and safety of blinatumomab is established in acute lymphoblastic leukemia (ALL), having received US Food and Drug Administration-accelerated approval in 2014 and full approval for relapsed or refractory (R/R) B-cell precursor (BCP) ALL in 2017. Blinatumomab gained accelerated approval for the treatment of BCP-ALL with minimal residual disease (MRD) in 2018, the first approval for this indication. It was also approved by the European Medicines Agency for Philadelphia chromosome (Ph)-negative, R/R BCP-ALL in November 2015. Blinatumomab has approval in 57 countries, including Japan, all member countries of the European Union, Canada, and Australia for R/R BCP-ALL in adults and children.[28]

BLINATUMOMAB FOR THE TREATMENT OF PATIENTS WITH BCP-ALL

Blinatumomab has revolutionized the treatment of BCP-ALL, increasing overall survival (OS) and reducing the incidence of selected adverse events (AEs) versus standard-of-care (SOC) chemotherapy. The safety and efficacy of blinatumomab for BCP-ALL in adults and children were demonstrated by several pivotal trials, including randomized controlled trials (Table 1).[29-32] Only data from 2 single-arm studies (clinicaltrials.gov identifiers NCT01626495 and NCT01029366) are available for CAR T-cell therapy, in which 25 pediatric patients (aged 5-22 years) and 5 older patients (aged 26-60 years) with R/R BCP-ALL and T-cell ALL were treated. However, the results are encouraging (a complete response [CR] in 90%, sustained remission with 6-month event-free survival in 67%, and an OS rate of 78% [median follow-up, 7 months; range, 1-24 months]).[33]

The TOWER study (A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-Precursor ALL; clinicaltrials.gov identifier NCT02013167) compared the effects of blinatumomab monotherapy against SOC chemotherapy in heavily pretreated adults with Ph-negative, R/R BCP-ALL.[29] The trial was stopped early because of the survival benefit observed. AEs in the blinatumomab group were consistent with those observed in previous studies, and exposure-adjusted AE rates were lower for blinatumomab versus SOC.[34] Blinatumomab is also effective in adults with Ph-positive, R/R BCP-ALL and in children with Ph-negative, R/R BCP-ALL.[30,32]

Some 30% to 50% of adults with BCP-ALL in complete hematologic remission exhibit persistent MRD. Blinatumomab was evaluated in the single-arm, phase 2 BLAST study (A Confirmatory Multicenter, Single-Arm Study to Assess the Efficacy, Safety, and Tolerability of the BiTE Antibody Blinatumomab in Adult Patients With MRD of B-Precursor Acute Lymphoblastic Leukemia; clinicaltrials.gov identifier NCT01207388) of patients with BCP-ALL in first or later complete remission with MRD, inducing a complete MRD response in most patients, with significantly longer relapse-free survival and OS. Seventy-eight percent of MRD-positive patients achieved MRD negativity after blinatumomab therapy (Table 1). The 5-year OS analysis showed a median OS of 36.5 months, and more than one-half of those who achieved a complete MRD response after the first cycle of blinatumomab were alive at 5 years, suggesting that the treatment might be curative in some patients.[35] Cytokine release syndrome (CRS)-associated AEs were observed infrequently.[31] Additional studies evaluating blinatumomab in frontline settings and combination therapies are ongoing (eg, NCT03023878 and NCT03340766).

CD19-targeted therapies have been associated with failure because of CD19 antigen loss after treatment, with rates ranging from 8% to 35% for blinatumomab and from 39% to 65% for CAR T-cell therapies.[36-40] The mechanisms leading to therapy failure are poorly understood but may include immunoediting, whereby antigen loss is caused by a T-cell–dependent immunoselection process that allows escape of tumor cells.[41] Lineage switch and epitope loss under therapy pressure have also been suggested as mechanisms of tumor escape, although, with regard to epitope loss, a recent study found that some CD19 isoforms contributing to CAR T-cell escape preexisted at diagnosis; this finding suggests that the application of combined treatment approaches might be beneficial.[38,42] Inhibitory T-cell signaling is another mechanism

TABLE 1. Details of the TOWER, ALCANTARA, BLAST, and Pediatric Registrational Blinatumomab Studies

Study	Patients	Study Design	Outcome	Adverse Events
TOWER (NCT02013167; Kantarjian 2017[29])[a]	Heavily pretreated adults with Ph−, R/R BCP-ALL	Phase 3, prospective, randomized (2:1 blinatumomab [n = 271] or SOC chemotherapy [n = 134]) Primary outcome, OS	• Median OS, 7.7 mo (95% CI, 5.6-9.6 mo) blinatumomab vs 4 mo (95% CI, 2.9-5.3 mo) SOC • Prespecified stopping boundary was reached; hazard ratio of death, 0.71 (95% CI, 0.55-0.93; $P = .01$) • Remission rates ≤12 wk after treatment significantly higher in blinatumomab vs SOC; CR, 34% vs 16%, respectively ($P < .001$); CR, CRh, or Cri, 44% vs 25%, respectively ($P < .001$) ◦ Median duration of remission in patients with CR, CRh, or Cri: 7.3 mo (95% CI, 5.8-9.9 mo) blinatumomab vs 4.6 mo (95% CI, 1.8-19.0 mo) SOC • MRD negativity achieved 78% blinatumomab vs 48% SOC (treatment difference, 28%; 95% CI, 9%-47%) among patients with CR, CRh, or CRi • 6-mo EFS, 31% blinatumomab vs 12% SOC	• AEs: 99% occurrence in each group • SAEs: 62% blinatumomab vs 45% SOC • SAE rate adjusted for treatment exposure: 349.4 per 100 patient-y blinatumomab vs 641.9 per 100 patient-y SOC • AEs grade ≥3: 87% blinatumomab vs 92% SOC • CRS grade ≥3: 4.9% blinatumomab vs 0% SOC • Neurologic AEs grade ≥3: 9.4% blinatumomab vs 8.3% SOC • Fatal AEs: 19% blinatumomab vs 17% SOC; overall EAE rate adjusted for treatment exposure time significantly lower for blinatumomab versus SOC: ◦ Any grade AEs: 46.16 vs 137.64 events per patient-y ($P < .001$) ◦ Grade 3 AEs: 10.73 vs 45.27 events per patient-y ($P < .001$) ◦ Fatal AEs: 0.57 vs 1.28 events per patient-y ($P < .005$) • EAE rate of grade ≥3 CRS higher for blinatumomab than for SOC (0.16 vs 0 events per patient-y; $P = .038$)
ALCANTARA (NCT02000427; Martinelli 2017[30])[b]	Adults with Ph+, R/R BCP-ALL who failed ≥1 second-generation or later TKI or were intolerant to second-generation or later TKIs and intolerant or refractory to imatinib (N = 45)	Phase 2, open-label, single-arm Primary endpoint, CR or CRh within first 2 cycles	• 36% (95% CI, 22%-51%) achieved CR/CRh in first 2 cycles • 86% Of CR/CRh responders achieved complete MRD • Median RFS: 6.7 mo (95% CI, 4.4 mo to NE); median OS: 7.1 mo (95% CI, 5.6 mo to NE)	• Grade ≥3 TEAEs, 82% • 44% Of TEAEs thought blinatumomab-related; most common were febrile neutropenia (11%) and increased ALT (11%) • 11% Had fatal AEs, 1 (septic shock) considered treatment related • CRS (grade 1 or 2), 7% • 47% Experienced neurologic symptoms, most common paresthesia (13%) ◦ Grade 3 neurologic events in 7%
BLAST (NCT01207388; Gokbuget 2018[31])[c]	Adults with BCP-ALL in first or later hematologic CR with persistent or recurrent MRD ($\geq 10^{-3}$; N = 116)	Phase 2, open-label, single-arm Primary endpoint, complete MRD response after 1 cycle	• 78% Of evaluable patients achieved complete MRD in cycle 1, 80% after 2 cycles; median OS, 36.5 mo • Landmark analyses by complete MRD response ◦ Median RFS: 23.6 mo with complete MRD vs 5.7 mo without complete MRD ($P = .002$) ◦ Median OS: 38.9 vs 12.5 mo, respectively ($P = .002$)	Rate of AEs was similar to other blinatumomab studies; all patients experienced ≥1 AE • 33% Grade 3, 27% grade 4 • 3% Had grade ≤3 CRS, all during cycle 1 • 53% Any grade neurologic events ◦ Grade 3, 10%; grade 4, 3% • Two fatal AEs reported in the first cycle, 1 considered treatment related (atypical pneumonitis with H1N1 influenza)

TABLE 1. *Continued*

Study	Patients	Study Design	Outcome	Adverse Events
Pediatric Registrational Study (NCT01471782; von Stackelberg 2016[32])[d]	Pediatric and adolescent patients with R/R BCP-ALL	Open-label, phase 1/2 study: phase 1 investigated dose escalation (n = 49), and phase 2 was an extended cohort efficacy study (n = 44) Primary endpoints: MTD (phase 1) and CR rate within the first 2 cycles (phase 2)	• The MTD was 15 μg/m^2/d; recommended dosage 5 μg/m^2/d for the first 7 d, followed by 15 μg/m^2/d thereafter • 39% (95% CI, 27%-51%) achieved CR in first 2 cycles; 52% achieved complete MRD response • Median RFS for those who achieved CR: 4.4 mo (95% CI, 2.3-7.6 mo) • Median OS for all patients: 7.5 mo (95% CI, 4.0-11.8 mo)	• 8% Had DLT in cycle 1 (phase 1); most frequent grade ≥3 AEs: anemia (36%), thrombocytopenia (21%), febrile neutropenia (17%), and hypokalemia (17%) • 9% Had fatal AEs • 11% Treated with recommended dose had any grade CRS; grade 3, 4%, grade 4, 1% • 4% Had grade 3 neurologic events; 3% interrupted treatment after grade 2 seizures

Abbreviations: –, negative; +, positive; AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; BCP, B-cell precursor; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, incomplete hematologic recovery; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; EAE, exposure-adjusted event; EFS, event-free survival; MRD, minimal residual disease; MTD, maximum tolerated dose; NE, not estimable; OS, overall survival; Ph–, Philadelphia chromosome-negative; Ph+, Philadelphia chromosome-positive; R/R, relapsed or refractory; RFS, relapse-free survival; SAE, serious adverse event; SOC, standard of care; TEAEs, treatment-emergent adverse events; TKI, tyrosine kinase inhibitor.

[a]TOWER: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL) (clinicaltrials.gov identifier NCT02013167).

[b]ALCANTRA: A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the Bispecific T-Cell Engager (BiTE) Antibody Blinatumomab in Adult Subjects With Relapsed/Refractory Philadelphia Positive B-Precursor Acute Lymphoblastic Leukemia (clinicaltrials.gov identifier NCT02000427).

[c]BLAST: A Confirmatory Multicenter, Single-Arm Study to Assess the Efficacy, Safety, and Tolerability of the BiTE Antibody Blinatumomab in Adult Patients With Minimal Residual Disease (MRD) of B-Precursor Acute Lymphoblastic Leukemia (clinicaltrials.gov identifier NCT01207388).

[d]Pediatric Registrational Study: A Single-Arm Multicenter Phase II Study Preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE Antibody Blinatumomab (MT103) in Pediatric and Adolescent Patients With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL) (clinicaltrials.gov identifier NCT01471782).

associated with immunotherapy failure. Here, the inhibitory programmed death ligand-1 (PD-L1) is of interest because it is increased in B-cell ALL cells from patients who are refractory to blinatumomab and can confer resistance to CD3 BiTE molecules.[43] This inhibition could be overturned by designing a CD28/PD-L1 BiTE to trigger the CD28 co-stimulatory signal, instead of the inhibitory signaling pathway generally observed upon binding of the T cell to PD-L1–expressing cancer cells.[43] Dual-targeted CAR T cells are also being investigated to offset tumor antigen loss, either by modification of individual T cells with 2 CAR molecules and 2 different binding domains (dual-signaling CAR), or with 1 CAR molecule containing 2 different binding domains in tandem (TanCAR).[44]

AEs and Management

The most common AEs in blinatumomab clinical trials are pyrexia, neutropenia, and thrombocytopenia.[45] Key risks include CRS, neurotoxicity, and medication errors.[46] Neurotoxicity is also observed with CD19-specific CAR T-cell therapies, although factors other than CD19 might be involved.[47] The results of an ongoing phase 1/1b study on CD20/CD3 targets found that grade ≥3 neurologic AEs were rare (3% of all grade 3).[48] The CRS response with blinatumomab is usually mild but, in rare cases, can be severe and life-threatening.[45] Premedication with corticosteroids can reduce inflammatory reactions; the infusion of prednisone or dexamethasone before the first dose of blinatumomab and step-up dosing is recommended to reduce the risk of CRS.[45] This preemptive use of corticosteroids has provided a rationale for dexamethasone premedication when using other BiTE molecules, although it is not clear whether the effect can be generalized across the BiTE platform, and other CRS management strategies are under investigation. Interleukin 6 is a cytokine mediator of CRS and is elevated in patients with CRS.[34,49] The interleukin 6 receptor antagonist tocilizumab has been used to treat severe CRS after CAR T-cell therapy.[49] Inhibitors of tumor necrosis factor-α have also been used clinically to manage CRS.[33]

Half-Life–Extended BiTE Molecules

One characteristic of canonical BiTE molecules is their short half-life of 2 to 4 hours, which necessitates administration with continuous intravenous infusion[28,50]; this is typically administered using 2-day, 4-day, or 7-day infusion bags (depending on country approval), so outpatient administration is possible.[45,50] Full-length monoclonal antibodies have a longer half-life because of neonatal crystallizable fragment (Fc) receptor-mediated (Rn) recycling.

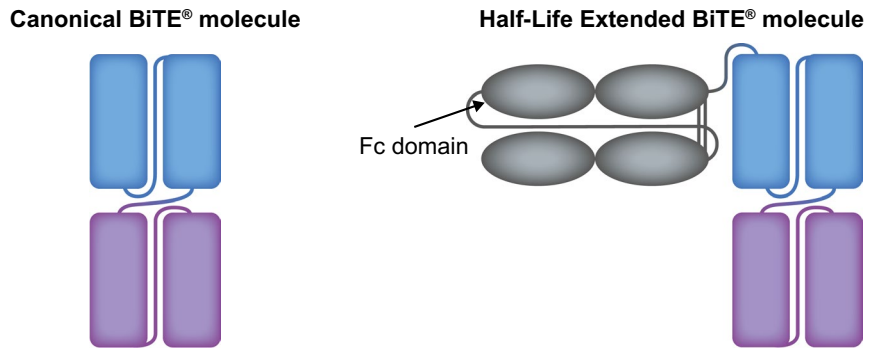

FIGURE 2. Canonical and half-life extended varieties of bispecific T-cell engager (BiTE) molecules are illustrated. Fc indicates crystallizable fragment.

TABLE 2. Tumor-Antigen Targets for Investigational Bispecific T-Cell Engager (BiTE) Molecules

Target	Cancer	BiTE Molecule	Type of BiTE	Study No.
CD19	DLBCL, MCL, FL	AMG 562	HLE	NCT03571828
CD33	AML	AMG 330	Canonical	NCT02520427
		AMG 673	HLE	NCT03224819
FLT3	AML	AMG 427	HLE	NCT03541369
BCMA	MM	AMG 420 (formerly BI 836909)	Canonical	NCT02514239
				NCT03836053
		AMG 701	HLE	NCT03287908
PSMA	Prostate	AMG 160	HLE	NCT03792841
		AMG 212	Canonical	NCT01723475
EGFRvIII	Glioblastoma	AMG 596	Canonical	NCT03296696
DLL3	Small-cell lung	AMG 757	HLE	NCT03319940
MUC17	Gastric	AMG 199	HLE	NCT04117958
				NCT20180290
CLDN18.2	Gastric	AMG 910	HLE	NCT04260191

Abbreviations: AMG, Amgen identification number; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen; CLDN18.2, claudin-18 isoform 2; DLBCL, diffuse large B-cell lymphoma; DLL3, δ-like protein 3; EGFRvIII, epidermal growth factor receptor vIII; FL, follicular lymphoma; FLT3, FMS-like tyrosine kinase 3; HLE, half-life extended; MCL, mantle cell lymphoma; MM, multiple myeloma; MUC17, mucin 17; NCT, clinicaltrials.gov national clinical trials identification number; PSMA, prostate-specific membrane antigen.

Canonical BiTE molecules lack the Fc portion responsible for FcRn binding and are not expected to undergo FcRn recycling; this likely contributes to their short half-lives (Fig. 2). Although continuous intravenous infusions can be burdensome for patients, a short half-life is beneficial in the event of serious AEs, because stopping infusion reduces serum levels quickly, generally leading to faster resolution of the AE.

The extension of serum half-life potentially will make administration easier for patients; therefore, half-life–extended (HLE) BiTE molecules (a canonical BiTE molecule fused to an Fc domain) (Fig. 2) have been developed. Comparative studies in nonhuman primates indicate that HLE BiTE molecules retain in vivo and in vitro activity similar to canonical BiTE molecules[51,52] and have demonstrated that fusing a CD19 BiTE molecule to the Fc domain resulted in a half-life of 210 hours after a single intravenous dose, potentially allowing once-weekly dosing.[52] Work on an anti-BCMA HLE BiTE molecule has indicated suitability for once-weekly dosing in patients with MM.[53] Several HLE BiTE molecules are in development, including AMG 160 (antiprostate-specific membrane antigen [anti-PSMA]), AMG 199 (antimucin 17 [anti-MUC17]), AMG 562 (anti-CD19), AMG 673 (anti-CD33), AMG 701 (anti-BCMA), AMG 910 (anti-CLDN18.2), and AMG 757 (anti-DLL3) (Table 2).[54]

TUMOR-SPECIFIC BITE ANTIGEN TARGETS

Hematologic Malignancies

CD19

Because CD19 is broadly and consistently expressed throughout B-cell development, it is an attractive target across all B-cell malignancies. Blinatumomab is being investigated in additional B-cell malignancies, including non-Hodgkin lymphoma, as both monotherapy and combination therapy (eg, NCT03114865, NCT02910063,

and NCT03072771). As an alternative to continuous intravenous dosing, subcutaneous delivery is being investigated in a phase 1b study (NCT02961881). The first-in-human study of the CD19 HLE BiTE molecule AMG 562 in patients with R/R diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma is recruiting (NCT03571828) (Table 2).

B-cell maturation antigen

B-cell maturation factor, also known as tumor necrosis factor receptor superfamily 17 or CD269, is a promising target expressed on the malignant cells of most patients with MM. A phase 1 study of CAR T-cell therapy targeting BCMA, involving patients with R/R MM (N = 33), showed an objective response rate of 85%, with a 45% CR rate and a median progression-free survival of 11.8 months. However, that study was not randomized, thus potentially confounding the results. It also produced a relatively high rate of AEs, with 97% of patients having grade ≥3 AEs, including hematologic and neurologic toxicity and CRS.[55]

AMG 420 (formerly BI 836909) is a BiTE molecule that, in preclinical studies, triggered the lysis of BCMA-expressing cells.[56] The AMG 420 first-in-human phase 1 dose-escalation study treated patients with R/R MM who had received ≥2 prior treatment lines. The maximum tolerated dose was 400 μg daily; at that dose, the overall response rate was 70% (7 of 10 patients), and 5 of the 7 patients achieved an MRD-negative CR. Grade 3 peripheral polyneuropathy was a dose-limiting toxicity in 1 patient (2.5%) at 400 μg daily but resolved with intravenous immunoglobulin and corticosteroids.[57] AMG 701 is an anti-BCMA HLE BiTE molecule that has shown promising in vitro antimyeloma activity as a monotherapy in an ongoing phase 1 trial (NCT03287908).[58]

CD33

The CD33 antigen is expressed in acute myeloid leukemia (AML), myelodysplastic syndrome, and chronic myeloid leukemia.[59] The suitability of CD33 as an antigen target for BiTE technology was confirmed in a study assessing its expression in patients with AML, and the cytotoxicity of the CD33 BiTE molecule AMG 330, using primary AML blasts and AML cell lines, also was established.[60,61] An ongoing phase 1 dose-escalation study of AMG 330 in patients with R/R AML is assessing the safety, pharmacokinetics, pharmacodynamics, and maximum tolerated dose. Preliminary data are encouraging; AMG 330 dosed at up to 480 μg daily is tolerable and has antileukemic activity in heavily pretreated patients. Also under development is the CD33 HLE BiTE molecule AMG 673.[54,62]

FMS-like tyrosine kinase 3

The FMS-like tyrosine kinase 3 (FLT3) antigen has been detected in most AML blasts and leukemic stem cells, whereas cell surface expression on nonmalignant cells is limited to immature hematopoietic progenitor cells. The oral FLT3/receptor tyrosine kinase AXL inhibitor gilteritinib has shown benefit in treating adults with FLT3-mutated, R/R AML (approximately 25% of patients with AML carry the FLT3-internal tandem duplication mutation), but the need remains for a therapy targeting FLT3 regardless of mutational status. AMG 427 is an FLT3 HLE BiTE molecule with potent activity in vitro, ex vivo, and in vivo in animal models. It recognizes an extracellular portion of FLT3 that is present regardless of mutation status and is currently being evaluated as monotherapy in a phase 1 study (NCT03541369) in patients with R/R AML.

Solid Tumors

Prostate-specific membrane antigen

PSMA is highly expressed in poorly differentiated, metastatic, and castration-resistant prostate cancer (mCRPC). Pasotuxizumab (AMG 212/BAY2010112) is an anti-PSMA canonical BiTE molecule.[63] In a phase 1 study using continuous intravenous pasotuxizumab to treat 16 patients with mCRPC who were refractory SOC therapy (NCT01723475), antitumor activity was dose-dependent, with 2 patients achieving a durable prostate-specific antigen response beyond 1 year.[64] Serious AEs were consistent with other BiTE therapies.[64,65] This is the first study showing that a BiTE therapy can be efficacious in solid tumors. AMG 160 is an anti-PSMA HLE BiTE molecule also being investigated for the treatment of mCRPC (NCT03792841) and should allow more convenient dosing, with short-term infusion every 2 weeks.[66]

Epidermal growth factor receptor vIII

Although brain cancers are not common, glioblastoma is the most aggressive primary malignant brain tumor (5-year survival rate. <5%).[67] Therapies for glioblastoma have advanced, but the nonspecific nature of the surgery, radiation, and chemotherapeutic regimens are broadly destructive. Epidermal growth factor receptor vIII (EGFRvIII) is a tumor-specific mutant of the EGFR tyrosine kinase that promotes tumor-cell growth and is expressed in approximately one-third of glioblastomas; AMG 596 is a BiTE-targeting EGFRvIII and is designed for the treatment of glioblastoma. Preclinical experiments demonstrated that AMG 596 potently mediates the lysis of EGFRvIII-positive tumor cell lines with half-maximal

effective concentration values <1 pM. It also significantly prolonged the survival of tumor-bearing mice in an EGFRvIII BiTE orthotopic tumor model ($P < .001$) and caused no toxicity in a dose range-finding study in cynomolgus monkeys. A first-in-human sequential dose-escalation, dose-expansion clinical trial is taking place for patients with EGFRvIII-positive glioblastoma. The preliminary clinical data show that AMG 596 may be well tolerated and offer antitumor activity in recurrent glioblastoma, with 1 patient achieving a sustained, confirmed partial response and 4 exhibiting stable disease (N = 19; NCT03296696).[68]

Delta-like protein 3

DLL3 is a Notch ligand highly expressed in small-cell lung cancer (SCLC) but not in normal lung tissue, suggesting that it is important in the tumorigenesis of SCLC.[69] AMG 757 is an HLE BiTE molecule that targets DLL3; in preclinical studies, it showed low potency against SCLC lines in vitro, significant inhibition of tumor growth in vivo, and an excellent safety profile in nonhuman primates. This suggests that AMG 757 may offer a new therapeutic option for patients with SCLC, and it has entered phase 1 clinical trials (NCT03319940).[70]

Mucin 17

MUC17 is a membrane-bound mucin that is overexpressed in gastric cancer and has been identified as a gastric cancer suppressor protein with therapeutic potential.[71] The HLE BiTE molecule AMG 199 has entered a phase 1 clinical trial to evaluate its safety and tolerability in patients with MUC17-positive gastric and gastroesophageal junction cancers (NCT04117958).

Claudin-18 isoform 2

Claudin-18 isoform 2 (CLDN18.2) is an epithelial surface marker for gastric, esophageal, pancreatic, lung, and ovarian cancers.[72] AMG 910 is a novel HLE BiTE molecule designed to direct T cells toward CLDN18.2-expressing cells. A phase 1 study is in preparation to evaluate AMG 910 in patients with gastric and gastroesophageal junction adenocarcinomas (NCT04260191).

CONCLUSIONS

Despite advances in the field of immuno-oncology, many patients with cancer still have critical unmet needs. As demonstrated with blinatumomab, BiTE therapies have the potential to provide deep and durable responses by eliminating MRD. Their off-the-shelf use provides an innovative T-cell treatment to patients with an immediate need. The development of HLE BiTE molecules and subcutaneous administration of blinatumomab also aim to improve the patient experience by providing dosing flexibility.[52,73] To date, the BiTE immuno-oncology platform has a relatively low rate of immune-related grade ≥3 AEs, including CRS.[29] The ability to harness the power of the T cell and direct it to tumor-antigen targets has the potential to transform cancer treatment by setting new standards, such as complete MRD response and expansion of cure fraction. The approval of blinatumomab and the emerging clinical data from BiTE pipeline molecules show the potential of this platform to provide meaningful advances in oncology.

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CONFLICT OF INTEREST DISCLOSURES

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