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REVIEW

Bispecific Antibodies in Multiple Myeloma: Present and Future

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ABSTRACT Despite many recent advances in therapy, there is still no plateau in overall survival curves in multiple myeloma. Bispecific antibodies are a novel immunotherapeutic approach designed to bind antigens on malignant plasma cells and cytotoxic immune effector cells. Early-phase clinical trials targeting B-cell maturation antigen (BCMA), GPRC5D, and FcRH5 have demonstrated a favorable safety profile, with mainly low-grade cytokine release syndrome, cytopenias, and infections. Although dose escalation is ongoing in several studies, early efficacy data show response rates in the most active dose cohorts between 61% and 83% with many deep responses; however, durability remains to be established. Further clinical trial data are eagerly anticipated.

Significance: Overall survival of triple-class refractory multiple myeloma remains poor. Bispecific antibodies are a novel immunotherapeutic modality with a favorable safety profile and impressive preliminary efficacy in heavily treated patients. Although more data are needed, bispecifics will likely become an integral part of the multiple myeloma treatment paradigm in the near future. Studies in earlier lines of therapy and in combination with other active anti–multiple myeloma agents will help further define the role of bispecifics in multiple myeloma.

INTRODUCTION

Although there have been many advances in the treatment of multiple myeloma, there is still an unmet need for patients who are relapsed/refractory to currently available therapies. In particular, patients who are penta-refractory [refractory to two immunomodulatory drugs (IMiD), two proteasome inhibitors (PI), and an anti-CD38 monoclonal antibody] have been shown to have a median overall survival (OS) of less than 6 months (1). Immunotherapeutic approaches have been developed over recent years to harness the patient's immune system to destroy the malignant plasma cells. These developments include chimeric antigen receptor (CAR)-T cell therapy, antibody–drug conjugates (ADC), and, more recently, bispecific antibodies. Although each modality has its advantages and disadvantages, phase I trials of bispecific antibodies in multiple myeloma have shown early promise as a readily available off-the-shelf treatment with deep responses and limited incidence of grade ≥3 adverse events.

Bispecific antibodies are designed to bind both a target on the malignant plasma cells and on cytotoxic immune effector cells [T cells/natural killer (NK) cells] to create an immunologic synapse, leading to T/NK-cell activation and destruction of malignant plasma cells (Fig. 1; ref. 2). Bispecific antibodies have been developed with and without an Fc region. Although molecules lacking an Fc region have been shown to easily penetrate tumors due to their small size (3, 4), they require frequent or continuous infusion due to their short half-life. Bispecific antibodies with Fc regions have been shown to have an extended half-life, enabling less frequent dosing (5). For this reason, all of the bispecifics in ongoing phase I and II trials (with the exception of AMG420, which has been discontinued) have included an Fc region in their antibody structure. As of the writing of this article, there are currently at least 17 ongoing phase I/II trials (and two discontinued) with four different antigen targets (Table 1). All of these studies target CD3 on T cells; however, preclinical studies are also investigating NK-cell engagers as a novel mechanism of action, with early success (6–10). Additionally, trispecific antibodies, which are currently in preclinical investigation, attempt to add T-cell costimulatory proteins to decrease T-cell anergy (11, 12) or target dual myeloma antigens while engaging NK cells (7).

In addition to the ongoing phase I/II trials, there are multiple preclinical bispecific agents under development (Table 2). These preclinical agents target multiple myeloma cells by way

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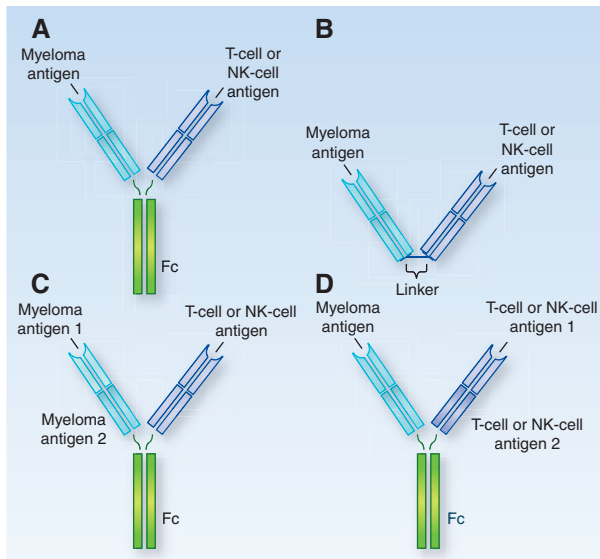
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Figure 1. Bispecific and trispecific antibody structure. Bispecific antibodies. **A,** Bispecific T-cell and NK-cell engagers bring immune effector cells in proximity to specific antigen-expressing myeloma cells to promote direct cell-mediated cytotoxicity. The Fc portion provides stability and a longer half-life in the circulation, allowing for intermittent rather than continuous dosing. **B,** Bispecific compounds lacking an Fc portion have a very short half-life and require continuous infusions. These are only representative schematics; there is significant variability in antibody structure across compounds, leading to differing pharmacokinetic and pharmacodynamic profiles. **C,** Trispecific antibody targeting an immune effector cell and two distinct myeloma antigens. **D,** Trispecific antibody with costimulation of the immune effector cell to enhance cytotoxicity.

of BCMA, CD138, CD38, SLAMF7, and GPRC5D, and additionally target CD3, CD16a, NKp30, or NKG2D to recruit either T cells or NK cells. These studies have shown early preclinical success and suggest potential for future phase I trials in multiple myeloma (9, 12–26).

VIABLE TARGETS FOR BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

To maximize efficacy and minimize toxicity, bispecific antibodies should target an antigen that is unique and specific to multiple myeloma cells, with minimal expression in other healthy tissues. Although there are numerous potential myeloma cell targets (Fig. 2), four targets have been used in current phase I trials: BCMA, CD38, GPRC5D, and FcRH5.

BCMA

B-cell maturation antigen (BCMA), or CD269, is an antigen that is expressed on both malignant and normal plasma cells at high levels (27, 28). It is a type III transmembrane glycoprotein in the tumor necrosis factor receptor superfamily, whose function is to regulate B-cell proliferation, maturation, survival, and differentiation to plasma cells through binding of its ligands, a proliferation-inducing ligand (APRIL) and B-cell–activating factor (BAFF; refs. 29–34). APRIL and BAFF signaling via BCMA are essential for humoral immunity, and blocking this interaction prevented antibody formation to the immunogenic carrier protein keyhole limpet hemocyanin and Pneumovax in mice (35). BCMA is almost exclu-

sively expressed on mature B lymphocytes, plasmablasts, and plasma cells, while remaining undetectable in naïve B cells and hematopoietic stem cells. Although BCMA expression is also undetectable in most nonhematologic tissues, it has been found to have some expression in the testis, trachea, and gastrointestinal tract possibly due to the presence of plasma cells (36). BCMA has been shown to have increased expression on malignant plasma cells compared with normal plasma cells (27, 37) and is upregulated during disease progression from monoclonal gammopathy of undetermined significance to smoldering multiple myeloma to active multiple myeloma (38). Higher expression of soluble BCMA, thought to be from gamma-secretase–induced shedding, has been associated with worse outcomes in multiple myeloma (27). There are currently six bispecifics in clinical trials targeting BCMA.

CD38

CD38 is a surface glycoprotein that has been found to be an activation marker (39), an adhesion molecule (40), and an ectoenzyme involved in the metabolism of NAD^+ and NADP (41, 42). CD38 is highly expressed on plasma cells, but is also found at lower levels on other hematologic cells including NK, lymphoid and myeloid cells, red blood cells, and platelets (43). CD38 expression has also been found at low levels on prostatic epithelial tissue, pancreatic islet cells, airway striated muscle cells, renal tubules, ganglia cells, and corneal cells and in the perikarya and dendrites of some neurons (44–47). This non–plasma cell expression of CD38 accounts for many of the side effects of the anti-CD38 antibodies daratumumab and isatuximab, and would presumably be a concern for bispecific antibodies with a CD38 target. Some examples of these side effects include bronchospasm during infusion, angle closure glaucoma, and myopic shift (48, 49). CD38 expression on plasma cells has also been shown to be downregulated after the first infusion of anti-CD38 antibodies, potentially generating resistance and inducing tumor escape over time (42, 50); however, clinical trials with daratumumab have shown durable responses in multiple myeloma (51–54). Two bispecifics targeting CD38 are in phase I trials. In addition, there is evidence that daratumumab causes depletion of $CD38^+$ myeloid-derived suppressor cells and $CD38^+$ regulatory T cells while inducing a clonal expansion of cytotoxic and helper T cells (55). This enhanced T-cell response can potentially be harnessed to increase T-cell engagement with bispecifics, and studies have begun adding daratumumab to non–CD38-targeting bispecifics (anti-BCMA and anti-GPRC5D) to test this hypothesis.

GPRC5D

The orphan G protein–coupled receptor class C group 5 member D (GPRC5D) is a relatively novel target for multiple myeloma immunotherapy. It is an orphan G protein–coupled receptor with unknown function that is highly expressed on malignant bone marrow plasma cells, as well as hard keratinized structures that include the hair shaft, nail, and central region of the tongue (56–58). High expression of GPRC5D has been associated with poor prognosis in multiple myeloma (59). GPRC5D has been used as a target in CAR-T therapy for multiple myeloma, with promising results in preclinical studies (56, 60), and is now a target for the bispecific antibody JNJ-64407564 (talquetamab) in four phase I trials.

Table 1. Clinical trials for bispecific antibodies in multiple myeloma

Agent	Targets	Sponsor	Phase	Clinical trial ID	Status
AMG420	BCMAxCD3	Amgen	I	NCT03836053	Completed
AMG701	BCMAxCD3	Amgen	I/II	NCT03287908[a]	Ongoing
CC-93269	BCMAxCD3	Bristol Myers Squibb	I	NCT03486067	Ongoing
PF-06863135	BCMAxCD3	Pfizer	I/II	NCT04649359	Ongoing
				NCT03269136[a]	Ongoing
REGN5458	BCMAxCD3	Regeneron	I/II	NCT03761108	Ongoing
REGN5459	BCMAxCD3	Regeneron	I	NCT04083534	Ongoing
JNJ-64007957 (teclistamab)	BCMAxCD3	Janssen	I	NCT03145181	Ongoing
			I	NCT04696809	Ongoing
			I/II	NCT04557098	Ongoing
			Ib	NCT04108195[b]	Ongoing
			Ib	NCT04586426[b]	Ongoing
TNB-383B	BCMAxCD3	TeneoBio	I	NCT03933735	Ongoing
GBR1342	CD38xCD3	Ichnos Sciences	I/II	NCT03309111	Ongoing
AMG424	CD38xCD3	Amgen	I	NCT03445663	Terminated
JNJ-64407564 (talquetamab)	GPRC5DxCD3	Janssen	I/II	NCT04634552	Ongoing
			I	NCT03399799	Ongoing
			Ib	NCT04108195[b]	Ongoing
			Ib	NCT04586426[b]	Ongoing
BFCR4350A (cevostamab)	FcRH5xCD3	Genentech	I	NCT03275103	Ongoing

[a]Combination study including non–bispecific antibody treatment.

[b]Trial includes JNJ-64007957 (teclistamab) and JNJ-64407564 (talquetamab).

FcRH5

The Fc receptor-homolog 5 (FcRH5) is a surface protein in the immunoglobulin superfamily that has been implicated in proliferation and isotype expression in the development of antigen-primed B cells (61–63). It is expressed only in the B-cell lineage with expression starting in pre–B cells and increasing expression through maturation to mature B cells and plasma cells (64). FcRH5 has also been shown to be more highly expressed in multiple myeloma plasma cells compared with normal plasma cells (61, 64, 65) and may be even more highly expressed in cell lines with 1q21 abnormalities (65, 66). Antibodies to FcRH5 were also found to internalize in preclinical models, making it a potential target for ADC, although a phase I trial was unsuccessful (67). Nonetheless, FcRH5, with its restricted expression to B-cell lineage and its upregulation in multiple myeloma, is the target of the bispecific BFCR4350Aa (cevostamab) in an ongoing phase I trial.

PHASE I TRIALS IN MULTIPLE MYELOMA

AMG420, a BCMAxCD3 bispecific T-cell engager, was the first to complete its phase I trial in multiple myeloma (68). As it did not have an Fc portion, it had a short half-life and was administered continuously through a pump for 4 weeks out of 6. Forty-two patients with at least two prior lines of therapy were enrolled, with 36% double refractory to an IMiD and PI. Dose-limiting toxicities (DLT) included grade 3

cytokine release syndrome (CRS) and grade 3 polyneuropathy. CRS occurred in 38% of patients, serious infections in 33% (including 12% central line infections), and grade 3 polyneuropathy in two (5%) patients. The polyneuropathies resolved after 2 to 3 months. At the maximum tolerated dose, 7/10 (70%) demonstrated a response. The development of this compound was subsequently discontinued in favor of a longer half-life bispecific antibody, AMG701. As a result, the following section focuses on compounds still in development, all of which have extended half-lives.

Safety

As of the writing of this article, there have been phase I data from eight additional trials, all reported from conference proceedings and not peer-reviewed publications (69–76). Two studies reached their recommended phase II dose (RP2D), with many studies reporting DLTs. These DLTs included acute kidney injury, elevated AST/ALT, delirium, confusion, thrombocytopenia, increased lipase, maculopapular rash, and pneumonia. These DLTs were generally manageable with supportive care. To date, there are no data available on study discontinuation due to adverse effects. The main adverse events are summarized below, with detailed data on individual trials presented in Table 3. As these are first-in-human phase I trials, there are no comparator arms to determine whether certain adverse effects occurred at a higher rate than expected for a heavily relapsed myeloma population.

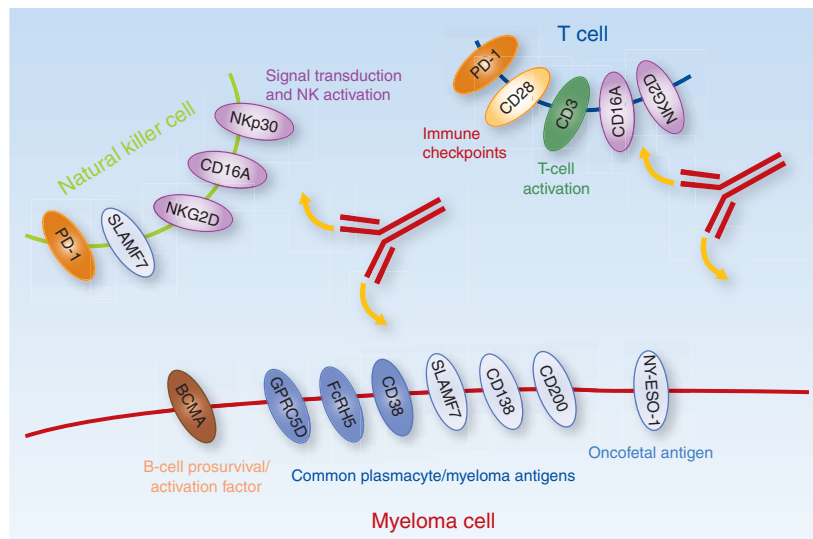**Table 2.** Preclinical bispecific and trispecific antibodies in multiple myeloma

Target	Drug	Sponsor	Notes
BCMAxCD3	EM801	Bristol Myers Squibb	Active also in high-risk patients and non–cross-resistant with previous lines of treatment (14)
BCMAxCD3	AP163	Ampsource Biopharma Shanghai Inc.	Induces less cytokine secretion than other bispecifics *in vitro* (16)
BCMAxNKp30	CTX-8573	Compass Therapeutics	Antitumor effect in mice even with low BCMA expression (9)
BCMAxCD16a	AFM26	Affimed Therapeutics	NK-cell engager; may have superior safety profile over CD3 T-cell engagers (15)
BCMAxCD16a	RO7297089	Genentech	Has a favorable safety profile and represents a novel MOA among other BCMA-targeting modalities (10)
BCMAxMICA	2A9-MICA	China Pharmaceutical University	MICA binds NKG2D on NK cells to induce multiple myeloma cell death *in vitro* and in a mouse model (24)
BCMAxCD200xCD16a	Gantke et al.	Affimed Therapeutics	Results in increase in avidity leading to preferential lysis of antigen double-positive cells compared with antigen single-positive cells (7)
CD138xCD3	STL001	Jiangsu, China	Nanomolar-level affinity to recombinant human CD138 protein and shows more potent antitumor activity against RPMI-8226 cells than that of separate aCD3-ScFv-hIgFc and aCD138-ScFv-hIgFc, or the isotype mAb *in vitro* or *in vivo* (17)
CD138xCD3	h-STL002, m-STL002	Jiangsu, China	Shows potent cytotoxicity against multiple myeloma RPMI-8226 cell line through T-cell activation (18)
CD38xCD3xCD28	Wu et al.	Sanofi	Demonstrates *in vitro* multiple myeloma cell killing 3–4 log higher than daratumumab (12)
CD38xCD3	Sorrento CD38/CD3	Sorrento Therapeutics	Demonstrates more potent tumor cell killing than daratumumab (19)
CD38xCD3	Bi 38–3	Inserm	Kills multiple myeloma cells *in vitro* and in a mouse model with no toxicity to B, T, and NK cells (23)
SLAMF7xNKG2D	SLAMF7-NKG2D	Ohio State University	*In vivo*, survival was significantly prolonged using SLAMF7-NKG2D biAb in a xenograft NOD-SCID$^{IL2\gamma c-/-}$ (NSG) mouse model engrafted with both human PBMCs and multiple myeloma cell lines (22)
GPRC5DxCD3	GPRC5DxCD3 TRAB	Chugai Pharmaceutical	Suppresses tumor growth of GPRC5D-positive myeloma cells through the activation of T cells *in vitro* and *in vivo* in xenograft models (20)
NY-ESO-1xCD3	ImmTAC-NYE	Immunocore	Produces lysis of multiple myeloma cell line *in vitro* (25)
A2/NY-ESO-1xCD3	Maruta et al.	Ehime University, Japan	Antimyeloma activity *in vitro* similar to CAR-T construct (26)

Abbreviations: biAb, bispecific antibody; mAb, monoclonal antibody; MOA, mechanism of action; PBMC, peripheral blood mononuclear cell.

Cytokine Release Syndrome

CRS is an acute systemic inflammatory syndrome caused by immunotherapies including CAR-T cells and bispecific antibodies. The pathophysiology involves activation of T cells and other immune effector cells with significant cytokine release. The severity of CRS is thought to result from a combination of disease burden, type of underlying malignancy, and type and dose of immunotherapy (77, 78). Fever is the only necessary symptom of CRS, but other possible clinical manifestations are wide-ranging and include hypotension, altered mental status, and hypoxia. There are different grading systems for CRS, making it difficult to compare CRS within and between immunotherapeutic modalities (79). In the six trials of anti-BCMA bispecific antibodies, the range of any-grade CRS was 39% to 95%. CRS of grade ≥3 ranged from 0% to 9%. In the anti-GPRC5D trial, CRS was found in 54% of patients with 3% grade ≥3. In the anti-FcRH5 trial, CRS was found in 76% of patients, with 2% grade ≥3. Across all studies, the use of tocilizumab and corticosteroids to treat CRS was 9% to 40% and 0% to 17%, respectively. Both the median time to onset and median duration of

Figure 2. Bispecific and trispecific antibody targets in multiple myeloma. Filling color denotes functional class of the target antigen; filling intensity denotes stage of translational development: clinical (darker) or preclinical (lighter). NY-ESO-1 antigen is presented by MHC class I, which requires therapeutic antibody to recognize NY-ESO-1 in complex with patient-specific MHC-I allele. PD-1 has been targeted in combination with bispecific antibodies but is not itself a direct target of bispecifics.

CRS ranged from 12 to 48 hours, with median time to onset generally quicker with intravenous administration (24 hours) compared with subcutaneous administration (48 hours). CRS was generally confined to the first cycle, and all patients recovered with no sequelae. Step-up dosing was used in most studies to attempt to mitigate the initial intensity of CRS.

Neurotoxicity

Neurotoxicity in these trials ranged from 5% to 28% at any grade and 0% to 2% at grade ≥3. Reported neurologic symptoms included headache, confusion, aphasia, cognitive disorder, and encephalopathy. Many of these symptoms were in the setting of CRS and resolved after CRS treatment. Of note, the AMG402 study, in the setting of continuous dosing (due to its short half-life), had a high rate of neuropathy. Neuropathy was not found to be a major side effect in all other reported trials based on presented data. Recently, the FDA placed a hold on PF-06863135 due to three cases of peripheral neuropathy.

Hematologic

Hematologic side effects across all trials that presented these data included anemia (any grade 21%–42%, grade ≥3 17%–42%), neutropenia (any grade 16%–57%, grade ≥3 14%–53%), lymphopenia (any grade 15%–40%, grade ≥3 12%–36%), leukopenia (any grade 23%–32%, grade ≥3 14%–16%), and thrombocytopenia (all 8%–40%, grade ≥3 6%–25%). As of this writing, there are no data on the timing and duration of these cytopenias. The dose–response relationship is also unknown from the early data. The mechanism of cytopenias is not currently understood as the targets of the bispecifics are not present on other cell lineages. Cytopenias can be seen even in patients attaining responses with these agents. Therefore, one hypothesis is a "bystander" effect from the release of cytokines and destruction of plasma cells in the bone marrow, though there is currently no evidence to support or refute this possibility.

Infection

In the six trials that reported, infection was found in 21% to 52% of patients, with grade ≥3 in 8% to 30%. The source and type of infection were not widely reported. The populations of patients in these phase I trials were all relapsed or refractory and were heavily pretreated. There is evidence of cumulative multifactorial immunosuppression with reduction of CD4+, CD45+, CD19+, and NK cells in relapsed/refractory patients with multiple lines of therapy (80). Treatment-emergent hypogammaglobulinemia has also been noted but has not been well characterized in studies to date. The relatively low rate of ≥ grade 3+ infections with anti-GPRC5D therapy and serious/unusual infections with the other agents raises the possibility that expression of target antigens on nonmyelomatous B cells could play a role. Preclinically, BCMA signaling is essential for generation of humoral immunity, which may predispose BCMA-treated patients to hypogammaglobulinemia, infectious complications, and lack of response to vaccines. The latter is particularly important in the era of COVID-19. At our institution, we found that multiple myeloma patients receiving BCMA-directed therapies had an odds ratio of 10.3 of not developing IgG antibodies to SARS-CoV-2 vaccination compared to non-BCMA–treated patients (81). Larger numbers of patients, longer follow-up, and ideally a control arm will be needed to truly elucidate the contribution of bispecific antibody treatment to infectious risk.

Other

Common nonhematologic side effects across all trials included fatigue (17%–35%), nausea (17%–31%), pyrexia (16%–31%), and diarrhea (12%–31%), while back pain, headache, and

Table 3. Safety profile

Agent	AMG701 (69)	CC-93269 (75)	PF-06863135 (76)	REGN5458 (73)	JNJ-64007957 (teclistamab) (72)	TNB-383B (70)	JNJ-64407564 (talquetamab) (74)	BFCR4350A (cevostamab) (71)
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Patients (N)	65	19	30	49	149 (84 i.v., 65 s.c.)	58	157 (102 i.v., 55 s.c.)	53
CRS (grade ≥3)	65% (9%)	90% (5%)	73.3% (0%)	39% (0%)	55% (0%)	45% (0%)	54% (3%)	76% (2%)
Infection (grade ≥3)	(17%)	NR (26%)	NR (30%)	47% (18%)	52% (15%)	21% (14%)	38% (8%)	NR
Anemia (grade ≥3)	42%	NR (42%)	20% (16.7%)	37% (22%)	55% (32%)	21% (17%)	48% (27%)	28% (19%)
Neutropenia (grade ≥3)	25%	NR (53%)	33.3% (26.7%)	16% (14%)	57% (46%)	19% (16%)	47% (31%)	17% (15%)
Lymphopenia (grade ≥3)	NR	NR	16% (16%)	18% (12%)	NR	NR	40% (36%)	15% (15%)
Thrombocytopenia (grade ≥3)	21%	NR (21%)	8% (5%)	18% (6%)	40% (22%)	17% (14%)	32% (13%)	32% (25%)
Neurotoxicity (grade ≥3)	NR	NR	20%	12% (0%)	5% (1%)	NR	6% (2%)	28% (0%)
Other common SE (grade ≥3)	Diarrhea 31%, hypophosphatemia 31%	NR	NR	Fatigue 35% (6%), nausea 31% (0%), pyrexia 31% (2%), back pain 27% (4%)	Pyrexia 30% (0%), diarrhea 23% (1%), nausea 22% (1%), fatigue 22% (1%), headache 22% (0%), cough 21% (2%)	Fatigue 24% (2%), headache 22% (2%), nausea 21% (0%)	Skin-related disorder 45%, dysgeusia 38%, fatigue 29% (1%), headache 27% (1%), pyrexia 27% (1%), diarrhea 25% (3%), nail disorders 17%	Hypomagnesemia 28% (0%), diarrhea 28% (2%), hypokalemia 21% (4%)

Abbreviations: i.v., intravenous; NR, not reported; s.c., subcutaneous; SE, side effect.

cough, and vomiting were also documented in some of the trials. Electrolyte abnormalities included hypophosphatemia, hypomagnesemia, and hypokalemia. The anti-GPRC5D antibody trial was unique in causing skin-related effects (45%), dysgeusia (38%), and nail disorders (17%), relating to the expression of GPRC5D on these hard keratinized structures. Although the majority of skin-related adverse events were grade 1/2, there were two DLTs (grade 3 maculopapular rashes). Data on tolerability and discontinuation are not yet publicly available. The anti-FcRH5 antibody trial was unique in causing AST increases in 15% of patients, though at this time, there is no detail on possible causes, including whether this occurred during CRS.

Efficacy

Triple-refractory and penta-refractory multiple myeloma patients have been shown to have a median OS of less than 1 year with an overall response rate (ORR) of 30% and 29%, respectively, to the next line of therapy, decreasing with each subsequent regimen (1). Monotherapy trials in this population that have led to FDA approval, including carfilzomib, pomalidomide, daratumumab, selinexor, belantamab mafodotin, and melflufen, have achieved an approximately 20% to 30% ORR and 3- to 4-month progression-free survival (PFS; refs. 82–87). The inclusion criteria in the bispecific phase I trials included relapsed/refractory multiple myeloma with ≥3 lines of therapy including an IMiD, a PI, and an anti-CD38 Ab; relapsed/refractory multiple myeloma for which no established therapy is available; or relapsed/refractory multiple myeloma and intolerant to other therapies. Triple-refractory patients comprised 62% to 100% of the population in the trials that reported these data, and the median number of prior lines of therapy was five to eight over a median of 5.6 to 7 years since diagnosis.

Although safety is the primary objective of these phase I dose-escalation trials, preliminary efficacy data are available

Table 4. Efficacy results

Agent	AMG701 (69)	CC-93269 (75)	PF-06863135 (76)	REGN5458 (73)	JNJ-64007957 (teclistamab) (72)	TNB-383B (70)	JNJ-64407564 (talquetamab) (74)	BFCR4350A (cevostamab) (71)
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Patients (N)	65	19	30	49	149 (84 i.v., 65 s.c.)	58	157 (102 i.v., 55 s.c.)	53
Treatment	Weekly i.v.	Weekly i.v.	Weekly s.c.	Weekly i.v.	Weekly i.v. or s.c.	i.v. q3w	Weekly i.v. or s.c.	i.v. q3w
Median prior lines	6	6	8	5	6	6	6	6
Triple-class refractory	62%	IMiD 84%, PI 90%, Dara 89%	NR; 23% prior BCMA-directed	100%	81%	64%	82%; 17% prior BCMA directed	72%; 21% prior BCMA directed
ORR at therapeutic dose (only two trials have reached RP2D)	26% all patients 5/6 (83%) most recent cohort	10/12 (83%) ≥6 mg i.v.	16/20 (80%) 215–1,000 µg/kg s.c.	5/8 (63%) 96 mg i.v.	16/22 (73%) 1,500 µg/kg s.c. (RP2D)	12/15 (80%) 40–60 mg i.v.	9/13 (69%) 405 µg/kg s.c. (RP2D)	11/18 (61%) 3.6/90 mg–3.6/132 mg i.v. 5/8 (63%) for prior BCMA exposure
Duration of response	17/21 (81%) ongoing at median 5.6 months	NR	NR	14/19 (74%) ongoing at median 6 months	32/25 (91%) s.c. ongoing at median 6.5 months	22/27 (81%) ongoing at median 4.5 months	17/17 (100%) ongoing at median 3.7 months at ≥405 µg/kg s.c.	11/18 (61%) ongoing at median 10.3 months at all doses

Abbreviations: Dara, daratumumab; i.v., intravenous; NR, not reported; q3w, every 3 weeks; s.c., subcutaneous.

for the most active dose cohorts, ranging from 6 to 22 patients (Table 4). Importantly, these trials are at differing stages of maturity, with only two having reached their RP2D, and as a result, ORRs are likely to change with more patients enrolled and longer follow-up. The ORR in these cohorts ranged from 61% to 83%, with a very good partial response (VGPR) rate of 39% to 78%. Two studies reported RP2D data. JNJ-64007957 (teclistamab) had 73% ORR at RP2D (55% ≥VGPR), with 70% ORR in triple- refractory and 75% ORR in penta-refractory patients. JNJ-64407564 (talquetamab) had a 69% ORR at RP2D (39% with ≥VGPR), with 67% ORR in triple-refractory (nine patients) and 100% ORR in penta-refractory (two patients); 17% of patients had received prior BCMA-directed therapy, but there are no results available for these patients at this time. The BFCR4350A (cevostamab) study had 21% with prior BCMA therapy; 5/8 (63%) of these patients had a response. Many of the studies reported minimal residual disease (MRD) negativity in evaluable patients.

Median duration of response (DOR) has not been reached, as most of these phase I trials are still ongoing and many patients are still responding and receiving treatment. Follow-up times vary across trials; at a median follow-up of 3.7 to 10.3 months, the majority of patients (61%–100%) across

several trials have maintained their response. Median time to first response across all trials at all doses was 3 to 4 weeks.

Although further efficacy data are needed with larger numbers of patients and longer duration of follow-up, these preliminary response rates compare very favorably with recently approved drugs in multiple myeloma. The depth of response and likely DOR are impressive for a single agent in a heavily pretreated and refractory population. Additional phase I and II data are eagerly anticipated and will help inform the optimal use of bispecifics in multiple myeloma.

COMBINATION STUDIES

Despite the impressive preliminary efficacy of single-agent bispecifics, multiple myeloma remains a genetically heterogeneous disease (88), and relapses are still occurring. Multidrug therapy has long been standard of care for multiple myeloma, especially in relapsed and refractory patients, with several trials showing a benefit in PFS and sometimes OS with the addition of a third agent (52, 53, 89–96). Given the overall favorable toxicity profile of bispecifics, combination studies are the next logical step to improve further on efficacy.

At least four phase I/II trials are currently ongoing testing bispecific antibodies with/without one or more additional agents. The NCT03287908 trial is assessing a BCMAxCD3 antibody as monotherapy or in combination with pomalidomide with/without dexamethasone. The NCT03269136 trial is assessing a BCMAxCD3 bispecific antibody as monotherapy or in combination with either an anti–PD-1 monoclonal antibody, lenalidomide, or pomalidomide. The NCT04108195 trial has four treatment arms: BCMAxCD3 + daratumumab, GPRC5DxCD3 + daratumumab, BCMAxCD3 + daratumumab + pomalidomide, and GPRC5DxCD3 + daratumumab + pomalidomide. Lastly, the NCT04586426 trial combines BCMAxCD3 and GPRC5DxCD3 bispecific antibodies. These trials are ongoing, and no data have been reported yet.

Combination studies with anti-CD38 antibodies have a particularly strong preclinical rationale. Based on peripheral blood and bone marrow samples from patients on monotherapy trials, daratumumab was shown to decrease CD38+ myeloid-derived suppressor cells and CD38+ regulatory T cells, while causing a robust increase in cytotoxic and helper T cells in a majority of patients (47). In addition, there was a clonal expansion of T cells that correlated with myeloma response. Administering daratumumab alongside a bispecific antibody could potentially prime the patient's T cells and then optimally redirect them to the tumor cells. One preclinical study found that pretreatment with daratumumab increased efficacy of their BCMAxCD3 bispecific antibody in bone marrow samples (13).

FUTURE PERSPECTIVES

Bispecific antibodies represent a promising class of therapeutics for multiple myeloma and will likely be integrated into the multiple myeloma treatment paradigm in the near future. However, there are still many unanswered questions and unexplored opportunities. Mechanisms of resistance are not well understood at this time and deserve further study to inform the rational sequencing/combinations of the various bispecifics. If immune checkpoints are overexpressed at the time of progression, it would provide a rationale for combination therapy with immune-checkpoint inhibitors, whereas if loss of efficacy is from decline in T-cell function, then perhaps anti-CD38 antibodies could be used to salvage these patients. Although some combination studies are in progress as described above, there are countless opportunities for combination therapy, particularly with agents that do not overlap with the main non-CRS toxicities of bispecifics, which include cytopenias and infections.

Although novel treatments in multiple myeloma are conventionally studied in patients who have exhausted most or all available therapies, there is significant potential for bispecifics to move into earlier lines of therapy. Many multiple myeloma patients will not be able to receive multiple lines of therapy, whether due to comorbidities, toxicities from treatment, or early mortality, and, additionally, each successive line of therapy brings shorter remissions (97). Importantly, T-cell function declines as a result of multiple myeloma, its therapies, and aging, and there is evidence of

T-cell exhaustion as a distinguishing feature of relapse in multiple myeloma (98, 99). As such, there is a need to utilize T-cell–redirecting therapies and achieve deep and durable remissions early in the treatment course when patients can receive the most benefit. Given the high response rates, deep responses (including MRD negative), and potential durability of response, as well as limited toxicity and convenient dosing schedules, bispecifics may ultimately prove most useful in the upfront or early relapse setting. In addition, high-risk groups, including elderly/frail patients, high-risk cytogenetics, renal failure, and extramedullary disease, have not benefited from novel therapies to the same degree as standard-risk patients. Clinical trials of bispecifics in these patient populations are urgently needed.

At this time, the toxicities of bispecifics are not fully understood. Although low-grade CRS and neurotoxicity are common, it is not possible yet to predict who will be at highest risk and should be monitored in the hospital for the first dose versus those who could potentially be safely monitored at home. Further work is needed to better understand patient characteristics and biomarkers that may lead to higher risk of CRS and neurotoxicity in order to implement appropriate dosing (step-up or priming doses), monitoring strategies, and possible empiric use of tocilizumab/corticosteroids. Subcutaneous bispecifics have been shown to achieve similar plasma concentrations as intravenous formulations but with a slower time to maximal concentration and potentially less severe CRS, although this requires additional study. Cytopenias are not yet well characterized in terms of duration and need for supportive care, and further insight is needed into the mechanisms of this toxicity. Lastly, given that all of these bispecifics target normal plasma cells in addition to myeloma cells, the contribution of hypogammaglobulinemia to infectious risk needs to be elucidated, as this may inform prophylactic strategies, including the use of subcutaneous or intravenous immunoglobulin, as well as vaccination strategies, particularly regarding COVID-19.

Finally, with the recent approval of the first BCMA-directed CAR-T therapy in multiple myeloma, idecabtagene vicleucel (ide-cel), many questions linger about the utilization of bispecifics versus CAR-T in the future. As of now, there are no head-to-head trials comparing these modalities, and cross-trial comparisons of bispecific and CAR-T studies are not advisable given the small numbers of patients, differing patient populations, variable disease characteristics, multiple dosing schedules, and bridging chemotherapy for CAR-T patients. Until further trials are conducted, choosing between the two modalities will depend on a variety of practical considerations. Bispecifics are off-the-shelf products and induce rapid responses, which is ideal for rapidly progressing patients who may not be able to wait several weeks for the manufacture of CAR-T cells. Allogeneic CAR-Ts represent an opportunity for off-the-shelf CAR-Ts; however, these are still early in phase I trials. Additionally, CRS is typically milder with bispecifics (almost all grade 1/2), which may be easier to tolerate for elderly or frail patients. Bispecifics require ongoing treatment, in contrast to a one-time intervention with CAR-T, and may be less practical for patients who live far from academic medical centers or who otherwise are unable to

maintain a consistent follow-up schedule. At this time, there are no data to inform the optimal duration of therapy with bispecifics. There is a theoretical risk of decreasing the efficacy of bispecifics if administered soon after CAR-T given the prolonged lymphodepletion from CAR-T conditioning therapy, which would favor sequencing bispecifics prior to CAR-T. Sequencing of targets is poorly understood at this time, and there will be a significant unmet need for post-BCMA therapies given the recent approval of ide-cel and the BCMA-targeted ADC belantamab mafodotin. Both bispecifics and CAR-T are expected to move into earlier lines of treatment given their high efficacy. However, as multiple myeloma remains a heterogeneous disease, combination therapies will be essential to prevent relapse. Bispecifics may be more easily incorporated with currently approved myeloma therapies given their dosing schedule and the ability to hold doses for toxicity, whereas there are currently several strategies to engineer CAR-T cells to overcome resistance, which are outside the scope of this review. Overall, both bispecifics and CAR-Ts have shown unprecedented response rates in heavily treated patients. As they usher in a new era of immunotherapy in multiple myeloma, it is heartening to have such powerful agents in our arsenal to personalize therapy for patients with multiple myeloma as we continue the search for a cure.

Authors' Disclosures

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