How to Train Your T Cells: Overcoming Immune Dysfunction in Multiple Myeloma

Adam D. Cohen[1], Noopur Raje[2], Jessica A. Fowler[3], Khalid Mezzi[3], Emma C. Scott[3], and Madhav V. Dhodapkar[4]

ABSTRACT

The progression of multiple myeloma, a hematologic malignancy characterized by unregulated plasma cell growth, is associated with increasing innate and adaptive immune system dysfunction, notably in the T-cell repertoire. Although treatment advances in multiple myeloma have led to deeper and more durable clinical responses, the disease remains incurable for most patients. Therapeutic strategies aimed at overcoming the immunosuppressive tumor microenvironment and activating the host immune system have recently shown promise in multiple myeloma, particularly in the relapsed and/or refractory disease setting. As the efficacy of T-cell–dependent immuno-oncology therapy is likely affected by the health of the endogenous T-cell repertoire, these therapies may also provide benefit in alternate treatment settings (e.g., precursor disease; after stem cell transplantation). This review describes T-cell–associated changes during the evolution of multiple myeloma and provides an overview of T-cell–dependent immuno-oncology approaches under investigation. Vaccine and checkpoint inhibitor interventions are being explored across the multiple myeloma disease continuum; treatment modalities that redirect patient T cells to elicit an anti–multiple myeloma response, namely, chimeric antigen receptor (CAR) T cells and bispecific antibodies [including BiTE (bispecific T-cell engager) molecules], have been primarily evaluated to date in the relapsed and/or refractory disease setting. CAR T cells and bispecific antibodies/antibody constructs directed against B-cell maturation antigen have generated excitement, with clinical data demonstrating deep responses. An increased understanding of the complex interplay between the immune system and multiple myeloma throughout the disease course will aid in maximizing the potential for T-cell–dependent immuno-oncology strategies in multiple myeloma.

Introduction

Multiple myeloma is a clonal, multistep, plasma cell malignancy (1, 2). Multiple myeloma often begins with premalignant monoclonal gammopathy of undetermined significance (MGUS), followed by asymptomatic smoldering multiple myeloma (SMM) and active multiple myeloma (3). As the disease advances, the immune system demonstrates progressive impairment (4, 5).

The introduction of immunomodulatory drugs (IMiD), proteasome inhibitors (PI), and monoclonal antibodies (mAb) has improved patient outcomes, partially exerting anti–multiple myeloma activity through immunomodulation (6). Nevertheless, multiple myeloma remains incurable, becoming more aggressive with poor outcomes when treatment refractoriness occurs (7). The role of T-cell dysfunction in multiple myeloma and the success of T-cell–directed therapy in other malignancies warrant investigation of treatments enhancing T-cell anti–multiple myeloma activity (8). This review discusses the role of T cells and T-cell–directed therapies across the multiple myeloma disease continuum.

Evolution of T-cell Immunity in Multiple Myeloma Disease Progression

Reduced T-cell immunity has been associated with multiple myeloma disease progression (**Fig. 1**). However, even in patients with MGUS, increased levels of immunosuppressive regulatory T cells (Treg; ref. 9) and T-cell exhaustion (10) have been reported. An immune profiling study found that T cells from patients with SMM had an aberrant phenotypic profile, including reduced expression of activation markers, compared with those from age-matched healthy controls (5). Early changes in the T-cell population, including the presence of antigen-specific immunity and an enrichment of bone marrow (BM) stem-like/resident memory (TRM) T cells may prevent attrition of protective immunity and subsequent disease progression (10–12).

Progression to multiple myeloma has been associated with further immune dysfunction due to an altered T-cell repertoire, with features of terminally differentiated T cells and loss of antigen-specific T-cell function (**Fig. 1**). In multiple myeloma, loss of stem-like/TRM T cells (10) as well as increases in Tregs (9, 13) and proinflammatory Th17 cells (9, 14, 15) have been observed. These changes may have implications for T-cell–directed therapy. For example, loss of stem-like/TRM T cells may affect the durability of T-cell redirection or responsiveness to immune-checkpoint inhibitors (CPI). In a study comparing T-cell function in patients with MGUS versus multiple myeloma, T cells from patients with multiple myeloma were unable to mount responses to tumor cells (16). This was in contrast to T cells from patients with MGUS, which retained *ex vivo* antitumor activity (16). Taken together, these observations indicate that T cells in multiple myeloma lose the ability to naturally control tumor progression (16).

[1]Department of Medicine, Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania. [2]Departments of Hematology/Oncology and Medicine, Center for Multiple Myeloma, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. [3]Amgen, Inc., Thousand Oaks, California. [4]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia.

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Corresponding Author: Adam D. Cohen, Abramson Cancer Center, University of Pennsylvania, PCAM 12-South, 12-175, 3400 Civic Center Boulevard, Philadelphia, PA 19104. Phone: 215-615-5853; Fax: 215-615-5887; E-mail: adam.cohen@uphs.upenn.edu

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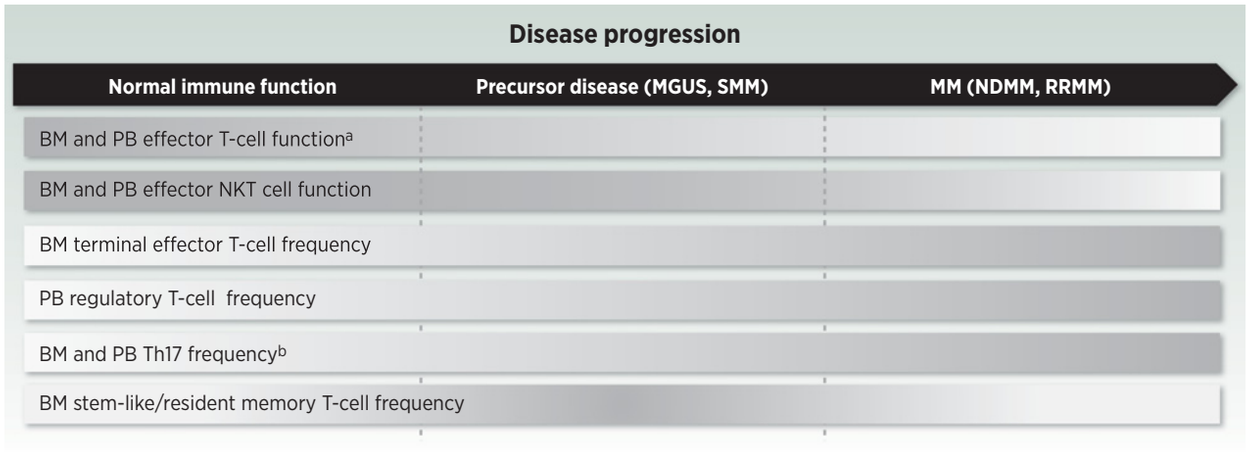

Figure 1.

Changes in the T-cell repertoire during multiple myeloma disease progression. Bars with gradients denote changes in T-cell populations (9, 10, 13–17, 21, 85, 86); darker shades correspond to increased levels, whereas lighter shades correspond to reduced levels. BM, bone marrow; MGUS, monoclonal gammopathy of undetermined significance; NKT, natural killer T cell; PB, peripheral blood; SMM, smoldering multiple myeloma; Th, T helper cell. [a]Referenced studies do not include BM and PB of age-matched healthy donors (16, 21). [b]Referenced studies do not include PB of patients with precursor disease or direct comparisons of BM Th17 frequency between age-matched healthy donors and patients with precursor disease (14, 15).

Several mechanisms for multiple myeloma–associated reductions in T-cell immunity/responsiveness have been proposed, including T-cell exhaustion, anergy, and/or senescence (17). Reduced T-cell recognition of multiple myeloma may also be due to ineffective antigen processing/presentation *in vivo* by tumor cells or dendritic cells (DC) (18–20). In one study, T cells from multiple myeloma tumor beds were found to elicit strong, multiple myeloma–specific cytolytic responses only after *ex vivo* stimulation with autologous DCs (21). This suggests that endogenous T cells from patients with multiple myeloma can be activated to mount an antitumor response (21, 22).

T-cell–Dependent Immuno-oncology Therapies in Multiple Myeloma

Understanding the mechanisms affecting T-cell immunity provides opportunities for therapy development. Here, we discuss developments in T-cell–dependent immuno-oncology therapies in multiple myeloma, including vaccines, CPIs, cellular therapies, and bispecific antibodies (bsAb)/antibody constructs. MAbs (e.g., daratumumab, elotuzumab, and antibody drug conjugates) and NK cell–based therapies in multiple myeloma have been recently reviewed (23, 24) and are beyond the scope of this review.

Vaccines

Anticancer vaccination aims to re-educate host immunity, stimulate/expand tumor-specific effector cells, and generate long-term memory (25, 26). Vaccine efficacy and response time depend on effector cell function/proliferation and tumor burden (26). Current anti–multiple myeloma vaccine strategies are targeting disease stages with lower tumor burden and/or immunosuppression (26), including stem cell transplantation (SCT), precursor disease, and minimal residual disease (MRD) settings.

Recent anti–multiple myeloma vaccination approaches can be categorized into targeted antigen– and whole cell–based methodologies. Targeted antigen approaches include protein/peptide-based vaccines that introduce tumor-associated antigens (TAA) to recruit native DCs for antigen processing/presentation and subsequent multiple myeloma–specific effector cell expansion (25). In the peritransplantation setting, studies have explored vaccines targeting MAGE-A3, hTERT, or survivin in conjunction with vaccine-primed autologous lymphocyte infusion (27–29). In SMM, a multipeptide vaccine targeting XBP1, CD138, and SLAMF7/CS1 (PVX-410) demonstrated single-agent immunogenicity that was enhanced with lenalidomide (30). Ongoing studies are evaluating PVX-410 with other combinations in precursor disease.

To elicit broader anti–multiple myeloma immune responses, whole cell–based methodologies present a greater spectrum of TAAs in the context of DC-mediated costimulation (26). An allogeneic vaccine deepened responses in one study: 3 of 4 patients with stable near-complete response (nCR) achieved complete response (CR) postvaccination (31). In the autologous SCT (autoSCT) setting, an autologous DC/multiple myeloma hybridoma vaccine converted 24% of patients with partial response posttransplantation to CR/nCR postvaccination (32). These results have led to ongoing phase II trials; studies testing vaccines targeting neoantigens are also emerging (**Fig. 2**; Supplementary Table S1).

CPIs

The overactivation of inhibitory immune-checkpoint pathways [e.g., programmed cell death protein-1 (PD-1)/PD-ligand 1 (PD-L1) pathway] in cancer suppresses immunosurveillance (33). CPIs that block these pathways enable tumor-reactive cells to mount immune responses (34). CPIs have been effective in other malignancies (33, 35), but their role in multiple myeloma remains unclear. Although nivolumab (anti–PD-1) had no significant single-agent activity in relapsed/refractory multiple myeloma (36), two phase I/II studies using pembrolizumab (anti–PD-1) plus an IMiD and dexamethasone showed overall response rates (ORR) of 44% to 60% in patients with relapsed/refractory multiple myeloma (37, 38).

However, in two phase III trials, patients with newly diagnosed multiple myeloma (NDMM) or relapsed/refractory multiple myeloma

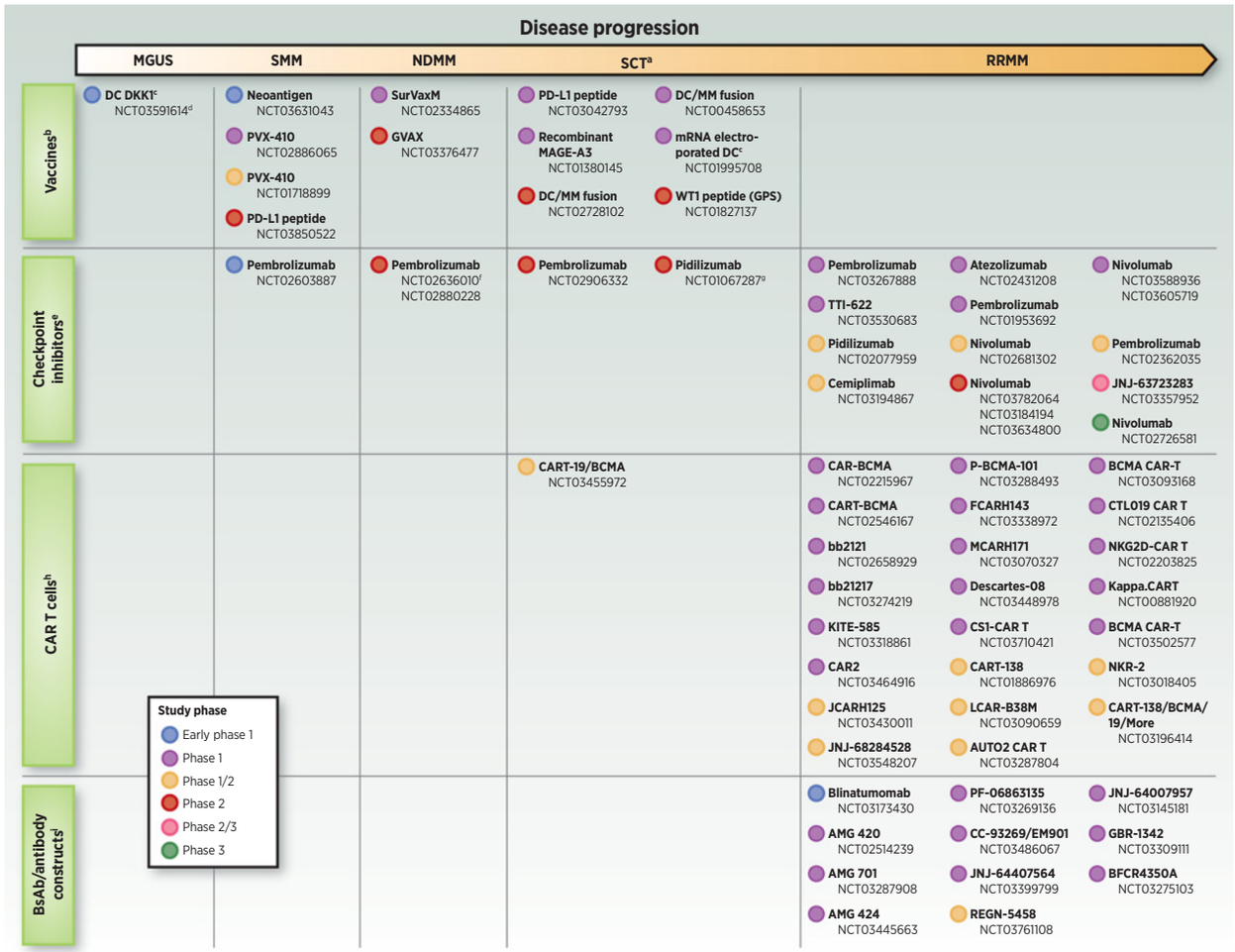

Figure 2.

Select T-cell–dependent immuno-oncology studies across the multiple myeloma disease continuum. Studies include early stages of disease (MGUS, SMM, and NDMM), patients with multiple myeloma and low tumor burden (transplant setting), and patients in the relapsed and/or refractory multiple myeloma setting. BCMA, B-cell maturation antigen; bsAb, bispecific antibody; CAR T, chimeric antigen receptor T cell; CPI, checkpoint inhibitor; DC, dendritic cell; GPS, galinpepimut-S; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed and/or refractory multiple myeloma; SCT, stem cell transplantation; SMM, smoldering multiple myeloma. Based on www.clinicaltrials.gov search conducted on February 20, 2019. [a]SCT studies may include NDMM or RRMM patients (i.e., not mutually exclusive). [b]Studies in RRMM are not shown, as the focus of more recent vaccine therapy trials has been for disease stages with lower tumor burden/immunosuppression. [c]Autologous DC vaccine. [d]Study also includes SMM and multiple myeloma patients. [e]Studies evaluating pembrolizumab/immunomodulatory drug combinations in RRMM are not included due to clinical holds placed on some of these studies. [f]Study also includes patients at first relapse. [g]In conjunction with DC/multiple myeloma vaccine. [h]Following the completion of our clinicaltrials.gov search, a phase I/II study of CT053, a BCMA-targeting CAR T-cell therapy, has opened (NCT03975907). [i]Following the completion of our clinicaltrials.gov search, a phase I study of TNB-383B, a BCMA-targeting bsAb/antibody construct, has entered clinical trials (NCT03933735).

who received pembrolizumab plus an IMiD and dexamethasone experienced greater rates of grade ≥3 immune-related adverse events (AE)/death compared with standard of care, without appreciable improvements in response (39, 40). These safety concerns led to the suspension of both trials by the Food and Drug Administration (FDA); several other CPI/IMiD combination studies were halted (34). The lack of CPI success in multiple myeloma remains unexplained; one hypothesis is reduced CPI response due to T-cell senescence (17).

Ongoing efforts are evaluating PD-1/PD-L1 inhibitors with other mAbs, vaccines, and as consolidation therapy post-SCT (Supplementary Table S2). Other CPI targets (e.g., Lag-3, Tim-3, and TIGIT) have demonstrated preclinical efficacy in multiple myeloma models (41, 42). Given their potential for enhancing T-cell activation, agonistic antibodies targeting costimulatory receptors (e.g., CD137/4-1BB, OX40) are also under investigation (41).

Cellular Therapies: Chimeric Antigen Receptor (CAR) T Cells, Transgenic T-cell Receptor (Tg TCR) T Cells, and Marrow-Infiltrating Lymphocytes (MIL)

CAR T cells are autologous T cells genetically modified *ex vivo* to express a novel receptor containing an extracellular antigen-binding

domain, to bypass major histocompatibility complex (MHC)–dependent binding to TAAs, and intracellular signaling domains for T-cell activation/costimulation (43). T-cell activation is initiated following immune synapse (IS) formation, which facilitates lytic granule-mediated apoptosis of the target cell. Notably, the CAR T cell–induced IS differs in composition and subdomain arrangement compared with the classic TCR-induced IS (e.g., smaller/patchy actin ring, disorganized distribution of signaling molecule Lck, and lack of an adhesion ring); these differences were associated with faster destruction and detachment from target cells (44).

Anti-CD19 CAR T cells demonstrated significant clinical activity in patients with relapsed/refractory B-cell leukemia and lymphoma (45–47). In multiple myeloma, CAR T-cell therapies targeting B-cell maturation antigen (BCMA) have shown the most promise to date (48–50). BCMA demonstrates relatively restricted expression on plasma cells and is expressed on multiple myeloma cells of virtually all patients with varying intensity (49). Preclinical studies have also demonstrated a role for BCMA in promoting multiple myeloma progression *in vivo* (51, 52). Therefore, BCMA represents a rational anti–multiple myeloma target.

Early studies of BCMA-targeting CAR T-cell therapy in patients with refractory multiple myeloma (median 7–9.5 prior lines) reported ORRs of 64%–90% in patients treated at optimal doses (>10^8 CAR T cells), including induction of MRD-negative CRs (53–55). Response durability and progression-free survival (PFS) have been more variable, but PFS was ∼11.8 months in the first 33 patients treated with the anti-BCMA CAR T-cell therapy bb2121 (53). In another anti-BCMA CAR T-cell trial in less heavily pretreated patients ($n = 57$, median 3 prior lines), ORR was 88% (68% CR), and median PFS was ∼15 months (56). Multiple anti-BCMA CAR T-cell trials have since opened (**Tables 1** and **2**), and preliminary findings have supported this initial activity. Longer follow-up is needed to determine response durability.

Current CAR T-cell manufacturing processes may impede prompt treatment of aggressive disease, and a significant proportion of leukopheresed patients (8%–14% in 2 recent trials; refs. 53 and 54) may never receive treatment due to rapid progression/clinical deterioration. Faster manufacturing protocols (57), allogeneic CAR T-cell products (58), and/or earlier treatment may help overcome this limitation.

CAR T-cell–associated toxicities include target-specific and -nonspecific effects of immune activation, particularly cytokine release syndrome (CRS) and neurotoxicity (49). Most anti-BCMA CAR T-cell studies in multiple myeloma have reported any-grade CRS rates >60%; rates of grade ≥3 CRS are variable, but have been up to 41% (**Table 1**). CRS can usually be abrogated with tocilizumab (anti-IL6R mAb). Neurotoxicity has been reported in up to 42% of patients (53), comparable with anti-CD19 CAR T cells; neurotoxicity has usually been self-limited and/or responded to steroids, though severe cases have been observed (53–55).

Another important consideration for CAR T cells is lymphodepletion, a strategy used to deplete immunosuppressive cell populations and improve CAR T-cell proliferation and engraftment (59). Lymphodepletion has enhanced the clinical benefit of CAR T-cell therapy in hematologic malignancies (60, 61), suggesting that preconditioning is an important procedure for this therapeutic class. In one multiple myeloma study, short-term CAR T-cell expansion was more consistently observed in patients who received cyclophosphamide lymphodepletion than those who did not (54).

Other adoptive cellular therapies are also under investigation. Autologous Tg TCR T cells are *ex vivo*–modified to express TCRs targeting extracellular or intracellular TAAs, albeit with MHC-restricted recognition (49, 62). Tg TCR T cells targeting NY-ESO-1 were well tolerated in patients with HLA A0201$^+$ multiple myeloma ($n = 20$; median 3 prior lines) when infused (day 2) after autoSCT; nCR/CR was seen in 14 of 20 (70%) patients, with a median PFS of 19.1 months (63). A trial investigating NY-ESO-1 Tg TCR T cells lacking PD-1 administered without autoSCT is ongoing (NCT03399448). MILs harbor a greater proportion of activated, memory, multiple myeloma-specific T cells, and show greater *ex vivo* anti–multiple myeloma activity than peripheral blood lymphocytes (64). In a phase I study, 22 patients with multiple myeloma (45% relapsed/refractory) received *ex vivo*–activated MIL (day 3) following autoSCT. Anti–multiple myeloma immune responses were significantly greater post-MIL infusion, and stronger immune activity correlated with deeper clinical responses (65). ORR was 54%; in patients who achieved ≥90% and <90% reduction in disease burden, median PFS was 25.1 months and 11.8 months, respectively (65). These results led to an ongoing phase II trial of MILs + autoSCT (NCT01045460).

Bispecific Antibodies (bsAb)/Antibody Constructs

BsAbs/antibody constructs are engineered to simultaneously engage endogenous T cells and tumor cells via binding to CD3 and any extracellular TAA, respectively, activating the T cells to attack the tumor cells (66). Advantages of bsAbs/antibody constructs include their ability to act independently of MHC/TCR specificity, costimulation, or peptide antigen presentation (67, 68). Furthermore, these molecules do not require *ex vivo* T-cell manipulation (68), enabling immediate treatment initiation. Upon T-cell recruitment to a cancer cell, an IS forms that is virtually indistinguishable from the endogenous TCR-induced synapse (69). IS formation induces the release of cytotoxic granules (e.g., perforin, granzymes) from the activated T cell, leading to tumor cell death. BsAbs/antibody constructs promote serial lysis and sustained T-cell activation, leading to polyclonal expansion of memory T cells (67, 70, 71). The bsAb/antibody construct with the most clinical experience to date is the BiTE (bispecific T-cell engager) platform, which utilizes 2 single-chain variable domains connected by a short linker. The resulting protein has a short serum half-life, requiring continuous infusion. An example is blinatumomab, which targets CD3 and CD19. Blinatumomab demonstrated clinical activity in relapsed/refractory acute lymphoblastic leukemia (ALL; refs. 72, 73), leading to FDA approval in 2014. Toxicities include CRS and neurotoxicity, which usually improve with infusion cessation and, if needed, steroid and/or tocilizumab administration.

The first bsAb/antibody construct with available clinical data in multiple myeloma is the BCMA-targeting molecule AMG 420 (**Table 1**). In a phase I dose-escalation study, patients with relapsed and/or refractory multiple myeloma ($n = 42$; median 4 prior lines) were continuously infused with AMG 420 (0.2–800 μg/d; 4 weeks on/2 weeks off, up to 10 cycles; ref. 74). The most frequently reported serious AEs were infections (31%) and peripheral polyneuropathy (5%); CRS was observed in 38% of patients, mostly grade 1. The 800 μg/d dose was not tolerable in this study (2/3 patients experienced dose-limiting toxicities). At 400 μg/d (recommended dose for this study), 70% (7/10) of patients responded, including 5 MRD-negative stringent CRs. The median time to response was 1 month,

Table 1. CAR T-cell and bsAb/antibody construct trials in patients with relapsed and/or refractory multiple myeloma with published data.

Therapy class: target(s)	Identifier (reference)	Phase	*N*			Patient population			Immuno-oncology agent and regimen(s)	ORR	≥CR	Safety		
			Eligible patients enrolled	Received study treatment	Evaluable for safety/efficacy	Median (range) age, years	Prior lines of therapy	High-risk cytogenetics				Common AEs	CRS	Neurotoxicity
CAR T: BCMA	NCT02215967 (55)	1	19 (at highest dose level)	16 (at highest dose level)	16 (at highest dose level)	Not reported	Median (range): 9.5 (3–19)	High-risk defined by del (17p), t(14;16), t (14;20), or t (4;14): 40% at highest dose	CAR-BCMA T cells with Cy/Flu (0.3–9 × 10^6/kg)	81% (13/16)	13% (2/16)	CRS, hypotension	Any grade: 94% (15/16); Grade ≥3: 38% (6/16)	Occurred in the setting of severe CRS, limited to confusion or delirium; 1 patient experienced encephalopathy and muscle weakness in all extremities
	NCT02546167 (54)	1	29	25	25	58 (44–75)	Median (range): 7 (3–13)	High-risk defined by complex karyotype, gain 1q, del(17p), t (14;16), and/or t (4;14): 96% (24/25)	CART-BCMA cells (1–5 × 10^8) alone (Cohort 1) CART-BCMA cells (1–5 × 10^7) with Cy (Cohort 2) CART-BCMA cells (1–5 × 10^8) with Cy (Cohort 3)	Cohort 1: 44% (4/9); Cohort 2: 20% (1/5); Cohort 3: 64% (7/11)	Cohort 1: 11% (1/9); Cohort 2: 0%; Cohort 3: 9% (1/11)	Grade ≥3: • Leukopenia (44% [11/25]); • Neutropenia (44% [11/25]); • Lymphopenia (36% [9/25])	Any grade: 88% (22/25); Grade ≥3: 32% (8/25)	Any grade: 32% (8/25); Grade ≥3 12% (3/25)
	NCT02658929 (53)	1	36	33	33	60 (37–75)	Median (range): 7 (3–23)	High risk defined by del(17p), t (4;14), or t (14;16): 45% (15/33)	bb2121 CAR T cells (50–800 × 10^6) with Cy/Flu	85% (28/33); 90% (27/30) in patients receiving 150–800 × 10^6 CAR^+ T cells	45% (15/33)	Any grade: • Neutropenia (85% [28/33]); • CRS (76% [25/33]); • Leukopenia (61% [20/33]); • Anemia (58% [19/33]); • Thrombocytopenia (58% [19/33])	Any grade: 76% (25/33); Grade ≥3: 6% (2/33)	Any grade neurologic toxic effect: 42% (14/33); Grade ≥3 neurologic toxic effect: 3% (1/33)
	NCT03090659 (56, 93)	1	57	57	57	At 1 of 4 clinical centers: 54 (27–72)	Median (range): 3 (1–9)	Not reported	LCAR-B38M CAR T cells (median, 0.5 × 10^6 cells/kg) with Cy	88% (50/57)	68% (39/57)	Any grade: • Pyrexia (91% [52/57]); • CRS (89% [51/57]); • Thrombocytopenia (49% [28/57]);	Any grade: 89% (51/57); Grade ≥3: 7% (4/57)	Any grade: 2% (1/57); Grade ≥3: 0%
		1	17	17	17	At 3 of 4 clinical centers: Range: 35–73	≥3 prior therapies: 71%	t(4;14) and del (17p): 35% (6/17) Gain(1q): 65% (11/17) Del(13q): 35% (6/17)	LCAR-B38M CAR T cells (median, 0.6 × 10^6 cells/kg) with Cy or Cy/Flu	88% (15/17)	76% (13/17)	Any grade: • Fever: 100% (17/17); • CRS: 100% (17/17); • Cytopenia: 82% (14/17); • Liver dysfunction: 53% (9/17)	Any grade: 100% (17/17); Grade ≥3: 41% (7/17)	Not reported

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Table 1. CAR T-cell and bsAb/antibody construct trials in patients with relapsed and/or refractory multiple myeloma with published data. (Cont'd)

Therapy class: target(s)	Identifier (reference)	Phase	N			Patient population			Immuno-oncology agent and regimen(s)	ORR	≥CR	Safety		
			Eligible patients enrolled	Received study treatment	Evaluable for safety/efficacy	Median (range) age, years	Prior lines of therapy	High-risk cytogenetics				Common AEs	CRS	Neurotoxicity
	NCT03274219 (91)	1	13	12	12	63 (44–69)	Median (range): 7 (4–17)	Del(17p), t(4;14), t(14;16): 58% (7/12)	bb21217 CAR T cells (150×10^6) with Cy/Flu	83% (10/12)	25% (3/12)	Grade ≥3: • Neutropenia (83% [10/12]) • Thrombocytopenia (50% [6/12]) • Anemia (42% [5/12]) • Leukopenia (42% [5/12])	Any grade: 67% (8/12); Grade ≥3: 8% (1/12)	Any grade: 25% (3/12); Grade ≥3: 8% (1/12)
	NCT03288493 (87)	1	Not reported	12	Safety: 12; Efficacy: 9 (3, Cohort 1; 6 Cohort 2)	Not reported	Range: 3–9	High-risk: 64%	P-BCMA-101 CAR T cells ($48–430 \times 10^6$) with Cy/Flu (Cohorts 1–3)	Cohorts 2 and 3: 83% (5/6)	Cohorts 2 and 3: 17% (1/6)	Grade ≥3: • Cytopenia • Febrile neutropenia	Any grade: 8% (1/12); Grade ≥3: 0%	Any grade: 0%
	N/A (94)	N/A	Not reported	16	Safety: 16; Efficacy: 13	55 (39–67)	Median (range): 4 (2–10)	Not reported	CT053 CAR T cells with Cy/Flu	100% (13/13)	15% (2/13)	Grade ≥3 CAR T-related AEs: • Thrombocytopenia (19% [3/16]); • Leukopenia (19% [3/16]); • Anemia, neutropenia, fever (13% [2/16] each)	Any grade: 19% (3/16); Grade ≥3: 6% (1/16)	Any grade: 0%
	NCT03338972 (88)	1	Not reported	7	Safety: 7; Efficacy: 6	63 (49–76)	Median (range): 8 (6–11)	Del(17p), t(4;14), and/or t(14;16): 100% (7/7)	FCARH143 CAR T cells with lymphodepletion	4 weeks after treatment: 100%	Not reported	Not reported	CRS was limited to grade 1 or 2 in severity and reported in all patients except 1	No events reported
	NCT03430011 (95)	1/2	19	13	8	53 (36–66)	Median (range): 10 (4–15)	IMWG high-risk cytogenetics: 50% (4/8)	JCARH125 CAR T cells with Cy/Flu	88% (7/8)[a]	38% (3/8)[a]	Not reported	Any grade: 75% (6/8)]; Grade ≥3: 0%	Any grade neurologic AE: 38% (3/8) Grade ≥3 neurologic AE: 13% (1/8)
	NCT03070327 (96)	1	Not reported	11	Safety: 10; Efficacy: 11	Not reported	Median (range): 6 (4–14)	High-risk: 82% (9/11)	MCARH171 CAR T cells ($72–818 \times 10^6$) with Cy/Flu	64% (7/11)	Not reported	Not reported	Any grade: 60% (6/10); Grade ≥3: 20% (2/10)	Any grade neurotoxicity: 10% (1/10) Grade ≥3 neurotoxicity: 0%
	NCT03093168 (97)	1	Not reported	17	14	Not reported	≥3 prior regimens for study eligibility	Not reported	BCMA CAR T cells (9×10^6 cells/kg) with Cy/Flu	79% (11/14)	50% (7/14)	Grade ≥3 nonhematologic AEs: • Pneumonia (14% [2/14]); • Hypophosphatemia (14% [2/14]); • Hypocalcemia (14% [2/14])	Grade ≥3: 7% (1/14)	Grade ≥3 neurotoxicity: 7% (1/14)

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			Eligible patients enrolled	Received study treatment	Evaluable for safety/efficacy	Median (range) age, years	Prior lines of therapy	High-risk cytogenetics				Common AEs	CRS	Neurotoxicity
	ChiCTR1800018137 (98)	Not reported	Not reported	9	9	Not reported	Median (range): 4 (3–5)	Not reported	CT103A CAR T cells (3 + 3 dose escalation at 1, 3, 6×10^6/kg) with Cy/Flu	100% (9/9)	44% (4/9)	Not reported	Grade 0–2 CRS observed in first 2 dose groups	Not reported
	NCT03661554 (99)	1	Not reported	16	13 at day 28[b]; 7 at 10 weeks	Not reported	Average 10 prior lines	Not reported	CART-BCMA cells (2–10 $\times 10^6$ CAR^+ cells/kg) with Cy/Flu	85% (11/13) at 28 d; 100% (7/7) at 10 weeks	43% (3/7) at 10 weeks	Not reported	Grade ≥3: 2 patients; grade 0–2 CRS observed in other patients	Not reported
CAR T: CD19	NCT02135406 (100)	1	12	10	10	61 (48–68)	Median (range): 6 (2–10)	Majority of patients had high-risk genetic or clinical characteristics	CTL019 CAR T cells with autoSCT	80% (8/10)	0%	Grade ≥3 AEs probably or possibly related to CTL019: autologous GVHD (gastrointestinal) and mucositis (10% [1/10] each)	Any grade: 10% (1/10); Grade ≥3: 0%	Not reported
CAR T: CD19+BCMA	NCT03196414 (89)	1/2	Not reported	8	Safety: 8; Efficacy: 5	Not reported	Not reported	Not reported	CART-19 and CART-BCMA cells as split dose (40:60) with Cy/Flu	80% (4/5)	0%	Any grade AE • Acute CRS (100% [8/8]) • Fatigue (100% [8/8]) • Cytopenia (100% [8/8]) • Anemia (75% [6/8])	Any grade: 100% (8/8)	Any grade neurotoxicity: 0%
	ChiCTROIC-17011272 (101)	2	22	21	21	58 years (IQR, 49.5–61)	Median (range): 6 (4–17)	Del(17p), t (14;16), t(14;20), or t(4;14): 24% (5/21)	CD19 CAR T cells (1×10^6 cells/kg) and anti-BCMA CAR T cells (1×10^6 cells/kg) with Cy/Flu	95% (20/21)	57% (12/21)	Any grade AE • Hypoimmunoglobulinemia (100% [21/21]) • B-cell aplasia (100% [21/21]) • Hematologic (95% [20/21]) • CRS (90% [19/21])	Any grade: 90% (19/21); Grade ≥3: 5% (1/21)	Any grade: 10% (2/21)
CAR T: NKG2D	NCT02203825 (102)	1	Not reported for MM cohort	5[c]	5[c]	Not reported	All patients had ≥5 prior therapies	Not reported	NKG2D-CAR T cells alone	0%	Not reported	Not reported for MM cohort	Grade ≥3: 0%	Grade ≥3 neurotoxicity: 0%
CAR T: CD38+BCMA	ChiCTR1800018143 (103)	1	Not reported	12	12	Not reported	All enrolled patients had ≥2 prior therapies or are double-relapsed or relapse after ASCT	67% (8/12) with genetic abnormalities	Anti-BCMA and anti-CD38 dual-target CAR T with Cy/Flu	83% (10/12)	42% (5/12)	Any grade AE • Hematologic toxicities in almost all patients • CRS (83% [10/12]) • Hepatotoxicity (17% [2/12]) • Nephrotoxicity (8% [1/12])	Any grade: 83% (10/12); Grade ≥3: 33% (4/12)	No neurotoxicity observed
CAR T: CD138	NCT01886976 (104)	1/2	5	5	5	Range, 48 to 68 years	Patients had received 5 to 18 prior chemotherapies	Not reported	CART-138 CAR T cells with conditioning	0%	0%	Grade ≥3: Fever (80% [4/5])	Not reported	Not reported

(Continued on the following page)

Table 1. CAR T-cell and bsAb/antibody construct trials in patients with relapsed and/or refractory multiple myeloma with published data. (Cont'd)

Therapy class: target(s)	Identifier (reference)	Phase	*N*			Patient population			Immuno-oncology agent and regimen(s)	ORR	≥CR	Safety		
			Eligible patients enrolled	Received study treatment	Evaluable for safety/efficacy	Median (range) age, years	Prior lines of therapy	High-risk cytogenetics				Common AEs	CRS	Neurotoxicity
CAR T: kappa LC	NCT00881920 (105)	1	Not reported	7[c]	7[c]	Range, 43 to 69 years	All patients had ≥1 prior therapy	Not reported	Kappa.CAR T alone or with Cy	0%	0%	Most common AEs reported in MM, NHL, and CLL cohorts were anemia, leukopenia, fatigue, hyper- or hypokalemia, and elevated aspartate aminotransferase	No patients had symptoms associated with severe CRS	Not reported
BiTE: BCMA × CD3	NCT02514239 (74)	1	Not reported	42	42	65 (39–79)	Median (range): 4 (2–13) prior lines	Standard-risk: 55%; Intermediate-risk: 40% High-risk: 2%	AMG 420 single agent (0.2 μg/d – 800 μg/d, 4 weeks on/ 2 weeks off, up to 10 cycles)	31% (13/42); 400 μg/d: 70% (7/10)	21% (9/42); 400 μg/d: 50% (5/10)	SAEs: • Infection (31% [13/42]) • Peripheral PN (5% [2/42]) Treatment-related SAE: • Grade 3 peripheral PN (5% [2/42]) • Grade 3 edema (2% [1/42])	Any grade: 38% (16/42); Grade ≥3: 2% (1/42)	2 patients reported peripheral PN as a DLT (1 at 800 μg/d, 1 at 400 μg/d dose deescalation). Both patients had grade 3 peripheral PN events, which were considered treatment-related SAEs
BsAb/ antibody construct: BCMA × CD3	NCT03269136, (77)	1	Not reported	5	5	Not reported	Not reported	Not reported	PF-06863135 (PF-3135) single agent	Not reported	Not reported	SAEs: • Grade 1 fever (not related to PF-3135) ($n = 1$) Treatment-emergent AE (all-causality): • The majority have been grade ≤2 • Grade 3 ALT/AST elevation ($n = 1$)	No CRS events have been reported	Not reported

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; autoSCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CR, complete response; CRP, C-reactive protein; CRS, cytokine release syndrome; Cy, cyclophosphamide; DLT, dose-limiting toxicity; Flu, fludarabine; GVHD, graft-versus-host disease; IL6, interleukin 6; IMWG, International Myeloma Working Group; IQR, interquartile range; mPFS, median progression-free survival; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PN, polyneuropathy; SAE, serious adverse event.

[a]Includes confirmed and unconfirmed responses.

[b]Three patients with extramedullary disease were evaluated as partial response at day 28 but were excluded from the efficacy analysis.

[c]MM patient values only.

and response duration is 5.6 to 10.4 months to date, with several ongoing at the time of presentation (74). A phase Ib/II multicenter study has recently opened (NCT03836053).

Several additional T-cell redirecting bsAb/antibody constructs have entered clinical trials, with no efficacy data yet available (**Fig. 2** and **Table 2**). Other BCMA-targeting investigational constructs include PF-06863135, AMG 701, JNJ-64007957, CC-93269/EM901, REGN-5458, and TNB-383B. BsAbs/antibody constructs targeting alternative multiple myeloma surface antigens include GBR-1342 and AMG 424 (anti-CD38), BFCR4350A (anti-FcRH5), and JNJ-64407654 (anti-GPRC5D). Each product differs in construction, binding sites, and affinities; however, most contain an Fc domain, creating an "IgG-like" molecule. Advantages of this type of molecule include a longer half-life (allowing for intermittent dosing; ref. 75), retention (in some constructs) of Fc-mediated effector functions (76), and potential subcutaneous administration. A theoretical disadvantage of this approach is more prolonged toxicity, but preliminary results from a phase I study ($n = 5$) of the IgG-like, BCMA-specific bsAb/antibody construct PF-06863135 showed a promising safety profile (77). Comparisons of safety/efficacy profiles with canonical BiTE molecules may be available within the next year. Research investigating trispecific antibodies (e.g., HPN217; ref. 78) is also emerging.

Challenges and Future Strategies of T-cell–Dependent Immuno-oncology Therapy

Although the immuno-oncology field has evolved rapidly and shown promise in multiple myeloma, T-cell–dependent immuno-oncology therapies face several challenges (**Fig. 3**). With the large number of available multiple myeloma therapies and many promising immuno-oncology approaches under investigation, determining the optimal treatment setting (considering disease stage, phenotype, and kinetics) and sequence within the current multiple myeloma treatment paradigm is complex.

Several classes of immuno-oncology agents have shown promise and recaptured immune responses in relapsed and/or refractory multiple myeloma, supporting their role in this setting. However, efficacy may be enhanced in a less dysregulated immune microenvironment, providing a rationale for evaluating these therapies earlier in the disease course. For example, in heavily pretreated patients with multiple myeloma, BCMA CAR T-cell expansion and response were associated with a preserved CD4:CD8 ratio and an increased frequency of $CD45RO^{-}CD27^{+}CD8^{+}$ T cells, reflective of naïve and stem cell memory T cells, prior to T-cell collection/manufacturing (54, 79). This phenotype was present more frequently in multiple myeloma patients with T cells harvested earlier in the disease course (80). Similarly, although bsAbs/antibody constructs have advantageous features that may help overcome immune-escape mechanisms in multiple myeloma, their activity may still be affected by endogenous T-cell quality (81). Therefore, bsAb/antibody construct efficacy may also be greater in less immunosuppressed patients. Further studies will help determine whether T-cell phenotype and/or function remain predictive of clinical outcomes with other CAR T-cell and bsAb/antibody constructs in multiple myeloma. The data thus far suggest that efficacy may be improved when the endogenous T-cell repertoire is in a healthier state (48). Vaccine, CPI, and CAR T-cell therapies are currently being evaluated as consolidation of first remission in NDMM, and vaccines are being studied even in MGUS/SMM (**Fig. 2**). BsAbs/antibody constructs may also be applicable across the multiple myeloma disease continuum.

The posttransplantation consolidation setting provides another opportunity for immuno-oncology therapy, as immunosuppressive cell numbers drop following SCT (34). Furthermore, as myeloablative therapy frees the BM niche, immuno-oncology treatment may repopulate the niche with tumor-reactive cells. Vaccines and CPIs are under investigation in the transplantation setting (**Fig. 2**); CAR T-cell and bsAb/antibody construct efficacy may also be enhanced in this setting. In a pilot study, tandem autoSCT and combined anti-CD19/BCMA CAR T-cell administration for high-risk NDMM patients resulted in dramatic CAR T-cell expansion, possibly due to deeper and more prolonged lymphopenia post-SCT, with promising efficacy and safety (82). Notably, the T-cell population utilized by CAR T cells and bsAbs/antibody constructs in this setting would likely differ: CAR T cells would likely be manufactured from T cells harvested before transplantation, whereas bsAbs/antibody constructs would engage T cells established posttransplantation.

Finally, determining the optimal treatment sequence, patient selection (high-risk patients, frail patients, etc.), potential for combination with current standard of care and/or other immuno-oncology therapies, and overall cost of these therapies will be important areas of future work and ongoing clinical trials (**Fig. 2**). Several additional factors require further investigation. First, it will be important to understand how immuno-oncology therapies used at relapse may be affected by prior exposure to treatments with immunomodulatory actions, including IMiDs (may enhance effector cell cytotoxic activity), PIs (capable of inducing immunogenic cell death; activating DCs; ref. 6), and anti-CD38 mAbs (may deplete immunosuppressive cell populations; expand helper and cytotoxic T cells; ref. 83). The first-line use of daratumumab will likely increase, with a consequent need for effective therapies for patients with daratumumab-refractory disease. Second, investigating the potential cross-resistance between immuno-oncology agents targeting the same antigen is warranted. Finally, retreatment at relapse with the same immuno-oncology product used at diagnosis may be feasible (84), depending on several factors (e.g., response to initial therapy, target antigen loss), and merits further study in multiple myeloma.

Conclusion

Progressive immune dysfunction is a hallmark of the multiple myeloma disease course. This has led to the development of numerous treatment strategies aimed at overcoming the immunosuppressive tumor microenvironment and stimulating the host immune system to elicit an antitumor response. The promising preliminary efficacy of T-cell–dependent immuno-oncology therapies (e.g., CAR T cells, bsAbs/antibody constructs) has generated excitement, particularly in heavily pretreated multiple myeloma patients with limited treatment options. As immuno-oncology innovations continue to demonstrate activity, opportunities remain to improve clinical benefit, tolerability, and access. Advances in our understanding of the interactions between the immune system and the multiple myeloma disease continuum will be critical in guiding future investigations to optimize immune system redirection and provide the greatest outcomes for patients with multiple myeloma.

Table 2. Ongoing CAR T-cell and bsAb/antibody construct trials in patients with relapsed and/or refractory multiple myeloma with unpublished data.

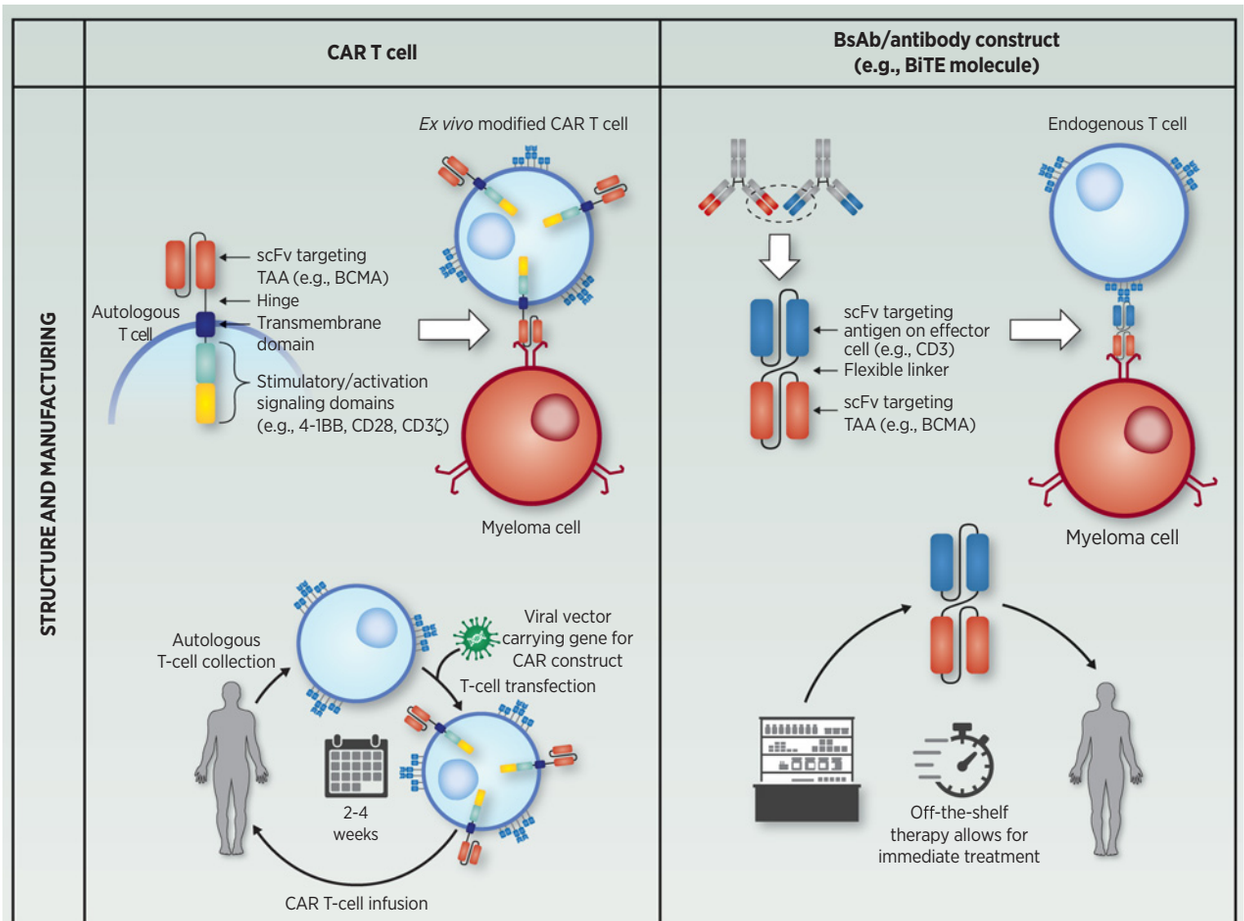
Therapy class	Target	Product	Clinical trial identifier (phase)	*N*	Patient population	Regimen(s)
CAR T cell[a]	BCMA	JNJ-68284528	NCT03548207 (phase Ib/II)	84 (est.)	Relapsed or refractory MM	JNJ-68284528 with lymphodepletion
		KITE-585	NCT03318861 (phase I)	64 (est.)	Relapsed/refractory MM	KITE-585 CAR T cells with Cy/Flu
		Descartes-08	NCT03448978 (phase I)	15 (est.)	Refractory MM	Descartes-08 with Cy/Flu
		BCMA CAR T	NCT03502577 (phase I)	18 (est.)	Relapsed or refractory MM	BCMA CAR T cells and LY3039478 with Cy/Flu
	APRIL	AUTO2	NCT03287804 (phase I/II)	80 (est.)	Relapsed or refractory MM	AUTO2 (15–350 $\times$ 10^6 cells) with Cy/Flu
	CD38	CAR2	NCT03464916 (phase I)	72 (est.)	Relapsed or refractory MM	CAR2 cells alone
	SLAMF7/CS1	CS1-CAR T	NCT03710421 (phase I)	30 (est.)	Relapsed or refractory MM	CS1-CAR T with Cy/Flu
	NKG2D	NKR-2 (CYAD-01)	NCT03018405 (phase I/II, THINK)	146 (est.)	Relapsed or refractory MM (or AML/MDS)	NKR-2 (3×10^8–3×10^9 cells) cells alone
	BCMA+CD138	CART-138/BCMA	NCT03196414 (phase I/II)	10 (est.)	Relapsed and refractory MM	CART-138/BCMA with Cy/Flu
BsAb/antibody construct[b]	BCMA $\times$ CD3	AMG 701	NCT03287908 (phase I)	115 (est.)	Relapsed or refractory MM	Single agent
		JNJ-64007957	NCT03145181 (phase I)	60 (est.)	Relapsed or refractory MM	Single agent
		REGN-5458	NCT03761108 (phase I/II)	56 (est.)	Relapsed or refractory MM	Single agent
		CC-93269 (EM901)	NCT03486067 (phase I)	120 (est.)	Relapsed and refractory MM	Single agent
	CD38 $\times$ CD3	AMG 424	NCT03445663 (phase I)	120 (est.)	Relapsed or refractory MM	Single agent
		GBR-1342	NCT03309111 (phase I)	125 (est.)	Previously treated MM	Single agent
	FcRH5 $\times$ CD3	BFCR4350A	NCT03275103 (phase I)	80 (est.)	Relapsed or refractory MM	Single agent
	GPRC5D $\times$ CD3	JNJ-64407564	NCT03399799 (phase I)	87 (est.)	Relapsed or refractory MM	Single agent
	CD19 $\times$ CD3	Blinatumomab	NCT03173430 (early phase I)	20 (est.)	Refractory MM	Blinatumomab-autoSCT

Abbreviations: AML, acute myeloid leukemia; autoSCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; bsAb, bispecific antibody; CAR, chimeric antigen receptor; Cy, cyclophosphamide; est., estimated; Flu, fludarabine; MDS, myelodysplastic syndrome; MM, multiple myeloma.

Based on www.clinicaltrials.gov search conducted on February 20, 2019.

[a]Following the completion of our clinicaltrials.gov search, a phase I/II study of CT053, a BCMA-targeting CAR T-cell therapy, has opened (NCT03975907).

[b]Following the completion of our clinicaltrials.gov search, a phase I study of TNB-383B, a BCMA-targeting bsAb/antibody construct, has entered clinical trials (NCT03933735).



CHALLENGES AND STRATEGIES FOR IMPROVEMENT

Challenge	Strategies for improvement
Immunogenicity (e.g., HAMA)	• Fully human product
Manufacturing time	• Allogeneic product • More rapid manufacturing protocols
Target antigen loss/ antigen-negative relapse	• Gamma-secretase inhibition for BCMA (e.g., NCT03502577) • Dual antigen-targeting product
Persistence	• MIL-based product • Preferential transduction of T_{CM} and T_{SCM} cell • PI3K inhibitor during manufacturing • Product with defined CD4:CD8 ratio
Safety (CRS, neurotoxicity)	• Tocilizumab to treat or prevent therapy-associated CRS • Consensus grading criteria and management algorithms for CRS and neurologic toxicity • Safety switches

Challenge	Strategies for improvement
Immunogenicity (e.g., HAMA)	• Humanize mAbs • Generate mAbs from phage display libraries based on human sequence
Target antigen loss/ antigen-negative relapse	• Infusion of 2 bsAbs/antibody constructs targeting separate TAAs
Frequency of administration	• Extended half-life product
Safety (CRS, neurotoxicity, infections)	• Tocilizumab to treat or prevent therapy-associated CRS • Consensus grading criteria and management algorithms for CRS and neurologic toxicity • Careful evaluation of infections in future clinical trials to enable development of optimal management guidelines

Figure 3.

Comparison of CAR T-cell and bsAb/antibody construct immuno-oncology approaches in multiple myeloma. Similarities and differences in structure and manufacturing (43, 49, 68), as well as challenges and current strategies for improvement (75, 82, 87–92). BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; bsAb, bispecific antibody; CAR, chimeric antigen receptor; CM, central memory; CRS, cytokine release syndrome; HAMA, human anti-mouse antibody; mAb, monoclonal antibody; MIL, marrow-infiltrating lymphocyte; scFV, single-chain variable fragment; SCM, stem cell memory; TAA, tumor-associated antigen; TCR, T-cell receptor.

Disclosure of Potential Conflicts of Interest

A. D. Cohen is a paid consultant for Janssen, Celgene, Takeda, GlaxoSmithKline, Kite Pharma, Oncopeptides, and Seattle Genetics, and reports receiving commercial research grants from and holds ownership interest in Novartis. J. A. Fowler, K. Mezzi, and E. C. Scott are employees of, and own stock in, Amgen. M. V. Dhodapkar is a paid consultant for Amgen, Janssen, Roche, and Kite Pharma. No potential conflicts of interest were disclosed by the other author.

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