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BCMA-targeted biologic therapies: the next standard of care in multiple myeloma therapy

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Abstract

With recent advances in myeloma therapy patients can achieve long-term remissions, but eventually relapses will occur. Triple-class refractory myeloma disease that is refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and penta-refractory myeloma—disease that is refractory to 2 proteasome inhibitors, 2 immunomodulatory agents, and an anti-CD38 antibody are associated with a particularly poor prognosis and novel treatments are desperately needed to address these patients. Targeting B cell maturation antigen (BCMA), which is ubiquitously expressed on plasma cells, has emerged as a well-tolerated and highly efficacious strategy in patients with relapsed and refractory myeloma. Several mechanisms of targeting BCMA are currently under investigation including antibody drug conjugates, bispecific antibodies, and chimeric antigen receptor T and NK cells, all with unique side effect profiles. Early phase clinical trials showed unprecedented response rates in highly refractory myeloma patients leading to the recent approvals of some of these agents. Still, many questions remain with regard to this target including: how best to target it, how to treat patients who have progressed on a BCMA targeting therapy and if response rates will deepen if these agents are used in earlier lines of therapy. In this review, we examine the rationale for targeting BCMA and summarize the data for several agents across multiple classes of BCMA-targeting therapeutics paying special attention to the diverse mechanisms and unique challenges of each therapeutic class.

1 Introduction:

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells which represents 18% of all hematologic malignancies and 1.8% of all cancers in the US [1, 2].

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With the recent advent and widespread adoption of novel therapies-including proteasome inhibitors (PIs), immunomodulatory agents (IMiDs) and anti-CD38 monoclonal antibodies-in addition to high-dose chemotherapy and autologous stem cell transplant the median overall survival of newly diagnosed MM patients now approaches 10 years with some patients surviving significantly longer [3–8]. Unfortunately, all patients will eventually relapse and patients who are triple class refractory (refractory to a PI, an IMiD and an anti-CD38 antibody) and especially penta-refractory patients (refractory to 2 PIs, 2 IMiDs and an anti-CD38 antibody) have a particularly poor prognosis of < 6 months [9–12]. Additionally, duration of response with subsequent therapies after relapses typically becomes progressively shorter as MM becomes more refractory [13–15]. This underlies the urgent need for novel targets and treatment modalities in the refractory MM patient population.

2 BCMA in MM:

B cell maturation antigen (BCMA) also known as TNFRSF17 or CD269 is a type III transmembrane glycoprotein and non-tyrosine kinase receptor in the tumor necrosis factor receptor (TNFR) superfamily [16, 17]. BCMA expression is nearly absent on naïve and memory B cells but is selectively induced during plasma cell differentiation and is ubiquitously expressed on plasmablasts and plasma cells [18, 19]. Expression is rare in other tissues, with only low-level BCMA mRNA and protein expression seen in areas with endogenous plasma cell populations (i.e., the testes, GI tract, and trachea) [20–23]. BCMA, along with B-cell activation factor receptor (BAFF-R) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), regulate B cell maturation and differentiation into plasma cells [24, 25]. BCMA −/− mice are able to generate short-lived plasma cells but are significantly deficient in long-lived plasma cells compared to wild type suggesting that BCMA is critical to maintaining a sustained humoral immune response [19, 26]. Similarly, murine models of BCMA overexpression promote in vivo MM cell growth [17]. Notably, BCMA expression is significantly higher in myeloma cells then normal plasma cells and levels also increase with progression from monoclonal gammopathy of undetermined significance (MGUS), to smoldering multiple myeloma (SMM) and active MM [20, 27, 28].

BCMA has two agonist ligands: a proliferation inducing ligand (APRIL) and B cell activation factor (BAFF) with APRIL having ~100 fold the affinity for BCMA than BAFF [29]. APRIL is primarily secreted by bone marrow stromal cells, osteoclasts, and macrophages in a paracrine fashion [17]. Serum levels of APRIL are higher in myeloma patients than healthy volunteers and correlate with ISS stage of newly diagnosed MM patients [17, 30–33]. Inhibition of APRIL with a monoclonal antibody led to decreased MM cell growth in a mouse xenograft models and the addition of APRIL to MM cell lines inhibited dexamethasone induced apoptosis [17, 32]. The downstream effects of BCMA binding to ligand are myriad and include activation of the NF-κβ, RAS/MAPK, and PI3K/AKT signaling pathways ultimately leading to the osteoclast mediated bone degradation, cell adhesion, and angiogenesis all of which promote MM proliferation and progression[17, 32, 34–36].

While BCMA is synthesized as a cell surface protein, cleavage of the extracellular domain and part of the transmembrane domain by γ-secretase results in the formation of a soluble form of BCMA (sBCMA) [37, 38]. Levels of sBCMA are significantly higher in MM patients than healthy controls and correlate with more advanced disease and poorer prognosis [28, 37, 39–44]. While smaller studies have shown that change in levels of sBCMA may serve as a surrogate of disease response to BCMA targeting therapy, this was not the case in the phase 1 DREAMM-1 study of the belantamab mafodotin (GSK2857916) a BCMA antibody-drug conjugate which is the largest study to date to report on the correlation of sBCMA levels and response to treatment [40, 43, 45]. These divergent findings may be explained by the finding of Chen et al who have shown that high levels of sBCMA may interfere with BCMA-targeted therapies by sequestering the antibody leading to less binding to surface BCMA [42]. This has led to the of investigation of administration of γ-secretase inhibitors (GSIs) to decrease surface BCMA shedding. Preclinical studies have shown that exposure to a GSI decreases sBCMA levels, increases surface BCMA expression and number of MM cells expressing surface BCMA, and increases responses to BCMA chimeric antigen receptor (CAR-T) therapy [46]. This noteworthy finding has led to early phase clinical trials evaluating the safety and efficacy of the combination of a GSI and BCMA targeting therapy in MM patients [47]. Alternatively, MEDI2228 another BCMA antibody-drug conjugate with preferential binding to surface BCMA, has shown improved cytotoxicity in preclinical models with high levels of sBCMA and has shown impressive efficacy in a phase 1 clinical trial of relapsed refractory MM patients (NCT3489525) [44, 48].

The efficacy of BCMA targeting in preclinical models and the potential for activity in MM patients who are refractory to conventional therapy has led to a wealth of research that has yielded multiple agents that target BMCA through a variety of mechanisms (Figure 1). Below we review these agents' mechanisms of action and summarize the most recent data for relevant clinical trials.

3 BCMA ADCs (Table 1)peer

Antibody drug conjugates (ADCs) are monoclonal antibodies (mAb) directed towards a highly expressed antigen on the cell surface of MM cells with the goal of delivering a toxic "warhead" payload bound to a linker [49–51]. When the mAb or antibody fragment binds to its target, it gets internalized and the cytotoxic drug is released by either linker cleavage or antibody dissolution, leading to cell damage and death. This modality allows for very specific drug delivery with limited off-target toxicities. Payloads must be stable to travel to the antigen site bound to the mAb and amass intracellular concentrations that are toxic to the target cells. Commonly used agents for myeloma include tubulin polymerase inhibitors like auristatin, RNA polymerase inhibitors like amanitin, or DNA-targeting agents [52–54]. While several different ADC targets are being studied for MM, compounds targeting BCMA with a multitude of cytotoxic warheads are the most mature [48, 49].

3.1 Belantamab mafodotin (GSK2857916)

The agent that spearheaded BCMA targeting ADCs in MM is belantamab mafodotin, a first in class humanized IgG1 monoclonal engineered antibody that is afucosylated and is bound to a microtubule inhibitor monomethyl auristatin-F (MMAF) through a protease resistant maleimidocaproyl linker [55]. Once the ADC is bound and internalized by the targeted cell, the payload is released and binds to tubulin leading to cell cycle arrest and eventually apoptosis [56]. More recent data also suggests an important role of immune mediated cellular killing through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) [57, 58]. The phase I DREAMM-1 study enrolled 73 MM patients previously treated with stem cell transplant, alkyalators, proteasome inhibitors, and immunomodulators and consisted of two parts: a dose-escalation portion of 38 patients treated every three weeks, and a 35-patient dose-expansion. There was no maximum tolerated dose reached or dose limiting toxicities. The most common non-hematologic side effect was corneal toxicity which occurred in 63% of those who participated in part two (treating dose of 3.4mg/kg). Of these toxicities, 54% were grade 1 and 2 with no treatment discontinuations. Regarding grade 3 and 4 hematologic toxicities, thrombocytopenia was seen in 34% and anemia was seen in 14% of participants. Responses were seen in 60% of patients treated in the dose expansion with a median PFS of 12 months and duration of response of 14.3 months [45, 59].

The phase II registrational trial (DREAMM-2) used the recommended dose from the prior study (3.4mg/kg every 3 weeks) and added a second arm at a dose of 2.5 mg/kg to evaluate safety and activity of the drug in 196 patients in eight countries. All participants had received 3 or more prior lines of therapy and were refractory or intolerant to an IMiD, PI, and an anti-CD38 antibody therapy. Overall, response rates were 31% in the 2.5mg/kg arm and 34% in the 3.4mg/kg group. Median PFS was 2.9 months in the 2.5mg/kg arm and 4.9 months in the 3.4mg/kg arm and median duration of response was 11 months [60]. The most common grade 3 and 4 adverse events were similar to the prior study and included keratopathy in 27% of patients treated with the 2.5 mg dose and 21% of patients on the 3.4 mg arm, as well as thrombocytopenia (20% and 33% respectively) and anemia (20% and 25%) [61, 62]. These results in heavily pre-treated patients with manageable toxicities led to FDA approval on August 5, 2020 at a dose of 2.5 mg/kg every three weeks in patients with at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 antibody [56]. Given the incidence of keratopathy attributed to MMAF which was seen in 70% of all patients treated, a REMS program was established requiring ophthalmologic evaluations prior to each administration [50, 61, 63].

While the DREAMM-2 study did show that belantamab mafadotin has single-agent activity in RRMM, studies are currently evaluating using this agent in combination with other MM therapies at earlier stages of disease with the hope of improved response rates [56, 64, 65]. Preliminary data presented in 18 patients treated in with belantamab mafadotin, bortezomib, and dexamethasone showed response rates of 78% and had comparable adverse events [66, 67]. When combined (at two different dose levels) with pomalidomide and dexamethasone, response rates increased to 82–95% [68, 69]. Given the increased frequency of ocular toxicity, decreased doses at 1.92 mg/kg and frequency of every 4 weeks were

performed [70]. Other combinations with agents such as lenalidomide, daratumumab, and pembrolizomab are being tested for safety and response rates in RRMM patients [71]. The interest in using BCMA-targeted therapy upfront to achieve deeper responses has led to a clinical trial in treatment-naïve transplant ineligible patients to determine if the addition of belantamab mafadotin to conventional induction therapy could induce deeper response and change the course of the disease [72].

3.2 MEDI2228

MEDI2228 is a fully human antibody with a cleavable linker containing the DNA cross-linking agent pyrrolobenzodiazepine (PBD) dimer tesirine [73]. In preclinical studies, MEDI2228 activated critical DNA damage responses (DDR) via phosphorylation of ATM/ATR kinases, checkpoint kinases (CHK)1/2, and H2AX leading to apoptotic cell death. Additionally, MEDI2228 was more efficacious than MMAF in preclinical testing regardless of amount of soluble BCMA, tumor microenvironment conditions, or presence of high risk cytogenetics [74]. Results of a first-in-human phase I study with 82 patients who had received at least 3 prior lines of therapy showed response rates of 61% and duration of response was not reached. Unlike MMAF-containing agents, no keratopathies were reported but it did cause photophobia in 53% of those who received therapeutic doses. Additional non-hematologic toxicities included rash (29%), dry eyes (20%), and pleural effusions (20%) Thrombocytopenia was the most common hematologic toxicity and was seen in 33% of patients [48]. The maximum tolerated dose was 0.14 mg/kg every three weeks. Unfortunately, development of MEDI2228 was halted given the crowded landscape of BCMA-targeted ADCs and significant toxicity seen with this agent [75].

3.3 CC-99712

This agent contains a maytansinoid toxic payload that forms part of the microtubular polymerization inhibitors and is attached to a non-cleavable linker [76, 77]. A Phase I dose escalation to determine maximum tolerated dose (MTD) and expansion arms to establish safety is ongoing.

3.4 HDP-101

HDP-101 is a BCMA ADC with a novel amanitin derivative as its payload which inhibits formation of mRNA in the targeted cell. This mechanism is unique in that it is works independently of mitotic cell division making it effective in less proliferative, more dormant clones [78, 79]. The first-in-human phase I/IIa study plans to enroll 36 patients in the dose-escalation phase and 30 patients in the dose-expansion portion [79]. There is special interest in patients with 17p deletion given the increased susceptibility seen in preclinical studies when compared to wild-type myeloma cells [80].

4 BCMA bispecifics (Table 2)

A different modality of BCMA-directed immunotherapy is through bispecific antibodies. These constructs are engineered proteins that mimic the antibody activity but have two different binding domains, one that targets a tumor-specific antigen, and another that binds to T cells with the goal of eliciting interactions between immune-effector cells and

MM cells to provoke T cell mediated cellular death [81]. The most common epitopes in immune cells are CD3 and CD16, while the most studied target in myeloma cells is BCMA, although other targets are currently under evaluation. While several different models are currently being used in immunotherapy such as those that resemble the traditional IgG structure and others that lack the Fc region, all contain at least 2 antigen-binding fragments (Fab). Early phase trials with these agents have shown excellent efficacy but have also been notable for the risk of cytokine release syndrome (CRS) and, more rarely, immune effector cell-associated neurotoxicity syndrome (ICANS). Briefly, CRS is a systemic inflammatory response thought to be secondary to activation of bystander immune and nonimmune cells leading to a significant cytokine (particularly IL-1, and IL-6) release [82, 83]. Clinical manifestations of mild CRS include, fever, fatigue, headache, arthralgias, and myalgias and can typically be managed with antipyretics, intravenous fluids, and the anti-IL-6 antibody tocilizumab. More severe cases can progress to hypotension, shock, DIC, and multiorgan system failure and require more aggressive care including vasopressors, high-dose corticosteroids, and supplemental oxygen[84–86]. It should be noted that these symptoms are often difficult to differentiate from systemic infection so empiric anti-infectives are recommended. ICANS is a form of toxic encephalopathy and a less common complication of T-cell mediated therapies. Clinical manifestations of ICANs are diverse with symptoms as varied as headache, aphasia, confusion, impaired fine motor skills and somnolence. More severe cases can progress to seizures, cerebral edema, and coma [87]. The pathophysiology of ICANS is less well understood but is thought to be related to cytokine mediated disruption of the blood-brain-barrier leading to cytokine and immune cell accumulation in the CNS resulting in direct neuronal injury [88, 89]. ICANS is typically managed with high-dose corticosteroids (and tocilizumab if coexisting CRS) [90]. Below we will focus on the constructs that target BCMA and have demonstrated clinical activity against MM.

4.1 AMG 420

The first bispecific to demonstrate positive results in MM was AMG 420. This agent, termed bi-specific T cell engager (BiTE®), consists of two single-chain variable fragments with one targeting CD3 and the other BCMA. The first in human phase I study required a continuous infusion given its very short half-life and was administered over 4 weeks with a 2-week break between cycles. Forty-two patients were enrolled in the dose-escalation phase that established 400 μg/d as the MTD. Cytokine release syndrome (CRS) was seen in 38% of treated patients and 29% developed infections. Of the 10 patients treated at the 400 μg/d dose, 70% achieved a response and 5 obtained minimal residual disease (MRD) negative status (defined as 10^{-4}) [91]. A phase I study to confirm the MTD in multiple countries was opened but discontinued prior to completing enrollment given the risk of infections and significant patient burden of the continuous infusion. Additionally, several agents including AMG 701 (see below) had been developed with longer half-lives which allowed for a more amenable dosing schedule.

4.2 AMG 701

This BiTE® was designed to overcome the short half-life of AMG 420. It includes a tandem scFv and an Fc portion that prolongs the construct's stability [92]. Preclinical models

demonstrated dosing could be on a weekly basis as a single agent or in combination with immunomodulators with good T cell-dependent cellular toxicity (TDCC) [93]. A phase I trial to evaluate the safety and activity in humans included 75 patients. Preliminary data reported a 61% incidence of CRS with 5 cases being grade 3 that reversed with treatment [94]. Other common adverse events included anemia (43%), neutropenia (23%), and diarrhea (31%). Treatment-related neurotoxicity was seen in 6 patients. Responses to treatment were seen at doses of 3mg and higher, but final dose for the expansion portion dose has not been established yet. This study plans to open arms of combination therapy with lenalidomide and/or pomalidomide in the near future.

4.3 CC-93269

This bi-specific agent is an asymmetric bi-valent IgG compound that binds to CD3 (monovalently) and BCMA (bivalently) [95]. Data from the first 30 patients who participated in the dose escalation portion of a phase I study as a once-a-week single agent showed response rates of 43% overall, but 83% in patients treated with the 6mg dose and higher. Additionally, 92% of the responders achieved MRD negativity at 10^{-5}. Median number of prior lines of therapy was 5. CRS was reported in 77% of cases with most being grade 1 or 2, however 1 death was associated with CRS but was also complicated by coexisting infection. Given the high rate of CRS this study has implemented prophylactic dexamethasone in all patients receiving doses ≥6 mg [96].

4.4 Teclistamab (JNJ-64007957)

Teclistamab is an IgG4 engineered antibody targeting CD3 and BCMA that showed cytotoxic activity in vitro by T cell activation and cytokine release [97]. The phase I study evaluated treatment as single agent to evaluate route of administration, safety, and dosing supported. Early data supported weekly dosing and subcutaneous (SQ) administration based on PK sampling. The most common toxicities included CRS (56%), neutropenia (26%), and anemia (23%) with two grade 4 dose-limiting toxicities: delirium and thrombocytopenia [98]. Updated data from the recommended phase II dose (1500 μg/kg weekly SQ dosing) given to 40 patients that formed part of the phase I study showed 65% response rates with a median of 5 prior lines of therapy. The study included a step-up dosing of 60 μg/kg and 300 μg/kg to reduce toxicities and reported 70% CRS with none being grade 3 or 4 [99, 100]. The longest duration on therapy reported has been 18 months. The combination of teclistamab with daratumumab +/− pomalidomide is being investigated for synergistic effects [100, 101].

4.5 Elranatamab (PF-06863135)

Elranatamab is a humanized monoclonal antibody that targets BCMA and CD3 like other agents, but unlike other agents it is paired to an IgG2a Fc backbone using hinge mutation technology [102]. Preclinical data showed a half-life of 4–6 days that led to the dosing of the first-in-human study [103]. The phase I dose-escalation study has evaluated SQ monotherapy in 50 patients and elranatmab in combination with lenalidomide or pomalidomide in an additional 8 patients. Overall response rate was for the monotherapy was 70% at doses of 215 μg/kg or higher with 30% CR/sCR. Safety profile consisted of 73% CRS, 57% anemia, 53% thrombocytopenia and injection site reaction, with neutropenia

in 40% of cases. Notably, 10 patients enrolled were previously treated with a BCMA-directed therapy (either an ADC or CAR-T). The response rate among this subset was 70% suggesting that this agent has activity in the population. Duration of response and final recommended phase II dosing have not yet been established. [104, 105].

4.6 REGN5458

REGN5458 is a fully humanized bispecific antibody with an Fc region and Fab arms that bind to CD3 and BCMA [106]. REGN5458showed more rapid cellular killing than BCMA CAR-Ts in preclinical activity against myeloma cell lines, primary myeloma cells, and murine xenograft models[107]. Preliminary data of the dose-escalation portion of a phase I study with 73 patients showed a tolerable safety profile with 38% of patients having grade 1 or 2 CRS using a weekly IV dosing schema which transitioned to every other week at maintenance. Other commons side effects included anemia in 32% of cases, fatigue (45%), and fever (36%). Three patients (4%) had grade 2 ICANS. Overall response rates were 51% among all doses and 75% at doses of 200–800 mg [109]. Of those who responded, 86% achieved a VGPR or better. A follow-up registrational phase II study is currently enrolling. REGN5459 is a similar bispecific antibody therapy targeting CD3 and BCMA but contains different binding characteristics. It is currently under investigation in early phase clinical trials which are expected to report results in 2023 [106].

4.7 ABBV-383 (Formally TNB-383B)

ABBV-383 is a fully human triple chain IgG4 antibody with 2 anti-BCMA domains to favor cell surface binding [110]. The IgG4 silenced backbone confers a half-life of 18 days, making every 3-week intravenous dosing a possibility. A phase I, first-in-human study of single-agent ABBV-383 dosed every 3 weeks in 118 RRMM patients who had received a median of 5 prior lines was recently reported. Safety profile showed 69% rate of CRS with 4% grade 3 events. Other toxicities included neutropenia (32%), anemia (28%), thrombocytopenia (23%), diarrhea (27%) and nausea (27%). Overall response rate at doses of ≥ 40mg was 60% with more than 40% achieving a VGPR or better [111, 112]. The convenience of its dosing and efficacy has led to plans for a phase II study.

5 BCMA CAR-Ts (Table 3)

Chimeric antigen receptor T cells (CAR-Ts) are T cells modified to contain an extracellular ligand binding domain made up of a fusion protein-most commonly a single-chain variable fragment (scFv) of a monoclonal antibody-designed to recognize one or more tumor-associated antigens (TAAs) on cancer cells. The ligand binding domain is fixed to extracellular spacer elements and a transmembrane domain, connected to a CD3ζ intracellular activation domain and one or more intracellular costimulatory domains (typically CD28, 4–1BB, CD27 and/or OX40) [113–117]. As they can recognize intact proteins and don’t require antigen presentation by antigen presenting cells, they are able to bypass several mechanisms of immune tolerance in contrast to HLA restricted traditional T cell receptors [118, 119]. Once bound to TAAs CAR-Ts initiate signaling through T cell activation and subsequent release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon γ (IFN-γ), interleukin 2 (IL-2), and interleukin 6 (IL-6)

leading to cytolysis [120, 121]. CAR-Ts are generated through leukapheresis of autologous CD3+ T cells followed by introduction of the scFv and co-stimulatory domains with a viral or retroviral vector, however, subtle differences in production are now being correlated to efficacy of specific products (described in more detail below). Prior to infusion of the CAR-T product, patients receive lymphodepleting conditioning chemotherapy (typically with fludarabine and cyclophosphamide) in hopes of decreasing endogenous T cells, especially regulatory T-cells, and increasing the levels of proliferative cytokines IL-7 and IL-15 to create a more favorable environment for the CAR-T cells to inhabit [77, 122, 123]. This technology has most notably been used to create autologous CAR-Ts directed against CD19 which have shown unprecedented results in refractory B cell malignancies and received FDA approval for B Cell ALL and relapsed refractory DLBCL in 2017 [124, 125]. Similar to the bispecific antibodies there is a risk of CRS and ICANS with CAR-T infusion. Rates of ICANS in particular tend to be higher in CAR-T trials then in similarly powered bispecific antibody trials.

BCMA is the most widely studied target of CAR-Ts for MM. Preclinical models of human myeloma demonstrated significant efficacy of autologous BCMA CAR-Ts even against myeloma cells with little expression of cellular BCMA [126, 127]. Currently, at least 15 autologous BMCA targeting CAR-Ts-each with unique antigen targets or molecular structure-are under investigation in clinical trials with other constructs targeting both BCMA and an additional antigen in early-stage trials [125, 128–133]. Recently, trials of allogenic CAR-Ts targeting BCMA have opened which have several advantages over autologous CAR-Ts which are discussed below [125]. Below we summarize the available data on specific BCMA targeting CAR-Ts.

5.1 Idecabtagene vicleucel (ide-cel; bb2121, Abecma)

Ide-cel is a second-generation CAR which uses a lentiviral vector to transduce a BCMA targeting scFv fused to a 4–1BB co-stimulatory and CD3ζ signaling domains [126, 134]. Preclinical studies of ide-cel showed potent activity in MM cell lines expressing cellular BCMA regardless of sBCMA levels [126]. Based on this data a multicenter phase I study of ide-cel in 33 relapsed/refractory multiple myeloma (RRMM) patients who had received ≥ 3 prior lines of treatment was undertaken and showed an overall response rate (ORR) of 85% with 45% of patients achieving a complete response (CR) or better. Sixteen patients were evaluated for minimal residual disease (MRD) status with 15 (94%) MRD negative at 10^{-5} and 3 (19%) MRD negative at 10^{-6}. Median PFS was 11.8 months. Cytokine release syndrome (CRS) occurred in 25 (76%) patients, with 2 (6%) patients (6%) having grade 3 CRS and no patients experiencing grade 4 CRS. Median time to onset of CRS was 1 day. Immune effector cell-associated neurotoxicity syndrome (ICANS) was seen in 14 (42%) of patients, but most were grade 1–2 with only 1 patient having ≥ 3 ICANS [134].

Based on this data a multicenter phase II trial of 128 RRMM who had received ≥ 3 prior lines of therapy including an IMiD, PI, and an anti-CD38 monoclonal antibody was opened. Patients were infused with 150×10^6 to 450×10^6 CAR-T cells. ORR was 73%, with 42 (33%) patients having a CR or better. Overall MRD negative rate (at 10^{-5}) was 26%, but it was 79% in the patients who achieved a CR or better. Notably, these response rates

were relatively preserved across patients with high-risk features including penta-refractory disease, extramedullary disease, and high-risk cytogenetics. Median PFS was 8.8 months and 20.2 months in patient achieving a CR or better. CRS was seen in 84% of patients with only 7 (5%) patients having ≥ grade 3. Similarly, ICANS was seen in 18% of patients with only 4 (3%) patients having ≥ grade 3. Interestingly, 93% of patients who progressed still had detectable levels of cellular BCMA on their MM cells suggesting that antigen loss is not a dominant mechanism for resistance [135, 136]. Based on these findings, ide-cel was approved for the treatment of adults with RRMM after four or more prior lines of therapy including an IMiD, PI, and anti-CD38 monoclonal antibody by the US Food and Drug Administration (FDA) in March 2021.

Several other studies are currently evaluating the utility of ide-cel in various populations including: use in front line therapy as consolidation in place of ASCT in high-risk MM, patients with suboptimal response or early relapse after ASCT, in combination with standard of care backbones, and the phase 3 trial of ide-cel vs standard of care in patients with relapsed disease after 2–4 prior lines of therapy [137–139]. Additionally, a newer formulation termed bb21217, has recently been developed. This agent is produced when bb2121 CAR-T cells are cultured in the presence of the PI3K inhibitor bb007 to select for more memory T cells in hopes of increasing the persistence of the CAR-T product in the host [140, 141]. Results of 46 RRMM patients treated with bb21217 in a multi-center phase I clinical trial showed a 55% ORR with 18% CR or better. CRS was seen in 67% of patients with median onset at 3 days. The majority of CRS was low-grade however, with only 2 patients having ≥ grade 3. ICANS was seen in 22% of patients with 3 patients with ≥ grade 3. Notably, biomarker analysis showed that increased levels of memory T cell markers in the drug product correlated with a sustained clinical response at 6 months [142].

5.2 Ciltacabtagene autoleucel (cilta-cel; LCAR-B38M; JNJ-68284528)

Similar to ide-cel, cilta-cel uses a lentiviral vector to create a construct with a CD3ζ activation domain, and 4–1BB costimulatory domain. Cilta-cel's antigen binding domain contains bispecifc scFvs targeting two distinct BCMA epitopes, VHH1 and VHH2 [143]. This bi-epitope binding confers higher avidity and specificity to BCMA. Initially, cilta-cel was investigated in a phase I trial of 74 RRMM patients conducted at 4 institutions in China who had progressive disease after ≥ 3 prior lines of therapy. Data presented on the first 57 patients enrolled showed an ORR of 88%, with 68% of patients achieving a CR or better. MRD negativity at 10^{-4} was achieved in 63% of patients. Median PFS was 15 months. CRS was seen in 90% of patients with the vast majority (82%) being grade 1 of 2 and only 4 (7%) patients with ≥ grade 3. ICANS was observed in 1 (2%) patient and was only grade 1 [144].

Based on these findings the phase Ib/II CARTITUDE-1 clinical trial was conducted in RRMM patients in the United States and Japan. Patients were required to have been treated with ≥ 3 prior lines or were double refractory to an IMiD and a PI and had previously received an anti-CD38 antibody. 97 RRMM patients (median 6 prior lines) were treated with cilta-cel (29 in the phase 1b portion, 68 in the phase 2 portion). Notably, 84% of patients were penta-exposed and 42% of patient were penta-refractory. ORR was 98%, with 95% of patients achieving a VGPR or better. Of the 61 patients evaluable, MRD negativity at

10^{-5} was achieved in 92% of patients. Median PFS has not been reached at 12.4 months. CRS was seen in 95% of patients with the vast majority (91%) being grade 1 of 2. ICANS was observed in 16.5% of patients and was predominately grade 1 or 2 with only 2% ≥ grade 3. Grade 3 and 4 hematologic toxicities were very common with specific rates of 92% neutropenia, 68% anemia, and 60% thrombocytopenia see across all cohorts [144–147]. Based on these data cilta-cel was granted breakthrough therapy designation from the FDA.

This has led to the multicohort, open-label, phase 2 CARTITUDE-2 trial which enrolled patients previously treated with 1–3 prior lines. Recently, data on the first 20 patients were presented. Median prior lines of therapy were 2 and all patients were previouly exposed to a PI and an IMiD. Nearly all (95%) of patient were previously treated with an alkylating agent, and 65% of patient had received prior daratumumab. ORR was 95% and responses were at least a VGPR. Of the 13 evaluable patients 92% were MRD negative at 10^{-5}. Grade 3/4 hematologic toxicity was common (neutropenia 95%, anemia 45%, thrombocytopenia 35%), as was CRS (95%), but was predominately grade 1 or 2 (10% grade 3 or 4). ICANS was seen in 15% of patients and all were grade 1 or 2. At a median follow-up of 9.7 months PFS was not yet reached [148]. Recently additional cohorts have opened investigating the use of cilta-cel as consolidation after induction therapy and as second line therapy in patients with suboptimal response to stem cell transplant.

A phase III trial (CARTITUDE-5) comparing the efficacy of cilta-cel versus pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd) in patients with lenalidomide-refractory MM is ongoing (NCT04181827).

5.3 Orvacabtagene Autoleucel (orva-cel; JCARH125)

Orva-cel is a BCMA-targeting CAR-T product containing a lentiviral CAR construct with a fully human scFv, an optimized spacer, and 4–1BB co-stimulatory and CD3ζ activation domains. In a multicenter phase I/II trial of patients with RRMM who received ≥ 3 prior lines including a PI, IMiD, anti-CD38 antibody and autologous stem cell transplant (ASCT). Results of 62 evaluable patients treated with the higher dose levels (300, 450, and 600 × 10^6 CAR-T cells) showed a 92% ORR with 36% of patients achieving a CR or better. Remarkably, 100% of patients treated at the highest dose (600 × 10^6) were MRD negative at 10^{-5}. CRS was seen in 89% of patients, but only 3% experienced ≥ grade 3; ICANS was seen in 13% of patients and only 3% experienced ≥ grade 3 symptoms. Notably, all patients with high baseline sBCMA responded to the agent [149–151]. Unfortunately, commercial development of ovra-cel was recently discontinued in favor of an alternative second-generation CAR-T (CC-98633) with a more rapid production time in hopes that more patients will be able to avoid bridging therapy if they can receive their CAR-T product more quickly.

5.4 CT103A

CT103A is a second-generation chimeric antigen receptor (CAR) utilizing a fully human BCMA-specific single-chain fragment variant (25C2) with high binding affinity to BCMA bound to 4–1BB co-stimulatory and CD3ζ activation domains. A multicenter phase I trial of this agent was conducted in China and enrolled 24 RRMM patients who had received 2

more prior lines. The ORR was 88% with 79% achieving a CR or better. Median PFS was 18.8 months. Among 20 subjects who underwent evaluation for MRD status, 17 were MRD negative at 10^{-4}. CRS was seen in 63% of patients, all of which was grade 1 or 2. Onset of CRS was 1–4 days. ICANS was seen in 3 patients and with 1 patient having grade 3 symptoms [152, 153].

5.5 MCARH171

MCARH171 is a second-generation CAR-T composed of a humanized scFv, a 4–1BB costimulatory domain, and a truncated epidermal growth factor receptor safety signal. An phase I dose escalation trial of MCARH171 is currently ongoing. Data on 11 RRMM patients had been present which showed an ORR of 64%, with a median duration of response of 106 days. Of the 10 evaluable patients 6 (60%) experienced CRS with 2 (20%) having grade 3 symptoms. One (10%) patient had grade 2 ICANS [154].

5.6 Combination and Bispecific CAR-Ts

Combinations of multiple CAR-Ts and CAR-Ts targeting more than one antigen are currently in development. The most popular combination is BCMA and CD19. This combination is based on the finding that a small component of MM cells express CD19, and these cells are considered to be less-differentiated and therefore may lack conventional MM markers such as BCMA. [155, 156].

A phase II single-center clinical trial at the Affiliated Hospital of Xuzhou Medical University in China looked at co-infusion with both a BCMA and CD19 CAR-T. A total of 21 RRMM patients received the two CAR-T products. ORR was 95% with 57% achieving a CR or better. PFS had not been reached at median follow-up of 6 months. CRS was seen in 90% of patients, but only 1 patient had grade 3 or higher. Interestingly, only 2 (10%) patients had any ICANS symptoms [132].

The University of Pennsylvania conducted a trial of a combination of BCMA and CD19 CAR-Ts as consolidation therapy in patients responding to their prior therapy. The study was conducted in two parts: Part A of the trial enrolled 7 patients treated with ≥ 3rd line (or ≥ 2nd line if previously exposed to all major agents) who had achieved a minor response or better to their last line of therapy; Part B enrolled high-risk patients responding to 1st or 2nd line therapy. The patients on part A were treated with both CAR-Ts, while the part B patients were randomized to receive the BCMA CAR-T with or without the CD19 CAR-T followed by maintenance with an IMiD. Of the 10 patients evaluable for response (6 from part A; 4 from part B-including 2 patients who received both agents), all evaluable patients achieved ≥ PR after CAR-T infusion. Of the 5 patients evaluable for MRD negativity, only one was MRD negative at 10^{-5}. Subsequently, 5 of the 10 evaluable patients (all of whom received the combination of both CAR-Ts) had progressed suggesting that the addition of the CD19 CAR-T did not clearly prevent progression in this population compared to a BCMA CAR-T monotherapy. CRS was seen in 8 (80%) of all patients, but was all grade 1 or 2. No neurotoxicity was seen [131].

5.7 Bispecific CAR-Ts

BCMA and CD19 bispecific CAR-Ts have shown efficacy in preclinical models and have begun early phase clinical trials [157, 158]. Early results of 5 patients treated in a first in human phase I clinical trial with a BCMA and CD19 bispecific CAR-T were encouraging with all patients having a clinical response and only grade 1 CRS seen in 3 patients [158].

BM38 is bispecific CAR-T that targets both BCMA and CD38 that is currently being evaluated in a phase I clinical trial of RRMM patient who have received at least 2 prior treatment regimens, including a PI and an IMiD. Preliminary data of 16 patients showed an 88% response rate with 50% sCRs. CRS was seen in 63% of patients with 25% ≥ grade 3. At a median follow-up of 8.4 months PFS had not yet been reached [159].

5.8 Allogenic BCMA CAR-Ts

Allogeneic CAR-Ts have several advantages over autologous CAR-Ts. Specifically, they allow for immediate availability as opposed to the 2–4 week turnaround time for autologous products-ideally limiting the need for bridging therapy, improved standardization of the CAR-T cell product, redosing or combination of CAR-T cells directed against different targets, and potential cost savings due to a more scalable process [125, 160–162]. Several allogenic BCMA targeting products are currently under evaluation in early phase clinical trials for MM patients. Data for 19 RRMM patients treated with ALLO-715 an allogenic BCMA CAR-T were recently presented. Patients had received ≥3 prior lines of therapy including an IMiD, a PI, and anti-CD38 monoclonal antibody. The trial is evaluating several different lymphodepleting chemotherapy regimens prior to ALLO-715 administration. ORR in the 15 evaluable patients was 33% but was significantly higher in the higher cell doses. CRS was only reported in 24% of patients and all were grade 1 or 2. No ICANs or GVHD was appreciated [163].

5.9 BCMA CAR-NKs

NK cells are innate immune effector cells that lack antigen-specific receptors and express high levels of CD56. They recognize abnormal cells (including virally infected cells and tumor cells) without prior sensitization in a non-HLA restricted manner through a combination of surface stimulatory and inhibitory receptors that target ligands on target cells [164, 165]. Notably, mature NK cells can be transplanted into a different host without losing their function of causing graft vs host [166]. Recently BCMA directed CAR-NK cells have been developed from immortalized NK cell lines and have shown activity in preclinical models [167]. Two phase 1 trials are currently investigating these agents in RRMM patients.

9 Conclusions and Future Directions

While BCMA directed therapies have proven highly efficacious especially compared to therapies directed to alternative targets in RRMM, none of the agents currently being evaluated have proven curative and relapses are still inevitable. Additionally, each class of agents has unique toxicities and logistical challenges which may serve to further limit their widespread availability. Autologous CAR-Ts require leukapheresis and infusion at a tertiary care facility due to the risk of CRS/ICANS, logistics of leukapheresis and significant

hematologic AEs. While conventional trials have looked at CAR-Ts as a single infusion without additional therapy allowing a patient an attractive treatment-free interval, it is widely thought that limited CAR-T expansion and persistence within the hostile tumor microenvironment represents significant mechanisms of CAR-T resistance and prevents durable clinical remission following CAR-T therapy [168]. To combat these challenges strategies employing maintenance regimens, addition of different therapies, and other considerations are under evaluation to help prolong the CAR-T product's lifespan and increase its efficacy are currently under investigation. In addition, efforts are currently underway to improve the throughput of CAR-T production to decrease the "vein to vein" time (defined as the time between leukapheresis of donor and infusion of CAR-T product) in hopes to decrease the need for bridging chemotherapy and disease escape while waiting for product availability.

The concept of T cell exhaustion through multiple mechanisms is a well-known entity contributing to various malignancies including MM [169–171]. Previous studies suggest that antigen-independent tonic signaling by CARs, perhaps due to the physical interactions between CARs or scFv dimerization, limits CAR-T cells potency by induction of exhaustion pathways which is somewhat abrogated by co-stimulatory domains [172, 173]. This has led to speculation that the combination of checkpoint inhibition with CAR-Ts may be able to further abrogate T cell exhaustion, but this would need to be approached cautiously to avoid additional toxicities.

Bispecific antibodies may be more accessible but still require at least initial infusions at a tertiary care facility given the risk for CRS/ICANS seen in with initiation of therapy. Eventually, subsequent doses may able to be given locally for convenience given the improved safety profile and lower rates of toxicities after the first dose, especially with newer agents. The use of bispecific antibodies in conjunction with standard of care backbones is under investigation to evaluate for increased efficacy without additional toxicity. Ideally, utilizing T cell stimulating agents earlier in therapy when patients are more chemotherapy naïve may lead to more robust and durable responses compared to later in their treatment course when they are at higher risk for T cell exhaustion. To this end, the sequencing of when to incorporate a BCMA targeting therapy is currently being investigated with several BCMA targeting therapies are being evaluated in earlier lines of therapy including newly diagnosed MM patients. The hope is that the addition of these agents to upfront therapy backbone will induce deeper, longer-lasting responses. However, this must be weighed against the potential for additional toxicity and cost that this strategy will elicit. Additionally, the question of whether a patient who progresses on a BCMA targeting therapy would still derive benefit from an alternative BCMA directed therapy is still unanswered. While the preliminary data with elranatamab suggests activity with this agent after treatment with a BCMA CAR-T or ADC it is unclear whether this represents a class effect or is specific to this agent. Currently, trials are enrolling to assess this question. Taken together BMCA targeting therapies are an important addition to the armamentarium of myeloma physicians and provide an excellent treatment choice for RRMM patients. Time will tell if their addition to earlier lines of therapy and/or NDMM treatment will induce deeper, more durable responses and if their effects can be accentuated with adjunctive therapies. Additionally, new agents and better supportive care are helping to ameliorate

the toxicities unique to each class of BCMA targeting agents which should allow their widespread use as more agents become commercially available.

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Key Points

- B-cell maturation antigen (BCMA) is selectively expressed on plasmablasts and plasma cells, making it an ideal therapeutic target for treatment of multiple myeloma.
- Antibody drug conjugates, bispecific antibodies and chimeric antigen receptor T cell therapies targeting BCMA have shown excellent clinical activity, but are associated with different safety profiles.

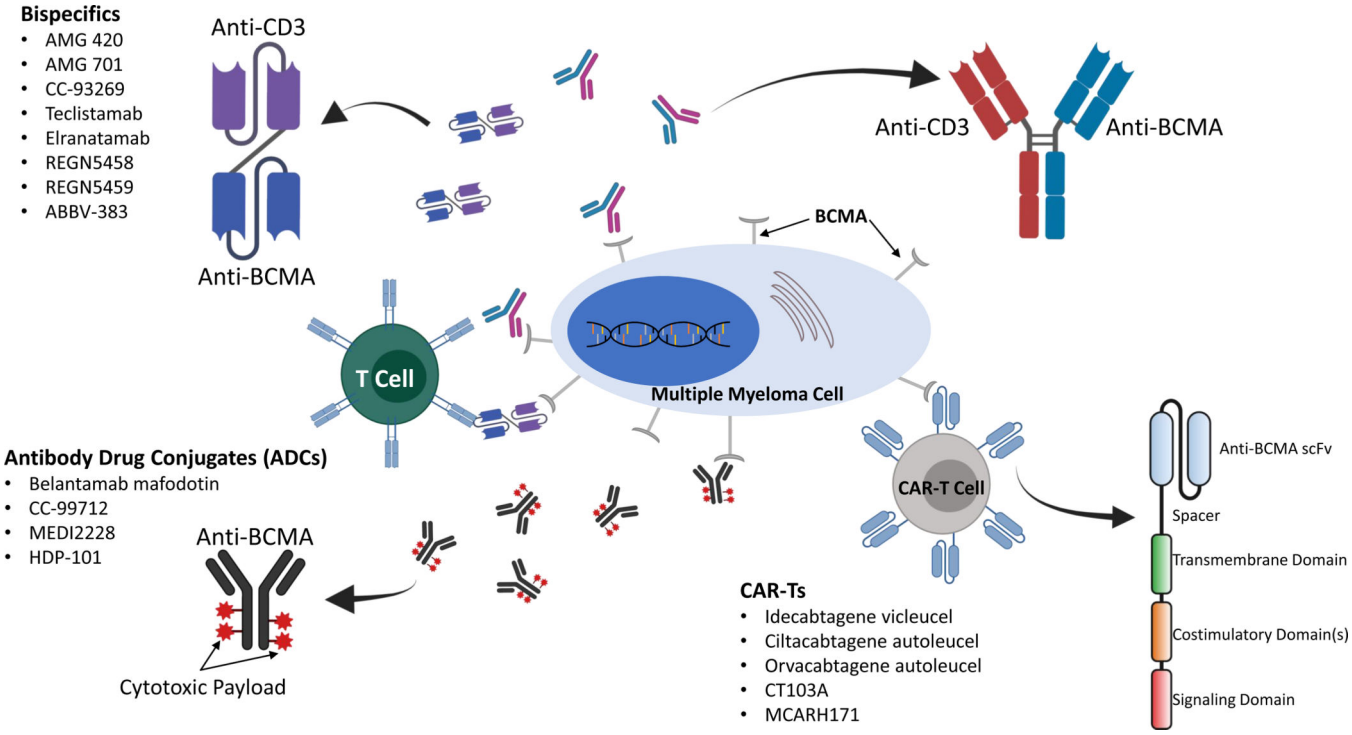

Fig 1:

Mechanisms of action of BCMA targeting therapies (antibody-drug conjugates, bispecific antibodies, and CAR-Ts) see text for details

Table 1:

BCMA ADCs

Drug	Trial ID	Patient Population	Regimen	Phase	n	Median Prior Lines (Range)	ORR (%)	≥VGPR (%)	PFS (months)	AE's of Interest	Ref
Belantamab Mafadotin (GSK2857916)	NCT02064387 (DREAMM-1)	RRMM	Monotherapy	1	73 (35 patients in part 2)	NR (67% ≥ 5)	60[a]	51.4[a]	12[a]	Corneal Toxicity[a]: 63% grade 1 or 2 9% grade 3	45
	NCT03525678 (DREAMM-2)			2	97 (2.5 mg/kg)	7 (3–21)	31	19	2.9	Corneal Toxicity: 43% grade 1 or 2 27% grade 3	60–61
	NCT03544281 (DREAMM-6)				99 (3.4 mg/kg)	6 (3–21)	34	20	4.9	Corneal Toxicity: 54% grade 1 or 2 20% grade 3 1% grade 4	
	NCT02064387 (DREAMM-1)	≥1 prior lines	Combination with Vd or Rd	1/2	18 with BVd[b]	3 (1–11)	78	50	NR	Corneal Toxicity: 44% grade 1 or 2 56% grade 3	66
	NCT04484623 (DREAMM-8)	≥1 prior lines	Combination with Pd or Rd	1/2	60	3 (1–5)	89	74	NR	Corneal Toxicity: 73% grade 3	68
MEDI2228	NCT03489525	RRMM	Monotherapy	1	8241 patients treated at MTD (0.14 mg/kg)	NR (2–11)	66[c]	27[c]	NR	Photophobia[c]: 41% grade 1 or 2 17% grade 3 or 4	48

[a]At the recommended part 2 dose (3.4 mg/kg)

[b]Only the data on the 18 patients treated with BVd (2.5mg/kg belantamab mafadotin) have been presented

[c]Represents patients treated at the MTD (0.14mg/kg)

Abbreviations: AE: Adverse event; ORR: Overall response rate; VGPR: Very good partial response; PFS: progression-free survival; RRMM: relapsed refractory multiple myeloma; Vd: bortezomib and dexamethasone; Rd: lenalidomide and dexamethasone; Pd: Pomalidomide dexamethasone;BVd: belantamab mafadotin, bortezomib and dexamethasone; NR: not reported; MTD: maximum tolerated dose

Table 2:

BCMA Bispecific Antibodies

Drug	Trial ID	Patient Population	Regimen	Phase	n	Median Prior Lines (Range)	ORR (%)	≥VGPR (%)	PFS (months)	CRS Rate	Ref
AMG 420	NCT03836053	RRMM	Monotherapy	1	42	5 (2–14)	31	24	NR	36% grade 1 or 2 2% grade 3	91
AMG 701	NCT03287908	RRMM	Monotherapy	1	75	6 (1–25)	26	17	NR	53% grade 1 or 2 7% grade 3	94
CC-93269	NCT03486067	RRMM	Monotherapy	1	19	6 (3–12)	53 (83% in patients treated with ≥6 mg dose)	37 (58% in patients treated with ≥6 mg dose	NR	68% grade 1 or 2 21% grade 3	96
Teclistamab (JNJ-64007957)	NCT03145181 (MajesTEC-1)	RRMM	Monotherapy	1	84 IV	6 (2–14)	38[a]	30[a]	NR	56% grade 1 or 2 0% grade 3 or 4	100–101
					72 SC	5 (2–14)	63	58		60% grade 1 or 2 0% grade 3 or 4	
Elranatamab (PF-06863135)	NCT03269136 (MagnetisMM-1)	RRMM	Monotherapy	1	50 SC	8 (3–15)	70[b]	65[b]	NR	83% grade 1 or 2 0% grade 3 or 4	104–105
REGN5458	NCT03761108	RRMM	Monotherapy	1	73	5 (2–17)	51	44	NR	38% grade 1 or 2 0% grade 3 or 4	109
ABBV-383 (TNB-383B)	NCT03933735	RRMM	Monotherapy	1	118	5 (1–15)	47 (801% at doses ≥ 40mg)	33 (73% at doses ≥ 40mg)	NR	52% grade 1 or 2 3% grade 3 or 4	111–112

[a]Only includes patients dosed ≥38.4 mg/kg

[b]Only includes patients dosed ≥215 mg/kg

Abbreviations: ORR: Overall response rate; VGPR: Very good partial response; PFS: progression-free survival; CRS: Cytokine release syndrome; RRMM: relapsed refractory multiple myeloma; IV: Intravenous; SC: subcutaneous; NR: not reported; MTD: maximum tolerated dose.

Table 3:

BCMA CAR-Ts

Drug	Trial ID	Patient Population	Regimen	Phase	n	Median Prior Lines (Range)	ORR (%)	≥VGPR (%)	PFS (months)	CRS Rate	ICANS Rate	Ref
Idecabtagene vicleucel (bb2121, ide-cel, Abecma)	NCT03361748 (KarMMa-2)	RRMM	Monotherapy	2	128	6 (3–16)	73	53	8.8	78% grade 1 or 2 5% grade 3 or 4	15% grade 1 or 2 3% grade 3 or 4	137–139
Ciltacabtagene autoleucel (JNJ-68284528, cilta-cel)	NCT03548207 (CARTITUDE-1)	RRMM	Monotherapy	1/2	97	6 (3–18)	98	95	61% at 24-months	90% grade 1 or 2 5% grade 3 or 4	14% grade 1 or 2 2% grade 3 or 4	147
	NCT04133636 (CARTITUDE-2)	1–3 prior lines	Monotherapy	2	20	2 (1–3)	95	95	NR	85% grade 1 or 2 10% grade 3 or 4	15% grade 1 or 2 0% grade 3 or 4	148
Orvacabtagene autoleucel (JCARH125, orva-cel)	NCT03430011 (EVOLVE)	RRMM	Monotherapy	1/2	62	7 (2–24)	92	68	NR	85% grade 1 or 2 3% grade 3 or 4	10% grade 1 or 2 3% grade 3 or 4	149–151
CT053	NCT03716856 NCT03302403 NCT03380039	RRMM	Monotherapy	1	24	4.5 (2–11)	88	NR	NR	63% grade 1 or 2 0% grade 3 or 4	8% grade 1 or 2 4% grade 3 or 4	152–153
MCARH171	NCT03070327	RRMM	Monotherapy	1	11	6 (4–14)	64	NR	NR	40% grade 1 or 2 20% grade 3 or 4	10% grade 1 or 2 0% grade 3 or 4	154

Abbreviations: ORR: Overall response rate; VGPR: Very good partial response; PFS: progression-free survival; CRS: Cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity syndrome; RRMM: relapsed refractory multiple myeloma; NR: not reported.