REVIEW

Targeting B Cell Maturation Antigen in Patients with Multiple Myeloma: Current Perspectives

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Abstract: Relapsed/refractory multiple myeloma remains a challenging disease necessitating the development of more effective treatment options. In the past decade, myeloma therapies have made significant advancements with the introduction of new treatment modalities. One of the new major targets for these novel therapeutics has been B-cell maturation antigen (BCMA), which is expressed on mature B-lymphocytes and plasma cells. There are three main categories of BCMA-targeted therapies currently available, including bispecific antibodies (BsAbs), antibody drug conjugates (ADCs), and chimeric antigen receptor (CAR) T-cell therapies. In this review, we discuss the existing BCMA-targeted therapies and provide insights into currently available treatment and future developments, with a particular focus on clinical efficacy and common drug-related adverse events.

Keywords: BCMA, multiple myeloma, bispecific antibody, BiTE, CAR T cells, B-cell maturation antigen

Introduction

Multiple myeloma (MM) is a clonal proliferation of plasma cells, which arises from B lymphocytes.[1,2] MM accounts for nearly 2% of all cancers and cancer-related deaths with the 5-year relative survival rate of 58%.[3] Although clinical outcomes have improved over the last decade, the prognosis for patients with high-risk disease or relapsed/refractory (R/R) disease remains poor, highlighting the need for newer treatment approaches.[4–6] Many potential targets in MM have been identified which includes CD24, CD38, CD56, CD138, signaling lymphocytic activation molecule family member 7 (SLAMF7), programmed cell death-ligand 1 (PD-L1).[7–10] However, many normal cells also express these receptors on their surface raising the possibility for systemic adverse reactions, while others have failed to show response in clinical trials.[11–13] There are other novel targets such as G protein-coupled receptor class C, group 5, member D (GPRC5D) and integrin β_7 with targeted agents under investigation.[14–17] One promising target in the treatment of MM is B-cell maturation antigen (BCMA), which is specifically expressed on mature B-lymphocytes and plasma cells, but not in other normal cells.[18–20] In this review, we discuss the rationale behind targeting BCMA and the available BCMA-targeted therapies.

Rationale of BCMA

BCMA, also known as TNFRSF17 or CD269, is a transmembrane glycoprotein and a member of the tumor necrosis factor (TNF) receptor family. It is expressed on mature B-lymphocytes and is overexpressed on malignant plasma cells. Activation of BCMA leads to the survival of plasma cells, and it serves as a binding site for a proliferation-inducing ligand (APRIL) and B cell activating factor of the TNF family (BAFF), which are crucial for normal B-cell and plasma cell development (Figure 1).[21–23]

APRIL has a higher affinity for BCMA compared to BAFF, and binding of APRIL or BAFF to BCMA triggers downstream gene expressions that play a significant role in the pathogenesis of MM[23,24] Soluble BCMA (sBCMA) levels have been shown to be elevated in patients with MM and correlate with the proportion of plasma cells in bone marrow biopsies in MM patients. Elevated sBCMA also carries prognostic implications in monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma.[25,26] In patients with MM, increased sBCMA levels
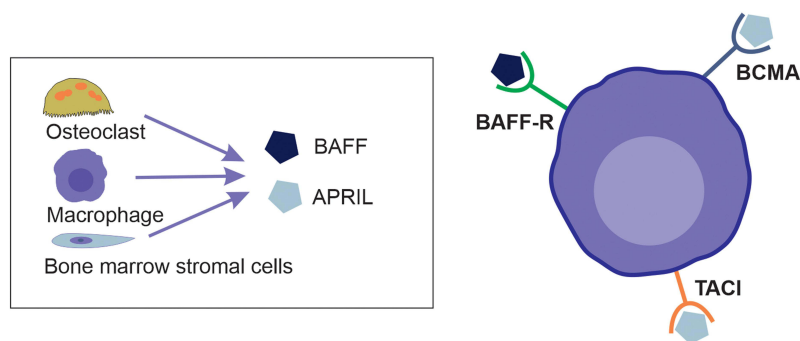
Figure 1 Myeloma cell with its receptors and substrates – BAFF and April which are mainly produced by osteoclast, macrophages and bone marrow stromal cells.

prevent circulating BAFF from performing its normal signaling and impairs B-cell development, resulting in lower polyclonal antibody levels.[27]

Currently, there are three main categories of targeted therapies for BCMA, including bispecific antibodies (BsAbs), antibody-drug conjugates (ADCs), and chimeric antigen receptor modified T-cell (CAR-T) therapy.

Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) consist of a monoclonal antibody that is directed towards a specific antigen on tumor cells and a cytotoxic payload that is connected to the antibody by a chemical linker. (Figure 2) ADCs are associated with reduced systemic toxicity compared to other classes of drugs due to their tumor cell-specific targeting.[28]

Belantamab mafodotin is a humanized IgG1 monoclonal antibody targeting BCMA, which is conjugated to a tubulin polymerization inhibitor known as monomethyl auristatin-F (MMAF or mafodotin) via a maleimidocaproyl (MC) linker that is resistant to proteolysis. Once the ADC attaches to the cell surface, it is internalized, and the active components are released, leading to antibody-mediated cytotoxicity and subsequent cell death.[29] Belantamab mafodotin was granted accelerated FDA approval in 2020 based on the DREAMM-2 study (NCT03525678) for the treatment of patients with R/R MM who had received at least three prior myeloma-directed therapies. However, it was withdrawn from the market in November 2022 due to results from the Phase III confirmatory trial, DREAMM-3 (NCT04162210), which showed that Belantamab mafodotin did not demonstrate superiority in progression-free survival (PFS) compared to pomalidomide and low-dose dexamethasone.[30–32] Additionally, high-grade keratopathy was a common adverse event (AE), with grade 3 keratopathy occurring in 54% of patients, which can be a limiting factor in delivering therapy.[33] It is currently only available through an expanded access protocol.[34]
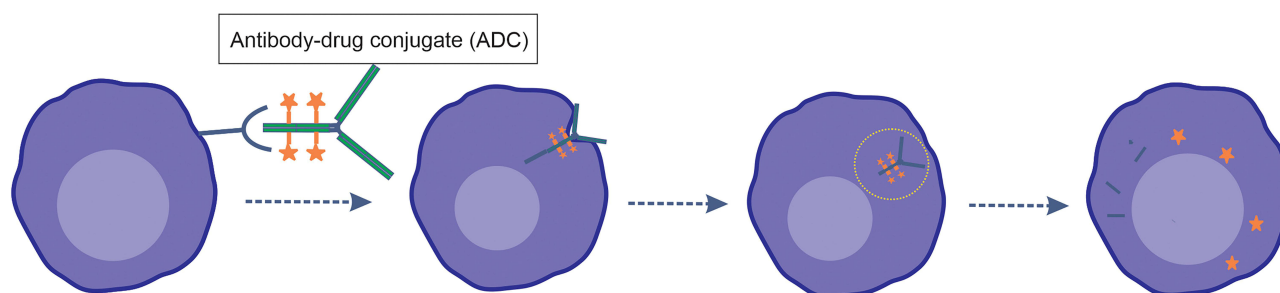

Figure 2 ADC binds to BCMA receptor in myeloma cell and gets internalized forming an endosome (yellow dotted circle) releasing toxic payload that leads to myeloma cell death.

Bispecific Antibodies

Bispecific antibodies (BsAbs) are unique molecules that can bind to two separate epitopes or antigens simultaneously. In the context of MM, commonly selected target-binding epitopes for BsAbs are BCMA on myeloma cells and CD3 receptor on T cells. (Figure 3) When the target is the CD3 receptor on T cells, these BsAbs are commonly referred to as bispecific T-cell engagers (BiTE).[35,36] (Figure 2) However, there are many other potential target sites, including GPRC5D, Fc receptor-homolog 5 (FcRH5), CD138, CD38, SLAMF7 on myeloma cells, as well as natural killer group 2 D (NKG2D), CD16A, and natural cytotoxicity receptor 3 (NKp30) on natural killer (NK) cells and T cells.[14,37–44] BsAbs form a cross-linkage between myeloma cells and T cells upon binding to their respective receptors. This interaction activates CD4+/CD8+ T cells which releases perforin, granzyme, and interferon-γ, resulting in lysis of myeloma cells.[45]

Teclistamab

Teclistamab is a humanized IgG4 BsAb that specifically targets BCMA on myeloma cells and CD3 receptor on T cells.[30] It is the only FDA approved BsAb for relapsed/refractory (R/R) MM, based on the results of the MajesTEC-1 study (NCT04557098).[46,47] This multicohort phase I/II trial enrolled 165 patients, including more than two-thirds of patients with triple-class refractory disease, who received weekly subcutaneous teclistamab. At a median follow-up of approximately 14 months, the overall response rate (ORR) was 63%, with 19.4% patients achieving very good partial response (VGPR), 32.7% stringent complete response (sCR), 6.7% complete response (CR). About one-fourth (44/165) of patients had negative minimal residual disease (MRD) assessed by next-generation sequencing with a threshold of 10^{-5} cells. Median duration of response (DOR) was about 18 months and median duration of progression-free survival (PFS) was 11.3 months.[47]

Cytokine release syndrome (CRS) occurred in 72.1% of patients, with grade 1 CRS in 50.3% of patients, grade 2 in 21.2%, and grade 3 or higher in 0.6% of patients. Neurotoxicity occurred in 24% of patients, with only 1% experiencing grade 3 or higher neurotoxicity.

Teclistamab and other BCMA targeting agents also target normal plasma cells, which can result in profound hypogammaglobulinemia increasing the risk of infections.[48–50] In the MajesTEC-1 study, infections were reported in 76.4% of patients, with COVID-19 occurring in 17.6% of patients, pneumonia in 18.2%, bronchitis 13.3%, cellulitis in 2.4%, and pneumocystis jirovecii (PJP) pneumonia in 3.6% of patients. There were also 41.2% reported deaths, with 24.8% attributed to progressive disease and 11.5% due to infections.

Cytopenias were also commonly observed, with neutropenia being the most frequent (all grade neutropenia in 70.9% of patients, with grade 3 neutropenia in 64.2%), anemia occurring in 52.1% of patients, and thrombocytopenia in 40% of patients.[47]

Based on these results, teclistamab appears to be a promising agent awaiting long-term outcomes and the results of future randomized clinical trials.

Elranatamab

Elranatamab (PF-06863135) is a BsAb that has received "breakthrough therapy" designation from the United States Food and Drug Administration (FDA), based on the results of the Phase II MagnetisMM-3 study (NCT04649359).[51–53] In this
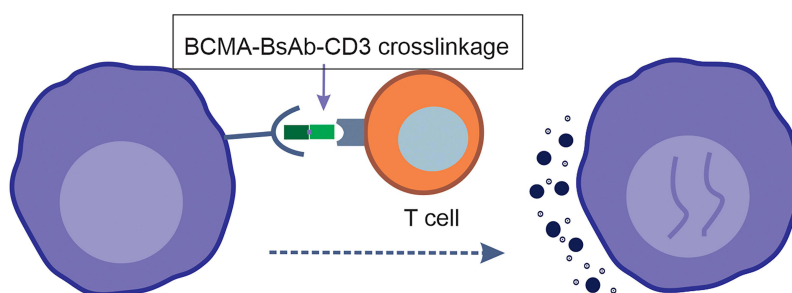

Figure 3 Bispecific antibody forms cross linkage with CD3 in T cell and BCMA receptor in myeloma cell that leads to activation of CD4+/CD8+ T-cell and release of cytotoxic cytokines ultimately causing myeloma cell death.

open-label, multicenter, single-arm trial, 123 patients received subcutaneous elranatamab weekly with a 2-step-up priming dose regimen. At a median follow-up of 6.8 months, patients achieved an ORR of 61%, with more than half achieving CR or better. Median time to response was noted to be 36 days.

Incidences of grade 1 and 2 CRS were reported in 71% of patients, with no events of grade 3 or higher CRS reported. Neurotoxicity was observed in 3.4%, all of which were either grade 1 or grade 2. Infections were reported in about 62% of patients, with upper respiratory tract infections occurring in 14.6% and pneumonia in 10.6%.

Peripheral neuropathy was reported in 17.1% of patients, with peripheral sensory neuropathy (4.9%), paresthesia (4.1%), and gait disturbance (2.4%) being the most common manifestations.[54]

Considering the risks and responses observed in the trial, elranatamab shows promise as a potential addition to the armamentarium of BsAbs, pending complete data from the phase II trial.

Linvoseltamab (REGN5458)

Linvoseltamab, a BCMAxCD3 BsAb, is currently in development and being studied in the LINKER-MM2 trial (NCT05137054). Phase 1/2 data from this trial involving 167 recruited patients showed that linvoseltamab achieved an ORR of 75% at doses greater than or equal to 200mg, with 37.5% of patients achieving CR or better. The most common AEs were CRS with an overall incidence of 47.9% (grade 1: 36.5%, grade 2: 10.8%, and grade 3: 0.6%), anemia (36.5%), fatigue (34.1%), neutropenia (28.7%), and thrombocytopenia (16.2%).[55–57] The trial is currently ongoing and is also being explored for potential benefits in combination with other anti-myeloma therapies.[58]

Pavurutamab (AMG701)

Pavurutamab is currently being evaluated in the phase 1/2 ParadigMM-1B trial (NCT03287908) to assess its efficacy as monotherapy or in combination with pomalidomide in patients with R/R MM.[59] According to preliminary results from the first in-human study, out of 75 patients treated for a median duration of approximately 6 weeks, the ORR was 36%. However, in 6 patients who received earlier dose escalation, the ORR was as high as 83%, among which 33.3% were VGPR and 50% were partial response (PR). The most common non-hematological AEs included CRS in 61% of patients, mostly grade 1 and grade 2 (53%), with grade 3 CRS occurring in 7% of patients. Hematological AEs included anemia (43%), neutropenia (23%), and thrombocytopenia (20%). Infections were reported in 13% of patients.[60]

Alnuctamab (CC-93269)

Alnuctamab (ALNUC; BMS-986349; CC-93269) is a humanized IgG antibody with bivalent affinity for BCMA and monovalent affinity for CD3.[61] In the first in-human study involving 70 patients (NCT03486067) treated with alnuctamab in a dose-escalation fashion, the ORR was 39%. Among the 10 patients who received a targeted escalated dose of ≥30mg, the ORR was 77%, that included 23% sCR/CR, 8% VGPR, and 46% PR. The median time to response was 4.3 weeks. Common AEs included CRS in 53% of patients, all limited to grade 1 or grade 2. Grade 1 neurotoxicity was observed in only one patient. Neutropenia was reported in 34% patients and anemia in 34%.[61,62] Alnuctamab continues to be evaluated in a Phase I trial, which is expected to be completed in 2027.[63]

ABBV-383

ABBV-383, previously known as TNB-383SB, is a BCMA x CD3 T-cell engaging BsAb currently in development (NCT03933735) with promising early results.[64] In a phase I study, 124 patients, who received ABBV-383 every 3 weeks, the ORR was 57%, out of which 43% was VGPR or better. However, when stratified to the dose escalation group, with patients receiving the drug at 40mg, the ORR increased to 83% with 67% achieving CR or better and 83% achieving VGPR or better. Among 58 patients in 60 mg dose escalation and expansion group, ORR was 60% with 29% CR or better and 43% VGPR or better.

CRS occurred in 83% of patients in the 40 mg group (with 0% classified as grade 2 or above), and in 72% of patients in the 60 mg group (with 2% classified as grade 2 or above). Infections were reported in 50% of patients in the 40mg cohort and 43% in the 60 mg cohort. Neutropenia (67%) and anemia (33%) were other common AEs reported.[65,66]

BsAbs have emerged as an important treatment modality for patients with R/R MM, showing promising responses. Teclistamab is currently the only commercially available BsAb for MM treatment, while others are still in early development. Additionally, there are ongoing studies exploring the use of BsAbs in combination with other anti-myeloma agents, although this approach may be associated with an increased risk of infections.[49,58,67,68] Table 1 provides a summary of BsAbs.

CAR-T Therapy

CAR-T cells are engineered to recognize and bind tumor antigens without the need for major histocompatibility complex (MHC)-mediated antigen presentation, leading to cytokine release, cytotoxicity, and tumor lysis. This process is illustrated in Figure 4.[69]

The first-in-human clinical trial that studied BCMA-targeting CAR-T cells took place in 2018, using γ-retrovirus as a vector to encode CAR-BCMA for transduction into T cells.[70] The manufacturing process of CAR T cells begins with autologous leukapheresis to obtain peripheral blood mononuclear cells, which are then sorted using magnetic cell sorting kits to enrich for CD3+ T lymphocytes. These T cells are then genetically modified using an inactivated lentivirus/retrovirus or a non-viral DNA modification system to introduce the CARs, followed by immunophenotyping, in-vitro expansion, formulation, and cryopreservation before infusion.[71–73]

Currently, there are several BCMA CAR-T therapies in development, but only idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have received FDA approval for the treatment of R/R MM (Table 2).[74,75]

Table 1 Summary of Bispecific Antibodies in Clinical Trials

Name of Drug	Clinical Trial	Status	N	ORR (%)	Level of Response	Median Duration of Response	CRS Any Grade (%)	CRS Grade 3 or Above (%)	Infections (%)
Teclistamab[47]	MajesTEC-1 (NCT04557098)	FDA approved	165	63	32.7% sCR, 6.7% CR, 19.4% VGPR, 4.2% PR	18 months	72	1	76.4
Elranatamab[53]	MagnetisMM-3 (NCT04649359)	Breakthrough therapy designation by FDA, completed Phase 2	123	61	NA	NA (not reached)	67	0	61.8
Linvoseltamab (REGN5458)[56]	LINKER-MM2 (NCT05137054)	Phase 1/2	167	75	NA	NA (not reached)	47.9	1.3	NA
Pavurutamab (AMG701)[60]	ParadigMM-1B (NCT03287908)	Phase 1/2	75	36 and 83$^\beta$	Among 5/6 patients, 3 PR, 2 VGPR	6 weeks	61	7	13
Alnuctamab (CC-93269)[61]	NCT03486067	Phase 1	70	39 and 77$^\beta$	NA	4.3 weeks	53	0	NA
ABBV-383[66]	NCT03933735	Phase 1	124	57, 60$^\gamma$ and 83$^\zeta$	67% CR or above, 83% VGPR or above$^\zeta$	NA (not reached)	72$^\gamma$ and 83$^\zeta$	2$^\gamma$ and 0$^\zeta$	43$^\gamma$ and 50$^\zeta$

Notes: $^\beta$At escalated doses. $^\gamma$60 mg escalation + expansion group. $^\zeta$40mg escalation group.
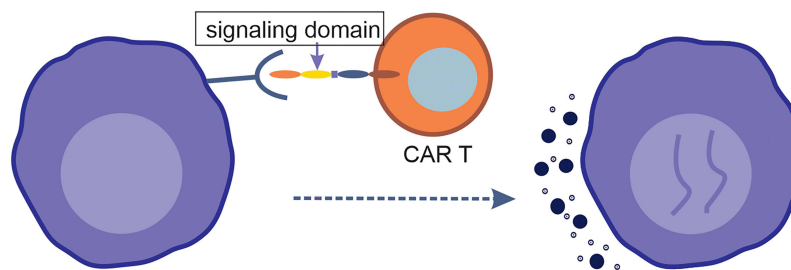
Figure 4 Signaling domain on CAR T cell binds to BCMA receptor on myeloma cell surface which leads to activation of CAR T cells and release of cytotoxic cytokines leading to myeloma cell lysis and death.
Abbreviations: BAFF, B cell-activating factor of the TNF family; BAFF-R, BAFF Receptor; BCMA, B cell maturation receptor; TACI, Transmembrane activator; APRIL, A proliferation-inducting ligand.

Idecabtagene Vicleucel

Idecabtagene vicleucel, also known as ide-cel or bb2121, demonstrated promising interim results in its phase 1 study (NCT02658929) with an ORR of 85% in 33 patients and a median DOR of 10.9 months. In the phase 2 KarMMA study (NCT03601078), which reported results on 128 out of 140 enrolled patients, ide-cel showed an ORR of 73%. The median PFS was 8.8 months with median DOR of 10.7 months.[90,91]

Recently published results from KarMMA-3 (NCT03651128), involving 386 patients from 12 countries, compared ide-cel to variable regimens in patients with triple-class-refractory (66%) or daratumumab-refractory (95%) MM. Both groups had similar distribution of Eastern Cooperative Oncology Group (ECOG) score, tumor burden, extramedullary disease, high-risk cytogenetics, and previous class exposures. Median follow-up duration was 18.6 months. In the ide-cel group, 71% of patients achieved an OR, with 35% sCR, 3% CR, 22% VGPR and 11% PR. MRD negativity was 20% (51/254) in the ide-cel group within 3 months, compared to 1/132 in the standard regimen group. Median DOR was 14.8 months, and PFS was 13.3 months in the ide-cel group, compared to 4.4 months in the standard regimen group. Common non-hematological AEs included CRS in 88% of patients, with 4% experiencing grade 3 or higher CRS, and neurotoxicity in 15% of patients, with 3% experiencing grade 3 or higher neurotoxicity. The most common hematological AEs were neutropenia (90%), anemia (66%), and thrombocytopenia (54%). Infections occurred in 58% of patients, with upper respiratory tract infection being the most common (12%) and pneumonia following thereafter (10%).[76] It is important to note that higher percentage of grade V all cause event occurred in the ide-cel group (14% vs 6%). Moreover grade III/IV neutropenia in patients treated with ide-cel was high at 76% with a median time to recover of 1.7 months.

Health-related quality of life was assessed using standardized questionnaires in patients enrolled in the KarMMA trial, and those who received ide-cel showed improvement in pain, physical functioning, fatigue, and overall quality of life lasting for 15–18 months.[92]

Ciltacabtagene Autoleucel

Ciltacabtagene autoleucel or cilta-cel (previously known as LCAR-B38M or JNJ-68284528) was first evaluated in the LEGEND-2 multicenter study in China (NCT03090659) in 57 patients. ORR was 88% with 68% achieving CR, 5% VGPR and 14% PR. MRD negativity was achieved in 63% patients. Median PFS was 15 months. Ninety percent patients experienced CRS with 7% having grade 3 or higher CRS. Others common AEs were leukopenia (30%), thrombocytopenia (23%).[93–95] A four-year follow-up data to this study was published in 2022 with 74 patients which showed a median PFS to 18 months with median duration of response of 23.3 months.[96] After promising results from the LEGEND-2 study, cilta-cel was further studied in CARTITUDE-1 phase 1b/2 study (NCT03548207) done in 113 patients from 16 USA centers. Patients received a single cilta-cel infusion at a target dose of 0.75×10^6 CAR T cells/kg and followed up at a median duration of 12.5 months. ORR was at a striking 97% among which 67% had achieved sCR with time-to-first response being 1 month. Twelve-month PFS was 77% and overall survival rate was 89%. CRS occurred in 95% patients with 4% being grade 3 or higher. The median time to onset of CRS was 7 days. ICANS occurred in 21% patients where 9% were grade 3 or higher. BCMA agents have also shown to cause delayed movement disorders and

Table 2 Summary of CAR-T Cell Therapies in Clinical Trials

Name of Drug	Clinical Trial	Status	N (Based on Latest Data)	ORR (%)	Level of Response	Median Duration of Response	CRS any Grade (%)	CRS Grade 3 or Higher (%)	Neurotoxicity (%)	Infections (%)
Idecabtagene (Ide-cel or bb2121)[76]	KarMMa-3 Phase 3 (NCT03651128) Earlier trials: KarMMa (NCT03361748), KarMMa-2 (NCT03601078)	FDA approved	386	71	35% sCR, 3% CR, 22% VGPR, 11% PR	14.8 months	88	4	15	58
Ciltacabtagene (Cilta-cel, LCAR-B38M or JNJ-68284528)[77]	CARTIFAN-1 Phase 2 (NCT03758417) Earlier trials: LEGEND-2 (NCT03090659), CARTITUDE-1 (NCT03548207)	FDA approved	48	85.4	79.2% sCR; 8.3% VGPR;	Not reached	97.9	35.4	4.2	85.4
Equecabtagene (CT 103A)[78]	FUMANBA-1 Phase ½ (NCT05066646) Earlier trial: ChiCTR1800018137	Fast track and regenerative medicine advanced therapy designation	103	95	74%≥CR; 17% VGPR, 4% PR	Not reached	93.2	1	1.9	NA
Bb21217[79]	CRB-402 (NCT03274219)	Phase 1	72	69	28% sCR/CR; 58% ≥VGPR	17 months	75	4.1	15	NA
Orvacabtagene (Orva-cel, JCARH-125)[80]	EVOLVE (NCT03430011)	Phase 1	51	91	39% sCR + CR, 25% VGPR, 27% PR	NA	NA	2	4 (grade 3 or above)	14% (grade 3 or above)
BMS-986354/CC-98633[81]	CC-98633-MM-001 (NCT04394650)	Phase 1	66	98.1	57.4% VGPR or better; 29.6% CR or better	NA	80	1.8	10.9	NA

(*Continued*)

Table 2 (Continued).

Name of Drug	Clinical Trial	Status	N (Based on Latest Data)	ORR (%)	Level of Response	Median Duration of Response	CRS any Grade (%)	CRS Grade 3 or Higher (%)	Neurotoxicity (%)	Infections (%)
Zevorcabtagene (Zevor-cel, CT053)[82]	LUMMICAR-2 (NCT03915184) Earlier trials: LUMMICAR-1	Phase 2	102	92.8	42.2% CR/sCR; 81.9% VGPR or better	Not reached	90.2	6.9	2	NA
MCARH171[83]	NCT03070327	Phase 1	11	64	NA	106 days	40	20	10	NA
ARI0002h[84]	CARTBCMA-HCB-01 (NCT04309981)	Phase 1 pilot study	35	96.3	44.4% sCR, 18.6% VGPR, 33.3 PR	1 month	87	0	0	NA
CS-1 BCMA bispecific CAR T[85]	NCT04662099	Phase 1	16	81	37.5% sCR, 18.75% VGPR, 25% PR	Not reached	38	6.2	0	NA
PHE885[86]	Phase 1: NCT04318327 Phase 2: NCT05172596	Phase 1 Currently in phase 2	7	100	17% CR, 33% VGPR, 50% PR	NA	100	0	33.3%	NA
C-CAR088[87]	NCT03815383, NCT03751293, NCT042295018, NCT04322292	Phase 1	31	96.4	42.9% sCR, 14.3% CR, 32.1% VGPR	Not reached	93.5	9.7	3.2	NA
FHVH33[88]	NCT03602612	Phase 1	25	92	72% sCR + VGPR	NA	NA	NA	NA	NA
UCARTCS1[89]	MELANI-01 (NCT04142619)	Phase 1	Only preclinical data available							

parkinsonian features.[97,98] In the CARTITUDE-1 trial, late neurotoxicity was reported in 12% and parkinsonism in 4% patients. There were 14 mortalities, 6 of which was attributed to treatment-related AEs. In terms of hematological AEs, neutropenia was the most common (95%), followed by anemia (68%), leukopenia (60%) and thrombocytopenia (60%). Infections occurred in 58% patients.[99] A follow-up study was conducted to above study which showed slightly better ORR at 97.9% with 82.5% achieving sCR. PFS at 27-month was 54.9% and OS was 70.4%.[100]

A phase-2 study is ongoing in China, called CARTIFAN-1 (NCT03758417) and data from 48 patients were published at a median follow-up of 26.4 months, that shows an ORR of 85.4%. 79.2% patients achieved sCR and MRD negativity of 40%. PFS & OS rates were 52.6% and 74.2% in 24-months respectively. Again, CRS occurred in most patients (97.9%) out of which 35.4% were grade 3 or higher. Neurotoxicity occurred in 4.2%, infections occurred in 85.4% patients, 37.5% were grade 3 or higher. There were 12 reported deaths, out of which 8 were attributed as treatment related.[77,101,102]

CAR-T cell therapies show promising outcomes, but comes at a cost of increased CRS, neurotoxicity and prolonged cytopenias, which may require stem cell boost. Besides, availability of treatment is limited, and there is also a component of disparity in access to treatment.[103] Therefore, patients can clinically decline awaiting treatment given the length of wait time.[104]

Mechanisms of BCMA Resistance

Both antigen and T-cell related mechanisms are responsible for resistance to BCMA treatment. T-cell mediated processes leading to BCMA-treatment resistance are T-cell senescence/exhaustion and development of immunosuppressive bone marrow microenvironment.[105] T-cell exhaustion and senescence are the primary mechanisms for BCMA resistance and refer to loss of cytokine producing and proliferating abilities respectively, which would otherwise play key roles in tumor lysis.[105]

One of the antigen-related mechanisms is antigen escape, that occurs because of dysregulated expression of MHC or changes in tumor-associated antigen epitopes.[106] Dual-targeting BCMA with another antigen has shown to prevent antigen escape-related relapse.[107,108] BCMA shedding from plasma cells driven by γ-secretase results in circulation of sBCMA, that can potentially lead to masking of antigen.[109] The third antigen-dependent process is the development of anti-scFv antibodies, which was more common with non-human scFv.[110] Use of humanized scFv has been shown to reduce production of anti-scFv antibodies, decreasing the risk for resistance.[109]

Future Directions

Allogeneic BCMA-targeted CAR T cells are being studied to address the logistical challenges with autologous CAR-T, that largely limits its access. UNIVERSAL is a phase 1, first-in-human trial of ALLO-715 (NCT04093596) used in escalating doses with an anti-CD52 antibody ALLO-647. ALLO-715 is an allogeneic CAR-T therapy comprising a second-generation anti-BCMA CAR containing humanized scFv and intracellular domains of 4–1BB and CD3ζ. T cell receptor alpha constant (TRAC) is knocked out of in this that reduces the risk of graft-versus-host disease (GVHD). Based on interim results of 48 patients with relapsed/refractory MM, 70.8% patients had a response with 45.8% VGPR or better and 25% with CR or sCR. Median duration of response was 8.4 months. CRS occurred in 55.8% patients with grade 3 or move in 2.3%, neurotoxicity was observed in 14% patients with no grade 3 or more events. Infections occurred in 53.5% patients with 23.3% above grade 3. No cases of GVHD were reported.[111]

Bispecific CAR-T has been studied using BCMA & CD24 CARs which showed both in-vitro and in-vivo cytotoxic activity against myeloma warranting further studies.[10] Similarly, anti-BCMA CAR-NK cells are being studied in pre-clinical phase in different models, with good results and may possess a place in the BCMA therapeutics shelf in the future.[112,113]

Currently, BCMA directed therapies are only available for R/R MM patients, but many trials are underway to explore their role at earlier stages and in combination with other myeloma therapies and in patients with high-risk disease (Table 3).

Table 3 Ongoing Trials in BCMA

Identifier	Title	Status	Interventions	Phase	Enrollment	Estimated Completion
ANTIBODY DRUG CONJUGATE (ADC)						
NCT03828292	An Open-label, Dose Escalation Study in Japanese Participants with Relapsed/Refractory Multiple Myeloma Who Have Failed Prior Anti Myeloma Treatments	Active, not recruiting	Drug: Belantamab mafodotin | Drug: Bortezomib | Drug: Dexamethasone | Drug: Pomalidomide	Phase 1	15	2023
NCT04549363	Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin	Recruiting	Drug: Belantamab mafodotin	Phase 3	25	2023
NCT04822337	Study of Carfilzomib, Lenalidomide, Dexamethasone and Belantamab Mafodotin in Multiple Myeloma	Recruiting	Drug: Carfilzomib, Lenalidomide, Dexamethasone, Belantamab Mafodotin	Phase 1 | Phase 2	70	2024
NCT05208307	Belantamab Mafodotin, Pomalidomide and Dexamethasone for the Treatment of High-Risk Myeloma	Recruiting	Biological: Belantamab Mafodotin | Drug: Dexamethasone | Drug: Pomalidomide	Phase 2	34	2024
NCT04036461	A Study of CC-99712, a BCMA Antibody-Drug Conjugate, in Participants with Relapsed and Refractory Multiple Myeloma	Recruiting	Drug: CC-99712 | Drug: BMS-986405	Phase 1	160	2025
NCT04398745	A Study of Belantamab Mafodotin Monotherapy in Multiple Myeloma Participants with Normal and Varying Degree of Impaired Renal Function	Recruiting	Drug: Belantamab mafodotin	Phase 1	36	2025
NCT04876248	Belantamab Mafodotin and Lenalidomide for the Treatment of Multiple Myeloma in Patients with Minimal Residual Disease Positive After Stem Cell Transplant	Recruiting	Biological: Belantamab Mafodotin | Drug: Lenalidomide	Phase 2	20	2025
NCT04680468	Study of Belantamab Mafodotin as Pre- and Post-autologous Stem Cell Transplant and Maintenance for Multiple Myeloma	Recruiting	Drug: Belantamab mafodotin	Phase 2	47	2026
NCT04246047	Evaluation of Efficacy and Safety of Belantamab Mafodotin, Bortezomib and Dexamethasone Versus Daratumumab, Bortezomib and Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma	Active, not recruiting	Drug: Belantamab mafodotin | Drug: Daratumumab | Drug: Bortezomib | Drug: Dexamethasone	Phase 3	575	2026
NCT04484623	Belantamab Mafodotin Plus Pomalidomide and Dexamethasone (Pd) Versus Bortezomib Plus Pd in Relapsed/Refractory Multiple Myeloma	Recruiting	Drug: Belantamab mafodotin | Drug: Pomalidomide | Drug: Dexamethasone | Drug: Bortezomib	Phase 3	300	2027

NCT04126200	Platform Study of Belantamab Mafodotin as Monotherapy and in Combination with Anti-cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 5)	Recruiting	Drug: Belantamab mafodotin | Drug: GSK3174998 | Drug: Feladilimab | Drug: Nirogacestat | Drug: Dostarlimab | Drug: Isatuximab | Drug: Lenalidomide | Drug: Dexamethasone | Drug: Pomalidomide	Phase 1 | Phase 2	464	2028
NCT05117008	Maintenance Belantamab Mafodotin (Blenrep®) After B-cell Maturation Antigen-Directed Chimeric Antigen Receptor T-cell Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma	Recruiting	Drug: Belantamab mafodotin	Phase 2	45	2032
BISPECIFIC ANTIBODIES						
NCT03269136	PF-06863135 As Single Agent And In Combination with Immunomodulatory Agents In Relapse/Refractory Multiple Myeloma	Active, not recruiting	Drug: PF-06863135 monotherapy IV or SC | Drug: PF-06863135 + dexamethasone | Drug: PF-06863135 + lenalidomide | Drug: PF-06863135 + pomalidomide	Phase 1	103	2023
NCT04798586	MAGNETISMM-2: Study of Elranatamab (PF-06863135) in Japanese Participants with Multiple Myeloma	Active, not recruiting	Drug: Elranatamab (PF-06863135)	Phase 1	4	2023
NCT04083534	First In Human (FIH) Study of REGN5459 in Adult Patients with Relapsed or Refractory Multiple Myeloma (MM)	Active, not recruiting	Drug: REGN5459	Phase 1 | Phase 2	43	2023
NCT04649359	MagnetisMM-3: Study Of Elranatamab (PF-06863135) Monotherapy in Participants with Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb	Active, not recruiting	Drug: Elranatamab (PF-06863135)	Phase 2	187	2024
NCT03145181	Dose Escalation Study of Teclistamab, a Humanized BCMA*CD3 Bispecific Antibody, in Participants with Relapsed or Refractory Multiple Myeloma	Recruiting	Drug: Teclistamab (IV) | Drug: Teclistamab (SC)	Phase 1	282	2025
NCT05228470	A Study of Elranatamab (PF-06863135) in Chinese Participants with Refractory Multiple Myeloma.	Recruiting	Drug: Elranatamab	Phase 2	36	2025
NCT05020236	MagnetisMM-5: Study of Elranatamab (PF-06863135) Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma	Recruiting	Drug: Elranatamab | Drug: Daratumumab | Drug: Pomalidomide | Drug: Dexamethasone	Phase 3	589	2025

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Table 3 (Continued).

Identifier	Title	Status	Interventions	Phase	Enrollment	Estimated Completion
NCT04696809	A Study of Teclistamab in Japanese Participants with Relapsed or Refractory Multiple Myeloma	Recruiting	Drug: Teclistamab	Phase 1 | Phase 2	38	2025
NCT04557098	A Study of Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma	Recruiting	Drug: Teclistamab	Phase 2	244	2025
NCT04735575	A Ph1/2 Study of EMB-06 in Participants with Relapsed or Refractory Myeloma	Recruiting	Biological: EMB-06	Phase 1 | Phase 2	66	2025
NCT03582033	A Safety Study of SEA-BCMA in Patients with Multiple Myeloma	Active, not recruiting	Drug: SEA-BCMA | Drug: dexamethasone | Drug: pomalidomide	Phase 1	83	2026
NCT05090566	MagnetisMM-4: Umbrella Study of Elranatamab (PF-06863135) in Combination with Anti-Cancer Treatments in Multiple Myeloma	Recruiting	Drug: Elranatamab + Nirogacestat | Drug: Elranatamab + lenalidomide + dexamethasone	Phase 2	105	2026
NCT03933735	A Study of TNB-383B in Participants with Relapsed or Refractory Multiple Myeloma	Active, not recruiting	Drug: TNB-383B	Phase 1 | Phase 2	220	2026
NCT05535244	A Study Evaluating the Efficacy and Safety of Cevostamab in Prior B Cell Maturation Antigen (BCMA)-Exposed Participants with Relapsed/Refractory Multiple Myeloma	Recruiting	Drug: Cevostamab | Drug: Tocilizumab	Phase 1 | Phase 2	140	2026
NCT05014412	A Study to Learn About the Study Medicine (Elranatamab) Either Alone or in Combination with Dexamethasone in Participants with Multiple Myeloma That Has Come Back After Responding to Treatment or Has Not Responded to Treatment	Recruiting	Drug: Elranatamab | Drug: Elranatamab+ dexamethasone	Phase 2	76	2026
NCT05675449	A Clinical Trial of Three Medicines (Elranatamab Plus Carfilzomib and Dexamethasone) in People with Relapsed Refractory Multiple Myeloma	Recruiting	Drug: Elranatamab | Drug: Carfilzomib	Phase 1	14	2026
NCT03486067	Study of CC-93269, a BCMA x CD3 T Cell Engaging Antibody, in Participants with Relapsed and Refractory Multiple Myeloma	Active, not recruiting	Drug: CC-93269	Phase 1	220	2027

NCT05623020	A Study to Learn About the Effects of the Combination of Elranatamab (PF-06863135), Daratumumab, and Lenalidomide Compared with Daratumumab, Lenalidomide, and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma Who Are Not Candidates for Transplant	Recruiting	Drug: Elranatamab	Drug: Daratumumab	Drug: Lenalidomide	Drug: Dexamethasone	Phase 3	676	2028
NCT05317416	Study with Elranatamab Versus Lenalidomide in Patients with Newly Diagnosed Multiple Myeloma After Transplant	Recruiting	Drug: Elranatamab	Drug: Lenalidomide	Phase 3	700	2029
NCT05137054	Linvolseltamab (Anti-BCMA x Anti-CD3 Bispecific Antibody) Plus Other Cancer Treatments for Participants with Relapsed/Refractory Multiple Myeloma (LINKER-MM2)	Recruiting	Drug: REGN5458	Drug: Daratumumab	Drug: Carfilzomib	Drug: Lenalidomide	Drug: Bortezomib	Drug: Pomalidomide	Drug: Isatuximab	Drug: Nirogacestat	Phase 1	245	2032
NCT03761108	Phase 1/2 Study of REGN5458 in Patients with Relapsed or Refractory Multiple Myeloma	Active, not recruiting	Drug: REGN5458	Phase 1 | Phase 2	309	2032
CAR T/NK cells						
NCT04162353	BCMA-CD19 cCAR in Multiple Myeloma and Plasmacytoid Lymphoma	Recruiting	Biological: BCMA-CD19 cCAR T cells	Phase 1	12	2021
NCT03943472	BCMA Chimeric Antigen Receptor Expressing T Cells Therapy for Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: Anti-BCMA CAR-T cells	Drug: Fludarabine	Drug: Cyclophosphamide	Drug: Immune inhibitors	Early Phase 1	10	2022
NCT04236011	BCMA and CD19 Targeted Fast Dual CAR-T for BCMA+ Refractory/Relapsed Multiple Myeloma	Recruiting	Biological: GC012F injection	Early Phase 1	15	2022
NCT05346198	Evaluate CART-BCMA in Patients with Relapsed and/or Refractory Multiple Myeloma	Recruiting	Drug: CART-BCMA	Phase 1	15	2023
NCT04637269	Anti-BCMA CAR-T Cell Therapy for the R/R Multiple Myeloma	Recruiting	Biological: anti-BCMA CAR-T	Early Phase 1	16	2023
NCT04271644	BCMA-Targeted CAR-T Cell Therapy for Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: BCMA CAR-T cells	Phase 1 | Phase 2	80	2023
NCT04272151	Safety and Efficacy of BCMA-Targeted CAR-T Therapy for Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: BCMA CAR-T cells	Phase 1 | Phase 2	40	2023

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Table 3 (Continued).

Identifier	Title	Status	Interventions	Phase	Enrollment	Estimated Completion
NCT04776330	A Clinical Research of BCMA-Targeted Prime CAR-T Cell Therapy in Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: BCMA targeted prime CAR-T cells	Phase 1 | Phase 2	80	2023
NCT03380039	Clinical Study of CAR-BCMA T Cells in Patients with Refractory or Relapsed Multiple Myeloma	Active, not recruiting	Genetic: CAR-BCMA T cells | Drug: Fludarabine | Drug: Cyclophosphamide	Not Applicable	6	2023
NCT05008536	Anti-BCMA CAR-NK Cell Therapy for the Relapsed or Refractory Multiple Myeloma	Recruiting	Biological: Anti-BCMA CAR-NK Cells | Drug: Fludarabine | Drug: Cytoxan	Early Phase 1	27	2023
NCT03716856	Clinical Study of CAR-BCMA T in Patients with Refractory or Relapsed Multiple Myeloma	Active, not recruiting	Genetic: CAR-BCMA T cells | Drug: Fludarabine | Drug: Cyclophosphamide	Phase 1	11	2023
NCT04662099	T Cells Expressing a Bispecific CAR Targeting CS1 and BCMA in Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: Conditioning chemotherapy followed by CAR T cell infusion	Phase 1	24	2023
NCT04714827	Targeting CD19 and BCMA CAR-T Cells Immunotherapy in Patients with Relapsed or Refractory Multiple Myeloma	Recruiting	Biological: CD19-CD22 CAR-T cells	Phase 1 | Phase 2	24	2023
NCT05201118	A Study of a Fully Human BCMA-targeting CAR (CT103A) Combined with Selinexor in Patients with Relapsed/ Refractory Extramedullary Multiple Myeloma	Recruiting	Drug: Selinexor | Drug: CT103A	Phase 1	20	2023
NCT05652530	Clinical Study of the Safety and Efficacy of BCMA CAR-NK	Recruiting	Drug: Chimeric Antigen Receptor NK Cell Injection Targeting BCMA (BCMA CAR-NK)	Early Phase 1	19	2023
NCT03455972	Study of T Cells Targeting CD19/BCMA (CART-19/BCMA) for High Risk Multiple Myeloma Followed with Auto-HSCT	Recruiting	Biological: anti-CD19 and anti-BCMA CAR | Drug: Immunomodulatory drugs	Phase 1 | Phase 2	15	2023
NCT03430011	Study Evaluating the Safety and Efficacy of JCARH125 in Subjects with Relapsed and/or Refractory Multiple Myeloma	Active, not recruiting	Biological: JCARH125 | Biological: JCARH125 + anakinra	Phase 1 | Phase 2	169	2023
NCT05336383	Phase II Study of Salvage Radiation Treatment After B-cell Maturation Antigen Chimeric Antigen Receptor T-cell Therapy for Relapsed Refractory Multiple Myeloma	Recruiting	Drug: Radiation Therapy	Phase 2	30	2023
NCT04935580	Study of FasT CAR-T GC012F Injection in High Risk TE NDMM Patients	Recruiting	Biological: GC012F injection	Phase 1 | Phase 2	20	2023

NCT03302403	Clinical Study of Redirected Autologous T Cells with a Chimeric Antigen Receptor in Patients with Malignant Tumors	Active, not recruiting	Genetic: CAR-CD19 T cell | Genetic: CAR-BCMA T cell | Genetic: CAR-GPC3 T cell | Genetic: CAR-CLD18 T cell | Drug: Fludarabine | Drug: Cyclophosphamide	Not Applicable	18	2023
NCT04196491	A Study to Evaluate the Safety of bb2121 in Subjects with High Risk, Newly Diagnosed Multiple Myeloma (NDMM)	Active, not recruiting	Biological: bb2121 | Drug: Fludarabine | Drug: Cyclophosphamide | Drug: Lenalidomide	Phase 1	13	2023
NCT04003168	Human BCMA Targeted T Cells Injection Therapy for BCMA-positive Relapsed/Refractory Multiple Myeloma	Recruiting	Drug: Human BCMA targeted T Cells Injection	Phase 1	18	2024
NCT05712083	A Study of BCMA CAR-T Cell Therapy for Newly Diagnosed Multiple Myeloma	Recruiting	Drug: BCMA CAR-T cells	Phase 2	40	2024
NCT03602612	T Cells Expressing a Novel Fully-Human Anti-BCMA CAR for Treating Multiple Myeloma	Active, not recruiting	Drug: Cyclophosphamide | Drug: Fludarabine | Biological: Anti-BCMA CAR T cells	Phase 1	35	2024
NCT04706936	Novel BCMA-targeted CAR-T Cell Therapy for Multiple Myeloma	Recruiting	Biological: anti-BCMA CAR-T | Drug: Cyclophosphamide | Drug: Fludarabine	Phase 1	25	2024
NCT03070327	BCMA Targeted CAR T Cells with or without Lenalidomide for the Treatment of Multiple Myeloma	Active, not recruiting	Biological: EGFRt/BCMA-41BBz CAR T cell | Drug: Cyclophosphamide | Drug: Lenalidomide.	Phase 1	20	2024
NCT05302648	To Evaluate the Safety and Efficacy of Human Derived Anti-BCMA CAR-T Injection for Subjects with R/R MM	Recruiting	Drug: Human Derived anti-BCMA CAR-T Injection	Early Phase 1	18	2024
NCT05066646	A Phase 1/2 Study of a Fully Human BCMA-targeting CAR (CT103A) in Patients with Relapsed/Refractory Multiple Myeloma (FUMANBA-1)	Recruiting	Drug: CT103A	Phase 1 | Phase 2	132	2024
NCT05150522	B Cell Maturation Antigen Targeted CAR-T Cells in Treatment with Relapsed and Refractory Multiple Myeloma	Recruiting	Biological: BCMA CAR-T cells	Phase 1 | Phase 2	10	2024
NCT04601935	A Single-center Exploratory Clinical Study to Evaluate the Safety, Tolerability, and Efficacy of a BCMA-targeted Universal LCAR-BCX Cells in Patients with Relapsed/Refractory Multiple Myeloma	Active, not recruiting	Biological: LCAR-BCX cells product	Phase 1	34	2024
NCT05412329	Study of Dual Targeted CD19/BCMA FASTCART GC012F in Relapsed/ Refractory Multiple Myeloma	Recruiting	Biological: GC012F injection	Phase 1	9	2024

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Table 3 (Continued).

Identifier	Title	Status	Interventions	Phase	Enrollment	Estimated Completion
NCT03994705	Descartes-11 in Multiple Myeloma	Active, not recruiting	Biological: Descartes-11 | Drug: Fludarabine | Drug: Cyclophosphamide	Phase 1 | Phase 2	25	2024
NCT03361748	Efficacy and Safety Study of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma	Active, not recruiting	Biological: bb2121	Phase 2	149	2024
NCT05618041	The Safety and Efficacy Investigation of CAR-T Cell Therapy for Patients with Hematological Malignancies	Recruiting	Biological: CAR-T Autologous T cell injection	Not Applicable	50	2024
NCT04677452	Dose Exploration Study OF JWCAR129, BCMA-Targeted CART for RRMM	Recruiting	Biological: JWCAR129	Phase 1	24	2024
NCT05266768	Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Preliminary Efficacy of IBI346#CIBI346Y002#	Recruiting	Drug: IBI346	Phase 1	36	2024
NCT05270928	Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Preliminary Efficacy of IBI346#CIBI346Y001#	Recruiting	Drug: IBI346	Phase 1	42	2024
NCT05430945	A Study of BCMA-targeted CAR-T Cells Therapy for Refractory/Relapsed Multiple Myeloma	Recruiting	Biological: BCMA Targeted CAR T-cells	Early Phase 1	100	2025
NCT05509530	Safety and Efficacy of Anti-BCMA/GPRC5D CAR-T Cell Therapy in Treating Relapsed and Refractory Multiple Myeloma (rr/MM)	Recruiting	Other: anti-BCMA/GPRC5D CAR-T CELL	Phase 2	30	2025
NCT03975907	Clinical Trial to Evaluate CT053 in Patients with Relapsed and/or Refractory Multiple Myeloma (LUMMICAR STUDY 1)	Recruiting	Biological: CAR-BCMA T Cells	Phase 1 | Phase 2	114	2025
NCT04318327	BCMA-directed CAR-T Cell Therapy in Adult Patients with Relapsed and/or Refractory Multiple Myeloma	Recruiting	Biological: PHE885	Phase 1	56	2025
NCT04287660	Study of BiRd Regimen Combined with BCMA CAR T-cell Therapy in Newly Diagnosed Multiple Myeloma (MM) Patients	Recruiting	Drug: clarithromycin, lenalidomide, dexamethasone and autologous BCMA-directed CAR T-cells	Phase 3	20	2025

NCT04309981	Clinical Trial Using Humanized CART Directed Against BCMA (ARI0002h) in Patients with Relapsed/Refractory Multiple Myeloma to Proteasome Inhibitors, Immunomodulators and Anti-CD38 Antibody.	Recruiting	Biological: Adult differentiated autologous T-cells with anti-BCMA specificity	Phase 1 | Phase 2	36	2025
NCT04133636	A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen (BCMA) in Participants with Multiple Myeloma	Recruiting	Drug: JNJ-68284528 | Drug: Lenalidomide | Drug: Daratumumab | Drug: Bortezomib | Drug: Dexamethasone	Phase 2	157	2025
NCT04394650	A Study of CC-98633, BCMA-targeted Chimeric Antigen Receptor (CAR) T Cells, in Participants with Relapsed and/or Refractory Multiple Myeloma	Active, not recruiting	Biological: CC-98633	Phase 1	150	2025
NCT05740891	AHSCT Combined with CAR-T Cells in the Treatment of Refractory and Relapsed Multiple Myeloma	Recruiting	Drug: BCMA CAR-T cells injection	Phase 1	50	2025
NCT05032820	MM CAR-T to Upgrade Response BMTCTN1902	Recruiting	Drug: Lenalidomide and bb2121	Phase 2	40	2025
NCT05632380	ASCT in Combination with C-CAR088 for Treating Patients with Ultra High-risk Multiple Myeloma (MM)	Recruiting	Procedure: Autologous hematopoietic stem cell transplantation | Biological: C-CAR088	Phase 1 | Phase 2	20	2025
NCT05172596	PHE885 CAR-T Therapy in Adult Participants with Relapsed and Refractory Multiple Myeloma	Recruiting	Biological: PHE885	Phase 2	136	2025
NCT03274219	Study of bb21217 in Multiple Myeloma	Active, not recruiting	Biological: bb21217	Phase 1	72	2025
NCT05396885	Study of CART-ddBMCA in Relapsed or Refractory Multiple Myeloma (iMMagine-1)	Recruiting	Biological: CART-ddBCMA	Phase 2	110	2025
NCT03196414	Study of T Cells Targeting CD138/BCMA/CD19/More Antigens (CART-138/BCMA/19/More) for Chemotherapy Refractory and Relapsed Multiple Myeloma	Recruiting	Biological: CART-138/BCMA/19/more	Phase 1 | Phase 2	10	2026
NCT03758417	A Study of LCAR-B38M CAR-T Cells, a Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen (BCMA) in Chinese Participants with Relapsed or Refractory Multiple Myeloma	Recruiting	Biological: LCAR-B38M CAR-T Cell	Phase 2	130	2026
NCT05376345	BCMA-targeted LCAR-BCDR Cells in Patients with Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: LCAR-BCDR cells product	Phase 1	32	2026

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Table 3 (Continued).

Identifier	Title	Status	Interventions	Phase	Enrollment	Estimated Completion
NCT04720313	NXC-201 (Formerly HBI0101) Multiple Myeloma	Recruiting	Drug: NXC-201 (formerly HBI0101)	Phase 1	48	2026
NCT04603872	CAR-T Cells Combined with Dasatinib for Patients with Relapsed and/or Refractory B-cell Hematological Malignancies	Recruiting	Drug: CD19/BCMA Targeted CAR T-cells and dasatinib | Drug: CD19/BCMA Targeted CAR T-cells	Early Phase 1	120	2026
NCT05528887	Study of CAR-T Cell Therapy in the Treatment of Relapsed/Refractory Hematological Malignancies	Recruiting	Biological: Autologous CAR-T cells | Drug: Fludarabine | Drug: Cyclophosphamide	Phase 1	10	2026
NCT05594797	Human BCMA Targeted T Cells Injection (BCMA CAR-T) for Subjects with R/R MM	Recruiting	Drug: Human BCMA Targeted T Cells Injection	Phase 2	100	2027
NCT05722418	CRISPR-Edited Allogeneic Anti-BCMA CAR-T Cell Therapy in Patients with Relapsed/Refractory Multiple Myeloma	Recruiting	Biological: CB-011	Phase 1	50	2027
NCT04093596	Safety and Efficacy of ALLO-715 BCMA Allogenic CAR T Cells in in Adults with Relapsed or Refractory Multiple Myeloma (UNIVERSAL)	Recruiting	Genetic: ALLO-715 | Biological: ALLO-647 | Drug: Fludarabine | Drug: Cyclophosphamide | Drug: Nirogacestat	Phase 1	132	2027
NCT05000450	Safety and Efficacy of ALLO-605 an Anti-BCMA Allogeneic CAR T Cell Therapy in Patients with Relapsed/Refractory Multiple Myeloma	Recruiting	Genetic: ALLO-605 | Biological: ALLO-647 | Drug: Fludarabine | Drug: Cyclophosphamide	Phase 1 | Phase 2	136	2027
NCT04181827	A Study Comparing JNJ-68284528, a CAR-T Therapy Directed Against B-cell Maturation Antigen (BCMA), Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Participants with Relapsed and Lenalidomide-Refractory Multiple Myeloma	Active, not recruiting	Drug: JNJ-68284528 | Drug: Pomalidomide | Drug: Bortezomib | Drug: Dexamethasone | Drug: Daratumumab	Phase 3	419	2027
NCT04244656	A Safety and Efficacy Study Evaluating CTX120 in Subjects with Relapsed or Refractory Multiple Myeloma	Active, not recruiting	Biological: CTX120	Phase 1	26	2027
NCT05243212	Study of CAR-BCMA, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma	Recruiting	Biological: CAR-BCMA	Phase 1 | Phase 2	75	2028

NCT03601078	An Efficacy and Safety Study of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma and in Subjects with High-Risk Multiple Myeloma	Recruiting	Biological: bb2121 | Drug: Lenalidomide	Phase 2	235	2030
NCT03741127	Long-Term Follow-Up Study for Subjects Treated with P-BCMA-101	Active, not recruiting	Drug: Rimiducid may be administered as indicated	Phase 1	100	2032
NCT03915184	Clinical Trial to Evaluate Zevor-cel (CT053) in Patients with Relapsed and/or Refractory Multiple Myeloma (LUMMICAR STUDY 2)	Recruiting	Biological: zevor-cel	Phase 1 | Phase 2	105	2034
NCT04923893	A Study of Bortezomib, Lenalidomide and Dexamethasone (VRd) Followed by Cilta-cel, a CAR-T Therapy Directed Against BCMA Versus VRd Followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants with Newly Diagnosed Multiple Myeloma for Whom ASCT is Not Planned as Initial Therapy	Recruiting	Drug: Bortezomib | Drug: Dexamethasone | Drug: Lenalidomide | Drug: Cilta-cel | Drug: Cyclophosphamide | Drug: Fludarabine	Phase 3	650	2034
NCT04155749	Master Protocol for the Phase 1 Study of Cell Therapies in Multiple Myeloma	Recruiting	Drug: CART-ddBCMA | Drug: ARC-T Plus Anti-BCMA SparX	Phase 1	65	2035
NCT03549442	Up-front CART-BCMA with or without huCART19 in High-risk Multiple Myeloma	Active, not recruiting	Combination Product: BCMA CART + huCART19 | Combination Product: CART BCMA or CART BCMA + huCART19 | Combination Product: Single-dose infusion of CART BCMA or CART BCMA + huCART19	Phase 1	40	2036
NCT04613557	Safety, Activity and Cell Kinetics of CYAD-211 in Patients with Relapsed or Refractory Multiple Myeloma	Recruiting	Biological: CYAD-211 | Drug: Endoxan | Drug: Fludara	Phase 1	12	2036
NCT05521802	A Study of C-CAR088 in Patients with Relapsed or Refractory Multiple Myeloma	Recruiting	Biological: B-cell maturation antigen (BCMA) directed chimeric antigen receptor (CAR)-T cell	Phase 1 | Phase 2	92	2037
NCT05577000	Anti-BCMA Chimeric Antigen Receptor T Cells for Relapsed or Refractory Multiple Myeloma	Recruiting	Biological: Manufactured Anti-BCMA CAR-T cells | Drug: Fludarabine | Drug: Cyclophosphamide	Phase 1	24	2039
NCT04960579	P-BCMA-ALLO1 Allogeneic CAR-T Cells in the Treatment of Subjects with Multiple Myeloma	Recruiting	Biological: P-BCMA-ALLO1 CAR-T cells | Drug: Rimiducid	Phase 1	135	2040
NCT05182073	FT576 in Subjects with Multiple Myeloma	Recruiting	Drug: FT576 (Allogenic CAR NK cells with BCMA expression) | Drug: Cyclophosphamide | Drug: Fludarabine | Drug: Daratumumab	Phase 1	168	2040

Conclusion

BCMA targeted therapy remains the core of treatment for R/R MM with new available agents and many in development that have shown encouraging results. Teclistamab, ide-cel and cilta-cel are the currently FDA approved agents with some in queue for approval. Overall, these add significantly to the treatment arsenal for patients with R/R MM. Other non-BCMA targeted therapies, particularly GPRC5D has shown good results in early clinical trials, but data to compare them with anti-BCMA agents is lacking.

Disclosure

The authors report no competing interests in this work.

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