BCMA-targeted immunotherapy for multiple myeloma

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Abstract

B cell maturation antigen (BCMA) is a novel treatment target for multiple myeloma (MM) due to its highly selective expression in malignant plasma cells (PCs). Multiple BCMA-targeted therapeutics, including antibody-drug conjugates (ADC), chimeric antigen receptor (CAR)-T cells, and bispecific T cell engagers (BiTE), have achieved remarkable clinical response in patients with relapsed and refractory MM. Belantamab mafodotin-blmf (GSK2857916), a BCMA-targeted ADC, has just been approved for highly refractory MM. In this article, we summarized the molecular and physiological properties of BCMA as well as BCMA-targeted immunotherapeutic agents in different stages of clinical development.

Keywords: B cell maturation antigen, BCMA, Belantamab mafodotin, CAR-T, Antibody-drug conjugate, Bispecific T cell engager

Introduction

Recent advances in novel therapeutics such as proteasome inhibitors (PI) and immunomodulatory drugs (IMiD) have significantly improved the treatment outcomes in patients with multiple myeloma (MM) [1–8]. However, most MM patients eventually relapse due to the development of drug resistance [9]. In addition, many of the current popular target antigens, such as CD38 and SLAMF7 (also known as CS1 or CD319), are also found in other normal tissues, thus leading to unwanted off-tumor toxicities [10, 11]. Therefore, novel treatment strategies are urgently needed, especially in high-risk relapsed/refractory (R/R) MM [12–15]. B cell maturation antigen (BCMA) or CD269, also known as tumor necrosis factor receptor superfamily member 17 (TNFRSF-17), is restrictively expressed in both normal and malignant plasma cells (PC) at high levels, which makes it an ideal target antigen for novel MM therapies [16, 17].

B cell maturation antigen (BCMA)

BCMA is encoded by a 2.92-kb TNFRSF17 gene located on the short arm of chromosome 16 (16p13.13) and composed of 3 exons separated by 2 introns (Fig. 1). BCMA is a 184 amino acid and 20.2-kDa type III transmembrane glycoprotein, with the extracellular N terminus containing a conserved motif of 6 cysteines [18–21]. BCMA was found to be a member of tumor necrosis factor (TNF) receptor (TNFR) superfamily [22]. There are four natural splice variants of human BCMA that present with different receptor binding affinities, membrane-anchoring ability, and intracellular domain signaling [19, 23].

BCMA, along with the other two functionally related TNFR superfamily members, B cell activating factor (BAFF; also called BlyS) receptor (BAFF-R) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), coordinates to regulate B cell proliferation maturation and survival, as well as differentiation into plasma cells (PCs) [24–30]. Unlike BAFF-R and TACI, BCMA is almost exclusively expressed on plasmablasts [31] and PCs [32]. It is also weakly detectable on some memory B cells committed...
to PC differentiation and on plasmacytoid dendritic cells [33]. BCMA is undetectable in naïve B cells, hematopoietic stem cells, or in normal non-hematologic tissues except for some organs such as the testis, trachea, and some portions of gastrointestinal duct due to the presence of PCs [34]. The upregulation of BCMA is induced by B lymphocyte-induced maturation protein1 (Blimp-1), an essential transcription factor involved in the development and survival of PCs [35]. In BCMA−/− mice, the long-term survival of PCs is impaired, but lack of BCMA has no effect in short-lived PCs, B cell development, or early humoral immune response, and the splenic architecture and germinal centers appear intact in these BCMA-deficient mice [32, 36]. Therefore, the presence of BCMA might be specifically required to enhance the survival of long-lived PCs.

Meanwhile, BCMA is identified on the surface of nearly all MM cell lines (80–100%) and is more abundantly present in malignant PCs than normal PCs [16, 37]. MM patients receiving allogeneic transplant often develop donor-derived anti-BCMA monoclonal antibodies (mAbs) after donor lymphocyte infusion and benefit from graft-versus-tumor response [38]. In contrast, TACI is expressed at a significantly lower concentration and BAFF-R is even hardly detectable on MM cells [39]. BCMA overexpression significantly promotes in vivo growth of xenografted MM cells in murine models [40]. Furthermore, BCMA expression is upregulated during MMogenesis and evolution, from normal to MGUS to SMM to active MM [41]. Higher levels of BCMA are associated with poorer outcomes [16], indicating that BCMA is a useful biomarker of disease activity and prognosis for MM.

BCMA has two agonist ligands: a proliferation-inducing ligand (APRIL) and BAFF, which are mainly secreted by bone marrow (BM) stromal cells, osteoclasts, and macrophages in a paracrine manner in the BM [40, 42–44] (Fig. 2). APRIL exhibits a much higher binding affinity to BCMA than BAFF [45], and it also binds to TACI [46], while BAFF restricts more selectivity to BAFF-R [45]. Thus, APRIL is more specific to PCs and correlates to more downstream pathophysiological activities [47]. MM cell lines had significantly reduced growth when xenografted in APRIL−/− mice [48]. In MM patients, the serum levels of APRIL and BAFF are elevated about 5-fold over those in the healthy controls [42], and the more advanced the stage of MM is, the higher concentration of ligands is detected [49]. Studies have shown that MM cells could stimulate osteoclasts to produce more APRIL which contributes to an immunosuppressive BM microenvironment [40, 50]. It has been suggested that adding APRIL blocking monoclonal antibodies (mAbs) to BCMA-directed immunotherapies might overcome MM cell-induced immunosuppressive BM microenvironment and thereby enhance the antibody-dependent cell-mediated cytotoxicity (ADCC) against MM cells [51].

Upon binding of the ligands to BCMA, multiple growth and survival signaling cascades are activated in MM cells, most frequently nuclear factor-κ-light-chain enhancer of activated B cells (NF-κB), but also including rat sarcoma/mitogen-activated protein kinase (RAS/MAPK), and phosphoinositide-3-kinase–protein kinase B/Akt (PI3K-PKB/Akt) signaling pathway [37, 52, 53]. These pathways result in proliferation stimulation by modulating cell cycle checkpoints, increased survival by

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**Fig. 1 BCMA gene and protein.** BCMA is encoded by the TNFRSF17 gene (BCMA gene) located on the short arm of chromosome 16 (16p13.13). The BCMA gene comprised of 3 exons separated by 2 introns. BCMA is a type III transmembrane glycoprotein, with an extracellular N terminus containing a conserved motif of 6 cysteines and an intracellular tumor necrosis factor receptor-associated factor (TRAF) binding domain that triggers the activation of nuclear factor-κ-light-chain enhancer of activated B cells (NF-κB) signaling.
upregulating anti-apoptotic proteins (e.g., Mcl-1, BCL-2, BCL-XL), and production of cell adhesion molecules (e.g., ICAM-1), angiogenesis factors (e.g., VEGF, IL-8), and immunosuppressive molecules (e.g., IL-10, PD-L1, TGF-β) [37, 40, 54]. In vitro studies have shown that BCMA overexpression can even trigger the activation of NF-κB and MAPK pathways in MM cells itself without stimulation of APRIL or BAFF [55]. In addition, there are many cross-talks between APRIL/BCMA signaling and other pathways. For example, APRIL interacts with CD138/syndecan-1 and heparan sulfate proteoglycans (HSPG) to promote proliferation and survival of MM cells [56]. Concomitant blockade of FGF-R3 and JAK2 leads to BCMA downregulation [57]. In vitro study also shows that BCMA co-immunoprecipitates with interferon regulatory factor-4 (IRF-4), a master transcription factor mediating survival of MM cells, further emphasizing its role in the oncogenesis of MM [58].

**Soluble BCMA (sBCMA)**

BCMA has a soluble form, sBCMA, derived from direct shedding of the membrane BCMA through γ-secretase activity. sBCMA retains the extracellular domain and a part of the transmembrane region [59]. sBCMA represents a potential biomarker for B cell involvement in human autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis [59, 60]. In MM patients, the serum level of sBCMA is found to be significantly elevated compared to healthy individuals [61]. A higher serum level of sBCMA independently correlates to a heavier disease burden, a worse clinical and radiological response, and a poorer prognosis [62]. A remarkable decrease in sBCMA level was observed in patients with good responses to BCMA-targeted immunotherapy, suggesting sBCMA as a new biomarker for monitoring response to MM therapy [63]. Interestingly, unlike sBCMA, many studies have shown that the level of cell-surface BCMA does not seem to affect the response to BCMA-targeted immunotherapy [64]. It is quite possible that the varied levels of surface BCMA in MM patients are simply the result of the shedding variations of the membrane BCMA. High level of sBCMA may interfere with BCMA-targeted immunotherapy by reducing the total amount of cell-surface
BCMA and sequestering circulating ligands or anti-BCMA antibodies, thereby inhibiting efficient binding to MM cells [65, 66]. It has been recently reported that a γ-secretase inhibitor (GSI, LY3039478/JSMD194) decreased sBCMA concentration, while increased cell-surface BCMA expression concurrently in MM cell lines, patient tumor cells, in murine models. This inhibitor significantly improved in vitro tumor recognition and in vivo anti-tumor efficacy of BCMA-specific chimeric antigen receptor (CAR)-T cells. Preclinical study has also discovered that short-term GSI administration to MM patients markedly increased the percentage of BCMA⁺ tumor cells [67]. Currently, a phase 1 clinical trial (NCT03502577) is ongoing to evaluate the safety and efficacy of combining CAR-T therapy with GSI, as well as cyclophosphamide (CTX), and fludarabine (FAMP) to treat patients with relapsed or persistent MM.

**BCMA-targeted immunotherapy**

Early studies on anti-BCMA antibodies showed robust cytotoxic activity against MM cells in vitro [68]. Currently, multiple innovative BCMA-targeted treatment modalities, including antibody-drug conjugate (ADC), CAR-T cells, and bispecific T cell engager (BiTE), are under active clinical development [13, 14, 69–77] (Fig. 3).

**BCMA antibody-drug conjugate (ADC)**

ADC composes of three essential components: a mAb that recognizes a tumor-specific antigen, a cytotoxic molecule often referred to as payload, and a chemical linker that connects the mAb and payload [78–81]. Upon binding to the corresponding antigen on the surface of tumor cells, ADC is internalized first and the linker is hydrolyzed inside of the lysosomes or endosomes, releasing the payloads that lead to cell death by damaging DNA or impeding microtubule assembly. ADC becomes attractive because it enhances targeted killing of tumors while sparing normal tissues, thereby minimizing toxicity. With the improvement of engineering technology, the newest generation of ADCs can be generated through site-specific conjugation and has homogenous drug-antibody ratio as well as better stability in circulation [80–82]. Multiple ADCs have been approved for clinical therapy of lymphoma and leukemia [79–81, 83, 84]. Multiple BCMA ADCs are under clinical development (Table 1).

**Belantamab mafodotin (GSK2857916; Blenrep; GlaxoSmithKline, GSK)**

Belantamab mafodotin (GSK2857916) is a humanized anti-BCMA IgG1 mAb conjugated to monomethyl auristatin F (MMAF, mafodotin) via a non-cleavable maleimidocaproyl (MC) linker. Mafodotin is released after complete proteolytic degradation of the whole mAb backbone as well as the linker by lysosomes. It then binds to tubulin and impedes microtubule assembly, leading to G2/M cell cycle arrest and subsequent cell apoptosis [80, 86]. Preclinical study discovered that GSK2857916 markedly inhibited BCMA⁺ MM cell growth in a dose- and time-dependent manner, with low bystander toxicity on surrounding BCMA⁻ cells. It also rapidly eliminated MM cells in subcutaneous and systemic MM mouse models, leading to tumor-free duration up to 3.5 months. Another study of GSK2857916...
demonstrated strong ADCC activity which was further enhanced by lenalidomide [33].

A multicenter, open-label, first-in-human phase 1 trial (DREAMM-1, NCT02064387) recruited 73 adult patients with R/R MM who failed autologous or allogenic stem cell transplantation (ASCT), alkylators, PI, and IMiDs. In the dose-escalation phase, 38 patients received GSK2857916 (0.03–4.60 mg/kg) through 1-h intravenous infusions once every 3 weeks. No dose-limiting toxicities (DLT) or maximum tolerated dose (MTD) were identified. 3.40 mg/kg every 3 weeks was selected as the recommended dose for the dose-expansion phase of study which enrolled 35 patients [74]. According to a recent update, 21 patients showed responses with an overall response rate (ORR) of 60%. Two (6%) patients achieved stringent complete response (sCR), 3 (9%) patients achieved complete response (CR), and 14 (40%) patients experienced very good partial response (VGPR). The median progression-free survival (mPFS) and median duration of response (mDOR) were 12 and 14.3 months, respectively. There were mostly grade 1–2 adverse events (AEs), with thrombocytopenia (35%) and anemia (17%) being the most common treatment-related serious AEs (grade ≥3 AEs). Grade 1–2 corneal events such as blurry vision (52%), dry eyes (37%), and photophobia (29%) were also frequently encountered. No cases of treatment-related death have been reported so far [85]. The response rate again did not appear to be associated with the expression level of cell-surface BCMA. However, non-responders were found to have a higher

| Name | Structure | Clinical trial information | Inclusion/exclusion criteria | Pt characteristics | Dosage | Major response | Most common AE |
|------|----------|---------------------------|------------------------------|---------------------|--------|---------------|----------------|
| Belantamab mafodotin (GSK2857916) | Linker: non-cleavable MC Payload: MMAF | Phase 1 NCT02064387, DREAMM-1 [74, 85] | R/R MM received or were refractory to ASCT, alkylators, PI, and IMID | 35 pts in dose expansion phase; median age 60; high-risk cytogenetics 13 (37%); 14 (40%) pts received > 5 prior lines; mDOR: 12.5 mo | 3.4 mg/kg every 3 wks | ORR 60%; sCR 2 (6%), CR 3 (9%), VGPR 14 (40%); mPFS 12 mo; mDOR 14.3 mo | G3+ thrombocytopenia (35%) anemia (17%); G1,2 corneal events: blurry vision (52%), dry eyes (37%), |
| MEDI2228 | Linker: protease-cleavable Payload: PBD | Phase 1 NCT03489525, R/R MM received or were refractory to ≥ 3 anti-MM therapies, including ASCT, alkylators, PI, IMID, and CD38 mAb | – | – | – | – | – |
| HDP-101 | Linker: non-cleavable MC Payload: Amanitin | Preclinical | – | – | – | – | – |

AE adverse event, CR complete response, G grade, mDOF median duration of follow-up, MC maleimidocaproyl, MMAF monomethyl auristatin F, mo month, mDOR median duration of response, mPFS median progression-free survival, ORR overall response rate, PBD pyrrolobenzodiazepine, PD progressive disease, pt patient, sCR stringent complete response, VGPR very good partial response, wk week
baseline level of circulating sBCMA than the responders. A higher dose of GSK2857916 (≥ 1.92 mg/kg) was required to bind a large fraction of sBCMA [64].

A multicenter randomized phase 2 trial (DREAMM-2, NCT03525676) is further evaluating the safety and efficacy of belantamab mafodotin (BLMF) in R/R MM [70]. There were 196 evaluable adults with R/R MM who had disease progression after receiving ≥ 3 previous lines of anti-MM treatments, were refractory to PIIs or IMiDs, were refractory or intolerant to an anti-CD38 mAb, and had undergone ASCT or were ineligible for transplant. These patients were randomized to receive either 2.5 mg/kg cohort and 34% in the 3.4 mg/kg cohort. The most common severe adverse events were keratopathy, thrombocytopenia, and anemia. There were two deaths potentially related to the BLMF therapy (one case of sepsis and one case of hemophagocytic lymphohistiocytosis). Belantamab mafodotin (Blenrep, GSK) was recently approved by FDA for the therapy of highly refractory MM.

Several other phase 1, 2, or 3 trials are currently recruiting to investigate different combination regimens incorporating BLMF in patients with R/R MM, such as BLMF + pomalidomide + dexamethasone (DREAMM-3, NCT03715478) [87]; BLMF + pembrolizumab (anti-PD-L1) (DREAMM-4, NCT03848845); BLMF + dexamethasone + lenalidomide (arm A); or bortezomib (arm B) (DREAMM-6, NCT03544281) [80]. Another phase 1/2 trial (DREAMM-5, NCT04126200) was planned to explore the synergistic effects combining BLMF with other novel anti-cancer agents, such as the T cell activating checkpoint mAbs: GSK3359609 (an IgG4 inducible T cell co-stimulatory agonist antibody that is Fc optimized to selectively enhance T cell function to enable anti-tumor responses), GSK3174998 (a humanized wild-type IgG1 anti-OX40 agonistic mAb), and PF-03084014 (a γ-secretase inhibitor) [88]. Recently, a phase 3 trial started recruiting to compare the efficacy and safety of BLMF to daratumumab in the combination regimen with bortezomib and dexamethasone (DREAMM-7, NCT04246047) [70].

HDP-101

HDP-101 is a fully humanized mAb conjugated to aminitin via a non-cleavable MC linker. Amanitin is a DNA-toxic agent that impedes the transcription process by binding to eukaryotic RNA polymerase I at very low concentrations irrespective of the proliferation status of the target cells. It appears to be superior to microtubule inhibitors which mainly target proliferating cells [89]. Preclinical study discovered that when administrated at pico- to nanomolar concentrations, HDP-101 exhibited profound cytotoxicity to BCMA+ myeloma cell lines and non-proliferating primary MM cells isolated from patients with R/R MM irrespective of BCMA expression level [90, 91]. Dose-dependent tumor regression after HDP-101 treatment was also observed in mouse xenograft models with both subcutaneous and systemic MM. In vivo study also showed a favorable safety profile in non-human primates that mainly consisted of transient, mild to moderate increase in liver enzymes and lactate dehydrogenase. HDP-101 is yet to be advanced to in-human clinical trials [91].

MEDI2228

MEDI2228 is a fully human antibody site-specifically conjugated to pyrrolobenzodiazepine (PBD) dimer via a protease-cleavable linker. PBD dimer is also a DNA-toxic agent that binds to the minor-groove and cross-links DNA, leading to DNA damage and apoptotic cell death. Preclinical study demonstrated that MEDI2228 exhibited profound anti-tumor activity against different cell lines of MM and plasma cell leukemia (PCL), including cells resistant to lenalidomide, regardless of the level of cell-surface BCMA expression. A single injection of MEDI2228 at doses as low as 0.1 mg/kg induced tumor regression in various MM xenograft models. In vitro study also reported that the anti-tumor activity persisted even in the presence of high concentration of sBCMA because the antibody component of MEDI2228 possessed strong binding to membrane-bound BCMA but weak affinity to monomeric human BCMA [92]. New reports suggested that MEDI2228 might synergize with anti-CD38 mAbs or bortezomib to enhance anti-myeloma effect [93, 94]. A dose-escalation phase 1 clinical trial (NCT03489525) is currently evaluating the pharmacokinetics, safety, and tolerability of MEDI2228 in patients with R/R MM.

BCMA-targeted CAR-T cells

CAR-T cell therapy is a novel immunotherapy that combines the advantage of target specificity of mAbs and cytotoxicity of T cells [12, 14, 95]. Molecular engineering of new generation of CARs makes CAR-T therapy more promising [69, 96–102]. Two CD19-engineered CAR-T cell products, axicabtagen ciloleucel (yescarta, Kite) and tisagenlecleucel (kymriah, Novartis), have been approved by the U.S. Food and Drug Administration (FDA) for therapy of advanced B cell malignancies [95]. Currently, more than 10 BCMA-targeted CAR-T products have entered early-phase clinical studies (Tables 2 and 3) [13, 14, 96]. Most of them showed high response rates, even in patients with high-risk features such as high-risk cytogenetics and extra-medullary disease at time of CAR-T cell infusion [115]. Cytokine release syndrome (CRS)
and neurotoxicity (NTX) are the common CAR-T-related adverse events [116–122]. However, a significant portion of responders eventually relapsed. Larger studies with longer follow-up investigating the association between response and survival are still warranted [123].

**CAR-BCMA**

One of the first anti-BCMA CAR-T cell products was developed through a γ-retroviral vector that encoded a second-generation CAR containing a murine BCMA scFv and a CD28 co-stimulatory domain. These engineered T cells gained the ability of BCMA recognition, cytokine production, proliferation, cytotoxicity, and in vivo tumor eradication [34].

The first-in-human dose-escalation phase 1 trial (NCT02215967) investigating the safety and efficacy of this CAR-BCMA cell therapy initially reported 12 patients with R/R MM [63]. Three doses of 300 mg/m² CTX plus 30 mg/m² FAMP were administered daily on days 5, 4, and 3 before a single dose of CAR-BCMA T cell infusion on day 0. Four dose levels of CAR-T cells were selected: 0.3, 1.0, 3.0, and 9.0 × 10⁶ cells/kg. Overall, 1 patient achieved sCR, 3 patients entered partial remission (PR), and 8 patients maintained stable disease (SD) for up to 16 weeks. Among the 6 patients receiving the 2 lowest dose levels, limited anti-myeloma activity and mild toxicity occurred. Better clinical responses were observed in the 2 higher dose groups. One patient treated on the third dose level obtained VGPR. Among the 2 patients treated on the fourth dose level, one patient achieved sCR for 17 weeks, with BM plasma cells eradicated after treatment, and the other patient underwent VGPR with BM plasma cells undetectable by flow cytometry 28 weeks after treatment and serum monoclonal protein decreased by more than 95%. However, patients receiving higher doses presented with more prolonged cytopenia and a higher risk of severe CRS. In addition, a remarkable decrease of sBCMA level after CAR-BCMA T cell infusion was observed in patients with the most impressive anti-myeloma responses [63].

9.0 × 10⁶ cells/kg was selected for the dose expansion study in 16 patients who failed an average of 9.5 prior lines of MM. The ORR was 81%, with 63% patients achieving VGPR or CR. Median event-free survival (mEFS) was 31 weeks. In addition to eradication of BM myeloma cells, soft tissue plasmacytomas were also eliminated. Negative minimal residual disease (MRD) (≤ 10⁻⁴ nucleated cells) was achieved in the BM in 11 responders. Higher peak blood CAR+ cell levels were associated with better anti-tumor responses. BCMA antigen loss was also observed which might contribute to therapy resistance and disease relapse. CRS toxicities were substantial especially in patients with high MM burdens but were generally reversible. NTX was limited to confusion or delirium in the setting of severe CRS. Cytopenia was frequently encountered early after CAR-BCMA T cell infusion in most patients and was attributable to the CTX and FAMP conditioning chemotherapy. Some cases with prolonged cytopenia were also reversible with treatment [124].

### Table 2

| Name               | Manufacturer                        | BCMA scFv         | Co-stimulatory | Transduction | Extra safety domain |
|--------------------|-------------------------------------|-------------------|----------------|--------------|---------------------|
| CAR-BCMA           | NCI                                 | Murine            | CD28           | γ-Retrovirus | No                  |
| Idecabtagene vicleucel; Bb2121 | Bluebird Bio and Celgene          | Murine            | 4-1BB          | Lentivirus   | No                  |
| Bb21217            | Bluebird Bio and Celgene            | Murine            | 4-1BB          | Lentivirus   | Yes, PI3K inhibitor |
| LCAR-B38M          | Nanjing Legend/Genscript Biotech    | Bi-epitope        | 4-1BB          | Lentivirus   | No                  |
| JNJ-4528           | Janssen Research & Development      | Bi-epitope        | 4-1BB          | Lentivirus   | No                  |
| CT053              | CARsgen Therapeutics                | Fully human       | 4-1BB          | Lentivirus   | No                  |
| P-BCMA-101         | Poseida Therapeutics                | Fully human anti-BCMA | 4-1BB      | PiggyBac™ (PB) DNA Modification System | No |
| CART-BCMA          | UPenn/Novartis                      | Fully human       | 4-1BB          | Lentivirus   | No                  |
| CT103A             | Nanjing Iaso Biotherapeutics        | Fully human       | 4-1BB          | Lentivirus   | No                  |
| JCAR-H125          | Juno Therapeutics                   | Fully human       | 4-1BB          | Lentivirus   | No                  |
| MCAH171            | MSKCC                               | Fully human       | 4-1BB          | γ-Retrovirus | Yes, tEGFR          |
| BCMA CAR-T         | HRAIN Biotech                       | Fully human       | 4-1BB          | γ-Retrovirus | Yes, tEGFR          |
| KITE-585           | Kite, Gilead company                | Fully human       | CD28           | Lentivirus   | No                  |

Yu et al. Journal of Hematology & Oncology (2020) 13:125 Page 7 of 24
| Name          | Clinical trial information | Inclusion/exclusion criteria | Pt characteristics | Pre-condition | Dosage | Pharmacokinetics | Major response | Most common AE |
|--------------|----------------------------|------------------------------|--------------------|---------------|--------|------------------|---------------|----------------|
| Idecabtagene  | Phase 1b                   | R/R MM who received or were  | 33 pts (21 in dose- | CTX + FAMP   | 150 or | Expansion at all dose | ORR 85%; CR 15 | G3+ neutropenia (85%), leucopenia (58%), thrombocytopenia (45%), anemia (45%); CRS 23 (70%) G1–2, 2 (6%) G3+; NTX 14 (42%) G1–2, 13 (39%) G3+ |
| Bb2121       | NCT02058929 [71]           | refractory to ≥ 3 prior lines, including PI, IMiD | escalation; 12 in dose expansion); median age 60; median prior lines 7; high-risk cytogenetics 13 (45%); mDOF 11.3 mo | FAMP          | 450 × 10^6 cells/pt | level, persist up to 1 yr | 11.8 mo | |
|              |                            |                              |                    |               |        |                  |               |                |
| Phase 2      | NCT0336174 [103]           | R/R MM who received or were  | 128 pts (54 received | CTX + FAMP   | 150–450 | Peak on d11, detectable in 29/49 (59%) pts at 6 mo and 11.8 mo | ORR 73.4%; CR 31.3% mPFS | All grades cytopenia (94%); CRS 107 (83.6%) G1–2, 7 (5.5%) G3+; NTX 19 (14.9%) G1–2, 4 (3.1%) G3+ |
| Bb21217      | NCT03274219 [104]          | refractory to ≥ 3 prior lines, including PI, IMiD, and CD38 mAb | 450 × 10^6 cells; median age 61; median prior lines 6; triple-refractory 108 (84%); penta-refractory 33 (26%); mDOF 11.3 mo | FAMP          | 106 cells/pt |                  |               |                |
|              |                            |                              |                    |               |        |                  |               |                |
| LCAR-B38M    | Phase 1/2                  | R/R MM who received or were  | 57 pts; median age | CTX           | Avg 0.5 | Detectable till 4 mo, at most 10 mo | ORR 88%; CR 42 (74%); VGPR 2 (4%); PR 6 (11%); mPFS 20 mo; 18-mo PFS 50%; 18-mo OS 68% | G3+ leukopenia (30%), thrombocytopenia (23%), increased AST (21%); CRS 46 (82%) G1–2, 4 (7%) G3+; NTX 1 (2%) G1–2 |
|              | NCT03090659 [105]          | refractory to ≥ 3 prior lines | 54 median prior lines 3; ASCT 10 (18%); mDOF 19 mo | FAMP          | 106 cells/kg 3 infusion or 3 split infusions |                  |               |                |
| JNJ-4528     | Phase 1b/2                 | R/R MM who received or were  | 17 pts; median age 55 median prior lines 5; ASCT 8 (47%); mDOF 22 mo | CTX ± FAMP | Avg 0.7 × 10^6 cells/kg 1 infusion or 3 split infusions | Peak on d6–30, detectable till up to 9 mo | ORR 88%; CR 14 (82%); VGPR 1 (4%); mPFS 12 mo; 1-yr PFS 52.9% 1-yr OS 82.3% | G3+ myelotoxicity 5 (29%); CRS 10 (59%) G1–2, 7 (41%) G3+; NTX 0 |
|              | NCT03548207 [107]          | refractory to ≥ 3 prior lines, including PI, IMiD, CD38 mAb | 450 × 10^6 cells/kg | FAMP          | Avg 0.75 × 10^6 cells/kg |                  |               |                |
| CT053        | Phase 1                    | R/R MM who received or were  | 24 pts; median age 60 median prior lines 45 high-risk cytogenetics 9 (38%); | CTX + FAMP   | 1.5 × 10^8 cells/pt | Peak on d7–21, detectable till 172d, at most 341d | ORR 87.5%; sCR 14 (71%); CR 5 (21%); VGPR 1 (4%); mPFS 281 d; PD 9 | G3+ leukopenia (87.5%), neutropenia (66.7%), lymphopenia (79.2%), thrombocytopenia (25%); CRS 15 (62.5%) G1–2; |
| Name            | Clinical trial information | Inclusion/exclusion criteria                                                                 | Pt characteristics | Pre-condition | Dosage | Pharmacokinetics | Major response                                                                                       | Most common AE                                      |
|-----------------|---------------------------|----------------------------------------------------------------------------------------------|--------------------|--------------|--------|-----------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| P-BCMA-101      | Phase 2                  | R/R MM who received or were refractory to ≥ 3 prior lines, including Pl, IMiD, CD38 mAb       | 12 pts; prior lines 3–9 mDOF 3 wk | CTX + FAMP   | 0.75–15 × 10^6 cells/kg | Peak at 2–3 wks, remain detectable at 3 mo | 6 pts in higher dose cohort: ORR 83%; sCR 1 VGPR 3 PR | G3+ cytopения и febrile neutropenia; CRS 1 (8%) G1–2; NTX 0 |
| CART-BCMA       | Phase 1b                 | R/R MM who received or were refractory to ≥ 3 prior lines, including Pl, IMID,                | 25 pts; median age 58; median prior lines 7; high-risk cytogenetics 24 (94%); ASCT 23 (92%); panta-refractory 11 (44%); mDOF 24 mo | None or CTX | 1–5 × 10^7 or 1–5 × 10^6 cells/pt | Peak on d10–14, remain detectable at 6 mo | ORR 48%; CR 2 (8%), VGPR 5 (20%), PR 5 (20%); best mPFS 125 d; PD 22 | G3+ leukopenia (44%), neutropenia (44%), lymphopenia (36%); CRS 14 (56%) G1–2, 8 (32%) G3+; NTX 5 (20%) G1–2, 3 (12%) G3+ |
| CT103A          | Phase 1                  | R/R MM who received or were refractory to ≥ 3 prior lines, including Pl, IMID,                | 16 pts; median prior lines 4; mDOF 195 d | CTX + FAMP   | 1–8 × 10^6 cells/kg | Peak at 2 wks, remain detectable at 6 mo | ORR 100%; CR/sCR 12 (75%), VGPR 2 (12.5%) | CRS 15 (94%) G1–2, 1 (6%) G3+; NTX 0; DLT 1 TRD 1 |
| JCARH125        | Phase 1/2                | R/R MM who received or were refractory to ≥ 3 prior lines, including Pl, IMID, CD38 mAb, ASCT 24 (94%); ASCT 23 (92%); panta-refractory 11 (44%); mDOF 5 wk | 8 pts; median age 53; median prior lines 10; ASCT 8 (88%); panta-refractory 4 (50%); mDOF 5 wk | CTX + FAMP   | 50 or 150 × 10^6 cells/pt | – | ORR 100%; sCR/CR 3 (37.5%), VGPR 2 (25%), PR 2 (25%); PD 0 | CRS 6 (75%) G1–2; NTX 2 (25%) G1–2, 1 (12.5%) G3+ |
| MCARH171        | Phase 1                  | R/R MM who received or were refractory to ≥ 2 prior lines, including Pl, IMID,                | 11 pts; median prior lines 6 | CTX + FAMP   | 72, 137, 475, 818 × 10^6 cells/pt 1 to 2 doses | Peak expansion found in dose cohort 475, 818 × 10^6 | ORR 64%; mDOR 106 d | CRS 4 (40%) G1–2, 2 (20%) G3+; NTX 1 (9%) G1–2 |
| BCMA CAR-T       | Phase 1                  | R/R MM who received or were refractory to ≥ 2 prior lines, including Pl, IMID; ≥5% cell-surface BCMA | 44 pts; median prior lines ≥ 2 mDOF ≥ 1 mo | CTX + FAMP   | 9 × 10^6 cells/kg | Expansion and persistence throughout the DOF | ORR 79.6%; sCR 2 (4.5%); CR 16 (36%), VGPR 8 (18%), PR 8 (18%); mPFS 15 mo; 2-yr PFS 49.16%; 2-yr OS 53.95% | CRS 10 (22.7%) G1–2, 3 (68%) G3+ |

*Avg average, ASCT autologous or allogenic stem cell transplantation, CR complete response, CRS cytokine release syndrome, CTX cyclophosphamide, d day, DLT dose-limiting toxicity, FAMP fludarabine, G grade, IMID immunomodulatory imide drugs, mDOF median duration of follow-up, mDOR median duration of response, mo month, mPFS median progression-free survival, NTX neurotoxicity, ORR overall response rate, OS overall survival, PD progressive disease, Pl proteasome inhibitor, PR partial response, pt patient, sCR stringent complete response, TRD treatment-related death, VGPR very good partial response, wk week, yr year*
Idecabtagene vicleucel (ide-cel; bb2121) and bb2121

Bb2121 product consists of autologous T cells transduced with a lentiviral vector encoding a second-generation CAR which incorporates a murine anti-BCMA scFv, a 4-1BB co-stimulatory motif and a CD3ζ T cell activation domain. Preclinical data showed that bb2121 demonstrated robust in vitro killing of MM cells independent of the BCMA expression levels or the presence of sBCMA. A single administration of bb2121 resulted in rapid and sustained tumor elimination and 100% survival in a mouse model of human MM [125].

Based on these findings, a multicenter phase 1 trial (CRB-401, NCT02658929) was initiated in patients with R/R MM who had failed at least 3 (median 7) previous lines of therapy, including a PI, an IMiD, or are double-refractory. Doses of 50 × 10^6, 150 × 10^6, 450 × 10^6, or 800 × 10^6 total CAR+ T cells were tested in the dose-escalation phase, of which 150 × 10^6 to 450 × 10^6 total CAR+ T cells were selected for the dose-expansion phase. Results of the first 33 consecutive patients with an average of 11.3 months follow-up were reported recently. The ORR was 85% (45% CR). The mPFS was 11.8 months. Sixteen responders who could be evaluated for MRD all obtained MRD-negative status and were found to have better outcome with an mPFS of 17.7 months. Better clinical responses were found in high-dose cohorts (≥150 × 10^6 total CAR+ cells) and in patients with high-risk cytogenetic profiles. Response rate appeared to be unrelated to the amount of tumorsurface BCMA. However, a greater depth of changes of sBCMA level after infusion was found to correlate with earlier and more durable responses. CAR-T cell expansion was observed at all dose levels and was associated with responses. CAR-T cells persisted up to 1 year after the infusion. Hematologic toxicity was the most common SAE. Non-hematologic toxic effects were primarily of grade 2 or lower. CRS was observed in 25 patients (76%), which was of grade 1 or 2 in 23 patients (70%) and grade 3 in 2 patients (6%). NTX occurred in 14 patients (42%) and were of grade 1 or 2 in 13 patients (39%) and grade 4 in 1 patient (3%) but was reversible. No cases of treatment-related death have been reported so far [71, 126, 127].

In view of the favorable safety profile and efficacy, a phase 2 clinical trial of bb2121 in patients with R/R MM (KarMMA, NCT03361748) has been started. Eligible participants are R/R MM patients who have received at least 3 prior lines of therapy including IMiD, PI, and CD38 mAb and were refractory to their last regimen. One dose of bb2121 (dose range: 150-450 × 10^6 total CAR+ cells) is given after lymphodepletion [71, 128]. According to a recent update, as of October 16, 2019, 128 patients received the infusion (4 patients received 150 × 10^6 total CAR+ cells, 70 patients received 300 × 10^6 total CAR+ cells, and 54 patients received 450 × 10^6 total CAR+ cells). Median number of prior therapies was 6. Median duration of follow-up (mDOF) was 11.3 months. Ninety-four patients (ORR 73.4%) showed responses, including 40 (31.3%) CR, and mPFS was 8.6 months. Those who received the dose of 450 × 10^6 total CAR+ cells achieved 81.5% ORR, 35.2% CR, and mPFS was 11.3 months, indicating that higher doses might be associated to better response and outcomes. CAR-T cell expansion peaks at day 11, with durable persistence, as circulating CAR-T cells were detectable in 29/49 (59%) patients at 6 months and 4/11 (36%) patients at 12 months post-infusion. Higher expansion was also observed when high dose was given. Most common AE was cytopenia (97%). One hundred seven (83.6%) patients encountered CRS including 7 (5.5%) grade ≥3 events and 1 death. Twenty-three (18%) patients encountered NTX including 4 (3.1%) grade ≥3 events [103].

Another phase 2 study (KarMMA-2, NCT03601078) looking at patients with high-risk MM including those with early relapse or inadequate response post-ASCT has also been initiated. In addition, a multicenter, randomized, open-label, phase 3 trial is recruiting to compare the efficacy and safety of bb2121 versus standard triplet regimens (daratumumab + pomalidomide + dexamethasone, or daratumumab + bortezomib + dexamethasone, or ixazomib + lenalidomide + dexamethasone) in patients with R/R MM (KarMMA-3, NCT03651128).

Bb21217 is constructed on the basis of the bb2121 CAR structure with an extra domain of bb007 which encodes a Phosphoinositide 3-kinases (PI3K) inhibitor to enrich the CAR-T cells displaying a memory-like phenotype. It has been suggested that selected CAR-T cells with this phenotype might be more potent and more persistent than unselected CAR-T cells. A first-in-human, multicenter phase 1 dose-escalation trial (CRB-402, NCT03274219) is ongoing to assess the safety, pharmacokinetics, efficacy, and duration of bb21217 CAR-T cells in patients with R/R MM who received ≥3 prior regimens, including a PI and an IMiD, or are double-refractory to both classes. Only patients with ≥50% BCMA expression detected by immunohistochemistry (IHC) on malignant PCs were enrolled. Four dose levels were planned: 150 × 10^6, 450 × 10^6, or 800 × 10^6, and 1200 × 10^6 total CAR+ T cells [104]. According to the latest update, 22 patients (median age 63) have received bb21217 infusion so far (12 at 150 × 10^6, 6 at 300 × 10^6, and 4 at 450 × 10^6). The median number of prior regimens received was 7. Eighteen patients (82%) had undergone ASCT, and 7 had high-risk cytogenetics. Eighteen patients were evaluable for initial (1 month) clinical responses. Among the 15 patients (83%) who responded, 6 have progressed. 10/10 evaluable
responders obtained undetectable MRD status. 6/8 patients evaluable at 6 months and 2/2 patients evaluable at 12 months presented with detectable CAR+ T cells in peripheral blood. Fifteen patients (68%) developed manageable CRS (5 grade 1, 2 grade 2, 1 grade 3). Five patients (23%) developed NTX (1 grade 1, 2 grade 2, 1 grade 3, 1 grade 4 featured by encephalopathy); all were successfully resolved [128]. However, no evidence is available to yet show bb21217 is more advanced than bb2121 in terms of persistence of clinical response at present.

**LCAR-B38M (JNJ-4528)**

LCAR-B38M, also known as JNJ-68284528 (JNJ-4528), is a bispecific second-generation CAR-T cell product directed against 2 distinct BCMA epitopes. This bi-epitope targeting significantly improves the binding avidity and distinguishes LCAR-B38M from all the other BCMA-targeted CAR-T products. An ongoing, single-arm, open-label, multicenter phase 1 trial (LEGEND-2, NCT03090659) of LCAR-B38M was initiated in patients with R/R MM in China. After achieving lymphodepletion with 3 doses of CTX 300 mg/m², weight-adjusted LCAR-B38M CAR-T cells (median, 0.5 × 10⁶ cells/kg [range, 0.07 to 2.1 × 10⁶]) were administered in 3 infusions (20, 30, and 50% of total dose) over 7 days. As of December 31, 2018, 57 eligible patients (median age 54) who failed at least 1 (median 3) prior regimens (must at least have contained bortezomib) have received the therapy with a mDOF of 19 months [76]. The ORR was 88% with 74% CR, 2 patients (4%) obtained VGPR, and 6 patients (11%) obtained PR. 39/42 (93%) patients with CR achieved undetectable MRD status. The median time to initial response was 1.2 month. The 18-month OS was 68% with an mDOR of 22 months for all responders and 27 months for MRD-negative patients. The 18-month PFS was 50% with an mPFS of 20 months for all patients and 28 months for MRD-negative patients. The clinical response was found to be related to neither the LCAR-B38M CAR-T cell dose nor the level of BCMA expression. LCAR-B38M became undetectable in peripheral blood in majority of patients at 4 months; however, it persisted up to 10 months in 5 patients. The most common SAEs were leukopenia (30%), thrombocytopenia (23%), and increased aspartate aminotransferase (AST) (21%). CRS was mostly grades 1 and 2, with only 4 patients (7%) experiencing grade 3 toxicity, which were all reversible. The median time to CRS onset was 9 days post-infusion. No statistically significant correlation was found between CRS and the dose of therapy. NTX was reported in 1 patient who presented with grade 1 aphasia, agitation, and seizure-like activity [75, 76, 105, 129].

In a separate report (NCT03090659), LCAR-B38M was tested in 17 patients (median age 55) with R/R MM who failed at least 3 prior lines of therapy enrolled from three clinical centers in China different from the aforementioned study. Two different treatment protocols were adopted by different sites. In 2 clinical centers, 8 patients received a lymphodepletion regimen of CTX 250 mg/m² + FAMP 25 mg/m², intravenously daily for 3 days, and then CAR-T cells split into 3 infusions (day 0, 3, and 6) 5 days after lymphodepletion, while in 1 clinical center, 9 patients received CTX 300 mg/m² intravenously daily for 3 days, and CAR-T cells were administered via only one infusion. The mean dose was 0.7 × 10⁶ (range, 0.2–1.5 × 10⁶) CAR-T cells/kg [106, 130]. As of July 20, 2019, the ORR was 88%. Fourteen patients (82%) achieved CR, and 1 patient (6%) underwent VGPR. All 14 CR patients obtained undetectable MRD status. The median time to first response was 1 month. At a mDOF of 22 months, 6 (38%) patients remain progression-free, with a mPFS of 12 months, 1-year PFS of 52.9%, and 1-year OS of 82.3%. Positive anti-LCAR-B38M antibody represented a risk factor for relapse or progressive disease (PD), while patients who underwent prior ASCT showed a more durable response. LCAR-B38M CAR-T cells peaked around day 6 to 30 and persisted in most patients up to 9 months. Regarding toxicities, grade ≥3 cytopenias occurred in 10 patients. All patients experienced grade 1–2 liver toxicity. CRS was observed in all patients. Ten patients experienced grade 1 or 2 CRS, and 7 patients had grade ≥3 CRS after infusion. One patient died of the concurrence of severe CRS and tumor lysis syndrome (TLS) despite the administration of hemodialysis, tocilizumab, etanercept, and other supportive care. The study pointed out several potential indicators for severe CRS such as the abundance of BCMA, cytogenetic marker del(17p), and the elevation of interleukin-6 (IL-6) [76, 130].

A U.S. phase 1b/2 trial (CARTITUDE-1, NCT03548207) is ongoing to assess the safety and efficacy of JNJ-4528 (LCAR-B38M), in patients with R/R MM who received ≥3 prior regimens or were double-refractory to a PI and IMiD, and received anti-CD38 antibody. A single infusion of JNJ-4528 at the targeted dose of 0.75 × 10⁶ CAR+ cells/kg (range 0.5–1.0 × 10⁶) was administered 5–7 days after initiation of the standard conditioning regimen with CTX and FAMP. According to a recent update, 29 patients (median age 61) who failed a median number of 5 prior lines entered the phase 1b portion of the study with a mDOF of 9 months. An ORR of 100% has been found, with 22 (76%) CRs, 6 (21%) VGPRs, and 1 (3%) partial response (PR). Median time to ≥CR was 2 months. The response rate was independent of baseline BCMA expression. MRD negativity at 10⁻⁵ or 10⁻⁶ in the BM was achieved in all evaluable patients at 6 months. At the time of data cutoff, 26/29 patients are progression-free, with 6-month progression-
free survival rate of 93%, and longest response ongoing at 15-month follow-up. Cytopenia was the most common SAE. Twenty-seven patients (93%) experienced grade 1 to 2 CRS, with 1 grade 3 case and 1 grade 5 event which became the DLT. Median time to CRS onset was 7 days post-infusion. Most CRS events lasted around 4 days and were manageable with support, tocilizumab, or corticosteroid therapy. Four patients experienced NTX with 3 grade 1 to 2 and 1 grade 3. One death related to grade 5 CRS and 1 non-treatment-related death (acute myeloid leukemia) were reported [107, 131]. Majority of patients reached the peak expansion of JNJ-4528 CAR+ cellular and transgene levels around 10–14 days post-infusion with a concurrent decline of sBCMA levels. JNJ-4528 CAR-T cells remained detectable in 22/28 patients at 6-month follow-up. At peak expansion, there was a preferential expansion of CD8+ CAR-T cells displaying predominantly a central memory (Tcm) phenotype (CCR7+ CD45RO+), which contributed to the high anti-tumor activity of JNJ-4528 at a relatively low dose. Serum cytokine levels also increased with the expansion of CAR-T cells. And increases in IL-6 correlated to the onset of CRS which was around day 7, similar to previous studies [107, 132]. In consistent with LEGEND-2, CARTITUDE-1 further confirmed the favorable efficacy and manageable toxicity profile of LCAR-B38M/JNJ-4528 CAR-T cell therapy. 0.75 × 10^6 CAR+ cells/kg was the recommended phase 2 dose for future development.

Currently, phase 2 investigation of LCAR-B38M/JNJ-4528 CAR+ T cell in patients with R/R MM has been initiated both in China (CARTIFAN-1, NCT03758417) and in the USA (CARTITUDE-2, NCT04133636). A phase 3 clinical trial is being planned to compare the efficacy and safety of JNJ-4528 to those of the standard therapy (PvD: Pomalidomide + Bortezomib + Dexamethasone; or DPd: Daratumumab + Pomalidomide + Dexamethasone) in patients with R/R MM (CARTITUDE-4, NCT04181827).

CT053
CT053 is another CAR-T cell product in development in China. It is a second-generation CAR incorporating a fully human anti-BCMA scFv which is much less immunogenic, a 4-1BB co-stimulatory motif and a CD3ζ activation domain. CT053 is being investigated in multiple phase 1 trials in China (NCT03716856, NCT03302403, NCT03380039, and NCT03975907) that recruited patients with R/R MM who failed at least 2 (average 4.5) prior regimens. Participants received one cycle of CT053 CAR-BCMA after FAMP/CTX conditioning. As of June 30, 2019, 24 eligible patients (median age 60) have been enrolled. Most of them received a single dose of 1.5 × 10^8 total CAR-T cells except 3 subjects who received 0.5 × 10^8, 1 × 10^8, and 1.8 × 10^8 cells, respectively. The ORR was 87.5% (21/24) including 14 sCR, 5 CR, 1 VGPR, and 1 PR. 17 out of 20 evaluable patients achieved MRD-negative status. Efficacy was observed even at the lowest dose (0.5 × 10^6) in a patient who maintained VGPR for 378+ days and achieved CR on day 437 and then sCR on day 502. mDOF was 333 days. Thirteen patients maintained CR/sCR. Nine patients have progressed so far with a mPFS of 281 days, 3 of whom died at the data cutoff date. Median T cell persistence was 172 days, and the longest was 341 days. Hematologic toxicity remained the most common treatment-related SAE. Fifteen of 24 patients (62.5%) experienced CRS, and all were low grades and recovered within 2–8 days. NTX was reported in 3 patients (12.5%) (2 grade 1, 1 reversible grade 3). No DLT has been observed at the time of analysis [108, 133]. Another multicenter phase 1b trial (NCT03915184) has started recruiting to evaluate the safety and efficacy of CT053 in R/R MM in the USA.

P-BCMA-101
P-BCMA-101 is a novel second-generation CAR-T product that incorporates a fully human anti-BCMA Centyrin™, 4-1BB co-stimulatory motif, and a CD3ζ activation domain. Centyrin is a fully human protein that presents with high specificity, binding affinity, more stability, and less immunogenicity. What makes it different from most CAR-T products is that P-BCMA-101 is produced using the piggyBac™ (PB) DNA Modification System instead of a viral vector [134]. Since the product does not depend on viral transfection, it may be more cost-effective. In addition, P-BCMA-101 contains a purified population of CAR+ cells with a high percentage of favorable stem cell memory T phenotype (T_{SCM}). Preclinical data demonstrated prominent efficacy in reducing tumor burden and preventing recurrence in various xenograft models with a single dose of P-BCMA-101 [135]. A phase 1 dose-escalation trial (NCT03288493) has enrolled 12 patients with heavily pretreated MM (≥ 3 [3–9] prior lines, including a PI and an IMiD, or double-refractory). These patients received one dose of P-BCMA-101 ranging from 0.75 × 10^6 to 15 × 10^6 cells/kg after being conditioned by CTX and FAMP. Of the 6 patients who received higher dose of therapy, an ORR of 83%, with 1 sCR, 1 VGPR, and 3 PR, had been achieved within 2 weeks. The response rate did not correlate to the level of BCMA expression. P-BCMA-101 cell level peaked at 2–3 weeks and remained detectable at the data cutoff point as far as 3 months. Cytopenia and febrile neutropenia were still the most common SAEs. Of note, there was a minimal rate of CRS and NTX. Only 1 case of maximum grade 2 CRS was identified. Therefore, this novel CAR-T agent might generate an improved therapeutic index [109].
Based on the data of phase 1, a pivotal phase 2 study (PRIME; NCT03288493) has been designed. The trial plans to enroll 100 adult R/R MM patients who have failed at least 3 prior lines of therapy, including a PI, an IMiD, and CD38 targeted therapy. No pre-specified level of BCMA expression is required. Of note, patients getting prior CAR-T cells or BCMA-targeted agents are also eligible for the study. A single intravenous dose of P-BCMA-101 CAR-T cells (6–15 x 10^6 cells/kg) will be administered after a standard 3-day CTX/FAMP conditioning regimen. Different from other CAR-T products, given the safety profile demonstrated during phase 1, no hospital admission is required and patients may receive P-BCMA-101 in an outpatient setting [136].

CART-BCMA
Another lentiviral-transduced CAR-T cell product, CART-BCMA, contains a fully human BCMA-specific scFv with CD3ζ and 4-1BB signaling domains. Preclinical study demonstrated high specificity for BCMA and robust anti-myeloma activity [137]. CART-BCMA has been evaluated in a phase 1b study (NCT02546167) in R/R MM. Twenty-five patients (median age 58) refractory to a median number of 7 prior lines were enrolled and randomized into 3 different treatment cohorts: (1) 1 to 5 x 10^8 CART-BCMA cells alone, (2) CTX 1.5 g/m^2 + 1 to 5 x 10^7 CART-BCMA cells, and (3) CTX 1.5 g/m^2 + 1 to 5 x 10^8 CART-BCMA cells. Responses were seen in all cohorts with or without lymphodepletion with ORR of 44% (4/9) in cohort 1, 20% (1/5) in cohort 2, and 64% (7/11) in cohort 3, including a total of 2 CR, 5 VGPR, and 5 PR. By the time of data cutoff, 3 patients remained progression-free. The mPFS was 65 days in cohort 1, 57 days in cohort 2, and 125 days in cohort 3. The study also discovered that better responses and CART-BCMA expansion were associated with higher CD4/CD8 T cell ratio and percentage of CD45RO-CD27+CD8+ T cells in the initial leukapheresis product. BCMA expression level was found to be decreased on residual MM cells of responders and increased in most patients with PD. Circulating CAR-T cell expansion generally peaked on days 10–14, remained detectable at 6 months in 14 of 17 (82%) patients tested, and persisted till 2.5 years after infusion in one patient with sCR. Hematologic toxicities were the most common SAE: leukopenia (44%), neutropenia (44%), and lymphopenia (36%). Grade 3–4 CRS and NTX were reported in 8 (32%) and 3 (12%) participants, respectively, thus making this product seemingly more toxic than other products. One patient died of candidemia and progressive MM following treatment for severe CRS and encephalopathy [110].

CT103A
CT103A is a novel BCMA-targeting CAR-T cell product developed with a lentiviral vector encoding a second-generation CAR structure with a fully human scFv, 4-1BB co-stimulatory, and CD3ζ activation domain. It is currently undergoing a single-center phase 1 investigation in China (ChiCTR1800018137). As of August 1, 2019, 16 patients with R/R MM refractory to a median number of 4 prior lines have been enrolled. All patients received CT103A in a dose-escalation trial (four doses at 1, 3, 6, 8 x 10^6/kg) after a CTX/FAMP conditioning regimen and were followed for an average of 195 days after infusion. The study showed an excellent response with an ORR of 100%, including 12 CR/sCR and 2 VGPR with 6 patients achieving CR/sCR within 2 weeks post-infusion. All 15 evaluable patients reached MRD-negative status. Circulating CT103A cells peaked at 2 weeks post-infusion and remained detectable in 12/16 patients at 6 months. All 16 patients developed low-grade CRS, with 1 grade 4 event at the dose of 6 x 10^6/kg which was considered as a DLT. No NTX was observed. One patient died of lung infection at day 19 post-infusion [111, 138]. Despite this encouraging preliminary result, further studies are still warranted to evaluate the safety and efficacy of this fully human BCMA-targeted CT103A.

JCARH125
JCARH125 is second-generation BCMA-targeted CAR-T product containing a fully human scFv, optimized spacer, 4-1BB co-stimulatory, and CD3ζ activation domain. Preclinical study demonstrated robust anti-tumor activity of JCARH125 against BCMA expressing cells as well as various xenograft models regardless of the antigen densities or the presence of sBCMA. Off-target activity was not observed [139]. A phase 1/2 multicenter trial (EVOLVE, NCT03430011) is investigating the safety and efficacy of JCARH125 in patients with high R/R MM, who have received ≥3 prior regimens, including ASCT, a PI, IMiD, and an anti-CD38 mAb, unless not a candidate. The first 2 dose levels at 50 and 150 x 10^6 CAR+ T cells have been studied. As of July 12, 2018, all 8 evaluable patients out of 19 enrolled (median age 53; median number of prior lines 10) showed objective response, with 2 sCR, 1 CR, 2 VGPR, 2 PR, and 1 mild response (MR). The mDOF was 5 weeks. No PD was identified at the cutoff date. Six patients experienced grade 1 or 2 CRS, and 3 patients experienced NTX with 1 grade 3 lethargy resolved within 24 h after receiving steroids [112]. This study is still ongoing.

MCARH171
MCARH171 is a second-generation CAR-T cell product incorporating a human BCMA scFv and a 4-1BB co-
stimulatory motif, as well as a truncated epidermal growth factor receptor (tEGFR) safety system. Preclinical studies observed rapid in vivo expansion of CAR-T cells, eradication of large tumor burden, and durable protection to tumor re-challenge [140]. A dose-escalation phase 1 trial (NCT03070327) is currently evaluating the safety and efficacy of MCARH171 in patients with R/R MM. In this trial, participants received conditioning regimen with FAMP and CTX followed by MCARH171 infusion in 1–2 divided doses. Four dose levels were tested: 72 × 10^6, 137 × 10^6, 475 × 10^6, 818 × 10^6 total CAR+ T cells. As of July 16, 2018, 11 patients who failed an average of 6 prior myeloma regimens have received the therapy. The ORR was 64%, and the mDOR was 106 days. High-dose cohorts demonstrated higher peak expansion and longer persistence of MCARH171 as well as more durable clinical responses than low-dose cohorts. CRS occurred in 6 patients (4 grade 1–2, 2 grade 3). One patient experienced grade 2 encephalopathy which resolved within 24 h. No DLT was found [113].

**BCMA CAR-T cells with tTEGFR**

A Chinese company (Hrain Biotechnology) has also developed a second-generation γ-retrovirus-mediated anti-BCMA CAR-that contains a fully human scFv, 4-1BB co-stimulatory, CD3ζ activation domain along with the tEGFR safety system to facilitate tracking of the BCMA-targeting CAR-T cells. A phase 1 trial (NCT03093168) has been launched to evaluate the safety and efficacy of this BCMA CAR-T cell product for treating R/R MM. This trial enrolled patients who failed at least 2 prior treatment regimens and have over 5% BCMA expression on PCs. A single dose of 9 × 10^6 CAR+ cells/kg CAR-T cells were administered following the standard CTX/ FAMP lymphodepletion regimen. As of March 1, 2019, 44 enrolled evaluable patients achieved an ORR of 79.6%, including 2 sCR, 16 CR, 8 VGPR, and 8 PR, and 16 patients reached MRD-negative status. At the data cutoff, mPFS was 15 months. The 24-months PFS and OS were 49.16% and 53.95%, respectively. Grade 1–2 CRS was identified in 10 (22.7%) patients, and 3 (6.8%) patients underwent manageable grade 3 CRS events. The study has been ongoing for more than 26 months so far [114].

**KITE-585**

KITE-585 is a second-generation lentiviral-transduced CAR-T cell product which has a fully human anti-BCMA scFv, a CD28 co-stimulatory domain, and a CD3ζ activation domain. KITE-585 demonstrated potent in vitro and in vivo activity against MM cell lines even in the presence of soluble BCMA and also eradicated xenografted MM tumors in mice [141, 142]. A first-in-human, open-label, multicenter phase 1 study (NCT03318861) has been planned to evaluate the safety and feasibility of KITE-585 in R/R MM patients [143]. However, development of this product has subsequently been terminated.

**Bispecific CAR-T cells**

Bispecific and multi-antigen-targeted CAR-T cells are under active development [97, 144]. Bispecific CAR-T cells targeting BCMA and another tumor-specific antigen such as CD19 and CD38 have recently been developed to improve clinical efficacy by reducing the risk of relapse due to antigen escape.

**CD19/BCMA bispecific CAR-T cells**

Even though CD19 expression is lost in normal plasma cells [145, 146], CD19 is found to be expressed in a minute subset of less differentiated myeloma clones and CD19-targeted CAR-T cell therapy is effective in certain MM patients [147–150]. CD19+/BCMA- MM cells with enhanced clonogenic potential might contribute to the relapse after anti-BCMA CAR-T cell therapy [151]. It has been reported that combined infusion of both anti-CD19 and anti-BCMA CAR-T cells was feasible and produced promising responses with manageable toxicities in patients with R/R MM [152]. However, the addition of anti-CD19 CAR-T did not clearly prevent progression after anti-BCMA CAR-T therapy according the interim result of an ongoing study [153]. A BCMA CD19 bispecific CAR-T product was recently manufactured in China. It was constructed by linking BCMA and CD19 scFv, joined by a CD8 hinge, transmembrane domain, co-stimulatory domain, and CD3ζ [154]. In preclinical study, BCMA-CD19 CAR-T cells were shown to be highly effective in eliminating MM tumor cells both in vitro and in vivo and appeared more cytotoxic than single CAR-T. A first-in-human trial has been initiated. Five patients with R/R MM were evaluated between 15 and 59 days post-CAR-T infusion. All patients showed responses within this short period of evaluation time, with 1 sCR, 3 VGPR, and 1 PR. The sCR patient maintained the status at the time or report (129 days). The CAR-T proliferation peak was reached on day 10. Three patients experienced grade 1 CRS. No SAEs were reported [154].

**BM38: CD38/BCMA bispecific CAR-T cells**

CD38 is a glycoprotein expressed on PCs and other lymphoid cell populations. Due to its high and uniform expression on myeloma cells, CD38 is an ideal target for novel therapeutic strategies especially mAbs (daratumumab and isatuximab) [155–157]. BM38, a bispecific CAR-T cell product targeting BCMA and CD38, incorporates the anti-CD38 and anti-BCMA scFv in tandem plus 4-1BB signaling and CD3ζ domains. A phase 1
dose-escalating trial has been launched in China (ChiCTR1800018143). As of 31 July 2019, 16 patients with R/R MM who had received 2 prior treatment regimens received BM38 CAR-T cell infusion (dose range 0.5, 1.0, 2.0, 3.0, and $4.0 \times 10^6$ cells/kg). mDOF was 36 weeks. Fourteen (87.5%) patients achieved ORR with 8 sCR, 2 VGPR, and 4 PR. Fourteen (87.5%) patients reached MRD-negative status, and all 5 (100%) extramedullary lesions were eliminated. The longest duration of sCR was over 51 weeks. Five out of the 8 sCR patients maintained sCR status, 2 transformed to VGPR, and 1 to PR at the cutoff date. The 9 months PFS rate was 75%. The dose $4.0 \times 10^6$ cells/kg was selected for future dose-expansion study. Ten (62.5%) patients experienced grade 1–2 CRS, and 4 patients had reversible grade ≥3 CRS. All hematological toxicities were relieved within the first month after infusion. No NTX, DLTs, or deaths were reported [158].

**CAR-NK cells targeting BCMA**

Natural killer (NK) cell engineering has recently emerged as a promising alternative approach for cancer therapy. NK cells belong to the innate immune system. Unlike T cells, NK cell activation does not require antigen presentation or strict human leukocyte antigen (HLA) matching. CAR-NK cells do not carry the risk of graft-versus-host disease (GVHD), and they can be generated from NK cell lines (such as NK92) or induced pluripotent stem cells (iPSCs) instead of autologous manufacturing. Therefore, CAR-NK cells can be standardized as an “off-the-shelf” therapy product. In addition, the cytotoxicity of NK cell is mediated via the release of perforin and granzyme as well as the expression of apoptosis-inducing ligands including FasL and TRAIL. So there is much less concern about the CRS seen in many CAR-T cell therapies [159, 160]. Several preclinical studies of CAR-NK cells have been performed in MM. CAR-NK-92MI cells transfected with anti-CD138 scFv presented with enhanced cytotoxicity toward CD138-positive MM cells [161]. CAR-NK 92 cells targeting SLAMF7 not only showed intensified in vitro cytolyis, but also anti-tumor activity in murine tumor models and prolonged mouse survival [162]. A phase 1 trial of a newly developed BCMA-specific CAR-NK 92 cell product has enrolled 20 R/R MM patients aged between 18 and 80 years old in China in May 2019 (NCT03940833). The trial is ongoing with no interim report yet.

**Bispecific T cell engager (BiTE) and trispecific T cell engager (TiTE)**

Bispecific T cell engager (BiTE) is a double scFv-containing molecule that binds concomitantly to CD3 and a tumor-specific antigen, facilitating T cell/cancer cell crosslinking, followed by CD4+CD8+ T cell activation. The activated T cells secrete interferon-γ, granzyme B, and perforin and exert profound T cell cytotoxicity against tumor cells without requiring antigen-presenting cells, MHC-I/peptide complex, and co-stimulatory molecules [163]. Blinatumomab (BLINCYTO®), the first CD19/CD3 BiTE, has been approved by FDA for the treatment of R/R CD19+ acute lymphocytic leukemia (ALL) [164–166]. BCMA BiTE agents are in clinical trials (Table 4).

**AMG 420 (BI 836909, Amgen)**

AMG 420, formerly BI836909, consists of two linked scFvs, with BCMA scFv positioned N-terminally, and the CD3ε scFv C-terminally followed by a hexahistidine (His6 tag). In vitro study showed that upon simultaneous binding to BCMA+ MM cells and CD3+ T cells, AMG 420 induced crosslinking of both cell types, formation of a cytolytic synapse and subsequently activation of T cells, and release of cytokines (IFNy, IL-2, IL-6, IL-10, TNFα) in a dose-dependent manner, leading to lysis of BCMA+ MM cells. However, BCMA- cells were not affected. The presence of BM stromal cells, sBCMA and APRIL, had very minimal impact on the activity of AMG 420. Ex vivo study showed that AMG 420 induced potent MM cell lysis in both newly diagnosed and R/R MM patient samples. AMG 420 also demonstrated robust tumor-depletion ability in various xenograft models of systemic or subcutaneous MM [170].

A first-in-human phase 1 dose-escalation study (NCT02514239) has started to look at the safety and efficacy of AMG 420 for patients with R/R MM who have failed at least two prior treatment lines including PI and IMiD. Patients with PC leukemia, extra-medullary disease, CNS involvement, or prior ASCT were excluded. In this study, 6-week cycles of AMG 420 (4 weeks continuous IV infusion +2 weeks off) were given for up to 5 cycles or until PD, toxicity, or withdrawal. Five more cycles could be given per investigator for perceived benefit. As of December 10, 2018, 42 patients received AMG 420 (0.2–800 μg/day). Median age was 65, median number of prior therapies was 4, and median number of treatment cycles was 2.5. Overall, 13/42 patients showed responses to treatment (6 sCRs, 3 CRs, 2 VGPRs, 2 PRs). Median time to any response was 1 month. Four hundred micrograms per day was determined to be a recommended dose for further investigation, since this dose led to 7/10 (70%) responses with 5 sCRs, 1 VGPR, and 1 PR. At the data cutoff, the DOR ranged between 5.6 and 10.4 months. Overall, 24 patients had PD. Three DLTs and 2 deaths from AEs were reported. SAEs occurred in 21 (50%) patients including infections (n = 12) and polyneuropathy (n = 2). Grade 2–3 CRS was also seen in 3 patients. The study is currently still ongoing [72, 73].
| Name (manufacturer) | Structure | Clinical trial information | Inclusion/exclusion criteria | Pt characteristics | Dosage | Major Response | Most common AE |
|---------------------|-----------|----------------------------|-----------------------------|-------------------|--------|----------------|----------------|
| AMG 420 (Amgen)     | BCMA/CD3  | Phase 1 NCT02514239 [72]   | R/R MM who received or were refractory to ≥ 2 prior lines, including PI and IMiD; PC leukemia, extra-medullary relapse, CNS involvement, or prior ASCT were excluded | 42 pts; median age 65; median prior lines 4 | 0.2–800 μg/d, 4 wks infusion +2 wks off, for up to 5 cycles. Avg 2.5 ± 2.6 cycles | ORR 31%; sCR 14%; CR 7%; VGPR 4.8%; PR 4.8% | G3+ infection 12 (28.5%); polyneuropathy 2 (4.8%); G2–3 CRS 3 (7%); DLT 3 (7%) |
| CC-93269 (Celgene) | BCMA (bivalent)/CD3 (monovalent) | Phase 1 NCT03486067 [167] | R/R MM who received or were refractory to ≥ 3 prior lines; hx of BCMA-directed therapy were excluded | 19 pts; median age 64; median prior lines 6; ASCT 16 (84%); all pts refractory to the last line | 0.15–10 mg/d for a 28-day cycle (D1, 8, 15, and 22 for Cycles 1–3; D1 and 15 for Cycles 4–6; and on D1 for Cycle 7). Median 4 cycles; Median DOT 146 wks | 12 pts w/ dose of ≥ 6 mg; ORR 10 (83.3%); sCR/CR 4 (33.3%); VGPR 7 (58.3%) | G3+ neutropenia (52.6%); anemia (42.1%); infections (26.3%); thrombocytopenia (21.1%); G1–2 CRS 17 (89.5%) |
| PF-06863135 (Pfizer) | BCMA/CD3, IgG2a backbone | Phase 1 NCT03269136 [168] | R/R MM who received or were refractory to ≥ 3 prior lines, including PI, IMiD, CD38 mAb | 17 pts; median age 61; median prior lines 11; 5 pts (29%) had prior BCMA-targeted therapy | Once weekly non-continuous infusion in 6 dose-escalation groups | Minimal response 1 (6%); SD 6 (35%); PD 9 (53%) | G3+ thrombocytopenia (24%); anemia (18%); G1–2 CRS (24%) |
| REGN5458 (Regeneron) | BCMA/CD3  | Phase 1 NCT03761108 [169] | R/R MM who received or were refractory to ≥ 3 prior lines, including PI, IMiD, CD38 mAb | 7 pts | 6 mg/kg. 16 weekly doses + maintenance 12 doses per 2 wks | ORR 4 (53.3%) | G1–2 CRS 3 (42.9%) |
| AMG 701 (Amgen)     | BCMA/CD3, extended half-life | Phase 1 NCT03287908 | R/R MM who received or were refractory to ≥ 3 prior lines, including PI, IMiD, CD38 mAb | – | – | – | – |
| TNB3338 (TeneoBio)  | BCMA (high affinity)/CD3 (low affinity), IgG4 backbone | Phase 1 NCT03933735 | R/R MM who received or were refractory to ≥ 3 prior lines, including PI, IMiD, CD38 mAb | – | – | – | – |

Avg average, CNS central nervous system, CR complete response, CRS cytokine release syndrome, d day, DOT duration of treatment, G grade, hx history, med median, ORR overall response rate, PC plasma cells, PD progressive disease, PR partial response, pt patient, R/R relapse or refractory, sCR stringent complete response, SD stable disease, VGPR very good partial response, wk week.
AMG 420 has already been granted fast track status by the FDA, and phase 2 development is expected to start.

**CC-93269 (BCMA-TCB2, EM901)**

CC-93269 is an asymmetric 2-arm humanized IgG T cell engager that binds bivalently to BCMA and monovalently to CD3 in a 2+1 format. In a preclinical study, CC-93269 promoted MM cell death and tumor regression in different animal models [171, 172]. A phase 1 dose-escalating trial (NCT03486067) evaluating CC-93269 in patients with R/R MM has recently reported its interim updates [167]. Only patients who had received ≥3 prior regimens but without prior BCMA-directed therapy were eligible for the study. Intravenous CC-93269 was administered on days 1, 8, 15, and 22 for Cycles 1–3, days 1 and 15 for Cycles 4–6, and day 1 for Cycle 7 and beyond, all in 28-day cycles. As of May 24, 2019, 19 patients with a median age of 64 and a median number of 6 prior treatments received CC-93269 therapy (dose range 0.15–10 mg). Median duration of treatment was 14.6 weeks or 4 cycles. Of the 12 patients treated with a dose of ≥6 mg, 10 patients showed responses (ORR 83.3%), including 7 VGPR (58.3%) and 4 sCR/CR (33.3%); 9 (75.0%) patients achieved MRD negativity. The median time to response was 4.2 weeks. One patient presented with PD. Most frequently encountered SAEs were neutropenia (52.6%), anemia (42.1%), infections (26.3%), and thrombocytopenia (21.1%), but no dose modifications were required. CRS were found in 17 (89.5%) patients but were mostly grades 1 and 2. This study is ongoing [167].

**PF-06863135 (PF-3135)**

PF-06863135 (PF-3135) is a humanized mAb bispecific to BCMA- and CD3- antigens. PF-3135 exhibited strong cytotoxicity to MM cell lines and different MM primary patient samples. A single injection of PF-3135 effectively inhibited tumor growth in a dose-dependent manner in various established mouse models [173]. A recent update on the ongoing, multicenter, phase 1 trial (NCT03269136) reported 17 patients with R/R MM who were treated with once weekly, non-continuous, IV infusion of PF-3135 in 6 dose-escalation groups. Median age was 61 years old (range 47–82). Median number of prior therapies was 11. Of note, 5 (29%) patients had received prior BCMA-targeted therapy including other BiTEs or CAR-T cells. Among the 16 evaluable patients, 1 (6%) patient had a minimal response and 6 (35%) patients had SD across all dose levels, while 9 (53%) patients had PD. Additional dose cohorts are being enrolled. There were mainly grade 1–2 AEs including CRS (24%), thrombocytopenia (24%), and anemia (18%). DLT of treatment-related febrile neutropenia was found in one patient on the highest dose level [168, 174].

**REGN5458**

REGN5458 is another human bispecific antibody against both BCMA and CD3. This agent showed strong cytotoxicity against MM cell lines and primary patient blasts regardless of tumor-surface level of BCMA. REGN5458 was even found to increase the surface level of BCMA. Animal studies also discovered rapid tumor clearance and growth suppression after REGN5458 was administered at doses as low as 0.4 mg/kg. Of note, the antitumor activity of REGN5458 was comparable to that of anti-BCMA CAR-T cells both in vitro and in vivo [175]. A phase 1 dose-escalating trial (NCT03761108) is currently investigating the safety and efficacy of REGN5458 in R/R MM. Eligible patients were those who had at least 3 prior regimens of treatment. Sixteen weekly doses of REGN5458 were given first, followed by a maintenance phase of 12 doses administered every 2 weeks. Patients with PD after initial response were allowed to be retreated. According to the most recent update in ASH 2019, 7 patients have received the therapy with 4 responses (ORR 53.3%). Three patients were treated at the dose of 6 mg/kg. In addition, 2 patients achieved MRD-negative status. Regarding safety, no DLTs were reported. Three patients had mild CRS [169].

**AMG 701**

AMG 701 is a BiTE similar to AMG 420 but with extended half-life. Preclinical studies showed that AMG 701 markedly induced T cell-mediated lysis of BCMA+ MM cells either resistant or sensitive to current anti-MM agents such as IMid or PI3, regardless of the BCMA expression level. It can also trigger robust immunomodulatory effects to overcome the immunocompromised BM microenvironment, such as upregulation of immune checkpoint molecules (PD1, TIM-3, LAG-3), enhanced production of cytokines (INFγ, TNFα), and increased CD8+/CD4+ T cell ratio [176]. AMG 701 in combination with IMid significantly increased long-term durable responses and reduced relapse in xenograft models [177]. Therefore, AMG 701 alone or in combination with IMid might improve outcome in MM patients. A phase 1 trial (NCT03287908) is currently ongoing in patients with R/R MM.

**TNB383B**

TNB383B is a novel bispecific monoclonal IgG4 antibody that consists of 2 heavy and 1 light chain(s) paired through knob-in-hole technology. The first heavy chain is comprised of two identical scFvs in sequence targeting human BCMA with high affinity and avidity. The second heavy chain and a kappa light chain recognize human CD3 with a low-activating potency. TNB383B was found to have strong ex vivo anti-MM efficacy with markedly reduced cytokine release in preclinical studies [178].
open-label, multicenter phase 1 trial (NCT03933735) is currently ongoing to evaluate the safety, pharmacokinetics, and efficacy of TNB383B in R/R MM who received at least 3 prior regimens of treatments. No interim result has been reported so far [179].

**BCMA-targeted therapeutics and future perspectives**

Even though BCMA-targeted agents achieved remarkable responses in patients with R/R MM, most of them are still at early stage of clinical development. CAR-T therapy has been reported to be effective for extramedullary plasma cell dyscrasia [71, 115, 130]. However, autologous BCMA CAR-T cells take at least 2–4 weeks to prepare and are mainly available in specialized medical centers, limiting its utility in individuals with rapid PD. For elderly patients (≥75 years old) and patients who have been heavily pretreated, it could be difficult to generate sufficient amount of autologous BCMA CAR-T cells [54, 180]. The high incidence of CRS and NTX as well as grade ≥3 hematologic AEs associated with the pre-conditioning lymphodepletion are also major concerns, even though the BCMA CAR-T cells were effective for R/R MM patients [124]. A phase 1/2 study (NCT03455972) is currently investigating combined infusion of BCMA- and CD19-specific CAR-T cells in patients with high-risk MM 14 to 20 days after ASCT. Structural modifications have been attempted to decrease the toxicity of CAR-T cell therapy, such as by adding an inhibitory CAR to reduce off-target responses [102, 181], applying a small molecule-gated system to facilitate remote control of CAR-T cells [182], or by attaching suicide genes to the engineered CAR [183]. Several strategies are also proposed to improve efficacy, such as bispecifically targeting both BCMA and another tumor-specific antigen to prevent antigen relapse as discussed above.

BiTE highly relies on the reserved function of T effector cells to generate cytotoxicity. Therefore, it is mainly recommended for patients who have received fewer prior lines of therapy [164, 165]. Compared to CAR-T cells, BiTE has a much shorter half-life; thus, continuous infusion is generally needed [184]. In addition, BiTE also causes SAEs including CRS and NTX. New BiTEs with structural modifications such as AMG 701 and TNB383B have been developed to extend half-life and reduce toxicity. Besides, BiTE combined with IMiD might improve the efficacy as discussed above.

ADC is an “off-the-shelf” product that facilitates direct killing of tumor cells via cytotoxic payloads while carrying a low risk of CRS and NTX. Compared with CAR-T cell product, it is also less expensive and requires less time to prepare. It is given as a bolus infusion in general, not requiring continuous IV administration. However, ADC is cleared by the malignant cells much faster via receptor-mediated endocytosis, thus requiring more frequent infusions. The concern for low payload penetration and bystander effect also limits its anti-tumor ability [80, 81]. Novel cytotoxic agents as payloads (e.g., α-amanitin, tubulysins, hizoxin, spliceostatins) and ADC structure modifications (e.g., non-IgG scaffolds or non-internalizing mAb scaffolds) are currently under development to improve the efficacy [185].

It remains undetermined whether any BCMA-targeted agents (ADC, CAR-T, or BiTE) offers a better therapeutic index. It is equally intriguing whether these agents can be combined concurrently or sequentially. One possible future perspective is that in patients with high MM burden, BCMA ADC could be used as a bridging therapy to quickly reduce tumor load. CAR-T and BiTE could then be administered to eliminate MRD for durable responses. Another question that needs to be addressed in the future is how to appropriately integrate these drugs into current treatment algorithms for MM. Several ongoing clinical trials are currently comparing different combination regimens incorporating BCMA-targeted agents with PIs, IMiDs, checkpoint blockades, or epigenetic inhibitors. The first BCMA-targeted ADC, belantamab mafodotin-blmf (GSK2857916), is already approved for clinical applications for R/R MM. BiTE and CAR-T cells targeting BCMA are promising. The BCMA-targeted immunotherapy is undoubtedly enriching the armamentarium against MM.

**Conclusion**

BCMA represents a specific biomarker of normal and malignant PCs. A variety of BCMA-targeted agents including ADC, CAR-T cells, and BiTE are currently in active clinical development. Belantamab mafodotin-blmf (GSK2857916), a BCMA-targeted ADC, has just been approved for highly refractory MM.

**Abbreviations**

ADC: Antibody-drug conjugate; ADCC: Antibody-dependent cell-mediated cytotoxicity; APRIL: A proliferation-inducing ligand; ASCT: Autologous or allogenic stem cell transplantation; BAFF: B cell activating factor; BCMA: B cell maturation antigen; BiTE: Bispecific T cell engager; CAR: Chimeric antigen receptor; CT: Complete response; CRS: Cytokine release syndrome; CTX: Cyclophosphamide; DLT: Dose-limiting toxicity; DOF: Duration of follow-up; FAMP: Fludarabine; IMID: Immunomodulatory imide drug; mAb: Monoclonal antibodies; mDOR: Median duration of response; MM: Multiple myeloma; mIFPS: Median progression-free survival; MRD: Minimal residual disease; MTD: Maximal tolerated dose; NTX: Neurotoxicity; ORR: Overall response rate; OS: Overall survival; P: Plasma cell; PD: Progressive disease; PI: Proteasome inhibitor; PR: Partial response; R/R: Relapsed and/or refractory; SAE: Severe adverse event; scCr: Stringent complete response; TLS: Tumor lysis syndrome; TRD: Treatment-related death; VGPR: Very good partial response

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