Targeting B Cell Maturation Antigen (BCMA) in Multiple Myeloma: Potential Uses of BCMA-Based Immunotherapy

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The approval of the first two monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab) in late 2015 for treating relapsed and refractory multiple myeloma (RRMM) was a critical advance for immunotherapies for multiple myeloma (MM). Importantly, the outcome of patients continues to improve with the incorporation of this new class of agents with current MM therapies. However, both antigens are also expressed on other normal tissues including hematopoietic lineages and immune effector cells, which may limit their long-term clinical use. B cell maturation antigen (BCMA), a transmembrane glycoprotein in the tumor necrosis factor receptor superfamily 17 (TNFRSF17), is expressed at significantly higher levels in all patient MM cells but not on other normal tissues except normal plasma cells. Importantly, it is an antigen targeted by chimeric antigen receptor (CAR) T-cells, which have already shown significant clinical activities in patients with RRMM who have undergone at least three prior treatments, including a proteasome inhibitor and an immunomodulatory agent. Moreover, the first anti-BCMA antibody–drug conjugate also has achieved significant clinical responses in patients who failed at least three prior lines of therapy, including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent. Both BCMA targeting immunotherapies were granted breakthrough status for patients with RRMM by FDA in Nov 2017. Other promising BCMA-based immunotherapeutic macromolecules including bispecific T-cell engagers, bispecific molecules, bispecific or trispecific antibodies, as well as improved forms of next generation CAR T cells, also demonstrate high anti-MM activity in preclinical and even early clinical studies. Here, we focus on the biology of this promising MM target antigen and then highlight preclinical and clinical data of current BCMA-targeted immunotherapies with various mechanisms of action. These crucial studies will enhance selective anti-MM response, transform the treatment paradigm, and extend disease-free survival in MM.

Keywords: multiple myeloma, B-cell maturation antigen, targeted immunotherapy, monoclonal antibody, chimeric antigen receptor T cell, monoclonal antibody drug conjugate, bi-specific antibody
INTRODUCTION

Multiple myeloma (MM), the second most common hematologic malignancy in the United States, accounts for 1% of malignancies and 10% of hematologic cancers (1). This tumor is characterized by the expansion of malignant plasma cells (PCs) in the bone marrow (BM), associated with excessive production of monoclonal immunoglobulins in blood and urine in patients. In addition, MM patients develop significant osteolytic bone lesions and have immunodeficiency that compromises both longevity and quality of life (2, 3). For the past two decades, the clinical outcome of MM patients has shown remarkable improvements primarily due to the incorporation of novel therapeutic agents into conventional treatments. Specifically, the addition of proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs) has significantly increased response rate, progression-free, and overall survival in both relapsed and newly diagnosed MM patients, compared with conventional therapies (4–7). The addition of monoclonal antibodies (MoAbs) elotuzumab and daratumumab as immunotherapies in MM has further improved patient outcome. The use of autologous stem cell transplantation also results in better outcome. However, MM remains incurable for most patients, since drug-resistant clones constantly emerge and evolve (8). Persistence of minimal residual disease (MRD) is often seen and patients with MRD-negativity also relapse. Particularly, the overall survival of patients with relapsed disease after PIs IMiDs, and MoAbs treatment is extremely low. Thus, more efficacious therapies and novel strategies are urgently needed if we are to develop curative therapies.

Multiple myeloma develops from a premalignant precursor condition monoclonal gammopathy of undetermined significance, progressing to smoldering MM, then active MM, majorities of which ultimately advancing to end-stage PC leukemia. Genetic and epigenetic processes are present initially and underlie this progression, including hyperdiploidy of chromosomes, translocation of immunoglobulin heavy chain, deregulation of cell cycle genes, alteration of NFκB pathways, and abnormal DNA methylation patterns (9–11). Besides complex molecular aberrations, MM cells are heavily dependent on their BM microenvironment to support their growth, survival, and the development of drug resistance. Tumor cells closely interact with BM accessory cells in bidirectional fashions via cell–cell contact and/or production of a variety of factors, which ultimately promotes MM cell expansion, while impairing immune surveillance and effector function against MM cells. These MM-supporting cells include BM stromal cells (BMSCs) (12, 13), osteoclasts (14), endothelial cells (15), macrophages (16), T regulatory cells (17–19), dendritic cells (20), plasmacytoid DCs (pDCs) (21), myeloid-derived suppressor cells (22), and mesenchymal cells (13, 23). These accessory cells secrete various cytokines including interleukin-6 (IL-6) (24), tumor growth factor β (TGFβ) (25, 26), macrophage inflammatory protein-1α (MIP-1α) (27), insulin-like growth factor (28), vascular endothelial growth factor (29), hepatocyte growth factor (30), B cell activating factor (BAFF) (31, 32), and a proliferation-inducing ligand (APRIL) (31, 33), which further maintain an MM-supporting or immunosuppressive BM microenvironment (34). For example, the key myeloma growth factor IL-6 and the critical immune inhibitory factor TGFβ are detected at high levels in the BM of MM patients. The interplay of these two cytokines may affect generation of Th17 cells both directly or via other pro-inflammatory cytokines, and thereby downregulate antitumor immune responses (35). Increased Th17 cells and decreased regulatory T cells (Tregs) with less immune suppression is noted in MM patients with long-term survival (36). Since Tregs can inhibit function of antigen-presenting cells and effector T cells (37), increased Treg number allows MM cells to escape from immune surveillance. In fact, immune-suppressive Treg markers Foxp3 and CTLA-4 are significantly upregulated in the BM aspirates of MM patients compared with normal donor controls (17), and increased Tregs are correlated with worse outcomes in MM (36, 38, 39). These studies indicate that molecular and cellular components suppress immune BM milieu, further enhancing MM progression.

Successful targeted anti-MM immunotherapies should both target MM cells and simultaneously restore antitumor activity of immune effector cells (40). Ideally, targets for effective immunotherapies should be selectively and strongly expressed on the surface of MM cells relative to normal cells. Compared with CD38 and SLAMF7, B cell maturation antigen (BCMA) demonstrates highly restricted expression on PCs but no other tissues, is, therefore, an excellent target for immunotherapy in MM (41, 42).

BCMA IS AN IMPORTANT SURFACE PROTEIN SUPPORTING THE SURVIVAL OF MM CELLS

B cell maturation antigen, also termed tumor necrosis factor receptor superfamily member 17 (TNFRSF17), is a type III transmembrane protein without a signal-peptide and containing cysteine-rich extracellular domains (43–45). Alignment of the human (44, 45) and murine BCMA protein sequences (43) revealed a conserved motif of six cysteines in the N-terminal part, which strongly suggests that the BCMA protein belongs to the tumor necrosis factor receptor (TNFR) superfamily. BCMA, along with two related TNFR superfamily B-cell activation factor receptor (BAFF-R) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), critically regulate B cell proliferation and survival, as well as maturation and differentiation into PCs. These three functionally related receptors support long-term survival of B cells at different stages of development by binding to BAFF and/or APRIL (46–49), their cognate ligands. Specifically, BCMA is only induced in late memory B cells committed to the PC differentiation and is present on all PCs (46, 50, 51). Expression of BCMA is induced, while BAFF-R is decreased, during PC differentiation from B cells. Studies from BCMA-knockdown mice further indicate that BCMA is most important for long-lived PC survival but is dispensable for overall B cell homeostasis (50, 52). A recent study showed that an enzyme, γ-secretase can cleave membrane BCMA, leading to decreased in membrane form BCMA and formation of soluble form BCMA (sBCMA) (53) (Figure 1).
Earlier studies show that overexpression of BCMA in 293 cells activates the mitogen-activated protein kinase pathway, especially JNK and p38 kinase, the nuclear factors NFκB and Elk-1, without stimulation of BAFF or APRIL (54). BCMA expression is positively regulated by B-lymphocyte-induced maturation protein 1 (Blimp-1), a gene controlling proliferation of PCs (55). In KMS12 MM cell line, BCMA co-immunoprecipitates with interferon regulatory factor-4, a master transcription factor mediating survival of MM cells (56). Importantly, BCMA overexpression or APRIL binding to BCMA in MM cells significantly promotes MM cell growth and survival in vivo (33, 57). Conversely, BCMA knockdown blocks MM cell proliferation and viability via downregulation of cell cycle progression and antiapoptosis molecules. APRIL and BAFF, via binding to BCMA and TACI, further activate NFκB pathways and upregulate antiapoptotic proteins (Mcl-1, Bcl-2, Bcl-xL) to protect MM cells against dexamethasone- and serum deprivation-induced cell death (31, 58) (Figure 1). These studies establish a pathophysiological role of BCMA and APRIL in MM.

**RATIONALE TO TARGETING BCMA IN MM**

B cell maturation antigen is exclusively expressed on the surface of plasmablasts and differentiated PCs, but not on memory B, naive B cells, CD34+ hematopoietic stem cells, and other normal tissue cells (41, 50, 51, 60–64). BCMA mRNA and protein are more highly expressed on malignant than normal PCs, as validated by multiple gene expression profiling (41, 42, 65, 66) and immunohistochemistry (IHC) studies (41). In the study by Carpenter et al. (41), cDNA copies of BCMA were detected by qPCR in several hematologic tissues including white blood cells, BM, lymph node, spleen, and tonsil. In normal tissues, low levels of BCMA cDNA copies were detected in the samples of testis, trachea and samples from gastrointestinal organs like...
duodenum, rectum, and stomach. When the expression was evaluated by IHC, BCMA protein expression was only detected on MM cells, lymphoid cells, or PCs from normal human organs such as duodenum, rectum, and stomach. However, BCMA protein expression was not detected on the other cell types in these organs (41). Another study examined BCMA expression on various blood cells and Hodgkin lymphoma cells using flow cytometry (63). BCMA expression was negative on naive and memory B cells, weak on founder B cells from germinal center (GC) and Reed–Sternberg cells, positive on GC B cells, but highly positive on plasmacytoid B cells. Based on these findings, BCMA protein is highly and specifically expressed on PCs, low levels of BCMA RNA detected in these normal organs would be due to existence of PCs.

Thus far, majorities of studies indicate that BCMA transcript, protein, and the serum BCMA level are significantly higher in MM cell lines and patient MM cells, when compared with normal donors. One recent study reported that median BCMA expression on patient MM cells was not to be higher compared to normal donors. One recent study reported that median BCMA in MM cell lines and patient MM cells, when compared with protein, and the serum BCMA level are significantly higher than wild-type mice under similar conditions (77). These results are characterized by high stability and high antitumor potency, with low bystander toxicity.

GSK2857916

GSK2857916 is a humanized and IgG1 mAb with high affinity to BCMA (Kd of ~0.5 nM) (42), which uses non-cleavable linker, maleimidocaproyl (mc), and a new class of antimitotic agents, monomethyl auristatin F, as payload. This structure is characterized by high stability and high antitumor potency, with low bystander toxicity.

GSK2857916 binds to all CD138+ and BCMA+ MM cell lines and patient MM cells. MM cell proliferation is inhibited via G2/M arrest in a dose-dependent manner, and apoptosis is induced by activation of caspase 3/7 and 8. There are minimal effects on surrounding BCMA-negative normal cells. GSK2857916 also triggers

BCMA-BASED IMMUNOTHERAPIES

The development of novel agents targeting BCMA is ongoing rapidly, especially following impressive clinical responses in relapsed MM patients using the first chimeric antigen receptor (CAR) T cell therapy (78). Currently, there are multiple BCMA-based treatment modalities including: ADC, bispecific T-cell engager (BiTE), CAR T cell (CAR T), bispecific molecule, and bi/trispecific Abs (Figure 2) (summarized in Table 1), as well as cancer vaccines.

ANTIBODY–DRUG CONJUGATES

Antibody–drug conjugate, one of the fastest growing class of cancer therapeutics, is composed of recombinant mAbs covalently bound to cytotoxic chemicals (payload) via synthetic chemical linkers (107). The mAbs first identify and bind to the antigen on the surface of tumor cells, and then is absorbed or internalized, together with the payload. After the ADC is internalized, the cytotoxic chemicals are released in the lysosomes and transported to cytosol to kill the tumor cells.

FIGURE 2 | B cell maturation antigen (BCMA)-based immunotherapies with multiple mechanisms of action against MM cells. Various BCMA-based treatment modalities are under clinical development are listed in Table 1 and shown here. BCMA-NK Bi or Tri Ab, not shown here, can also specifically induce effector cell-mediated lysis of MM cells. ADC, antibody drug conjugate; Bi, bispecific full-length immunoglobulin; BiTE, bispecific T-cell engager; CAR T, chimeric antigen receptor T cell; MM, multiple myeloma cell; NK, natural killer cell; Mφ, macrophage.
| Therapeutic format | Compound (or name) | Company/ sponsor | Characteristics | Clinical development | Reference |
|--------------------|-------------------|------------------|-----------------|----------------------|-----------|
| Antibody–drug conjugates | GSK2857916 | GlaxoSmithKline | 1. Humanized and afucosylated IgG1 mAb 2. BCMA binding affinity: Kd of ~0.5 nM 3. Anticancer drug: monomethyl auristatin F 4. Linker: Maleimidocaproyl (non-cleavable) | Phase 1 | (42, 79, 80) |
| HDP-101 | Heidelberg Pharma | 1. Antigen-targeted amanitin-conjugates 2. Humanized mAb 3. Anticancer agent: Amanitin 4. Linker: Maleimide (non-cleavable) | Preclinical | (81, 82) |
| MED2228 | MedImmune | 1. Fully humanized antibody 2. Anticancer drug: Pyrrolobenzodiazepine 3. Linker: Protease-cleavable linker | Preclinical | (83) |
| Bispecific T-cell engager | BI 836900 (Amg420)/ Amg701 | Boehringer Ingelheim/Amgen | 1. Bispecific single-chain variable fragment with hexahistidine tag 2. Targeting CD3 and BCMA | Preclinical | (84, 85) |
| CAR T | Anti-BCMA chimeric antigen receptor (CAR) | National Cancer Institute | 1. Transfection: γ-retroviral vector 2. Extracellular domain: murine scFv 3. Co-stimulation domain: CD28 | Phase 1 | (41, 78, 86) |
| bb2121 | Bluebird Bio Celgene | 1. Transfection: Lentivirus vector 2. Extracellular domain: Murine scFv 3. Co-stimulation domain: 4-1BB | Phase 1 | (87) |
| LCAR-B38M | Nanjing Legend Biotech | 1. Transfection: lentivirus vector 2. Extracellular domain: Bispecific variable fragments of llama heavy-chain antibodies 3. Co-stimulation domain: 4-1BB | Phase 1 | (88, 89) |
| CART-BCMA | Novartis | 1. Transfection: Lentivirus vector 2. Extracellular domain: fully human scFv 3. Co-stimulation domain: 4-1BB | Phase 1 | (90, 91) |
| KITE-S8S | Kite Pharma | 1. Transfection: lentivirus vector 2. Extracellular domain: fully human scFv 3. Co-stimulation domain: 4-1BB | Preclinical | (92) |
| BCMA CAR | Pfizer Collectis SA | 1. Transfection: lentivirus vector 2. Extracellular domain: fully human scFv 3. Co-stimulation domain: 4-1BB 4. Inactivation of the T cell receptor alpha chain 5. Contained a safety switch | Preclinical | (93) |
| P-BCMA-101 | Poseida Therapeutics | 1. In vitro transcribed mRNA and plasmid DNA, no viral transfection 2. Extracellular domain: human fibronectin type III domain 3. Contain a safety switch | Preclinical | (94–96) |
| FHVH74-CD828Z FHVH32-CD828Z FHVH33-CD828Z FHVH3-CD828Z | Tenebrio | 1. Antigen-recognition domains composed of single fully human FHVH without light chain variable region domain or linker 2. Co-stimulation domain: 4-1BB or CD28 | Preclinical | (97) |
| Descartes-06 | Cartesian Therapeutics | 1. CD8+ anti-BCMA CAR T-cells modified transiently by mRNA transfection | Preclinical | (98) |
| P-BCMA-ALLO1 | Poseida Therapeutics | 1. NextGEN™ (NG) CRISPR gene editing system to disrupt both TCR and MHCI expression 2. Non-viral piggyBac™ (PB) DNA transposition technology to produce CAR-T cells with highly desirable stem cell memory T cell subset | Preclinical | (99) |
| EGFRt/BCMA-41BBz | Juno | 1. Transfection: lentivirus 2. Extracellular domain: fully human scFv 3. Co-stimulation domain: 4-1BB 4. Suicidal gene: EGFRt | Phase 1 (recruiting) | (99) |

(Continued)
### TABLE 1 | Continued

| Therapeutic format | Compound (or name) | Company/ sponsor | Characteristics | Clinical development | Reference |
|-------------------|--------------------|------------------|-----------------|----------------------|-----------|
| Bispecific molecule | BCMA/CD3 bispecific | Pfizer, Alexo Therapeutics, Kodiak Sciences | 1. Fully-human IgG CD3 bispecific molecule with IgG2A backbone  
2. BCMA binding affinity: Kd 20 pM  
3. CD3 binding affinity: Kd ~40 nM | Preclinical | (100) |
| Bispecific antibody | EM801 | EngMab AG, Celgene | 1. Two-arm IgG1-based human antibody  
2. One CD3 and two BCMA binding sites  
3. BCMA-binding affinity: Kd of 10 nM  
4. CD3-binding affinity: Kd of 70 nM | Preclinical | (66) |
| aBCMA-TCB2/EM901 | Celgene | 1. Two-arm IgG1-based human antibody  
2. One CD3 and two BCMA-binding sites | Preclinical | (101) |
| Ab-957 | Janssen | 1. BOMAxCD3 bispecific antibody  
2. Ec50:  
   a. BCMA + cell: 0.06–0.45 nM  
   b. T-cell activation: 0.1–0.28 nM | Preclinical | (102) |
| AFM26 | Affirmed | 1. Targeting CD16A (NK cells) and BCMA  
2. NK-cell binding affinity: Kd of 1.2 nM | Preclinical | (103, 104) |
| TNB383B/TNB-384B | TeneoBio | 1. Targeting BCMA and CD3  
2. Very low or absence of cytokine release after TNB-383B treatment | Preclinical | (105) |
| Trispecific antibody | Anti-CD16A/BCMA/CD200 antibody | Affirmed | 1. Trispecific antibody format: CD16A/BCMA/CD200  
2. Bivalent binding to CD16A  
3. Monovalent binding to both BCMA and CD200 | Preclinical | (106) |

Every effort has been made to obtain reliable data from multiple sources including http://clinicaltrials.gov/, companies, and other web sites, but accuracy cannot be guaranteed.

*aMost recently, the BCMA/CD3 TCB CC-93269 (EM901) has entered clinical phase I testing (NCT03486067).

ADCC and antibody-dependent cellular-mediated phagocytosis against patient MM cells. The cytotoxicity against MM cells is further enhanced when GSK2857916 is combined with lenalidomide via effector-dependent and -independent manners. Most importantly, in both disseminated and subcutaneous human MM xenograft models in mice, GSK2857916 rapidly eliminates MM cells and generated little toxicity in mice treated with continuous dosing for nine times at 4 mg/kg, with tumor-free survival up to 3.5 months in mice (42).

GSK2857916 was evaluated in a phase 1 study of patients with relapsed and refractory multiple myeloma (RRMM), including dose-escalating and expansion parts (79, 80). GSK2857916 monotherapy has demonstrated a 60% response rate and a median progression-free survival of 7.9 months in a group of hard to treat and heavily pretreated RRMM (80). It has recently been awarded Breakthrough Therapy designation from FDA and received PRIME designation from the European Medicines Agency (EMA).

**HDP-101**

HDP-1, an antibody-targeted amanitin conjugate, is an anti-BCMA ADC with a novel payload amanitin, which binds to the RNA polymerase II in eukaryotic cells and inhibits cellular transcription at very low concentrations (108). HDP-1 was synthesized with the conjugation of maleimide-amanitin compounds and engineered cysteine residues in the heavy chain of the humanized anti-BCMA Thiomab (109, 110).

HDP-101 demonstrated potent in vitro cytotoxicity against BCMA-expressing MM cell lines at picomolar range, without effects on BCMA-negative cells. Significant tumor regression including complete remission was observed in the mouse xenograft model in a dose-dependent manner. The tolerability and therapeutic index were good after a series of HDP-101 administrations at different concentrations in Cynomolgus monkeys. Mild-to-moderate elevation of liver enzymes and lactate dehydrogenase were noted, but these abnormalities were transient. HDP-101 has a long half-life in serum (about 12 days) (81, 82).

**MEDI2228**

The structure of MEDI2228 includes a fully human antibody site-specifically conjugated to a pyrrolobenzodiazepine dimer via a protease-cleavable linker. This ADC is rapidly internalized into MM cells and trafficked to lysosomes.

MEDI2228 was highly active in 8 of 10 MM cell lines (IC50 range 6 to 210 ng/mL) including cell lines regardless of BCMA levels (83). MEDI2228 was also active in the presence of BMSCs. A single injection of MEDI2228 induced human MM xenograft regression in mice at very low doses (0.1 mg/kg). MEDI2228 was characterized by weak binding capacity to recombinant monomeric human BCMA, but strong binding to membrane-bound BCMA. It kills an average of 95% of tumor cells in the presence of sBCMA at levels up to 720 ng/mL, without impact on IC50. Clinical trials of this new anti-BCMA will be starting in mid-2018.

**BISPECIFIC T-CELL ENGAGER**

Bispecific T-cell engager is a single-chain variable fragment (scFv), composed of two linked mAbs (bispecific antibodies) targeting
mainly CD3 on the surface of T-cells and tumor-associated antigens. This unique structure allows BiTE to engage T-cells with tumor cells (111). After the binding, antitumor cytotoxicity and cytokine production of T cells are activated, and the formation of cytolytic immunological synapses are induced (112, 113). BiTE is also characterized by its small size (55 kDa), which makes it a highly potent and efficacious molecule to against cancer (114). However, the small size of BiTE is unstable due to short serum half-life, thus continuous infusion is required.

**BI 836909**

BI 836909 is the first bispecific scFv with two linked scFvs in MM (84). The scFv targeting BCMA is positioned in N-terminal, and the scFv targeting CD3ε is in C-terminal, followed by a hexahistidine (His6-tag). BI 836909 simultaneously bind to CD3+ T cell and BCMA-expressing MM cells. This makes a cross-link between both cells to induce formation of cytolytic synapse, ultimately leading to activation of T cells and lysis of BCMA+ MM cells. These cytotoxic activities were not observed in BCMA-negative cells. When cocultured with BM stromal cells, BI 836909 retains potent anti-MM activity. Additionally, soluble APRIL and BCMA have only a mild effect on the anti-MM activity of BI 836909.

In mouse xenograft studies, BI 836909 led to tumor shrinkage in a subcutaneous NCI-H929 xenograft model and prolonged survival in an orthotopic L-363 xenograft model. In a cynomolgus monkey study, administration of BI 836909 resulted in significant depletion of BCMA + PCs in the BM of monkeys (84).

A half-life extended anti-BCMA BiTE base on BI 836909 was recently reported to be effective in vitro and in vivo and is suitable for once-weekly dosing in MM patients (85).

**CAR T CELL THERAPY**

Adoptive transfer of T cells genetically modified to recognize tumor-associated antigens is a promising cancer treatment (115). By using techniques of genetic modification, T cells can express CAR, which are fusion proteins that have an antigen recognition region, usually scFv derived from antibody on the surface, and a costimulation domain in the cell. Unlike T cell receptor modified T cells, CAR T cells are not restricted by major histocompatibility complex (40).

In MM, several anti-BCMA CAR T cell therapies have shown impressive clinical activities (some reaching 90–100%) with more are developed and under preclinical and/or clinical investigations (see Table 1).

**OTHER TRIALS OF ANTI-BCMA CAR-T THERAPY**

The combined infusion of CD19 and BCMA-specific CAR T Cells for RRMM was investigated in an early phase study (NCT 03196414) (116). The cells contained respective anti-BCMA or anti-CD19 scFv transduced by lentivirus, OX40 and CD28 costimulatory moiety, and CD3z T-cell activation domain. Clinical efficacy was evaluated in five patients monitored for more than 4 weeks, and showed that ORR was 100%, including 1 sCR, 1 VGRP, 2 PR, and 1 SD (116).

**ANTI-BCMA CD3 BI- OR TRISPECIFIC MOLECULES**

**A Fully Human IgG CD3 Bispecific Molecule Targeting BCMA**

This fully-human IgG bispecific molecule is characterized by its long half-life (about 3 days in mice) (100). The molecule utilizes hinge mutation technology to pair anti-BCMA and anti-CD3 targeting arms and places them in an IgG2A backbone. The anti-MM cytotoxicity was observed in MM patient samples at very low concentration (EC50 = 0.093 ± 0.1 nM), lower than ADC. This molecule also effectively depleted BCMA-expressing normal plasma B cells. The evolution of toxicity in cynomolgus monkeys model showed favorable safety profile.

**EM801**

EM801 is asymmetric two-arm IgG1-based human antibody with two binding sites for BCMA and 1 binding site for CD3 (66). EM801 promotes activation of CD4+ and CD8+ T-cells accompanied with release of IFN-γ, granzyme B, and perforin, and CD3+ T-cell-dependent killing of MM cell lines. EM801 also induced significant cell death in malignant PCs by autologous T cells in BM samples of previously untreated and RRMM patients at very low concentrations (from 10 pM to 30 nM).

**BCMA-TCB2**

B cell maturation antigen-TCB2 is a bispecific antibody, which shares similar structure of EM801, but with higher affinity to BCMA (101). BCMA-TCB2 induces lysis of MM cells, activation of T cells, and natural emergence of the checkpoint inhibitor PD-1 on T cells at very low concentration. Combination of BCMA-TCB2 with lenalidomide or daratumumab significantly enhanced antymyeloma efficacy. NK cells were also activated after BCMA-TCB2 treatment.

**Ab-957**

Ab-957 is bispecific IgG-like Ab generated by Genmab DuoBody® technology to target CD3 on T-cells and BCMA on MM cells (102). Preclinical studies also show that Ab-957 potently induces specific cytotoxicity of BCMA + MM cells in vitro and in vivo, with a concomitant activation of T cells at very low concentration.

**AFM26**

AFM26 is a bispecific antibody, which targets BCMA on MM cells and CD16A on NK cells (103, 104). AFM26 induces potent NK-cell-mediated cytotoxicity in BCMA+ MM, even when BCMA expression of BCMA was low. AFM26 does not induce NK-cell depletion. It shows similar anti-MM activity, but less inflammatory cytokine secretion, than BiTEs.

**TNB383B and TNB-384B**

TNB383B and TNB-384B are bispecific antibodies targeting BCMA on MM cells and CD3 on T cells, which are generated
based on the basis of \textit{in silico} analysis of heavy chain only/fixed light chain antibody sequences (105). Both Abs showed significant anti-MM cytotoxicity at very low concentration (nano- or pico-molar) and eradicated MM cell growth in mice. In addition, markedly reduced or absence of cytokine release is observed after TNB-383B treatment.

**Anti-CD16A/BCMA/CD200 Antibody**

This trispecific antibody is characterized by bivalent binding to CD16A on NK cells and monovalent binding to BCMA and CD200 on MM cells (106). This dual-targeting structure may increase selectivity of MM cells coexpressing both antigens and improve safety.

**THERAPEUTIC AGENTS TARGETING APRIL**

Therapeutic agents blocking APRIL/BCMA are under investigated as well. A novel mouse anti-human APRIL antibody hAPRIL01A (01A) inhibits the binding of APRIL to BCMA and TACI (117). Importantly, 01A inhibited APRIL- and osteoclast-induced proliferation of MM cells and further induced apoptosis of MM cells in cocultures (33). 01A also enhances the cytotoxicity mediated by IMiDs and PI in the cocultures of MM cells with BCMA-negative BM accessory cells and effector cells. Furthermore, APRIL induces expression of genes involved in immunosuppression, such as PD-L1, TGF-β, and IL-10, are decreased in MM cells following 01A treatment (33). The early phase clinical trial of BION-1301, a fully humanized 01A mAb, is ongoing (118).

**PERSPECTIVES AND CONCLUSION**

Since its discovery in 1992, accumulating evidence has demonstrated that BCMA is a promising target for immunotherapy in MM (Table 2). CAR T therapy first demonstrated promising clinical efficacy in several phase 1 clinical trials in which high response rates are seen in heavily pretreated RRMM patients. GSK2857916, the first therapeutic BCMA-ADC, also shows impressive clinical efficacy and acceptable safety profile in RRMM resistant to multiple lines of current anti-MM treatments (Table 3). Similar efficacy in clinical trials can be anticipated for other anti-BCMA formats demonstrating highly selective anti-MM activity in preclinical studies.

Ongoing efforts are attempting to make BCMA CAR T therapy more potent, safe, and affordable for patients. To improve clinical efficacy, novel CAR T therapies are being developed to overcome relapse due to reduced tumor antigen, including modification of T cells with two distinct CAR molecules with two different binding domains, or one CAR molecule with two different binding domains in tandem (122–124). To reduce toxicities of conditioning chemotherapy, possible approaches include usage of less toxic conditioning chemotherapy, treating earlier in the disease course with less tumor burden, and improved supportive care (125). For prediction of severe cytokine releasing syndrome (CRS), several inflammation cytokines (especially IL-6) have been evaluated, and models have been established (125, 126). For the treatment of CRS, cytokine-directed therapy with anti-IL6 receptor inhibitor tocilizumab can abrogate toxicities (127, 128). Other strategies to reduce side effects include modification of CAR structure, such as incorporation of suicide genes into the engineered T cells (129–131); adding an inhibitory CAR on engineered T cells to reduce off-target immune response (132); or usage of a small molecule system to control CARs (133, 134). More

| Years | Major findings | Reference |
|-------|----------------|-----------|
| 1992  | BCMA gene was first found, which was located on chromosome band 16p13.1 in a human malignant T-cell lymphoma | (45) |
| 1994  | The structure of BCMA was investigated. BCMA is expressed in mature B cells | (44) |
| 1998  | BCMA gene was identified as a new member of the tumor necrosis factor receptor superfamily | (43) |
| 2000  | BCMA is the receptors of BAFF and a proliferation-inducing ligand | (47–49) |
|       | BCMA is expressed both on the surface and in an intracellular perinuclear structure of myeloma cell | (54) |
|       | Overexpressed BCMA can activate the MAPK pathway and the nuclear factors NF-κB and Elk-1 | |
| 2001  | In mouse model studies, knock out of BCMA had no significant impact on the life span of B cell. The humoral responses and memory responses remained intact | (52) |
| 2002  | Gene array study identified expression of BAFF, TACI, and BCMA in myeloma cells | (65) |
| 2004  | BCMA is necessary for the survival of long-lived bone marrow plasma cells (PCs) | (50) |
|       | BCMA is highly expressed in malignant PCs | (62) |
| 2007  | Anti-BCMA MoAb and antibody–drug conjugate (ADC) were synthesized | (119) |
|       | Preclinical study showed antitumor activity in myeloma cell lines | |
| 2013  | The first anti-BCMA chimeric antigen receptor (CAR) T was synthesized (by NCI) | (41) |
|       | This study confirmed BCMA to be exclusively expressed on malignant PCs | |
| 2014  | Anti-BCMA ADC (GSK2857916) showed antitumor activity by induction of apoptosis and ADCC | (42) |
| 2016  | First phase 1 clinical trial of anti-BCMA CAR T therapy reported | (78) |
|       | First phase 1 clinical trial of anti-BCMA ADC reported (GSK2857916) | (79) |
|       | Promising results of several phase 1 clinical trials | (78, 79, 90) |
| 2017  | High complete response rates to anti-BCMA CAR T therapy in relapsed and refractory multiple myeloma patients | (87, 88) |
**TABLE 3** | Summary of phase 1 clinical trials of anti-B cell maturation antigen (BCMA) agents.

| Name | Enrollment criteria | No. | Prior treatment | Protocol | Results and efficacy | Adverse event (AE) |
|------|---------------------|-----|-----------------|----------|----------------------|-------------------|
| **Antibody–drug conjugate** | RR MM or other hematologic malignancies expressing BCMA | Dose-escalating part 24 (multiple myeloma) | Dose-escalating part 24 (multiple myeloma) | IV infusion for 1 h ever 3 weeks | 1. 1 MR at 0.24 mg/kg 2. 1 VGPR, 3 PR, and 1 MR at doses ≥0.96 mg/kg 3. Clinical benefit rate: 25% | Overall: 23/24 (96%), nausea (42%), fatigue (38%), anemia (29%), chills (29%), pyrexia (29%), thrombocytopenia (29%), dry eye (21%), hypercalcemia (21%) Gr 3/4 SE (>10%): thrombocytopenia, anemia, and neutropenia Severe AEs: 8 (in 6 patients), including 1 unresolved limbal stem cell dysfunction Dose reduction: 4 patients IRR: 7/24 (29%) DLT (+) |
| **Expansion part** | | | | | 1. 1 sCR, 2 CR, 15 VGPR, and 3 PR 2. PFS: 7.9 months | 1. All patients had at least one AE 2. Corneal events (63%), thrombocytopenia/platelet count decreased (57%), anemia (29%), AST increased (29%), and cough (26%) 3. Gr 3/4 AE (≥10%): thrombocytopenia (34%) and anemia (14%) 4. Serious AEs were reported in 40% (14/35) of pts 5. IRRs: 8 (2 GR 1, 3 Gr 2, 3 Gr 3) |
| **Chimeric antigen receptor (CAR) T** | Anti-BCMA CAR (78) | RRMM | Median of 7 prior lines (range 3–13) | 1. Cy (300 mg/m²) 3 doses and Flu (30 mg/m²) 3 doses 2. Followed by dose escalation of CAR T from (0.3, 1, 3, 9) × 10⁶ cells/kg | 1 sCR, 2 VGPR, 1 PR, 8SD | Gr 3/4 AE: lymphopenia (100%), leukopenia (100%), neutropenia (100%), anemia (50%), thrombocytopenia (50%) |
| | bb2121 (120) | RRMM 50% BCMA expression on plasma cells | Median of 7 prior lines (range 3–14) | 1. Lymphodepletion: flu (30 mg/m²)/Cy (300 mg/m²) daily for 3 days 2. Followed by 1 infusion of bb2121 3. 3+3 design with planned dose levels of 50, 150, 450, 800, and 1,200 × 10⁶ CAR T cells | Median follow-up after bb2121 infusion: 15.4 weeks 1. ORR:89% (16/18) 2. ORR:100% (15/15, with 150 × 10⁶ or more CAR T cells) 4CR, 7 VGPR, 4PR (4 MRD-) 3. MTD: 80 × 10⁶ CAR + T-cells | 1. CRS: 15/21 (71%), grade3 (n = 2) 2. Gr 3/4 AE: lymphodepletion, hypotension (n = 4), CRS (n = 2), URI (n = 2), and syncope (n = 2) 3. No DLT 4. 1 death (cardiopulmonary arrest) more than 4 months after bb2121 infusion in a patient with an extensive cardiac history (disease status: sCR) |
| | LCAR-B38M (88, 121) | RRMM ≥3 prior regimens | 1. Median infusion cells: 4.7 (0.6–7.0) × 10⁶/kg, 3 infusions in 6 days | 1. ORR:100%, with 14 sCR, 4 VRPR, 1 PR | 1. CRS:14 (74%), Gr 3/4 (n = 2) 2. No neurologic AEs |

(Continued)
| Name                        | Enrollment criteria                                                                 | No.                                                                 | Prior treatment                                                                                       | Protocol                                                                                   | Results and efficacy | Adverse event (AE)                                                                 |
|-----------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------------|
| RRMM, with extramedullary involvement | RRMM 33 consented 28 eligible 21 infused Median 7 prior lines of therapy (range 3–11) 100% PI and IMiDs refractory 67% Dana refractory 95% had high-risk cytogenetics 67% del17p or TP53 mutation 29% extramedullary disease | 5 (2 with EMD) All relapsed after classical chemotherapy, IMiDs, and PIs 3 with prior auto-HSCT | 1. Pre-CAR-T treatment: fludarabine (25 mg/m²) and cyclophosphamide (250 mg/m²) daily for 3 days (d-5–d-3) 2. 0.62 x 10⁸/kg (median) CAR-T cells for 3 days (d0, d2, and d6) | 1. 1 CR, 1VGPR, 3 PR | 1. Most common AEs: CRS 2. DLT (−) TRM (−) |
| CART-BCMA (90) | RRMM                                                                 | 33 consented 28 eligible 21 infused | Median 7 prior lines of therapy (range 3–11) 100% PI and IMiDs refractory 67% Dana refractory 95% had high-risk cytogenetics 67% del17p or TP53 mutation 29% extramedullary disease | 1. 3 split-dose infusions of CAR T cells (10, 30, 60%) 2. 3 cohorts a. 1–5 x 10⁹ CART cells (n = 9) b. Cy 1,500 mg/m² + 1–5 x 10⁹ CART cells (n = 5) c. Cy 1,500 mg/m² + 1–5 x 10⁹ CART cells (n = 7) | 18 (86%) received full planned dose, and 3 received 40% of dose Efficacy Cohort 1: 1 sCR, 2 VGPR, 1 PR, 2 MR Cohort 2: 1 PR, 1 MR Cohort 3: 3 CR, 3 PR, 1 MR CAR T cell expansion By qPCR: 100% By FCM: 90% | 1. Cohort 1 data Grade 3/4 SE: hypophosphatemia (n = 3), hypocalcemia (n = 2), anemia, neutropenia, lymphopenia, thrombocytopenia, hypofibrinogenemia, fatigue, pneumonia, UTI, elevated ALP and AST, hypokalemia, hypertension, and pleural effusion 2. CRS Cohort 1: 18 (3 grade 3/4, with 4 receiving tocilizumab) Cohorts 2/3: 9 (3 grade 3, none requiring tocilizumab) 3. Neurotoxicity Cohort 1: 2 (grade 4 encephalopathy) Cohorts 2/3: 1 (grade 2 confusion/aphasia) 4. DLT (−) |

ALP, alkaline phosphatase; AST, aspartate aminotransferase; auto-HSCT, autologous hematopoietic stem cell transplantation; Bort, bortezomib; Car, carfilzomib; CRS, cytokine releasing syndrome; Cy, cyclophosphamide; Dana, daratumumab; DOR, duration of response; DLT, dose-limiting toxicity; EMD, extramedullary disease; Flu, fludarabine; FCM, flow cytometry; Gr, grade; IHC, immunohistochemistry; IMiD, immunomodulatory drug; IRR, infusion-related reaction; Len, lenalidomide; MoAb, monoclonal antibody; MR, minimal response; MRD, minimal residual disease; MTD, maximal tolerated dose; ORR, overall response rate; PCR, polymerase chain reaction; PD, progressive disease; PI, proteasome inhibitor; Pom, pomalidomide; PR, partial response; PRES, posterior reversible encephalopathy syndrome; RRMM, relapsed and refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; URI, upper airway infection; UTI, urinary tract infection; VGPR, very good partial response.
cost-effective, time-saving, and more accessible CAR T cell therapies are being developed, including allogeneic CAR T cells or CAR T cells utilizing novel manufacturing processes (93, 94).

For BCMA ADC, the first clinical trial has demonstrated efficacy and safety. ADC delivering highly toxic chemicals into the tumor cells is a highly selective therapy, which is critical since, the conjugated toxic chemicals are extremely deadly. Currently, several novel promising payloads are under development, including α-amanitin, tubulysins, hizoxin, or spliceostatins (135–137). To improve penetration, novel ADC formats such as non-IgG scaffolds or non-internalizing mAb scaffolds, may be applied to anti-BCMA ADC (138). Besides modification of ADC structure, combinations of ADC with other antitumor agents with different mechanisms of action are also under further investigation. Given that immune checkpoint inhibitors have clinical efficacy in several cancers, studies evaluating the clinical efficacy of combining immune checkpoint inhibitors with BCMA ADC are also warranted in MM (139).

Bispecific T-cell engagers are currently evaluated in preclinical studies. These anti-BCMA agents with excellent anti-MM effect will soon be investigated in clinical trials. Unlike CAR T cell therapy, BiTEs have a relatively short serum half-life and may not stimulate persistent immunity against cancer cells (140). Because it is difficult to maintain serum levels with bolus or intermittent infusion, continuous intravenous infusion may be needed (141). Importantly, long half-life molecules of BCMA BiTEs have been generated (85) and are currently being tested in a clinical trial. As CRS and neurotoxicity are also observed after BiTE treatment, close monitoring and adequate management for these side effects is very important (142). BCMA BiTEs mainly mediate their anti-MM effect by recruiting nearby cytotoxic T-cells to MM cells. However, the function of T cells is severely impaired in heavily pretreated MM patients (143, 144). To optimize BiTE anti-MM activity, studies are evaluating combination therapy with other anti-MM agents or immune checkpoint blockers.

Besides MM, anti-BCMA therapies may have therapeutic potential in other BCMA-expressing malignancies. For example, BAFF-R, BCMA, and TACI are all expressed on primary cells from patients with precursor B-cell acute lymphoblastic leukemia. Moreover, survival of leukemia cells is promoted by binding of BAFF and APRIL to their receptors, suggesting the therapeutic potential of targeting this signaling pathway (145).

Other malignancies, such as Waldenstrom macroglobulinemia and glioblastoma/astrocytomas, also express BCMA on their cell surface (146, 147) and may benefit from these BCMA targeted therapies.

As BCMA is exclusively expressed on PCs, anti-BCMA treatment will reduce the number of long-lived PCs. Since long-lived PCs play a critical role in maintaining humoral immunity, the impact of anti-BCMA therapy on immune function needs to be carefully and serially evaluated. To address this issue, more clinical observation and correlative studies are warranted. Another potential complicating factor in anti-BCMA immunotherapy is high serum level of sBCMA, cleaved from BCMA by γ-secretase. In MM patients, high levels of sBCMA have been detected, especially in the setting of progressive disease (68). In preclinical studies, sBCMA slightly influenced the potency (shift in EC50 values) but not the maximal lysis mediated by BI 836909 (84). GSK2857916 still induced significant MM1S cell lysis in the presence of MM1S culture supernatant (42). On the other hand, sBCMA level is markedly decreased in patients after successful CAR T cell therapy (78). More clinical studies are needed to determine whether the level of sBCMA can potentially interfere with efficacy of anti-BCMA treatment. Inhibition of γ-secretase to reduce the formation of sBCMA and enhance the expression of BCMA on MM cells is another novel treatment approach.

In conclusion, BCMA-based immunotherapy is a promising in MM. It is anticipated that most of these anti-BCMA approaches, alone and in combinations with immune checkpoint inhibitors, and as well as cancer vaccines, will be evaluated in clinical studies and offer the promise of more selective, better tolerated, anti-MM therapy.

AUTHOR CONTRIBUTIONS

Y-TT and S-FC reviewed literature and designed and wrote this paper. Y-TT and KA critically reviewed and edited the paper.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin (2018) 68(1):7–30. doi:10.3322/caac.21442
2. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc (2003) 78(1):21–33. doi:10.4065/78.1.21
3. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med (2011) 364(11):1046–60. doi:10.1056/NEJMra1011442
4. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med (2005) 352(24):2487–98. doi:10.1056/NEJMoa053445
5. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia (2014) 28(5):1122–8. doi:10.1038/leu.2013.313
6. San Miguel JF, Schlager R, Khuageva NK, Dimopoulos MA, Shlipergel O, Kroppf M, et al. Bortezomib plus melphalan and prednisone for initial treatment
of multiple myeloma. *N Engl J Med* (2008) 359(9):906–17. doi:10.1056/NEJMoa0804179
7. Rodrigo, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GERM study. *Blood* (2012) 120(8):1589–96. doi:10.1182/blood-2012-02-048922
8. Lauber JP, Voorhees PM, Hassoun H, Jakubowiak A, Loniad S, Richardson PG. Current strategies for treatment of relapsed/refractory multiple myeloma. *Expert Rev Hematol* (2014) 7(1):97–111. doi:10.1587/17440866.2014.882764
9. Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its preclinical precursor. *J Clin Invest* (2012) 122(10):3456–63. doi:10.1172/JCI61888
10. Morgan GI, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer* (2012) 12(5):335–48. doi:10.1038/nrc3257
11. Manier S, Salem KZ, Park J, Landau DA, Getz G, Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol* (2017) 14(2):100–13. doi:10.1038/nrclinonc.2016.122
12. Fowler JA, Mundy GR, Lwin ST, Edwards CM. Bone marrow stromal cells create a permissive microenvironment for myeloma development: a new stromal role for Wnt inhibitor Dkk1. *Cancer Res* (2012) 72(9):2183–9. doi:10.1158/0008-5472.CAN-11-2067
13. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nat Rev Cancer* (2007) 7(8):585–98. doi:10.1038/ncr2189
14. An G, Acharya C, Feng X, Wen K, Zhong M, Zhang L, et al. Osteoclasts promote immune suppressive microenvironment in multiple myeloma: therapeutic implication. *Blood* (2016) 128(12):1590–603. doi:10.1182/blood-2016-03-707547
15. Vacca A, Ria R, Semeraro F, Merchionne F, Coluccia M, Boccarelli A, et al. Endothelial cells in the bone marrow of patients with multiple myeloma. *Blood* (2003) 102(9):3340–8. doi:10.1182/blood-2003-04-1338
16. Zheng Y, Cai Z, Wang S, Zhang X, Qian J, Hong S, et al. Macrophages are abundant component of myeloma microenvironment and protect myeloma cells from chemotheraphy drug-induced apoptosis. *Blood* (2009) 114(17):3625–8. doi:10.1182/blood-2009-05-220285
17. Braga WM, da Silva BR, de Carvalho AC, Maekae YH, Bortoluzoo AR, Rizzatti EG, et al. FOXP3 and CTLA4 overexpression in multiple myeloma bone marrow as a sign of accumulation of CD4(+) T regulatory cells. *Cancer Immunol Immunother* (2014) 63(11):1189–97. doi:10.1007/s00262-014-1589-9
18. Feng X, Zhang L, Acharya C, An G, Wen K, Qiu L, et al. Targeting CD38 suppresses induction and function of T regulatory cells to mitigate immunosuppression in multiple myeloma. *Clin Cancer Res* (2017) 23(15):4290–300. doi:10.1158/1078-0432.CCR-16-3192
19. Kawano Y, Zavidij O, Park J, Moschetta M, Roccaro AM, et al. Blocking IFNAR1 inhibits multiple myeloma-driven Treg expansion and immunosuppression. *J Clin Invest* (2018) 126(8):2487–99. doi:10.1172/JCI88169
20. Leone P, Berardi S, Frassanito MA, Ria R, De Re V, Cicco S, et al. Dendritic cells accumulate in the bone marrow of myeloma patients where they protect tumor suppressor plasma cells from CD8(+) T-cell killing. *Blood* (2015) 126(12):1443–51. doi:10.1182/blood-2015-01-623975
21. Chauhan D, Singh AV, Brahmandam M, Carrasco R, Bandi M, Hideshima T, et al. Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. *Cancer Cell* (2009) 16(4):309–23. doi:10.1016/j.ccl.2009.04.018
22. Gorgun GT, Whitehill G, Anderson JL, Hideshima T, Cej M, Cagnetta A, et al. Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. *Cancer Cell* (2009) 16(4):309–23. doi:10.1016/j.ccl.2009.04.018
23. Corre J, Mahtouk K, Attal M, Gadelorge M, Huynh A, Fleury-Cappellesso S, et al. Bone marrow mesenchymal stem cells are abnormal in multiple myeloma. *Leukemia* (2007) 21(5):1079–88. doi:10.1038/sj.leu.2404621
24. Urashima M, Ogata A, Chauhan D, Vidrales MB, Troh G, Hoshi Y, et al. Interleukin-6 promotes multiple myeloma cell growth via phosphorylation of retinoblastoma protein. *Blood* (1996) 88(6):2219–27.
58. Neri P, Kumar S, Fulciniti MT, Vallet S, Chhetri S, Mukherjee S, et al. B-lymphocyte-induced maturation, alleviation of osteoclastogenesis in a severe combined immunodeficient human multiple myeloma model. J Clin Invest (2003) 112(2):286–97. doi:10.1172/JCI18025
59. Novak AJ, Darce JR, Arendt BK, Harder H, Henderson K, Kindsvogel W, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood (2004) 103(2):689–94. doi:10.1182/blood-2003-06-2043
60. Chiu A, Xu W, He B, Dillon SR, Gross JA, Sievers E, et al. Hodgkin lymphoma cells express TACI and BCMA receptors and generate survival and proliferation signals in response to BAFF and APRIL. Blood (2007) 109(2):729–39. doi:10.1182/blood-2006-04-015958
61. Lee L, Draper B, Chaplin N, Philip B, Chin M, Galas-Filipowicz D, et al. An APRIL-based chimeric antigen receptor for dual targeting of BCMA and TACI in multiple myeloma. Blood (2018) 131(7):746–58. doi:10.1182/blood-2017-05-781351
62. Claudio JO, Masih-Khan E, Tang H, Goncalves J, Voralia M, Li ZH, et al. A molecular complement of genes expressed in multiple myeloma. Blood (2002) 100(6):2175–86. doi:10.1182/blood-2002-01-0008
63. Seckinger A, Delgado JA, Moser S, Moreno L, Neuber B, Grab A, et al. Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody EM801 for multiple myeloma treatment. Cancer Cell (2017) 31(3):396–410. doi:10.4049/ccell.2017.02.002
64. Ghermezi M, Li M, Vardeny S, Harutyunyan NM, Gottlieb J, Berenson A, et al. Serum BAFF maturation antigen: a novel biomarker to predict outcomes for multiple myeloma patients. Haematologica (2017) 102(4):785–95. doi:10.3324/haematol.2016.150896
65. Sanchez E, Li M, Kitto A, Li J, Wang CS, Kirk DT, et al. Serum BAFF maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. Br J Haematol (2015) 168(6):727–38. doi:10.1111/j.1365-2457.2014.12924.x
66. Sanchez E, Smith EL, Yashar MA, Patil S, Li M, Porter AL, et al. The role of BAFF maturation antigen in the biology and management of, and as a potential therapeutic target in, multiple myeloma. Target Oncol (2018) 13(1):39–47. doi:10.1007/s11722-017-0538-x
67. Bellucci R, Alvey EP, Chiarretti S, Wu CJ, Zorn E, Weller E, et al. Graft-versus-tumor response in patients with multiple myeloma is associated with antibody response to BCMA, a plasma-cell membrane receptor. Blood (2005) 105(10):3945–50. doi:10.1182/blood-2004-11-4463
68. Fragoudaki M, Boula A, Tsirakis G, Pararas F, Spanoudakis M, Papadakis IS, et al. BAFF cell-activating factor: its clinical significance in multiple myeloma patients. Ann Hematol (2012) 91(9):1413–8. doi:10.1007/s00277-012-1470-x
69. Day ES, Cachero TG, Qian F, Sun Y, Wen D, Pelletier M, et al. Selectivity of BAFF, APRIL, and APRILI for binding to the TNF family receptors BAFFR/BR3 and BCMA. Biochemistry (2005) 44(16):1919–31. doi:10.1021/bi040827k
70. Wallweber HJ, Compaa DM, Starosvnik MA, Hymowitz SG. The crystal structure of a proliferation-inducing ligand, APRIL. J Mol Biol (2004) 343(2):283–90. doi:10.1016/j.jmb.2004.08.040
71. Moreaux J, Sprynski AC, Dillon SR, Mahtourak K, Jourdian M, Ythier A, et al. APRIL and TACI interact with syndecan-1 on the surface of multiple myeloma cells to form an essential survival loop. Eur J Haematol (2009) 83(2):119–29. doi:10.1111/j.1600-0609.2009.01262.x
72. Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. Immunotherapy (2015) 7(11):1187–99. doi:10.2217/imt.15.77
73. Hengeveld PJ, Kersten MJ. B-cell activating factor in the pathophysiology of multiple myeloma: a target for therapy? Blood Cancer J (2015) 5:e282. doi:10.1038/bjc.2015.3
74. Matthes T, McKee T, Dunand-Sautier I, Manfroi B, Park S, Passweg J, et al. Myelopoiesis dysregulation associated to sustained APRIL production in multiple myeloma-infiltrated bone marrow. Leukemia (2015) 29(9):1901–8. doi:10.1038/leu.2015.68
75. Ali SA, Shi V, Maric I, Wang M, Stonecek DF, Rose JJ, et al. T cells expressing an anti-B-cell maturation chimeric antigen receptor cause remissions of multiple myeloma. Blood (2016) 128(13):1688–700. doi:10.1182/blood-2016-04-711903
76. Cohen AD, Popat R, Trude S, Richardson PG, Libby IIIEN, Lendvai N, et al. First in human study with GSK2857916, an antibody drug conjugated to
microtubule-disrupting agent directed against b-cell maturation antigen (BCMA) in patients with relapsed/refractory multiple myeloma. Blood (2016) 128(22):2127.

79. Mathur R, Barnett BE, Hermanson D, He J, Zhang Z, Rengarajan S, et al. A novel BCMA-specific, centyrin-based, PiggyBac®-transposed CAR-T memory stem cells are effective against p53+/− and patient-derived multiple myeloma tumors. Blood (2016) 130(Suppl 1):3068.

80. Lam N, Alabanza I, Trinklein N, Buelow B, Kochenderfer JN. T cells expressing anti-B-cell maturation antigen (BCMA) chimeric antigen receptors with antigen recognition domains made up of only single human heavy chain variable domains specifically recognize BCMA and eradicate tumors in mice. Blood (2016) 128(22):2121.

81. Liu L, Xing L, Acharya CM, Wen K, Liu J, Hsieh P, et al. CD8+ anti-BCMA mRNA CAR T-cells effectively kill human multiple myeloma cells in vitro and in vivo. Blood (2017) 130(Suppl 1):3067.

82. Wang X, Barnett BE, Martin C, Hermanson D, Li X, Smith J, et al. Production of universal anti-BCMA CAR-T cells with reduced alloreactivity, but potent effector function for the treatment of multiple myeloma. Blood (2017) 130(Suppl 1):503.

83. Panowski SH, Kuo T, Chen A, Geng T, Van Blarcom TJ, Lindquist K, et al. Preclinical evaluation of a potent anti-BCMA CD3 bispecific molecule for the treatment of multiple myeloma. Blood (2016) 128(22):383.

84. Moreno L, Zabaleta A, Ailgnani D, Lasa M, Maiso P, Jelinek T, et al. New insights into the mechanism of action (MoA) of first-in-class IgG-based Bcma T-cell specific bispecific antibody (TCB) for the treatment of multiple myeloma (MM). Blood (2016) 128(22):2096.

85. Pillarsetti K, Baldwin E, Babich A, Majewski N, Barone L, Li Y, et al. Development of a new MAXCADC3 Dubody® antibody for multiple myeloma. Blood (2016) 128(22):2116.

86. Gantke T, Reusch U, Ellwanger K, Fueck I, Weichel M, Treder AFM – a novel CD16a-directed bispecific TandAb targeting bcma for multiple myeloma. Cancer Res (2017) 77(13 Suppl):5671. doi:10.1158/1538-7445.AM2017-5671.

87. Gantke T, Reusch U, Kellner C, Klaus K, Hanseke T, Nackmuss S, et al. AFM26 – targeting B cell maturation antigen (BCMA) for NK cell-mediated immunotherapy of multiple myeloma. Blood (2017) 130(Suppl 1):3082.

88. Buelow B, Pham D, Choudhry P, Dang K, Pratap P, Clarke S, et al. T cell engagement without cytokine storm: a novel Bcma x CD3 antibody killing myeloma cells with minimal cytokine secretion. Blood (2017) 130(Suppl 1):501.

89. Gantke T, Weichel M, Reusch U, Ellwanger K, Fueck I, Griep R, et al. Trispecific antibodies for selective CD16A-directed NK-cell engagement in multiple myeloma. Blood (2016) 128(22):4513.

90. McCombs JR, Owen SC. Antibody drug conjugates: design and selection of linker, payload and conjugation chemistry. AAPS J (2015) 17(2):339–51. doi:10.1208/s12248-014-9710-8.

91. Rudd MD, Luse DS. Amanitin greatly reduces the rate of transcription by RNA polymerase II ternary complexes but fails to inhibit some transcript cleavage modes. J Biol Chem (1996) 271(33):21549–58. doi:10.1074/jbc.271.33.21549.

92. Bhakta S, Raab H, Junutula JR. Engineering THIOmAbs for site-specific conjugation of thiol-reactive linkers. Methods Mol Biol (2013) 1045:189–203. doi:10.1007/978-1-62703-541-5_11.

93. Panowski S, Bhakta S, Raab H, Polakis P, Junutula JR. Site-specific antibody drug conjugates for cancer therapy: MAbs (2014) 6(1):34–45. doi:10.4161/mbas.27022.

94. Baueerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy. Cancer Res (2009) 69(12):4941–4. doi:10.1158/0008-5472.CAN-09-0547.

95. Rischwein K, Parr L, Pflanz S, Volkland J, Lumsden J, Klinger M, et al. Strictly target cell-dependent activation of T cells by bspecific single-chain antibody constructs of the BiTE class. J Immunother (2007) 30(8):798–807. doi:10.1097/CLI.0b013e318156750c.

96. Offner S, Hofmeister R, Romaniuk A, Kufer P, Baueerle PA. Induction of regular cytolytic T cell synapses by bispecific single-chain antibody constructs on MHC class I-negative tumor cells. Mol Immunol (2006) 43(6):763–71. doi:10.1016/j.molimm.2005.03.007.

97. Klein JS, Naganprapagam PN, Galimidi RP, Foglesong CP, West AP Jr, Bjorkman PJ. Examination of the contributions of size and avidity to the neutralization mechanisms of the anti-HIV antibodies b12 and 4E10. Proc Natl Acad Sci U S A (2009) 106(18):7385–90. doi:10.1073/pnas.0811427106.

98. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell therapy: a clinical path to effective cancer immunotherapy. Nat Rev Cancer (2008) 8(4):299–308. doi:10.1038/nrc2355.

99. Van L, Shang J, Kang L, Shi X, Zhou J, Jin S, et al. Combined infusion of CD19 and BCMA-specific chimeric antigen receptor T cells for RRMM: initial safety and efficacy report from a Clinical Pilot Study. Blood (2017) 130(Suppl 1):506.

100. Guadagnoli M, Kimberley FC, Phan U, Cameron K, Vink PM, Rodermond H, et al. Development and characterization of APRIL antagonistic monoclonal
antibodies for treatment of B-cell lymphomas. Blood (2011) 117(25): 6656–65. doi:10.1182/blood-2011-03-330852

118. Dudes J, Dziessen L, van Zandvoort P, van de Crommert J, Skoble J, Nair N, et al. Bion-1301, a first-in-class APRIL neutralizing antibody for the treatment of multiple myeloma: preclinical safety, and analysis of pharmacokinetics – pharmacodynamics relationship. Blood (2017) 130(Suppl 1):1827.

119. Ryan MC, Herimg M, Peckham D, McDonagh CF, Brown L, Kim KM, et al. Antibody targeting of B-cell maturation antigen on malignant plasma cells. Mol Cancer Ther (2007) 6(11):3009–18. doi:10.1158/1535-7163.MCT-07-0464

120. Berdeja JG, Lin Y, Raje N, Munshi N, Siegel D, Liedtke M, et al. Dur able clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: updated results from a Multicenter Study of bb2121 Anti-Bcma CAR T cell therapy. Blood (2017) 130(Suppl 1):740.

121. Mi J-Q, Fan X, Xu J, Liu Y, Zhuang Y, Yang S, et al. Effective treatment of relapsed/refractory multiple myeloma including extramedul lary involvement by BCMA-specific chimeric antigen receptor-modified T cells. Blood (2017) 130(Suppl 1):3115.

122. Ruella M, Barrett DM, Kenderian SS, Shes tova O, Hofmann TJ, Perazzelli J, et al. Dual CD19 and CD123 targeting prevents antigen-loss relapses after CD19-directed immunotherapies. J Clin Invest 2016) 126(10):3814–26. doi:10.1172/JCI87366

123. Zah E, Lin MY, Silva-Benedict A, Chen YY. T cells expressing CD19/CD20 bispecific chimeric antigen receptors prevent antigen escape by malignant B cells. Cancer Immunol Res (2016) 4(6):498–508. doi:10.1158/2326-6066.CIR-15-0231

124. Hegde M, Mukherjee M, Grada Z, Pignata A, Landi D, Navi SA, et al. Tandem CAR T cells targeting HER2 and IL13Ralpha2 mitigate tumor antigen escape. J Clin Invest 2016) 126(8):3036–52. doi:10.1172/JCI83416

125. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2012) 126(4):97–109. doi:10.1182/blood-2011-09-376277

126. Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, Frey N, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov (2016) 6(6):664–79. doi:10.1158/2159-8290.CD-16-0040

127. Teachey DT, Rheingold SR, Maude SL, Zuga maier G, Barrett DM, Seif AE, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood (2013) 121(26):5154–7. doi:10.1182/blood-2013-02-485623

128. Maude SL, Frey N, Shaw PA, Apelenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med (2014) 371(16):1507–17. doi:10.1056/NEJMoa1407222

129. Quintarelli C, Vera JF, Savoldo B, Giordano Attianese GM, Pule M, Foster AE, et al. Co-expression of cytokine and suicide genes to enhance the activity and safety of tumor-specific cytotoxic T lymphocytes. Blood (2007) 110(8): 2793–802. doi:10.1182/blood-2007-02-72843

130. Di Stasi A, Tey SK, Dotti G, Fujita Y, Kennedy-Nasser A, Martinez C, et al. Inducible apoptosis as a safety switch for adoptive cell therapy. N Engl J Med (2011) 365(18):1673–83. doi:10.1056/NEJMoa1106152

131. Ramos CA, Asgari Z, Liu E, Yvon E, Hoslop HE, Rooney CM, et al. An inducible caspase 9 suicide gene to improve the safety of mesenchymal stem cell therapies. Stem Cells 2010) 28(6):1107–15. doi:10.1002/stem.433

132. Fedorov VD, Themeli M, Sadelain M, PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses. Sci Transl Med (2013) 5(215):215ra172. doi:10.1126/scitranslmed.3006597

133. Juillerat A, Marechal A, Filhol JM, Valton J, Ducrert A, Poitot L, et al. Design of chimeric antigen receptors with integrated controllable transient functions. Sci Rep (2016) 6:18950. doi:10.1038/srep18950

134. Wu CY, Roybal KT, Puchner EM, Ounffer J, Lim WA. Remote control of therapeutic T cells through a small molecule-gated chimeric receptor. Science (2015) 350(6258):aab4077. doi:10.1126/science.aab4077

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