B-cell maturation antigen (BCMA) in multiple myeloma: the new frontier of targeted therapies

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***Abstract*:** Outcomes of patients with multiple myeloma (MM) who become refractory to standard therapies are particularly poor and novel agents are greatly needed to improve outcomes in such patients. B-cell maturation antigen (BCMA) has become an important therapeutic target in MM with three modalities of treatment in development including antibody–drug conjugates (ADCs), bispecific T-cell engagers (BITEs), and chimeric antigen receptor (CAR) T-cell therapies. Early clinical trials of anti-BCMA immunotherapeutics have demonstrated extremely promising results in heavily pretreated patients with relapsed/refractory MM (RRMM). Recently, belantamab mafodotin was the first anti-BCMA therapy to obtain approval in relapsed/refractory MM. This review summarizes the most updated efficacy and safety data from clinical studies of BCMA-targeted therapies with a focus on ADCs and BITEs. Additionally, important differences among the BCMA-targeted treatment modalities and their clinical implications are discussed.

Keywords: ADC, antibody–drug conjugate, BCMA, bifunctional antibodies, BITE, CAR T-cell, chimeric antigen receptor T-cell therapy, monoclonal antibody, multiple myeloma, myeloma, relapsed refractory multiple myeloma

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Introduction

Although the survival of patients with multiple myeloma (MM) has drastically improved over the last two decades due to advances in treatment, in particular with proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), MM remains incurable and patients eventually relapse. The addition of novel therapies, such as CD38 monoclonal antibodies (moAbs), to IMiD- and PI-backbone regimens has improved outcomes in patients with relapsed and refractory multiple myeloma (RRMM).[1–5] However, patients who become refractory to existing therapies have a very poor prognosis, with a median overall survival (OS) ranging from 5.6 to 9.2 months in those who are 'penta-refractory' (or refractory to 1 CD38 moAb + 2 IMiDs + 2 PIs) and 'triple-refractory and quad-refractory' (refractory to 1 CD38 moAb + 1 or 2 IMiDs + 1 PI, or 1 CD38 moAb + 1 IMiD + 1 or 2 PIs).[6] Subsequent treatment options in such patients are limited and novel agents for the treatment of RRMM are therefore needed.

B-cell maturation antigen (BCMA) has become an important target for the development of novel immunotherapeutics in MM. Recent reviews on BCMA-targeted therapies have been published, providing an overview on the biology of BCMA and preclinical and clinical studies of novel BCMA-based therapies.[7–9] The current modalities of BCMA-targeted therapies in development include antibody–drug conjugates (ADCs), bispecific T-cell engagers (BITEs), and chimeric antigen receptor (CAR)-modified T-cell therapies. This review summarizes the most updated efficacy and safety data from clinical studies of BCMA-targeted therapies with a comprehensive focus on currently available clinical trial data of ADCs and BITEs. Additionally, we highlight important differences among the BCMA-targeted treatment modalities and their clinical implications.

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B-cell maturation antigen

In brief, BCMA is a member of the tumor necrosis factor receptor superfamily and is highly expressed on mature B lymphocytes, with minimal expression on hematopoietic stem cells or nonhematopoietic tissue.[10] Moreover, in preclinical studies, overexpression of BCMA and the interaction with is ligand, a proliferation-inducing ligand (APRIL), was found to promote MM progression *in vivo* and augment MM cell growth and survival through induction of multiple signaling cascades, including protein kinase B (AKT), MAPK, and nuclear factor (NF)-κB.[11] Additionally, BCMA has been shown to be solubilized at high levels in serum of patients with MM (sBCMA).[12] This form of sBCMA binds to B-cell activating factor (BAFF). The role of BAFF is to stimulate normal B-cell and plasma cell development; however, this functioning is prevented when it is bound by BCMA in the serum, thereby leading to decreased polyclonal immunoglobulin levels in patients with MM.[12] Given the above, BCMA has been an ideal target for the development of therapeutics in MM.

Furthermore, sBCMA has been identified as a potential biomarker for monitoring disease status and OS of patients with MM.[13] sBCMA has been noted to be more highly expressed in the serum of patients with MM with progressive disease compared with those with responsive disease.[13] sBCMA levels above the median have also been correlated with shorter OS and progression-free survival (PFS).[13,14] Given its short half-life, levels of sBCMA also appear to respond more rapidly to therapy as compared to M-protein.[15,16] Clinical studies of BCMA-targeted therapies will help to further elucidate the role of sBCMA as a predictor of response to therapy and survival.

Anti-BCMA antibody–drug conjugates in multiple myeloma

ADCs are made up of a tumor-specific antibody and a cytotoxic payload joined together by a synthetic chemical linker.[17] Currently approved ADCs in other cancers include gemtuzumab ozogamicin (CD33 targeted),[18] brentuximab vedotin (CD30 targeted),[19] and inotuzumab ozogamicin (CD22 targeted),[20] in hematological malignancies as well as trastuzumab emtansine (HER2 targeted)[21] in breast cancer. As seen in these and other clinical studies of ADCs, ADCs often demonstrate a narrow therapeutic index and improving the therapeutic window of ADCs to optimize safety and efficacy remains an important aspect of clinical development of ADCs.[17]

Below we discuss the safety and efficacy data from the first-in-class anti-BCMA monoclonal antibody belantamab mafodotin, as well as other ADCs in early clinical development including AMG224, MEDI2228 and HDP-101 in RRMM (summarized in Table 1).

Belantamab mafodotin

Belantamab mafodotin is a humanized IgG1 monoclonal anti-BCMA antibody conjugated to the microtubule-disrupting agent monomethyl auristatin-F (MMAF), which leads to direct cell death following internalization and release of its cytotoxic moiety (cys-mcMMAF).[22,23] In the phase I clinical trial DREAMM-1 (ClinicalTrials.gov identifier: NCT02064387), belantamab mafodotin (previously known as GSK2857916) demonstrated impressive single-agent activity at a dose of 3.4 mg/kg with an overall response rate (ORR) of 60% and a median PFS of 12 months in a heavily pretreated, refractory patient population.[22] Moreover, of the 13 patients in the study with prior daratumumab treatment and who were refractory to both an IMiD and PI, the ORR was 38.5% with a median PFS of 6.2 months. Based on the preliminary results of the ongoing phase II, randomized DREAMM-2 clinical trial (ClinicalTrials.gov identifier: NCT03525678),[24] the US Food and Drug Administration (FDA) granted accelerated approval to belantamab mafodotin (Blenrep, GlaxoSmithKline) in August of 2020 as monotherapy for adult patients with RRMM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a PI and an IMiD, making it the first anti-BCMA therapy approved anywhere. In the DREAMM-2 trial, patients with RRMM who had received three or more lines of therapy and who were refractory to previous IMiDs and PIs as well as refractory or intolerant (or both) to an anti-CD38 monoclonal antibody were randomized to receive either 2.5 mg/kg or 3.4 mg/kg Blenrep *via* intravenous infusion every 3 weeks on day 1 of each cycle until disease progression or unacceptable toxicity. Of the 196 patients included in the intention-to-treat population ($n = 97$ in the 2.5 mg/kg cohort and $n = 99$ in the 3.4 mg/kg cohort), the ORR was 31% and 34% in the 2.5 mg/kg and 3.4 mg/kg cohorts,

Table 1. Clinical trials of anti-BCMA antibody–drug conjugates in RRMM.

Clinical trials with available data							
Trial	**Phase**	**Regimen**	**Study status**	***n***	**ORR (%)**	**Median PFS (mo)**	**AEs of interest**
DREAMM-1 (NCT02064387)	I	Belantamab mafodotin monotherapy	Completed	79	60	12	Keratopathy: 69% (majority Gr 1 or 2) Thrombocytopenia (all grades): 63% IRRs: 29% (majority Gr 1 or 2)
DREAMM-2 (NCT03525678)	II	Belantamab mafodotin monotherapy	Active, not recruiting	97 (2.5 mg/kg dosing cohort) 99 (3.4 mg/kg dosing cohort)	31 (2.5 mg/kg dosing cohort) 35 (3.4 mg/kg dosing cohort)	2.8 (2.5 mg/kg dosing cohort) 3.9 (3.4 mg/kg dosing cohort)	Keratopathy: 43% (Gr 1 or 2), 27% (Gr 3) (2.5 mg/kg cohort) 54% (Gr 1 or 2), 20% (Gr 3) (3.4 mg/kg cohort) Thrombocytopenia (all grades): 35% (2.5 mg/kg cohort) 58% (3.4 mg/kg cohort) IRRs: 18% (2.5 mg/kg cohort) (majority Gr 1 or 2) 15% (3.4 mg/kg cohort) (majority Gr 1 or 2)
DREAMM-6 (NCT03544281)	I/II	Belantamab mafodotin + bortezomib/dexamethasone (B-Vd) or lenalidomide/dexamethasone (B-Rd)	Recruiting	18 (B-Vd 2.5 mg/kg dosing cohort)*	78%	–	Keratopathy: 44% (Gr 1 or 2), 56% (Gr 3, no Gr 4 events) Thrombocytopenia: 61% (Gr 3 or 4) IRRs: 17% (all Gr 2)
AMG 224 (NCT02561962)	I	AMG 224 monotherapy	Active, not recruiting	40**	23%	–	Keratopathy: 36% (all Gr 1 or 2) Thrombocytopenia: 24% (Grade 3 or higher) IRRs: 3% (Gr 2)
MEDI2228 (NCT03489525)	I	MEDI2228 monotherapy	Recruiting	82	61% (0.14 mg/kg dosing cohort)	–	Keratopathy: not observed (0.14 mg/kg cohort) Thrombocytopenia: 32% (0.14 mg/kg cohort)

(Continued)

Table 1. (Continued)

Ongoing clinical trials				
Trial	**Phase**	**Regimen**	**Study status**	*n*
A phase I/II Multi-Center, Open Label, Dose Escalation Study to Determine the RP2D, Safety and Efficacy of GSK2857916 in Combination With Pomalidomide and Low-Dose Dexamethasone in Subjects With Relapsed and/or Refractory Multiple Myeloma (NCT03715478)	I/II	Belantamab mafodotin + pomalidomide (4 mg)/ dexamethasone	Recruiting	62
A phase I/II Single Arm Open-Label Study to Explore Safety and Clinical Activity of GSK2857916 Administered in Combination With Pembrolizumab in Subjects With Relapsed/Refractory Multiple Myeloma (DREAMM 4; NCT03848845)	II	Belantamab mafodotin (2.5 mg/kg and 3.4 mg/ kg) + pembrolizumab	Recruiting	40
Platform Study of Belantamab Mafodotin as Monotherapy and in Combination With Anti-cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 5; NCT04126200)	I/II	Belantamab mafodotin + GSK3174998 (sub-study 1) Belantamab mafodotin + GSK3359609 (sub-study 2) Belantamab mafodotin + nirogacestat (sub-study 3) Belantamab mafodotin + dostarlimab (sub-study 4) *versus* belantamab mafodotin monotherapy	Recruiting	464
DREAMM 7: A Multicenter, Open-Label, Randomized phase III Study to Evaluate the Efficacy and Safety of the Combination of Belantamab Mafodotin, Bortezomib, and Dexamethasone (B-Vd) Compared With the Combination of Daratumumab, Bortezomib and Dexamethasone (D-Vd) in Participants With Relapsed/Refractory Multiple Myeloma (DREAMM 7; NCT04246047)	III	Belantamab mafodotin + bortezomib/ dexamethasone *versus* Daratumumab + bortezomib/ dexamethasone	Recruiting	478
A phase III, Multicenter, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Belantamab Mafodotin in Combination With Pomalidomide and Dexamethasone (B-Pd) *versus* Pomalidomide Plus Bortezomib and Dexamethasone (PVd) in Participants With Relapsed/Refractory Multiple Myeloma (DREAMM 8; NCT04484623)	III	Belantamab mafodotin + pomalidomide/ dexamethasone *versus* Bortezomib + pomalidomide/ dexamethasone	Recruiting	450
A phase I, Open-label Study to Evaluate the Safety, Pharmacokinetics, Immunogenicity, and Preliminary Efficacy of MEDI2228 in Subjects With Relapsed/Refractory Multiple Myeloma (NCT03489525)	I	MEDI2228 monotherapy	Recruiting	142

*Preliminary efficacy and safety data have been presented for 18 patients treated with B-Vd (2.5 mg/kg dosing cohort) in the part 2 dose-expansion portion of study.
**Dose-escalation cohort.
AE, adverse event; BCMA, B-cell maturation antigen; Gr, grade; IRR, infusion-related reaction; mg/kg, milligram/kilogram; mo, months; *n*, sample size; NCT, ClinicalTrials.gov identifier; ORR, overall response rate; PFS, progression-free survival; RRMM, relapsed and refractory multiple myeloma.

respectively, with a very good partial response (VGPR) or better achieved in about 20% of patients in each cohort. At a median duration of follow-up of 6.3 months (2.5 mg/kg cohort) and 6.9 months (3.4 mg/kg cohort), the median duration of response (DOR) was not reached. Median PFS was 2.9 months and 4.9 months in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. OS data were not yet mature at the time of primary analysis. Given the short duration of follow-up in the primary analysis, longer follow-up is needed to assess durability of responses. Updated efficacy and safety data at median duration of follow-up of 9 months were recently presented, showing an ORR of 31% and 35%, median PFS of 2.8 and 3.9 months, median DOR 11 [95% confidence interval (CI): 4.2–not reached (NR)] and 6.2 (95% CI: 4.8–NR) months in the 2.5 mg/kg ($n = 97$) and 3.4 mg/kg ($n = 99$) cohorts, respectively.[25]

Efficacy results of the pivotal DREAMM-1 and DREAMM-2 studies and additional studies of Blenrep in combination with standard-of-care or novel agents that are ongoing are summarized in Table 1. DREAMM-6 is an ongoing, phase I/II, two-part, two-arm study of Blenrep combined with either bortezomib/dexamethasone (B-Vd) or lenalidomide/dexamethasone (B-Rd) with RRMM previously treated with $\geqslant 1$ prior line of therapy. Early efficacy and safety data from the Blenrep + Vd arm of the DREAMM-6 study (ClinicalTrials.gov identifier: NCT03544281) were recently presented.[26] A total of 59 patients have been treated to date in the B-Vd arm, with 18 patients having received 2.5 mg/kg of Blenrep as a single dose every 3 weeks combined with standard-dose Vd in 21-day cycles. At data cut-off, patients had received a median of 18.2 (6.0–46.4) weeks on treatment. Of the 18 patients who have received Blenrep 2.5 mg/kg + Vd in the part II dose-expansion portion of the study, the ORR was 78% with 50% achieving VGPR. DOR was not yet reached at time of analysis.

From the safety data available to date in the early phase trials of Blenrep, apart from hematologic toxicities, an important toxicity that has been observed has been keratopathy (changes to the corneal epithelium as seen by ophthalmologic examination which may occur with or without symptoms). In the DREAMM-1 study, corneal events were reported in 69% of patients, with the majority being Grade 1 or 2. The most common adverse events (AEs) reported in DREAMM-2 were Grade 1 or 2 keratopathy in 43% and 54% of the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively, and most common Grade 3 or 4 AEs were keratopathy in 27% and 21%, thrombocytopenia in 20% and 33%, and anemia in 20% and 25% of the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. The most commonly reported corneal symptoms were blurred vision and dry eyes. The majority of infusion-related reactions (IRRs) were Grade 1 and 2 and occurred in less than 20% of patients in both dosing cohorts. Dose reductions were necessary in 29% and 41% of patients in the 2.5 and 3.4 mg/kg cohorts, respectively, and dose reductions and dose delays due to keratopathy occurred in 23% and 27%, and 47% and 48% of the dosing cohorts, respectively. Early safety data in DREAMM-6 showed no unexpected safety signals with the combination of Blenrep + Vd. Grade 3 and 4 AEs occurred in 89% of patients, with Grade 3 and 4 thrombocytopenia occurring in 61% of patients and Grade 3 keratopathy occurring in 56% of patients (no Grade 4 corneal events were reported). In 28% of patients, AEs led to permanent discontinuation of study treatment. Understanding the underlying mechanisms of drug-induced keratopathy and effective management strategies will be very important going forward. Corneal events have been further characterized in both the DREAMM-1 and DREAMM-2 studies and guidelines for Blenrep dose modifications based on eye examination findings have been published.[27,28] Corneal examinations of patients on Blenrep should include a slit lamp examination to identify corneal changes and a best-corrected visual acuity assessment to detect changes from baseline. On slit lamp examination, corneal changes typically appear as small lesions within the corneal epithelium.[28] In a literature review, similar corneal findings have been reported with other MMAF-containing ADCs although the pathophysiology is not yet clearly understood.[28] Importantly, the DREAMM-2 ocular sub-study reported no benefit of prophylactic steroid drops to the development of corneal epitheliopathy compared with lubricant eye drops alone.[24] Of the 18% of patients experiencing changes in visual acuity in the DREAMM-2 study, 82% have recovered as of last follow-up and no permanent vision loss has been noted to date.[28] Management of corneal events generally includes dose delays and reductions until improvement of

symptoms. Moreover, future strategies to ameliorate drug-induced toxicities will likely include extending dosing intervals (i.e. every 4–6 week dosing *versus* every 3 week dosing).

AMG 224

AMG 224 is an anti-BCMA IgG1 antibody conjugated with mertansine (DM1), an anti-tubulin maytansinoid, through a non-cleavable linker and has shown clinical activity in a first-in-human phase I study.[29] Patients with RRMM having received ⩾3 prior lines of therapy including an IMiD and PI were included in the study. A total of 40 patients received study treatment (29 in the dose-escalation portion at doses of 30–250 mg and 11 in the dose-expansion portion at 3 mg/kg) and were a heavily pretreated patient population with a median of seven lines of prior therapy. The maximum tolerated dose (MTD) for AMG 224 monotherapy was determined to be 190 mg every 3 weeks. The ORR was 23% with a median DOR in the dose-escalation group of 14.7 (4.1–29.8) months. As seen with Blenrep, hematologic toxicities including thrombocytopenia and ocular toxicities were reported with AMG224. In the dose-escalation cohort, common Grade ⩾3 AEs were thrombocytopenia (24%) and anemia (21%); all treatment-emergent ocular AEs were Grade 1 or occurred in 21% of patients. In the dose-expansion cohort, common Grade ⩾3 treatment-emergent AEs (TEAEs) were thrombocytopenia (55%), neutropenia (27%), and anemia (18%); treatment-emergent ocular AEs were also all Grade 1 or 2 and occurred in 36% of patients. Overall, AMG in this phase I trial has demonstrated single-agent activity in a heavily pretreated RRMM patient population with a manageable safety profile, warranting further clinical development.

MEDI2228 and HDP-101

MEDI2228 is an anti-BCMA ADC composed of a fully human antibody site conjugated to a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer *via* a protease-cleavable linker, which leads to DNA damage and apoptotic cell death upon release. Preclinical models have demonstrated that MEDI2228 is cytotoxic to both MM cells and myeloma progenitor cells and remains active in the presence of clinically relevant levels of sBCMA.[30] Preclinical models have also shown synergistic activity of MEDI2228 combined with bortezomib and DNA damage-response inhibitors.[31] Results from a phase I, first-in-human, dose-escalation and expansion trial of MEDI2228 (ClinicalTrials.gov identifier: NCT03489525) in patients with RRMM who have progressed on three classes of standard-of-care anti-MM agents (including a PI, IMiD, and moAb) were presented at the 2020 American Society of Hematology (ASH) annual meeting.[32] MEDI2228 was administered in sequentially ascending dose levels (0.0125, 0.25, 0.05, 0.1, and 0.2 mg/kg) *via* intravenous infusion every 3 weeks. A total of 82 patients were enrolled. Patients had received 2–11 lines of prior therapy. The MTD was determined to be 0.14 mg/kg every 3 weeks. The most common TEAEs in the 0.14 mg/kg cohort included photophobia (54%), thrombocytopenia (32%), rash (30%), increased gamma-glutamyltransferase (24%), dry eye (20%), and pleural effusion (20%). Keratopathy or loss of visual acuity were not observed. Although clinical efficacy was demonstrated at all dose levels, the 0.14 mg/kg cohort exhibited the highest ORR at 61% with median DOR not reached. Of note, 90% of patients in the 0.14 mg/kg cohort had received prior daratumumab. In this heavily pretreated RRMM patient population who has received a PI, IMiD, and moAb, MEDI2228 0.14 mg/kg every 3 weeks appears to demonstrate impressive single-agent clinical activity.

HDP-101 is an anti-BCMA ADC linked to α-amantin, which binds to RNA polymerase II subunit A and inhibits cellular transcription. Preclinical evaluation of HDP-101 has demonstrated activity in myeloma cell line models, and preliminary data has shown that HDP-101 may be preferentially active in del17p myeloma.[33] Early phase in-human trials of HDP-101 are in development.

Anti-BCMA/CD3 bispecific antibodies in multiple myeloma

Bispecific antibodies are designed to have affinities for two different epitopes which allows for either monovalent or bivalent binding to two targets.[34] Immune cell-engaging bispecific antibodies bind to both the CD3 T-cell receptor and tumor-associated antigen, which forms a cytolytic synapse leading to release of perforin and cytotoxic granzyme-B and killing of the target cell.[34]

There are a number of BITEs targeting BCMA on MM cells and CD3 receptors on T-cells currently being studied in MM. Below we discuss the available safety and efficacy data from early phase trials of anti-BCMA/CD3 BITEs including teclistamab, AMG 420 and AMG 701, REGN5458, CC-93269, and PF-06863135 in RRMM (summarized in Table 2).

Teclistamab

Teclistamab (JNJ-64007957) is a humanized IgG4 bispecific monoclonal antibody that binds to both BCMA and CD3 receptors on T-cells. Initial results from the part 1 dose-escalation portion of the first-in-human phase I study of teclistamab (ClinicalTrials.gov identifier: NCT 03145181) in patients with RRMM who had previously been treated with a PI and an IMiD have been presented.[35] In the study, patients received teclistamab intravenously in dosing groups ranging from 0.3 μg/kg to 720 μg/kg. Patients had received a median of six prior lines of therapy (2–14) and 80% were triple-class refractory and 41% were penta-drug refractory. A total of 78 patients have been treated in the dose-escalation portion of the study, with response rates increased with higher doses of teclistamab. Of the 12 patients who received 270 μg/kg, the ORR was 67% (with 50% achieving VGPR or better). Response data for the 720 μg/kg was not yet mature. Additionally, of five patients evaluable for minimal residual disease (MRD) analysis, four (80%) achieved MRD negativity. The most common AEs of any grade were anemia, cytokine release syndrome (CRS), neutropenia, and thrombocytopenia occurring in 58%, 56%, 45% and 40% of patients, respectively. Grade 3 or higher anemia, neutropenia, and thrombocytopenia occurred in 36%, 38% and 24% of patients. All CRS events were Grade 1 or 2 and there was no treatment discontinuation due to CRS. Teclistamab appears to have an acceptable safety profile and the initial efficacy results are very encouraging particularly given the refractory patient population in this study. Updated results from this study and newly available data for subcutaneous teclistamab have been presented with 84 and 44 patients in the intravenous (0.3–720 μg/kg) and subcutaneous (80–3000 μg/kg) teclistamab arms, respectively.[36] Of 120 patients evaluable for response, the highest and most active dose levels were determined to be 270 μg/kg and 720 μg/kg weekly for intravenous administration and 720 μg/kg and 1500 μg/kg weekly for subcutaneous administration. Of 47 patients within these four dose levels, the ORR was 64%. Overall, this updated study analysis showed a relatively unchanged safety profile. Of note, CRS did tend to occur later with subcutaneous administration (median time to onset of 1 day *versus* 2 days for intravenous *versus* subcutaneous administration, respectively). Given the encouraging efficacy and safety data, a phase II monotherapy trial with subcutaneous teclistamamb at the recommended phase II dose of 1500 μg/kg is planned. Teclistamab is also being explored in a phase I study in combination with daratumumab (ClinicalTrials.gov identifier: NCT04108195).

AMG 420 and AMG 701

AMG 420, formerly known as BI-836909, is a BCMA/CD3 BITE molecule that has been investigated in patients with RRMM.[37] In the first-in-human dose-escalation study in patients with RRMM who had received at least two prior lines of therapy, including an IMiD and PI, AMG 420 was given at doses ranging from 0.2 μg/d to 800 μg/d for up to 10 cycles *via* continuous intravenous administration for 4 weeks on and 2 weeks off treatment in 6-week cycles. Forty-two patients were included in the analysis, with the study ORR being 31%. However, significant responses were observed at the 400 μg/d dose, with 7 (70%) of 10 patients responding, including 5 MRD-negative CRs, 1 VGPR, and 1 partial response (PR). The median DOR at this dose was 9 months. The MTD was determined to be 400 μg/d. Sixteen of 42 patients (38%) experienced CRS, with the majority (13/16) being Grade 1. The most common serious AEs of all grades were infection in 33% and polyneuropathy in 5%. Although AMG 420 demonstrated clinical activity in RRMM, continuous intravenous dosing poses a significant challenge. Thus, AMG 420 development has been suspended at this time and further clinical development of a half-life extended BCMA BITE molecule (AMG 701) is being pursued.

AMG 701 in preclinical studies has shown potent T-cell mediated lysis of MM cell lines *in vitro*, including IMiD-resistant cell lines.[38] Additionally, IMiD pre-treatment enhanced AMG 701-mediated T-cell dependent cytotoxicity against MM cells and induced a more pronounced immunomodulation even in the presence of osteoclasts or bone marrow stromal cells. Moreover, the combination of

Table 2. Clinical trials of anti-BCMA × CD3 T-cell engaging bispecific antibodies in RRMM.

Trial	Phase	Regimen	Study status	*n*	ORR (%)	AEs of interest
Clinical trials with available data						
Teclistamab (NCT03145181)	I	Teclistamab monotherapy	Recruiting	78	67% (*n* = 12)*	Anemia: 58% Neutropenia: 45% Thrombocytopenia: 40% (All Gr) CRS: 56% (Gr 1 and 2; no high-grade events) Infections: 19% (all Gr)
AMG 420 (NCT03836053)	I	AMG 420 monotherapy	Active, not recruiting	42	31%	CRS: 38% (majority Gr 1) Infections: 33% (all Grades)
AMG 701 (NCT03287908)	I	AMG 701 monotherapy	Recruiting	75	36%	Anemia: 43% Neutropenia: 23% Thrombocytopenia: 20% CRS: 61% (majority Gr 1 or 2)
REGN5458 (NCT03761108)	2-January	REGN5458 monotherapy	Recruiting	45	36%	Infections: 20% (Gr ⩾ 3) CRS: 38% (majority Gr 1)
CC-93269 (NCT03486067)	I	CC-93269 monotherapy	Recruiting	30	36% (3–6 mg dosing cohort) 89% (>6 mg dosing cohort)	Anemia: 37% Neutropenia: 43% Thrombocytopenia: 17% (Gr ⩾ 3) Infections:30% (Gr ⩾ 3) CRS: 77% (all Gr)
PF-06863135 (NCT03269136)	I	PF-06863135 monotherapy (IV** and SC† dosing)	Recruiting	16** 18†	1/16 (6%) MR** 6/16 (35%) SD** 33%†	Anemia**: 18% Thrombocytopenia**: 24% (all Gr) CRS**: 24% (all Gr) Anemia†: 50% Thrombocytopenia†: 39% (all Gr) CRS†: 61% (all Gr 1 or 2)
TNB-383B (NCT03933735)	I	TNB-383B monotherapy	Recruiting	38	52% [5.4–40 mg dosing cohorts]	Anemia: 16% Thrombocytopenia: 13% (Gr 3/4) CRS: 21% (all Gr 1 or 2)

(Continued)

Table 2. (Continued)

Ongoing clinical trials				
Trial	**Phase**	**Regimen**	**Study status**	***n***
A phase Ib Study of Subcutaneous Daratumumab Regimens in Combination With Bispecific T Cell Redirection Antibodies for the Treatment of Subjects With Multiple Myeloma (NCT04108195)	I	Daratumumab + teclistamab	Recruiting	100
A phase I/II Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of **AMG 701** in Subjects With Multiple Myeloma (ParadigMM-1B) (NCT03287908)	2-January	AMG 701 monotherapy	Recruiting	270
Phase I/II FIH Study of REGN5458 (Anti-BCMA × Anti-CD3 Bispecific Antibody) in Patients With Relapsed or Refractory Multiple Myeloma (NCT03761108)	2-January	REGN5458 monotherapy	Recruiting	74
A Multicenter, phase I (Open-label, Dose-escalation and Expansion Study of TNB-383B, a Bispecific Antibody Targeting BCMA in Subjects With Relapsed or Refractory Multiple Myeloma	I	TNB-383B monotherapy	Recruiting	72
(NCT03933735)				

*Efficacy data for 270 µg/kg dosing cohort, efficacy data for 720 µg/kg dosing cohort not yet mature.
**Efficacy and safety data for evaluable patients from intravenous PF-06863135 monotherapy dosing cohorts.
†Efficacy and safety data for evaluable patients from subcutaneous PF-06863135 monotherapy dosing cohorts.
AE, adverse event; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; Gr, grade; IV, intravenous; mg, milligram; MR, minimal response; *n*, sample size; NCT, ClinicalTrials.gov identifier; ORR, overall response rate; RRMM, relapsed and refractory multiple myeloma; SC, subcutaneous; SD, stable disease.

an IMiD and AMG 701 significantly enhanced anti-tumor activity in xenograft mouse models. These findings support the ongoing phase I trial of AMG 701 monotherapy in patients with RRMM (NCT03287908) and provide rationale for further investigation of AMG 701 in combination with IMiDs. Initial results of the ongoing phase I trial of AMG 701 monotherapy have been presented.[39] AMG 701 was administrated in three dosing cohorts (5–45 µg, 0.14–1.2 mg, and 1.6–12 mg) *via* weekly intravenous infusion in 4-week cycles until disease progression. Seventy-five patients received AMG 701. This was a heavily pretreated patient population with a median of 6 (1–25) prior lines of therapy, and 68% were triple-class refractory. The most common hematological and non-hematological AEs were anemia (43%), neutropenia (23%), thrombocytopenia (20%), diarrhea (31%), fatigue (25%), and fever (25%). CRS occurred in 61% of patients, with the majority being Grade 1 or 2. Overall at doses of 3–12 mg, the ORR was 36% (16/45). In six patients who underwent earlier escalation to achieve a target dose of

9 mg, the ORR was 83% (three PRs and two VGPRs). This encouraging early data supports further evaluation of AMG 701.

REGN5458

REGN5458 is another anti-BCMA and anti-CD3 bispecific antibody currently being evaluated in a phase I trials in patients with RRMM who have had >3 prior lines of therapy, including a PI, IMiD and anti-CD38 antibody or progression on or after an anti-CD38 antibody and refractory to a PI and IMiD (ClinicalTrials.gov identifier: NCT03761108). Safety and efficacy data for 45 patients enrolled in the dose-escalation portion of the study have been presented.[40] Patients had received a median of 5 (2–17) prior lines of therapy. All were refractory to an anti-CD38 moAb and 53% were penta-refractory. REGN5458 was administered over six dose levels from 3 mg to 96 mg. The most common treatment-related AEs included CRS (38%), fatigue (18%), nausea (18%), and myalgias (13%). Of patients experiencing CRS, 88% were Grade 1 and no patients experienced Grade 3 or greater CRS. Infection-related AEs occurred in 47% of patients, 20% of which were Grade ⩾3. The ORR across all dose levels was 36% and in the highest dose level was 60%. Moreover, the ORR was 17% in patients with extramedullary plasmacytomas. Additionally in this heavily pretreated population, responses were durable with a DOR of ⩾4 months in 44% and ⩾8 months in 19%. We await further data from the ongoing phase I dose-escalation and phase II portions of this trial.

CC-93269

CC-93269 is a bispecific antibody that binds BCMA and CD-3 T-cells. Initial results of the first-in-human phase I trial (ClinicalTrials.gov identifier: NCT03486067), evaluating the safety and tolerability of the agent in patients with RRMM who have received 3 or more prior regimens and were naïve to BCMA-directed therapy, have been presented.[41] CC-03269 was administered in doses ranging from 0.15 mg to 10 mg. Of the 30 patients that have received treatment, the ORR in patients treated with CC-93269 at the 3–6 mg and >6 mg dose were 36% and 89%, respectively. No responses were noted in the ⩽3 mg dosing group. Moreover, 17% of patients achieved a stringent complete response (sCR), and of the nine patients in the 10 mg dosing cohort, the sCR rate was 44%. As far as the safety profile, the majority of patients (97%) experienced a TEAE, with 73% having a Grade ⩾3 AE. The most common Grade ⩾3 AEs included neutropenia (43%), anemia (37%), infections (30%) and thrombocytopenia (17%). CRS of any grade was observed in 77% of patients. One patient death on trial was attributed to CRS, who had received an initial dose of 6 mg and a second dose of 10 mg. Ongoing enrollment and longer-term follow-up will more accurately delineate the safety and efficacy profile of CC-93269 and allow for determination of the recommended phase II dose.

PF-06863135

PF-06863135 (PF-3135) is a humanized bispecific anti-BCMA/CD3 monoclonal paired on an IgG2a backbone by hinge-mutation technology. Findings from the dose-escalation portion of an ongoing, multicenter, open-label, phase I study (ClinicalTrials.gov identifier: NCT03269136) of PF-3135 in patients with RRMM previously treated with a PI, IMiD, and an anti-CD38 moAb have been reported.[42] PF-3135 was administered intravenously once weekly in six dose-escalation groups. Of the 16 patients evaluable for efficacy, one (6%) patient had a minimal response and six (35%) patients had stable disease (SD) across dose levels. TEAEs of any grade were observed in 59% if patients, with the majority being Grade 1 and 2, including CRS (24%), thrombocytopenia (24%), anemia (18%), and pyrexia (18%). Given the preliminary evidence of anti-MM activity with intravenous PF-3135, subcutaneous dose escalation was also initiated in this study with the potential to reduce maximum concentration (C_{max}) and achieve a more favorable therapeutic window and initial safety and efficacy data has been presented.[43] Of 18 patients who received subcutaneous PF-3135, the ORR was 33% overall and 75% at the two highest dose levels (215 and 360 μg/kg). The most common TEAEs were CRS (61%), anemia (50%), thrombocytopenia (39%), injection site reaction (33%) and lymphopenia (33%). The majority of CRS were Grades 1 and 2, and subcutaneous administration of PF-3135 did reduce the C_{max}, allowing for administration of higher doses of drug without increased severity of observed CRS. This study is ongoing with additional dosing cohorts

accruing, including in combination with either PF-06801591 or lenalidomide.

TNB-383B

TNB-383B is a BCMA x CD3 bispecific T-cell redirecting antibody that incorporates a unique anti-CD3 moiety, which preferentially activates effector over regulatory T-cells, and 2 heavy-chain-only anti-BCMA moieties. Initial results of the first-in-human phase I dose-escalation and expansion trial of TNB-383B (ClinicalTrials.gov identifier: NCT03933735) in patients with RRMM who have had at least three prior lines of therapy (including a PI, IMiD, and anti-CD38 moAb) are reported.[44] TNB-383B was administered with escalating doses (0.025–40 mg) intravenously every 3 weeks. Patients enrolled had received a median of 7 (4–13) prior lines of therapy. Of 38 patients dosed, the most common AEs were CRS (21%) and headache (13%). All CRS events were Grade 1 or 2. At doses of 5.4–40 mg, the ORR was 52% with a median DOR of 9 (3–21) weeks. This study is ongoing.

CAR T-cell therapy in multiple myeloma

CARs consist of tumor-associated antigen-targeted single-chain variable fragments that are connected to intracellular signaling domains and costimulatory domains.[8] CAR T-cells are genetically modified T-cells that express a CAR against specific tumor-associated antigen. Upon binding, T-cell activation leads to cellular lysis and death.[8] CAR T-cell therapy in MM, specifically anti-BCMA CAR T-cell therapy, is more advanced in clinical development as compared to ADCs and bispecific antibodies. Early phase data of anti-BCMA CAR T-cell therapy has demonstrated impressive responses in RRMM. Recently published reviews as well as a meta-analysis provide a comprehensive summary of the efficacy and safety data of numerous CAR T-cell constructs currently in clinical trials.[7,8,45] Below, we highlight the most recent updates of the anti-BCMA CAR T-cell constructs bb2121, orvacabtagene autoleucel, and JNJ-68284528.

Idecabtagene vicleucel

Idecabtagene vicleucel (bb2121; Ide-cel) showed a manageable safety profile and promising clinical activity in patients with RRMM in the phase I study.[46] Initial results of the pivotal phase II KarMMa trial (ClinicalTrials.gov identifier: NCT03361748) of bb2121 in patients with RRMM who had received ⩾3 prior regimens (with previous exposure to an IMiD, PI, and anti-CD38 monoclonal antibody) and refractory to last line of therapy are very encouraging.[47] Ide-cel was administered at three dose levels: 150, 300, and 450×10^6 CAR T-cells. Eighty-four percent of patients were triple refractory. The ORR across 128 treated patients was 73%. CR or better and MRD negativity was achieved in 26% of patients. Clinically meaningful responses were observed across subgroups, including patients with high-risk cytogenetics and those with triple- and penta-refractory disease. At a median follow-up of 13.3 months, the median DOR was 10.7 (95% CI: 9.0–11.3) months and the median PFS was 8.8 (95% CI: 5.6–11.6) months. In patients who achieved CR/sCR, the median DOR was 19.0 months and median PFS was 20.2 months. Long-term follow-up data are needed to ascertain the durability of responses. Cytopenias were common, and infections occurred in 69% of patients. Any grade CRS was observed in 84% of patients, the majority of which was Grade 1. Five deaths occurred within 8 weeks of ide-cel infusion, three of which were attributed to AEs (CRS, aspergillus pneumonia, and gastrointestinal hemorrhage).

Orvacabtagene autoleucel

Orvacabtagene autoleucel (orva-cel, also known as JCARH125) is a fully human CAR T-cell therapy with a 4-1BB costimulatory domain currently being investigated in a multicenter phase I/II trial (ClinicalTrials.gov identifier: NCT03430011; EVOLVE) in patients with RRMM who have received ⩾3 prior regimens, a PI, an IMiD and an anti-CD38 monoclonal antibody. Updated results of 51 patients treated with higher dose levels (300, 450, and 600×10^6 CAR T-cells) in the phase I/II EVOLVE trial have been presented.[48] Of the 51 patients, 94% were triple-refractory and 48% were penta-refractory.

In this heavily pretreated RRMM patient population, the ORR across dosing cohorts was 92% with 36% of patients achieving CR/sCR. CRS of any grade occurred in 89% of patients, with only 3% experiencing Grade ⩾3 CRS. Grade ⩾3 neurological events occurred in 13% of patients. Cytopenias were common at all dose levels, with

Grade ⩾3 neutropenia, anemia, thrombocytopenia occurring in 90%, 48% and 47%, respectively. Grade ⩾3 infections occurred in 13% of patients. Importantly, CAR T-cell persistence was maintained in 69% of patients at month 6. Moreover, all patients with high baseline sBCMA achieved a PR or better. These results are very encouraging and enrollment at the recommended phase II dose of 600×10^6 CAR T-cells is ongoing.

Ciltacabtagene autolecel

Ciltacabtagene autolecel (cilta-cel, also known as JNJ-68284528 or JNJ-4528) contains two BCMA-targeting single-domain antibodies being investigated in the phase Ib/II study CARTITUDE-1 (ClinicalTrials.gov identifier: NCT03548207) in patients with RRMM who have received ⩾3 prior regimens or were double refractory to a PI and IMiD, and received anti-CD38 antibody. Preliminary phase Ib/II data from CARTITUDE-1 have been presented.[49] Cilta-cel was administered as a single infusion at a target dose of 0.75×10^6 ($0.5–1.0 \times 10^6$) CAR T-cells 5–7 days after start of lymphodepletion. A total of 97 patients have been enrolled (29 in phase Ib and 68 in phase II). Patients had received a median of 6 (3–18) prior lines of therapy, with 84% being penta-refractory. The ORR was 95% and median DOR not reached. The 6-month PFS and OS rates were 87% and 94%, respectively. Grade 3/4 hematological toxicities, including neutropenia, anemia, and thrombocytopenia, occurred in 91%, 68%, and 60% of patients. Overall, 95% of patients experienced CRS, with only 4% of observed CRS events being Grade 3 or 4. Grade ⩾3 neurological events occurred in 10% of patients. Given the impressive early efficacy results, JNJ-4528 has been granted Breakthrough Therapy Designation status by the US FDA and phase II (CARTITUDE-2; ClinicalTrials.gov identifier: NCT04133636) and phase III trials (CARTITUDE-4; ClinicalTrials.gov identifier: NCT04181827) are underway.

Clinical considerations of BCMA-targeted therapies

There are a number of differences between the BCMA-targeted modalities of treatment that have been discussed in previous reviews.[7,8,50] Outlined in Table 3 and highlighted below are key differences, such as production time, administration routes, toxicities, and immune-expansion capabilities, among the BCMA-targeted modalities and their implications on clinical practice.

A distinct difference between ADCs and BITEs as compared with CAR T-cell therapies is production time. ADCs and BITEs are available as 'off-the-shelf' reagents. Although CAR T-cell therapies have traditionally required a prolonged production process (typically on the order of weeks) given that a patient's leukocytes need to be collected and manufactured prior to treatment, 'off-the-shelf', or allogeneic CAR T-cell therapies, are also currently under development. CYAD-211 is an allogeneic CAR T-cell therapy planned for phase I study (ClinicalTrials.gov identifier: NCT04613557).

At present, in patients with rapidly progressive disease, CAR T-cell therapy may become practically challenging and necessitate bridging chemotherapy to make treatment with CAR T-cell therapy feasible. Both ADCs and BITEs have the advantage of immediate availability in such cases. An important consideration between the choice of ADC and BITE therapy is the concept of T-cell exhaustion.[50] BITEs may be more effective and should be considered in less heavily pretreated patients as they rely on endogenous T-cell effector function, which declines with each subsequent line of therapy. This concept may also affect the capability of BITE cells to produce potent and durable immune expansion in contrast to CAR T-cell therapies.

Early clinical trials of ADCs, BITEs, and CAR T-cell therapies have identified important therapy-related toxicities. Cytopenias are a common among the three modalities. Keratopathy is an emerging toxicity that has been observed with ADCs, although development of management strategies are underway, as discussed previously, to improve the risk profile. CRS and neurotoxicity observed with BITEs and CAR T-cell therapies have been overall manageable with agents such as IL-6 inhibitors and steroids. Unlike ADCs and BITEs, CAR T-cell therapies have added toxicity due to need for lymphodepletion.

Another drawback to inherent to BITEs are their short half-life, which require continuous infusion treatments that raise a practical challenge given they are less convenient than other administration

Table 3. Key differences among BCMA-targeted therapies in MM.

	ADCs	BITEs	CAR T-cells
Production time	"Off-the-shelf"	'Off-the-shelf'	Prolonged manufacturing time
Administration	–	Challenge of continuous infusion protocols	Require inpatient administration
Toxicities	1. IRRs 2. Thrombocytopenia 3. Keratopathy	1. CRS 2. Cytopenias	1. CRS 2. Neurotoxicity 3. Cytopenias 4. Toxicities related to lymphodepletion regimen
Immune expansion	Do not rely on patients' endogenous effector T-cells	Rely on patients' endogenous effector T-cells Decreased capability for *in vivo* T-cell immune expansion and persistence	Long-term *in vivo* T-cell immune expansion and persistence

ADC, antibody–drug conjugate; BITE, bispecific T-cell engager; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; IRR, infusion-related reaction; MM, multiple myeloma.

routes. Efforts are underway to develop half-life extended BITE molecules, such as AMG 701.

Conclusion

In summary, early clinical trials of BCMA-targeted immunotherapeutics have shown very promising efficacy results and manageable safety profiles in heavily pretreated patient populations with RRMM, supporting further clinical development of these agents in RRMM. As the first anti-BCMA therapy to gain approval, belantamab mafodotin has made way for a shifting paradigm in the treatment of MM. There are now a number of phase II and III trials of ADC and CAR T-cell therapies underway. KarMMa-3 (ClinicalTrials.gov identifier: NCT03651128) is a phase III study evaluating the efficacy and safety of bb2121 *versus* standard regimens in RRMM and CARTITUDE-4 (ClinicalTrials.gov identifier: NCT04181827) is a phase III study evaluating JNJ-68284528 *versus* pomalidomide/bortezomib/dexamethasone or daratumumab/pomalidomide/dexamethasone in RRMM. Moreover, studies of belantamab mafodotin in combination therapies are ongoing (DREAMM 5; ClinicalTrials.gov identifier: NCT04126200, DREAMM 7; ClinicalTrials.gov identifier: NCT04246047, and DREAMM 8; ClinicalTrials.gov identifier: NCT04484623). Belantamab mafodotin and bb2121 are additionally being studied in newly diagnosed MM (ClinicalTrials.gov identifier: NCT04091126 and KarMMa-4; ClinicalTrials.gov identifier: NCT04196491). As studies of BCMA-targeted therapies move to earlier lines of therapy, they may have the potential to induce deeper and more durable responses in less heavily pretreated and newly diagnosed MM patient populations. The results of these and other ongoing trials of anti-BCMA therapies will undoubtedly change the treatment landscape of MM yet again.

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References

1. Dimopoulos M, Quach H, Mateos MV, *et al.* Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet* 2020; 396: 186–197.
2. Dimopoulos MA, Oriol A, Nahi H, *et al.* Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 1319–1331.
3. Palumbo A, Chanan-Khan A, Weisel K, *et al.* Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 754–766.
4. Moreau P, Dimopoulos M-A, Mikhael J, *et al. Isatuximab plus carfilzomib and dexamethasone vs carfilzomib and dexamethasone in relapsed/refractory multiple myeloma (IKEMA): interim analysis of a phase 3 randomized, open-label study*. Presented at virtual edition of the 25th European Hematology Association (EHA) Annual Congress, 12 June 2020. Abstract LB2603.
5. Attal M, Richardson PG, Rajkumar SV, *et al.* Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet* 2019; 394: 2096–2107.
6. Gandhi UH, Cornell RF, Lakshman A, *et al.* Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; 33: 2266–2275.
7. Cho S-F, Lin L, Xing L, *et al.* BCMA-targeting therapy: driving a new era of immunotherapy in multiple myeloma. *Cancers (Basel)* 2020; 12: 1473.
8. Shah N, Chari A, Scott E, *et al.* B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia* 2020; 34: 985–1005.
9. Yu B, Jiang T and Liu D. BCMA-targeted immunotherapy for multiple myeloma. *J Hematol Oncol* 2020; 13: 125.
10. Novak AJ, Darce JR, Arendt BK, *et al.* Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. *Blood* 2004; 103: 689–694.
11. Tai YT, Acharya C, An G, *et al.* APRIL and BCMA promote human multiple myeloma growth and immunosuppression in the bone marrow microenvironment. *Blood* 2016; 127: 3225–3236.
12. Sanchez E, Gillespie A, Tang G, *et al.* Soluble B-cell maturation antigen mediates tumor-induced immune deficiency in multiple myeloma. *Clin Cancer Res* 2016; 22: 3383–3397.
13. Sanchez E, Li M, Kitto A, *et al.* Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. *Br J Haematol* 2012; 158: 727–738.
14. Ghermezi M, Li M, Vardanyan S, *et al.* Serum B-cell maturation antigen: a novel biomarker to predict outcomes for multiple myeloma patients. *Haematologica* 2017; 102: 785–795.
15. Bujarski S, Soof C, Chen H, *et al.* Serum B-cell maturation antigen levels to predict progression-free survival and responses among relapsed or refractory multiple myeloma patients treated on the phase I IRUX trial. *J Clin Oncol* 2018; 36(Suppl. 15): e24313.
16. Udd K, Soof C, Etessami S, *et al.* Changes in serum B-cell maturation antigen levels are a rapid and reliable indicator of treatment efficacy for patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2017; 7: e27–e28.
17. Coats S, Williams M, Kebble B, *et al.* Antibody-drug conjugates: future directions in clinical and translational strategies to improve the therapeutic index. *Clin Cancer Res* 2019; 25: 5441–5448.
18. Jen EY, Ko CW, Lee JE, *et al.* FDA approval: gemtuzumab ozogamicin for the treatment of adults with newly diagnosed CD33-positive acute myeloid leukemia. *Clin Cancer Res* 2018; 24: 3242–3246.
19. Yi JH, Kim SJ and Kim WS. Brentuximab vedotin: clinical updates and practical guidance. *Blood Res* 2017; 52: 243–253.
20. Lamb YN. Inotuzumab ozogamicin: first global approval. *Drugs* 2017; 77: 1603–1610.
21. Verma S, Miles D, Gianni L, *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791.
22. Trudel S, Lendvai N, Popat R, *et al.* Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety

and efficacy from dose expansion phase I study. *Blood Cancer J* 2019; 9: 37.

23. Tai YT, Mayes PA, Acharya C, *et al*. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood* 2014; 123: 3128–3138.
24. Lonial S, Lee HC, Badros A, *et al*. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020; 21: 207–221.
25. Lonial S, Lee HC, Badros A, *et al*. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). *J Clin Oncol* 2020; 38(Suppl. 15): 8536.
26. Nooka AK, Stockerl-Goldstein K, Quch H, *et al*. DREAMM-6: safety and tolerability of belantamab mafodotin in combination with bortezomib/dexamethasone in relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol* 2020; 38(Suppl. 15): 8502.
27. Popat R, Warcel D, O'Nions J, *et al*. Characterization of response and corneal events with extended follow-up after belantamab mafodotin (GSK2857916) monotherapy for patients with relapsed multiple myeloma: a case series from the first-time-in-human clinical trial. *Haematologica* 2020; 105: e261–e263.
28. Farooq AV, Degli Esposti S, Popat R, *et al*. Corneal epithelial findings in patients with multiple myeloma treated with antibody-drug conjugate belantamab mafodotin in the pivotal, randomized, DREAMM-2 study. *Ophthalmol Ther* 2020; 9: 889–911.
29. Lee HC, Raje NS, Landgren O, *et al*. Phase 1 study of the anti-BCMA antibody-drug conjugate AMG 224 in patients with relapsed/refractory multiple myeloma. *Leukemia*. Epub ahead of print 21 April 2020. DOI: 10.1038/s41375-020-0834-9.
30. Kinneer K, Flynn M, Thomas SB, *et al*. Preclinical assessment of an antibody-PBD conjugate that targets BCMA on multiple myeloma and myeloma progenitor cells. *Leukemia* 2019; 33: 766–771.
31. Tai Y-T, Xing L, Lin L, *et al*. MEDI2228, a novel BCMA pyrrolobenzodiazepine antibody drug conjugate, overcomes drug resistance and synergizes with bortezomib and DNA damage response inhibitors in multiple myeloma. *Clin Lymphoma Myeloma* 2019; 19(Suppl): E154–E155.
32. Kumar SK, Migkou M, Bhutani M, *et al*. Phase 1, first-in-human study of MEDI2228, a BCMA-targeted ADC in patients with relapsed/refractory multiple myeloma. *Blood* 2020; 136(Suppl. 1): abstract 179.
33. Singh RK, Jones RJ, Hong S, *et al*. HDP101, a novel B-Cell Maturation Antigen (BCMA)-targeted antibody conjugated to α-Amanitin, is active against myeloma with preferential efficacy against pre-clinical models of deletion 17p. *Blood* 2018; 132(Suppl. 1): 593.
34. Suurs FV, Lub-de Hooge MN, de Vries EGE, *et al*. A review of bispecific antibodies and antibody constructs in oncology and clinical challenges. *Pharmacol Ther* 2019; 201: 103–119.
35. Usmani SZ, Mateos M-V, Nahi H, *et al*. Phase I study of teclistamab, a humanized B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in relapsed/refractory multiple myeloma (R/R MM). *J Clin Oncol* 2020; 38(Suppl. 15): 100.
36. Garfall AL, Usmani SZ, Mateos M-V, *et al*. *Updated phase 1 results of teclistamab, a B-cell Maturation Antigen (BCMA) x CD3 bispecific antibody, in Relapsed and/or Refractory Multiple Myeloma (RRMM)*. Presented as part of the ASH2020 Virtual Scientific Program, 5–8 December 2020. Abstract 180.
37. Topp MS, Duell J, Zugmaier G, *et al*. Anti-B-cell maturation antigen BiTE molecule AMG 420 induces responses in multiple myeloma. *J Clin Oncol* 2020; 38: 775–783.
38. Cho S-F, Lin L, Xing L, *et al*. *AMG 701, a half-life extended anti-BCMA BiTE®, potently induces T cell-redirected lysis of human multiple myeloma cells and can be combined with IMiDs to overcome the immunosuppressive bone marrow microenvironment*. Presented at the 17th International Myeloma Workshop, 12–15 September 2019, Boston, MA. Abstract 169.
39. Harrison SJ, Minnema MC, Lee HC, *et al*. *A phase 1 First in Human (FIH) study of AMG 701, an anti-B-Cell Maturation Antigen (BCMA) Half-Life Extended (HLE) BiTE® (bispecific T-cell engager) molecule, in Relapsed/Refractory (RR) Multiple Myeloma (MM)*. Presented as part of the ASH2020 Virtual Scientific Program, 5–8 December 2020. Abstract 181.

40. Madduri D, Rosko A, Brayer J, *et al. REGN5458, a BCMA x CD3 bispecific monoclonal antibody, induces deep and durable responses in patients with Relapsed/Refractory Multiple Myeloma (RRMM)*. Presented as part of the ASH2020 Virtual Scientific Program, 5–8 December 2020. Abstract 291.

41. Costa LJ, Wong SW, Bermúdez A, *et al. First clinical study of the B-cell maturation antigen (BCMA) 2+1 T cell engager (TCE) CC-93269 in patients (pts) with relapsed/refractory multiple myeloma (RRMM): interim results of a phase 1 multicenter trial*. Presented at the 2019 ASH Annual Meeting, 7 December 2019, Orlando, FL.

42. Raje NS, Jakubowiak A, Gasparetto C, *et al.* Safety, clinical activity, pharmacokinetics, and pharmacodynamics from a phase I study of PF-06863135, a B-Cell Maturation Antigen (BCMA)-CD3 bispecific antibody, in patients with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* 2019; 34(Suppl. 1): 1869.

43. Lesokhin AM, Levy MY, Dalovisio AP, *et al. Preliminary safety, efficacy, pharmacokinetics, and pharmacodynamics of Subcutaneously (SC) administered PF-06863135, a B-Cell Maturation Antigen (BCMA)-CD3 bispecific antibody, in patients with Relapsed/Refractory Multiple Myeloma (RRMM)*. Presented as part of the ASH2020 Virtual Scientific Program, 5–8 December 2020. Abstract 3206.

44. Rodriguez C, D'Souza A, Shah N, *et al. Initial results of a phase I study of TNB-383B, a BCMA x CD3 bispecific T-cell redirecting antibody, in relapsed/refractory multiple myeloma*. Presented as part of the ASH2020 Virtual Scientific Program, 5–8 December 2020. Abstract 293.

45. Roex G, Timmers M, Wouters K, *et al.* Safety and clinical efficacy of BCMA CAR T-cell therapy in multiple myeloma. *J Hematol Oncol* 2020; 13: 164.

46. Raje N, Berdeja J, Lin Y, *et al.* Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med* 2019; 380: 1726–1737.

47. Munshi NC, Anderson LD, Shah N, *et al.* Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T-cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): initial KarMMa results. *J Clin Oncol* 2020; 38(Suppl. 15): 8503.

48. Mailankody S, Jakubowiak AJ, Htut M, *et al.* Orvacabtagene autoleucel (orva-cel), a B-cell maturation antigen (BCMA)-directed CAR T cell therapy for patients (pts) with relapsed/refractory multiple myeloma (RRMM): update of the phase 1/2 EVOLVE study (NCT03430011). *J Clin Oncol* 2020; 38(Suppl. 15): 8504.

49. Madduri D, Berdeja JG, Usmani SZ, *et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma*. Presented as part of the ASH2020 Virtual Scientific Program, 5–8 December 2020. Abstract 177.

50. Slaney CY, Wang P, Darcy PK, *et al.* CARs versus BiTEs: a comparison between T cell-redirection strategies for cancer treatment. *Cancer Discov* 2018; 8: 924–934.