The evolving status of immunotherapies in multiple myeloma: the future role of bispecific antibodies

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Summary

Treatment outcomes in multiple myeloma (MM) have improved dramatically over the past 10 years. However, patients with high-risk disease such as those with Stage III disease by the Revised International Staging System, the presence of adverse cytogenetics, or who are refractory to proteosome inhibitors, immunomodulatory drugs and monoclonal antibodies may have dismal outcomes. These patients represent an urgent ongoing need in MM. One of the hallmarks of MM is immune dysfunction and a tumour-permissive immune microenvironment. Ameliorating the immune-paresis could lead to improved outcomes. The role of immunotherapies has been growing at an exponential pace with numerous agents under development in clinical trials. In the present review, we provide an overview of immunotherapies in MM, focussing on bispecific antibodies (BsAbs). We review efficacy outcomes from the published clinical trials and consider the important safety aspects of these therapies, in particular the risk of cytokine-release syndrome and immune effector cell-associated neurotoxicity syndrome, and how these compare with patients receiving chimeric antigen receptor T cells. We discuss the MM epitopes being targeted by BsAbs, either in clinical or preclinical stages, and we consider where these therapies might best fit within the future ever-changing paradigm of MM treatment.

Keywords: myeloma, immunotherapy, antibody therapy, bispecific antibodies, cytokine-release syndrome.

Background

Multiple myeloma (MM) is the second commonest haematological malignancy affecting adults in the Western world.1 It is characterised by the clonal expansion of malignant plasma cells, which produce aberrant monoclonal immunoglobulins (Igs) and/or light chains. Associated sequela include hypercalcaemia, renal impairment, anaemia, lytic destruction of bones (these constitute the ‘CRAB’ criteria, which define symptomatic MM), alongside immunoparesis.2,3

Treatment and outcomes have improved dramatically over the past 10 years, particularly since the advent of the proteosome inhibitors (PIs), immunomodulatory imide drugs (IMiDs) and monoclonal antibodies (MoAbs). The median overall survival (OS) has doubled, and is now ~5 years4; however, older patients5 and those with high-risk disease features have considerably less favourable outcomes, and the majority of low-risk patients will eventually develop treatment-resistant clones and resistant disease.6-8 The Revised International Staging System (R-ISS) stratifies patients based on the presence of adverse cytogenetics [deletion 17p, translocation t(4;14) or t(4;16)], alongside elevated serum beta-2-microglobulin or lactate dehydrogenase levels. The 5-year OS is 82% for Stage I, low-risk patients, compared with 40% for Stage III, high-risk patients.4 Patients with ultra-high risk, or ‘double-hit’ myeloma, based on the presence of biallelic inactivation of tumour protein p53 (TP53), or 1q21 amplification and ISS Stage III disease have a median OS of <2 years.9 Patients who are refractory to all three classes of novel agents (triple refractory) have a survival of <1 year, and those with penta-refractory disease (refractory to two IMiDs, two PIs and a MoAb) have a dismal median OS of 5-6 months.10 Given this significant unmet need, novel therapies are urgently needed for these patients.

Why are immunotherapies attractive in myeloma?

One of the hallmarks of MM is the tumour-permissive microenvironment (TME). A complex interplay between MM cells, immune cells, and bone marrow (BM) stromal cells leads to immune-paresis, protecting and facilitating MM growth and survival.

The importance of the immune system in MM was first shown in patients undergoing allogeneic stem cell transplants (alloSCT). T-cell mediated graft-versus-host disease (GvHD) was found to be associated with improved relapse-free survival post-alloSCT,11 with a 5-year OS of 79% for those with
chronic GvHD, versus 43% without. Similar findings were shown in patients receiving donor lymphocyte infusions.\textsuperscript{12} AlloSCT represents the first available immunotherapy in MM; however, its use is limited by high transplant-related morbidity and mortality.

Immune dysfunction in MM has since been better characterised. Patients with MM are highly susceptible to infection, particularly in the early stages after diagnosis and reducing with response to treatment,\textsuperscript{13} which may partly reflect T-cell dysfunction. Changes in T-cell quantity and quality occur also during disease progression.\textsuperscript{14} BM-derived T cells from patients with monoclonal gammopathy of uncertain significance (MGUS) react to MM cells with robust cytokine production. The same does not occur using T cells from patients with MM, suggesting progressive T-cell dysfunction.\textsuperscript{15} This dysfunction is multifactorial. MM cells induce T-cell anergy partly through expression of checkpoint ligands and receptors such as programmed death-ligand 1 (PD-L1), which binds to programmed death receptor-1 (PD-1) leading to exhaustion, reduced cytokine production and impaired cell lysis.\textsuperscript{16} Increased PD-L1 expression on MM cells compared with healthy donor plasma cells or those from patients with MGUS has been demonstrated.\textsuperscript{17,18} Regulatory T cells (Tregs), an immunosuppressive subset of T cells, are elevated in MM patients’ blood, with levels correlating with disease burden. MM cells have been shown to induce formation of Tregs \textit{in vitro},\textsuperscript{19} promoting immune escape. Anti-MM therapies and autologous stem cell transplant (ASCT) also alter T-cell function, causing a reduction in naïve cluster of differentiation (CD)4 T-cells, and an increase in effector memory T cells and PD1-expressing CD4 T cells. MM treatment may therefore further exacerbate the immune dysregulation seen in MM.\textsuperscript{20}

Natural killer (NK) cells are a critical component of the innate immune system, required for tumour immune surveillance. MM cells and Tregs produce high levels of transforming growth factor beta, which impairs NK cytotoxicity, as does interleukin (IL)-6, produced by both MM and BM stromal cells (BMSCs).\textsuperscript{21} MM cells evade NK-detection through loss of NK-activating surface ligands and increased expression of NK-inhibiting ligands such as human leucocyte antigen (HLA) Class I antigens,\textsuperscript{22} and NK cells themselves show an exhausted phenotype in MM.\textsuperscript{23} The IMiD lenalidomide stimulates NK-mediated cytotoxicity. Lenalidomide is frequently administered with dexamethasone, which has been shown paradoxically to impair NK activity through suppression of CD4 T-cell production of IL-2.\textsuperscript{24}

Tumour-associated macrophages (TAM) are formed from circulating monocytes, which are recruited to the BM and activated by cytokines and chemokines produced by MM cells and BMSCs. TAMs are immunosuppressive and stimulate angiogenesis promoting MM spread.\textsuperscript{25} Other BM components contributing to the TME include myeloid-derived suppressor cells, which suppress T cells, and are found at five-times normal levels in patients with MM,\textsuperscript{26} as well as BMSCs which promote MM cell growth, migration and survival.\textsuperscript{27}

Reversing this immune-plegia, by enhancing the activity of suppressed populations of endogenous immune cells is an attractive prospect in MM. Many MM antigens also have immunoregulatory roles in addition to being present in the neoplastic cell surface. CD38, for example, regulates cell recruitment and cytokine release,\textsuperscript{28} and signalling lymphocyte activation molecule family member 7 (SLAMF7) is expressed on MM cells but also on NK cells, where it has an activating role.\textsuperscript{29} Table I describes the MM cell markers under investigation as targets for bispecific antibodies.

**Current immunotherapies in MM**

The role of immunotherapies in MM is growing, with various agents available that alter the immune function in differing ways.\textsuperscript{73}

**Monoclonal antibodies**

The first immune therapies were the MoAbs and several are now well established in clinical care. Daratumumab, which targets CD38 on MM cells, has shown impressive results when incorporated into established treatment regimens in newly diagnosed and relapsed MM. It is a humanised IgG kappa MoAb that kills MM cells through antibody-dependent T-cellular cytotoxicity (ADCC), antibody-dependent T-cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC).\textsuperscript{76,77}

In the relapse setting, daratumumab enhanced responses to bortezomib/dexamethasone and lenalidomide/dexamethasone in the seminal CASTOR and POLLUX trials respectively,\textsuperscript{78,79} leading to initial regulatory approval for relapsed patients. More recent combinations such as Daratumumab with pomalidomide/dexamethasone (Pd; APOLLO study\textsuperscript{80}) and daratumumab with carfilzomib, lenalidomide and dexamethasone (KRd; CANDOR study\textsuperscript{81}) have also shown improved progression-free survival (PFS) in the daratumumab arms.

In newly diagnosed ASCT-eligible MM, the addition of daratumumab to VTD (bortezomib, thalidomide and dexamethasone) and VRD (bortezomib, lenalidomide and dexamethasone) led to improved PFS and depth of response defined by minimal residual disease (MRD) status (CASSIOPEIA and GRIFFIN trials respectively).\textsuperscript{82,83} The same is true for non-transplant eligible patients when used in combination with lenalidomide/dexamethasone or bortezomib, melphalan and prednisolone (VMP; MAIA and ALCYONE respectively).\textsuperscript{84,85} and as a result, daratumumab has been approved in these settings by both the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA).

More recent studies, such as the MASTER study of daratumumab with KRd (Dara-KRd), followed by ASCT and response-adapted consolidation with additional cycles of Dara-KRd, focussed on the achievement of MRD-negative...
remissions as the primary end-point. Early results report high rates of MRD negativity, but longer follow-up is required to determine durability.86 Similarly, the MANHATTAN study assessed MRD negativity in 41 non-randomised patients receiving Dara-KRd without ASCT, reporting MRD negativity in 71% with 1-year PFS and OS rates of 98% and 100% respectively.87

Isatuximab, is another anti-CD38 MoAb. CD38 is not only a receptor, but also an ectoenzyme, with effects on calcium signalling.88 Isatuximab has a similar mechanism of action to daratumumab, but also inhibits the adenosine diphosphate (ADP) ribosyl-cyclase ectoenzymatic activities of CD38, leading in part to a reduction of adenosine in the BM.89 Higher adenosine levels correlate with disease progression and stage in MM,90 hence this action may provide additional anti-MM activity. Isatuximab was combined with pomalidomide and dexamethasone (Isa-Pd) in relapsed and/or refractory MM (RRMM), leading to a doubling of PFS (ICARIA-MM).91,92 The EMA and FDA approval for RRMM was subsequently granted in 2020.

Subgroup analysis of ICARIA-3 in high risk MM [del17p, t(4;14) or t(14;16)] showed a significant improvement in median PFS from 6-5 to 11-5 months in favour of Isa-Pd.93 Subgroup analysis of patients with renal impairment (estimated glomerular filtration rate <60 ml/min/1.73m²) also demonstrated the superiority of Isa-Pd, with a median PFS of 9.5 versus 3.7 months and a doubling of complete renal response rates.92 This was also the case in patients with renal impairment treated in the phase III IKEMA study of isatuximab with carfilzomib and dexamethasone (Isa-Kd) versus Kd in RRMM.94

Eloctuzumab is a humanised IgG1 MoAb directed at SLAMF7, which is highly expressed on MM cells,95 acting predominantly through ADCC. In RRMM, the addition of

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**Table I. Multiple myeloma cell markers in bispecific antibody clinical or pre-clinical trials.**

| Antigen   | Structure                                      | Expression                                                                 | Role                                                                                                             | Prognostic relevance                  |
|-----------|-----------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| BCMA      | Type III transmembrane glycoprotein of the tumour necrosis family receptor superfamily | MM cells, plasma cells, mature B lymphocytes90,32,33,34                     | Long-term survival of plasma cells;35 Ligand binding leads to upregulation of the anti-apoptotic proteins MCL-1 and BCL-2;56-38 | Soluble BCMA increases with disease progression;39 High soluble levels correlate with poor outcomes.40,41 |
| FcRH5 (CD305) | Membrane protein                                | MM cells, B cells and plasma cells42,43                                    | Regulates BCR signalling and binds to IgG32,45                                                                  | FcRH5 gene is located on chromosome 1q21, with overexpression in 1q gain44-46 |
| GPRC5D    | Transmembrane orphan receptor of the G protein-coupled receptor family47,48                 | MM cells, B cells and plasma cells49                                      | Function is poorly characterised but a role in MM cell proliferation has been postulated                         | Enhanced expression observed in certain high-risk cytogenetic MM groups, e.g. Del13q and t(4;14)47 |
| CD38      | Type II glycoprotein of the ADP-ribosyl cyclase family | MM cells, B cells and plasma cells50                                      | Regulation of calcium homeostasis, signalling and adhesion;51-53                                              | CD19 may identify MM stem cells       |
| CD19      | Type I transmembrane glycoprotein member of the immunoglobulin superfamily54                | B-cells. Low level expression by MM cells is seen using super-resolution microscopy55 | Modulates BCR-dependent and independent signalling;56-58                                                       | High soluble CD138 is a predictor of poor prognosis67-69 |
| SLAMF7    | Surface glycoprotein receptor of the signalling lymphocyte activation molecule family59 | MM cells, B-cells, plasma cells, CD8 T cells and NK cells60                | Acts as a ‘don’t eat me’ signal;59                                                                          | Enhanced expression at relapse and in patients with cytogenetic abnormalities70 |
| CD138     | Type I transmembrane protein of the syndecan proteoglycan family61                         | Epithelial cells, plasma cells, MM cells52,63                             | Adhesion, proliferation, angiogenesis, suppression of apoptosis and metastasis;64-66                          | High soluble CD138 is a predictor of poor prognosis67-69 |
| NY-ESO    | Member of the cancer/testis antigen family     | Healthy testis and placental cells, and a wide range of tumours including MM70 | Possible roles in cell cycle progression, self-renewal and differentiation;71-74                                 | Enhanced expression at relapse and in patients with cytogenetic abnormalities70 |

ADP, adenosine diphosphate; BCL-2, B-cell leukaemia/lymphoma 2; BCMA, B-cell maturation antigen; BCR, B-cell receptor; CD, cluster of differentiation; Fc, fragment crystallisable; FcRH5, Fc receptor homologue 5; GPRC5D, G protein-coupled receptor class C group 5 member D; IgG, immunoglobulin G; MCL-1, myeloid cell leukaemia-1; MM, multiple myeloma; NK, natural killer; NY-ESO, New York oesophageal squamous cell carcinoma; SLAMF7, lymphocyte activation molecule family member 7.

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elotuzumab to lenalidomide and dexamethasone (ELOQUENT-2). Hyperexpression of the mafodotin (GSK-2857916) is a first-in-class humanised IgG ADC directed against B-cell maturation antigen (BCMA) on the MM cell surface. Mechanisms of action includes ADCC, ADCP and delivery of the potent microtubule inhibitor monomethyl auristatin-F (MMAF), which stimulates apoptosis and release of immunogenic cell death markers. The phase I, dose escalation DREAMM-1 study reported overall response rate (ORR) of 60% and median PFS of 12 months in patients with RRMM. The open label phase II DREAMM-2 study reported an ORR of 31–35% and a very good partial response (VGPR) rate of ≥20% in a triple-class refractory cohort. PFS was less impressive compared with DREAMM-1, at 3–4 months, possibly reflective of suboptimal activity due to the inclusion of patients who were refractory to anti-CD38-directed therapy. The most commonly reported adverse events (AEs) were corneal events, predominantly blurred vision and dry eyes, and thrombocytopenia. Corneal events are thought to be secondary to uptake of the ADC by dividing corneal epithelial cells, representing a significant limitation to introduction of this agent into routine practice. The ongoing DREAMM-6 study of belantamab mafodotin in combination with lenalidomide/dexamethasone or bortezomib/dexamethasone in RRMM uses two doses of the ADC administered as a single or split dose. Whether splitting the dose can ameliorate ophthalmic toxicity waits to be seen. Belantamab mafodotin received orphan drug status by the FDA, with several trials ongoing of various therapeutic combinations including PIs, IMiDs, MoAbs, and checkpoint inhibitors (DREAMM-3, 9, 12 and 13 studies).

AMG 224 is a BCMA IgG1 antibody conjugated with mertansine (DM1), an anti-tubulin agent. The first-in-human phase I dose-escalation study treated 40 patients with RRMM. The ORR was 23% with a median duration of response of 15 months. Similar to belantamab mafodotin, thombocytopenia and corneal events were common occurrences.

Chimeric antigen receptor T cells

Chimeric antigen receptor T cells (CAR-T) are engineered to express modified T-cell receptors, directed against a specific tumour antigen. CAR-T-cells can recognise the designated tumour epitope without major histocompatibility class (MHC)-presentation and are independent of HLA class. A transmembrane domain connects the antigen-recognition domain to the T-cell activating CD3-zeta domain. Binding of the tumour epitope by the CAR thereby leads to cytotoxic activation of the T cell. The primary toxicity of CAR-T therapy is cytokine-release syndrome (CRS), secondary to the potent T-cell response generating a burst of cytokines, particularly IL-6. This can result in hypotension, hypoxia, immune effector cell-associated neurotoxicity syndrome (ICANS), multiorgan failure and fatality. Tocilizumab, an anti-IL-6 receptor antagonist, corticosteroids and supportive care form the main-stay of management.

The most promising CAR-T-cell studies in MM are against the BCMA target with >20 clinical trials published. The first-in-human trial of a BCMA-directed CAR-T was conducted by the National Cancer Institute (NCI), where 24 heavily pre-treated patients received one of four dose levels. The ORR at the highest dose was 81% with 63% attaining VGPR or better, although nearly 40% had Grade ≥3 CRS. Event-free survival was ~8 months with all patients relapsing.

Idecabtagene vicleucel (Ide-cel), previously known as bb2121, uses the same BCMA-binding moiety as the initial NCI study. In a phase I trial, when used at doses of ≥150 × 10^6, Ide-cel produced an ORR of 94% with a complete response (CR) rate of 56% in heavily pre-treated patients with RRMM. A total of 71% of patients had CRS, which was generally mild and only one-fifth required tocilizumab. In the subsequent phase II KarMMa trial, 128 of 140 enrolled patients received the target dose of 150–450 × 10^6 CAR-T cells. At median follow-up of 15–4 months, the ORR was 73%, with 33% achieving CR or better, 79% of whom were MRD negative to a level of 10^−5. The median PFS was 8–8 months, 84% had CRS, of which 5% was Grade ≥3. Based on these results, Ide-cel was granted FDA approval in March 2021.

A modification of the bb2121 CAR, termed bb21217, has the addition of a phosphoinositide-3 kinase inhibitor, which enriches the product for memory-like T cells, associated with increased persistence and efficacy. Early results have shown responses in six out of seven evaluable patients, with MRD negativity demonstrated in three of three responses tested.

Legend Biotech’s LCAR-B38M anti-BCMA CAR uses a novel Camalid heavy chain construct that recognises two separate epitopes of the BCMA antigen. The reported ORR was 88%, CR 68%, and 63% achieved MRD negativity. The median PFS after 8 months of follow-up was 15 months. In this study, CRS occurred in 90% of patients and was Grade ≥3 in 7%. InJ-4528 is a CAR-T product (also called cilta-cel, autoleucel or Cilta-cel), which uses the same CAR as LCAR-B38M. Cilta-cel is being trialed in the CARTITUDE-1 phase Ib/II clinical trial. In 97 patients with RRMM, the ORR was 97% with 67% obtaining stringent CR (sCR). The
12-month PFS and OS rates were 77% and 89% respectively. CRS occurred in 95% (Grade ≥3 in 4%) and neurotoxicity in 21% (Grade ≥3 in 10%). There were four deaths due to treatment-related AEs. In CARTITUDE-2, in which the efficacy of Cilta-cell was tested in various clinical settings in 20 patients with MM, the ORR was 95% and CR or sCR was 75%. CRS occurred in 85% (Grade ≥3 in 10%) and neurotoxicity in 20% (all Grade 1–2).

A meta-analysis of 447 patients with RRMM treated with anti-BCMA CAR-T-cells reported similar outcomes to these trials. The ORR was 84%, CR 43%, MRD negativity 83%, and PFS was 10 months after a median follow-up of 12 months. The rate of CRS was 73%, of which 10–15% was Grade ≥3.

Although these results are promising, CAR-T-cell therapies have some non-insignificant barriers to widespread application. They require patients to undergo apheresis, which may not be feasible in rapidly progressive disease. This was seen in KarMMa, where 9% of patients were unable to receive the product. They are extremely expensive, the majority of patients will experience CRS, particularly if disease burden is high, and current data do not yet suggest that CAR-T-cell therapy has curative potential in MM, with PFS durations of <1 year in the majority of cases. Loss of BCMA antigen expression has been seen at relapse, associated with chromosome 16p anomalies. How frequently this may occur, and to what extent it will impact efficacy of BCMA-directed CAR-Ts is not fully understood. CAR-Ts targeting multiple antigens are under investigation to improve specificity and abrogate the impact of BCMA loss, and up-front CAR-T-cell therapy is also being explored (e.g. ClinicalTrials.gov Identifier: NCT03549442).

**Checkpoint inhibitors**

The PD-1/PD-L1 axis is an important cause of T-cell exhaustion in MM. Disappointingly, incorporation of checkpoint inhibitors into the MM treatment pathway has had limited success to date. The phase I KEYNOTE-023 trial of the anti-PD-1 antibody pembrolizumab with lenalidomide/dexamethasone in RRMM yielded an encouraging ORR of 40%. However, two subsequent phase III clinical trials were placed on hold after interim analysis showed increased mortality in the investigator arm: KEYNOTE-183 consisted of pomalidomide/dexamethasone with or without pembrolizumab in RRMM, and KEYNOTE-185 compared the addition of pembrolizumab to lenalidomide/dexamethasone in NDMM. Several other trials using the PD-1 inhibitor nivolumab were also temporarily placed on hold after an excess of deaths was noted. Results from Checkmate 602 of pomalidomide/dexamethasone with or without nivolumab and elotuzumab, Checkmate 039 of nivolumab-daratumumab with or without pomalidomide/dexamethasone, and CA204142 of nivolumab-elotuzumab with or without pomalidomide/dexamethasone are awaited.

**Bispecific antibodies**

Bispecific T-cell antibodies (BsAbs) simultaneously bind a target epitope on cancer cells and CD3 on T cells, causing direct T-cell activation and tumour cell lysis. BsAbs may include a fragment crystallisable (Fc) region (IgG-like) or consist of only fragment antigen-binding (Fab) variable regions and linkers (non-IgG-like). Smaller non-IgG-like BsAbs require weekly continuous intravenous infusion, whereas the larger IgG-like BsAbs can be administered via 3 weekly infusion or subcutaneous (SC) injection. Several BsAbs are under evaluation in MM, with a number of early phase clinical studies reported and many ongoing. In the present review we will discuss the current state of BsAbs in MM, and the future of this area.

**Targets with agents in active clinical trials**

There are numerous possible targets for BsAbs in MM. The majority of active clinical trials concern BCMA-directed therapies; however, other MM epitopes are also under investigation. Potential targets and current antibodies under clinical development are summarised in Fig 1 and Table I.

**B-cell maturation antigen (BCMA)**

Seven studies have published regarding BsAbs binding to BCMA and CD3. Two products only have Fab regions, and five have Fc regions. Study characteristics and outcomes of all the studies described are detailed in Tables II and III.

The two products lacking an Fc region are AMGEN products, coined BiTEs® (Bispecific T-cell engagers). The phase I clinical trials of AMG 420 (previously termed BI 836909) and AMG 701, an extended half-life version with the same targets were published in 2020. AMG 420 is administered as a 28-day intravenous (IV) infusion followed by a 14-day break, whereas AMG 701 is given by IV infusion once a week and planned for a SC formulation.

Results from 117 patients have been reported, with an average age of 64 years (median of 63 years for AMG 420 and 65 years for AMG 701). Patients have had MM for ~5 years (median duration 5·2–5·9 years) and had received six to seven prior therapies. Over 80% had undergone previous ASCT, 39% had been exposed to an anti-CD38 antibody in the AMG 420 study, and 93% in AMG 701. Within the AMG 420 cohort, 36% (n = 15) were refractory to both a PI and IMiD, and 21% (n = 9) to daratumumab. In all, 68% of the AMG 701 group were triple refractory (n = 51).

In AMG 420, the most common serious AEs (SAEs) were infection (33%), elevated hepatic enzymes (12%) and polynephropathy (5%). In AMG 701, the most common SAEs were infection (17%), CRS (9%), and elevated pancreatic enzymes (3%). In AMG 420, CRS occurred in 38%, with one case of Grade 3 CRS only. One patient with Grade 2 CRS received tocilizumab. In AMG 701, CRS occurred in 61%,
with five Grade 3 cases (7%), which were treated with tocilizumab and corticosteroids.

In the AMG 420 study, the ORR was 31%, and 70% for the cohort (seven of 10 patients) who received the maximum tolerated dose (MTD) of 400 μg/day. Six patients (14%) attained an MRD-negative CR (<1 tumour cell/10⁴ normal cells by flow cytometry) and nine a CR or better (21%). In AMG 701, responses were reported for 72 patients. The ORR for all patients was 24%. For those receiving 3–12 mg doses (n = 45), the ORR was 36%, and 83% in the small group (n = 6) who received 9 mg doses with the earlier dose escalation protocol. Of the 17 patients who responded, 29% achieved a CR or better with 24% MRD negative by flow cytometry or next-generation sequencing (NGS) (<1 tumour cell/10⁴). In all, 80% of responders in the 9-mg group were triple refractory. Only one patient in the IV group had a minimal response. The ORR in the SC group was 33% and was 75% in those receiving doses of ≥215 μg/kg, with rates of VGPR or better of 45% and CR or better of 30%. The MTD was not reached. The most common AEs for SC elranatamab were lymphopenia (80%, 80% Grade ≥3), anaemia (57%, 46% Grade ≥3), injection-site reactions (53%, all Grade 1–2), thrombocytopenia (53%, 40% Grade ≥3) and neutropenia (40%, 34% Grade ≥3). CRS occurred in 73%, all of which were Grade 1–2.138,142,144

A total of 45 patients were treated with REGN5458. The median (range) age was 64 (41–81) years, number of prior therapies was 5 (2–17), 53% were penta class-refractory and 22.2% had ISS Stage 3 disease. The ORR was 36%, or 60% at the highest dose level. Of responders, 31% achieved a CR
Table II. Study and patient demographics of published studies.

| Bispecific antibody | Clinical trials identifier | Antibody structure | Target | Inclusion criteria | Prior BCMA-directed therapy allowed | No. patients | Age, years, median (range) | Median lines of therapy | Prior BCMA-directed therapy, % | Response to previous treatment | Adverse cytogenetics; other high-risk features |
|---------------------|---------------------------|--------------------|--------|-------------------|-------------------------------------|--------------|-----------------------------|---------------------------|-------------------------------|--------------------------------|------------------------------------------|
| AMG 420             | NCT02514239               | BiTE BCMA-CD3      | Progression after PI and IMiD | Yes | 42; 10 at 400 µg/day | 65 | 7 (3–14) | 0 | 36% refractory to PI/IMiD; 21% refractory to daratumumab | 33% high risk by IMWG |
| AMG 701             | NCT03287908               | Extended half-life, scFv plus Fc region BCMA-CD3 | Progression after PI and IMiD ± MoAb | No | 75 | 63 | 6 (1–25) | 0 | 68% triple-class refractory | 27% EMD |
| PF-0686135 (Elranatamab) | NCT03269136               | Full-length, humanised IgG2a BCMA-CD3 | RRMM treated with PI, IMiD and anti-CD38 MoAb | Yes | IV: 17 | 61 (47–82) | 11 | 29 | 87% triple-class refractory | 59% ≥1 Ch abnormality |
| REGN5458            | NCT03761108               | Fc Fab arms BCMA-CD3 | RRMM treated with PI, IMiD and anti-CD38 MoAb | No | 45 | 64 (41–81) | 6 (2–14) | 0 | 6% triple-class, 33–3% quad- and 53–3% penta-drug refractory | 22–2% ISS Stage 3 |
| Teltiostamab        | NCT03145181               | humanised, IgG Fc BCMA-CD3 | RRMM treated with PI, IMiD and anti-CD38 MoAb | No | 156 (84 IV; 72 SC), 40 received RP2D | 62.5 (39–84) (RP2D) | 5 (2–11) (RP2D) | 0 | 83% triple-class refractory, 35% penta-drug refractory (RP2D) |
| CC-93269            | NCT03486067               | 2-arm humanised IgG1 Fc, binds bivalently to BCMA and monovalently to CD3 in a 2 + 1 format BCMA-CD3 | RRMM, ≥3 prior lines | No | 30 | | | 0 | | | |

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| Bispecific antibody | Clinical trials identifier | Antibody structure | Target | Inclusion criteria | Prior BCMA-directed therapy allowed | No. patients | Age, years, median (range) | Median lines of therapy | Prior BCMA-directed therapy, % | Response to previous treatment | Adverse cytogenetics/other high-risk features |
|---------------------|---------------------------|--------------------|--------|-------------------|-------------------------------------|-------------|--------------------------|--------------------------|-------------------------------|--------------------------------|----------------------------------|
| TNB-383B            | NCT03933735              | IgG4 Fc, anti-CD3 moiety preferentially activates effector over Tregs. 2 heavy chain only anti-BCMA moieties | BCMA-CD3 | RRMM treated with PI, IMiD and anti-CD38 MoAb | No | 38 | 68 (37–83) | 7 (4–13) | 0 |  |
| BFCR4350A           | NCT03275103              | Humanised IgG1 Fc  | FcRL5-CD3 | RRMM for which no established therapy is available, appropriate, tolerated | Yes | 51 | 62 (33–80) | 6 (2–15) | 0 | 67% triple class-refractory |
| Talquetamab         | NCT03399799              | IgG4 Fc             | GPRC5D-CD3 | RRMM for which no established therapy is available, appropriate, tolerated | Yes | 174 (102 IV; 72 SC) 28 received R2PD | 61.5 (46–80) (RP2D) | 5.5 (2–14) (RP2D) | 21 (RP2D) | 71% triple class refractory, 18% penta-drug refractory (RP2D) | 22% ISS Stage 3 |

BCMA, B-cell maturation antigen; BCR, B-cell receptor; CD, cluster of differentiation; Ch, chromosome; EMD, extramedullary disease; Fab, fragment antigen-binding; Fc, fragment crystallizable; FcRH5, Fc receptor-homologue 5; GPRC5D, G protein-coupled receptor class C group 5 member D; IgG, immunoglobulin G; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISS, International Staging System; IV, intravenous; (RR)MM, (relapsed and/or refractory) multiple myeloma; MoAb, monoclonal antibody; PI, proteosome inhibitor; RP2D, recommended phase II dose; SC, subcutaneous; scFv, single-chain variable fragment; Tregs, regulatory T cells.
Table III. Study safety and efficacy outcomes of published studies.

| Bispecific antibody | Administration | MTD | DLTs | AEs/SAEs | CRS | ORR | Depth of response | Subgroup analysis | Duration of response |
|---------------------|----------------|-----|------|----------|-----|-----|-------------------|-------------------|---------------------|
| AMG 420             | Continuous 28 day IV infusion followed by 2 week break. Single-patient cohorts (0·2, 0·4, 0·8, 1·6 µg/day) were followed by cohorts of 3–6 patients (3·2, 6·5, 13, 25, 50, 100, 200, 400, 800 µg/day). | 400 µg/day | 2 patients at 800 µg/day dose: 1 Grade 3 CRS, 1 Grade 3 PN. 1 patient at 400 µg/day dose with baseline Grade 1 PN worsened to Grade 3. | SAEs: infection 33% (2 deaths), polyneuropathy 5%, 12% elevated hepatic enzymes | 38% (94%) | 31% overall, 70% for the 400 µg/day cohort | Responses first evident from 6·5 µg/day and most apparent at 400 µg/day. Of 13 responders, 6 MRD negative CR, 3 CR, 2 VGPR, 2 PR | 38% responders had high risk cytogenetics | 8–4 mon (2·5–15·5), MRD neg patients 9·6 mon (2·8–12·8) |
| AMG 701             | Weekly IV. The first 3 cohorts (dose 5–45 µg) had 1 patient each, the next cohorts (0·14–1·2 mg) had 3–4 patients, subsequent cohorts (1·6–12 mg) have 3–10 patients each. | Not reached | Grade 3 CRS (n = 5, 7%), 1 transient Grade 3 AF, 1 Grade 3 PN, 1 Grade 4 acidosis, 1 Grade 4 thrombocytopenia | AEs: anaemia 43%, neutropenia 23%, thrombocytopenia 20%, diarrhoea 31%, fatigue and fever 25%. | 61% (90%) | 61% (90%) | At doses of 1·6 mg or less (n = 27) there was 1 response at 0·8 mg. At doses of 3–12 mg (n = 45) ORR was 36%. In the cohort with earlier dose escalation with 9 mg, ORR was 83%. | Of 17 responders, 3 MRD negative sCR, 1 MRD negative CR, 1 sCR not yet MRD assessed, 6 VGPR, 6 PR | 80% of responders in the 9 mg group (4/5) are triple class-refractory | 3·8 months (1·9–7·4), maximum 23 months. At last assessment, on-going responses in 82% of responders |
| Bispecific antibody | Administration | MTD | DLTs | AEs/SAEs | CRS | ORR | Depth of response | Subgroup analysis | Duration of response |
|---------------------|----------------|-----|------|----------|-----|-----|------------------|------------------|-------------------|
| PF-06863135 (Elranatamab) | Weekly IV or SC (80, 130, 215, 360, 600 and 1000 µg/kg). IV not stated. | Not reached | 1 febrile neutropenia (IV dosing) | IV AEs: thrombocytopenia 24%, anaemia 18%, pyrexia 18% SC AEs: lymphopenia 80%, anaemia 57%, injection-site reaction 53%, thrombocytopenia 53%, neutropenia 40% Grade ≥3: lymphopenia 80%, anaemia 46%, thrombocytopenia 40%, neutropenia 34% | IV: 24% | 6% minimal response, 35% stable disease | ORR for doses ≥215 µg/kg 75% (n = 15/20) | For doses ≥215 µg/kg (n = 20) VGPR or better 45%, CR or better 30% | 3 of 4 patients with prior BCMA-directed therapy responder |
| REGN5458 | IV weekly, then every 2 weeks. 3–96 mg doses over six dose levels. | Not reached | 1 Grade 4 kidney injury, 1 Grade 3 transaminitis associated with CRS | AEs: fatigue and nausea 18%, myalgia 13%, infection 47%, Infusion related reactions 7%. Grade ≥3: anaemia 9%, lymphopenia 7%. Grade 5 AEs in 3 patients: 2 sepsis and 1 COVID-19 | 38% (Grade 1 88%) | 35.6% overall, 60% at the highest dose level | Of 16 responders, 5 achieved CR or better and 13 VGPR or better | ORR in patients with EMD 17% | 44% of responders had a duration of response of ≥4 months, 19% ≥8 months |
| Teclistamab | IV (0.3–720 µg/kg) and SC (80–3000 µg/kg). Given daily or weekly | 1500 µg/kg SC weekly chosen as RP2D | 1 Grade 4 delirium, 1 Grade 4 thrombocytopenia | AEs at RP2D: neutropenia 70% at RP2D (100% Grade 1–2). Median time to onset was later with SC dosing (day after SC injection vs. day of IV infusion) | 65% | ORR at RP2D 58% achieved VGPR or better, 30% CR or better | At RP2D 23 of 26 responders (88%) remain on treatment after median 5-3 months |
**Table III.** (Continued)

| Bipecific antibody | Administration | MTD | DLTs | AEs/SAEs | CRS | ORR | Depth of response | Subgroup analysis | Duration of response |
|--------------------|----------------|-----|------|----------|-----|-----|-------------------|------------------|--------------------|
| CC-93269 IV infusion days 1, 8, 15 and 22 of C1–3, D1 and 15 of C4–6 and D1 of C7 onwards. Doses 0.15–10 mg. | IV infusion days 1, 8, 15 and 22 of C1–3, D1 and 15 of C4–6 and D1 of C7 onwards. Doses 0.15–10 mg. | Not reached | 0 | Grade ≥3 AEs: neutropenia 43%, anaemia 37%, infections 30%, thrombocytopenia 17% | 77% (63% Grade 1, 30% Grade 2). 81% after the first or second dose. | ORR 43%. In patients receiving 10 mg (n = 9), ORR 89% | 12/13 responders were MRD negative. In the 10 mg group, 55% achieved CR or better | 5–3–40-6 weeks |
| TNB-383B Escalating doses (0-025–40 mg) IV every 3 weeks without step-up dosing | Escalating doses (0-025–40 mg) IV every 3 weeks without step-up dosing | Not reached | 1 Grade 3 | AEs: headache 13% Grade ≥3: anaemia 16%, thrombocytopenia 13% | 21% (63% Grade 1, 37% Grade 2). All after the first dose. | ORR 37%, 52% in patients receiving ≥5.4 mg | Of 14 responders, 3 achieved CR or better, 4 achieved VGPR or better | 9 weeks (3–27) |
| BFCR4350A IV infusion every 21 days. Arm A: step up dose given C1 D1 (0-05 mg-2.6 mg), target dose (0.15–132 mg) given C1D8. C2 onwards target dose given D1 | IV infusion every 21 days. Arm A: step up dose given C1 D1 (0-05 mg-2.6 mg), target dose (0.15–132 mg) given C1D8. C2 onwards target dose given D1 | Not reached | 1 Grade 3 | AEs: neutropenia and lymphopenia 12%, raised AST and thrombocytopenia 10% Grade ≥3: lymphopenia 12%, neutropenia 10%, anaemia and thrombocytopenia 6% | 75% (53% Grade 1, 45% Grade 2, 3% Grade 3). 85% resolved within 2 days | 46/51 evaluable. Responses seen in ≥3.6 mg dose levels. ORR 33%, or 52% in ≥3.6 mg cohort | Of 15 responders, 6 CR or sCR, 4 VGPR, 5 PR | Responses seen in patients with HR cyto(9/17), triple class-refractory (10/20), prior CD38 Ab (11/22) and CAR-Ts (2/3) |
| Talquetamab 102 IV (0–5–180 µg/kg) and 35 SC (5–800 µg/kg), 1 Grade 4 | 102 IV (0–5–180 µg/kg) and 35 SC (5–800 µg/kg), 1 Grade 4 | Increased lipase and 1 Grade 3 rash | 405 µg/kg SC weekly chosen as RP2D | AEs at RP2D: Neutropenia 64%, anaemia 57%, dysgeusia 57%, infections 32%, neurotoxicity 7%, skin related AEs 75% Grade ≥3 at RP2D: Neutropenia 54%, anaemia 29%, infections 4% | 79% at RP2D (4% Grade 3), median time to onset 1 day | ORR at RP2D 63% (n = 23) | At RP2D, 50% achieved VGPR or better | 6/15 responders had ongoing responses >6 months at data cut-off |

Ab, antibody; (S)AE, (serious) adverse event; AF, atrial fibrillation; AST, aspartate aminotransferase; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; COVID-19, coronavirus disease 2019; (s)CR, (stringent) complete response; CRS, cytokine-release syndrome; DLTs, dose-limiting toxicities; EMD, extramedullary disease; IV, intravenous; MRD, minimal residual disease; MTD, maximum tolerated dose; ORR, overall response rate; RP2D, recommended phase II dose; SC, subcutaneous; VGPR, very good partial response.
Responses were evaluable in 46 patients. The ORR was 33%, refractory disease and 55% had adverse cytogenetics. The risk of CRS. In all, 67% of the cohort had triple class-refractory disease and 35% penta class-refractory disease. The ORR was 65% at the RP2D, of which 58% achieved VGPR or better and 30% CR or better. Six of the seven evaluable patients in CR were MRD negative by NGS (×10^−4). AEs at RP2D were neutropenia (60%, 40% Grade ≥3) and neurotoxicity (3%, all Grade 1–2). CRS occurred in 70% (all Grade 1–2) at RP2D, with a median time to onset of 1 day.139,145

A total of 30 patients received CC-93269 IV. The ORR was 43% and 89% in those treated at the 10 mg dose. Of the 13 responders, 12 were MRD negative by Euroflow (×10^−5). The Grade ≥3 AEs were neutropenia (43%), anaemia (37%), infections (30%) and thrombocytopenia (17%). CRS occurred in 77%, of which 65% was Grade 1, and the majority confined to the first or second dose.140

TNB-383B was administered to 38 patients. The median (range) age was 68 (37–83) years and number of prior therapies was 7 (4–13). The ORR was 37% or 52% in patients receiving doses of ≥5.4 mg. Of patients who responded, 21% attained a CR or better and 50% a VGPR or better. Grade ≥3 anaemia occurred in 16% and thrombocytopenia in 13%. CRS was reported in 21% and was Grade 1 in 63% of cases.143

Fc receptor homologue 5 (FcRH5)
The one reported phase I clinical study of a BsAb directed against the Fc receptor-homologue 5 (FcRH5) concerns BFCR4350A (Cevostamab), a humanised IgG Fc antibody targeting FcRH5 and CD3. FcRH5 has a large extra-cellular region. Increased distance between the epitope and the target cell membrane has the potential to interfere with efficient T-cell synapse formation and BsAb efficacy.146 Cevostamab’s binding domain is within the most membrane-proximal portion of FcRH5, enabling efficient synapse formation.145 Moreover, FcRH5 is shed; however, the binding domain is not shed, preventing development of a sink effect.147 A total of 51 patients, with a median (range) age of 62 (33–80) years and 6 (2–15) prior lines of therapy received escalating intravenous doses of Cevostamab with a step-up dose to reduce the risk of CRS. In all, 67% of the cohort had triple class-refractory disease and 55% had adverse cytogenetics. Responses were evaluable in 46 patients. The ORR was 33%, or 52% in patients receiving doses of ≥3.6 mg (n = 29). CR or better was achieved in 21% (six of 29), with responses seen in patients with high-risk cytogenetics (nine of 17) and triple-refractory patients (10/20). The most frequent Grade ≥3 AEs were lymphopenia (12%), neutropenia (10%) and anaemia and thrombocytopenia (6% each). CRS occurred in 75%, was Grade 1–2 in all but one case, required tocilizumab and/or steroids in 47% and resolved within 2 days in 85%.148

G protein-coupled receptor class C group 5 member D (GPRC5D)
Talquetamab is an IgG Fc BsAb targeting GPRC5D and CD3. Several studies of talquetamab alone or in combination are ongoing (Table III) with results reported from the first-in-human study in RRMM. Escalating doses of IV or SC talquetamab were administered to 174 patients (102 IV, 72 SC). A total of 28 patients received the RP2D of 405 μg/kg weekly SC. The median (range) age of patients receiving the RP2D was 61.5 (46–80) years and prior lines of therapy was 5.5 (2–14), of which 71% were triple-class refractory, 18% were penta-refractory and 21% had received prior BCMA-directed therapy. Response data is available for 23 patients at RP2D. The ORR was 63% and 50% achieved VGPR or better. Most common AEs at RP2D were neutropenia (64%, 54% Grade ≥3), anaemia (57%, 29% Grade ≥3), infections (32%, 4% Grade ≥3), dysgeusia (57%), neurotoxicity (7%) and skin-related AEs (75%). CRS occurred in 79% (4% Grade 3) with a median time to onset of 1 day.149,150

Study design, outcomes and safety data from these studies are summarised in Tables II and III. Ongoing or planned studies are described in Table IV.

Discussion
The responses described in these studies are encouraging in heavily pre-treated patients, with including triple- and penta-class refractory cases. The attainment of MRD-negative responses in such patients is promising, although durability of responses is not yet known.

The importance of MRD has been provided by several trials and meta-analyses, which have shown superior PFS and OS in MRD-negative patients. MRD-positive patients in CR have similar outcomes to those only achieving a partial response (PR),151–153 and deeper levels of MRD negativity confer additional benefit.154,155 This highlights both the relevance of MRD testing and the putative value of novel therapies in this setting.

Similar to adoptive cellular therapies, CRS is a common side-effect of bispecific antibody therapy, occurring in 21–79% of patients across the nine reported clinical trials (median 65.5%). The majority of cases were Grade 1–2, with few Grade ≥3 events reported (maximum 10% in AMG701 and 12% in REGN5458). Requirements for tocilizumab and corticosteroids varied across the trials. Time to onset where reported was ~1 day faster for IV antibodies compared with SC (talquetamab, teclistamab), the majority of cases across studies were

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limited to the first dose, and mostly resolved within 2 days (SC PF-06863135, BFCR4350A).\textsuperscript{136,137,138,139,140,141,142,143,148,149} Although these data are immature, when compared with BCMA-directed CAR-T-cell therapy in MM, with reported rates of Grade ≥3 CRS of 4–41%,\textsuperscript{116,118,122,123,129,136,157,158} severe CRS seems to be less of a risk with bispecific antibodies. Haematological AEs were common but generally manageable, with few dose-limiting toxicities reported and MTD was not reached in several studies. Infections where documented, occurred in approximately 20–40%, without high rates of febrile neutropenia. Compared with CAR-T-cell therapies, BsAbs have other advantages particularly concerning the manufacturing process. Apheresis, T-cell transfection with a viral vector carrying the gene for the CAR construct, product purification and safety control measures, and re-infusion are not required. This process may take several weeks, which may not be feasible for patients with aggressive forms of disease.\textsuperscript{159} In KarMMa, 9% of patients did not receive the CAR-T-cell product.\textsuperscript{118} In a real-world setting, this may be more frequent.

BsAbs may be a more generalisable option, if effective, for a greater proportion of patients. Where they could provide most benefit within the treatment paradigm for MM, and for which patients is not yet known. There are some optimistic signs that BsAbs may be effective in patients with high-risk disease, although the small sample sizes in the current trials do not permit accurate subgroup analysis. In vitro data concerning INJ-7564 (GPRC5D-CD3) showed that the presence of adverse cytogenetic anomalies [del(17p), t(4;14) and t(14;16)] did not impair antibody efficacy.\textsuperscript{160} The AMG 420, AMG 701, REGN5458 and BFCR4350A studies have all reported responses in high-risk patients, defined variably by cytogenetics, refractoriness to previous therapies and extra-medullary disease.\textsuperscript{136,137,141,148} Longer follow-up and larger sample sizes are required to assess this further.

While immune dysregulation in MM makes immunotherapies an attractive prospect, progressive immune dysfunction also poses a challenge to their development. Interactions between PD-1 and PD-L1 are a well-studied mechanism of immune suppression. The potent T-cell activation caused by BsAbs induces expression of PD-L1 and other immune checkpoint ligands.\textsuperscript{161,162} The impact of PD-1/PD-L1 interaction was shown to limit the in vitro anti-MM activity of the FcRH5-CD3 BsAb, which was ameliorated by PD-L1 blockade.\textsuperscript{45} High levels of PD-1 expressing T cells have been shown to be associated with inferior MM cell lysis in response to treatment with JNJ-7564\textsuperscript{160} and poor responses to AMG 420 have been shown to be associated with high PD-1 expression on plasma cells.\textsuperscript{136} Elevated levels of immunosuppressive Tregs are associated with poor responses to blinatumomab (CD19-CD3) in patients with B-cell acute lymphocytic leukaemia (B-ALL),\textsuperscript{163} and poor MM cell lysis following JNJ-7564 treatment.\textsuperscript{160} Potential therapeutic options to ameliorate these effects include incorporating checkpoint inhibitors (e.g. pembrolizumab, nivolumab) into treatments, and lymphodepletion strategies to reduce Treg frequencies.

The immune dysregulation in MM is progressive, exacerbated by the impact of prior therapies on the BM.\textsuperscript{164,165} There is some evidence to suggest that BsAbs may be more effective when used earlier during the disease course. In a study of blinatumomab in B-ALL, robust expansion, activation and contraction of peripheral blood T cells, mimicking a naturally occurring T-cell response, was predominantly seen in patients with MRD and longer OS.\textsuperscript{166} CAR-T investigators have also raised the possibility that cellular therapies might be safer and more effective at an earlier time-point, given the reliance of CAR-Ts on the patient’s endogenous T-cell repertoire.\textsuperscript{167} Expansion and activity of a BCMA CAR-T-cell product was shown to be associated with preservation of the CD4:CD8 T-cell ratio and presence of naive and memory T cells prior to apheresis. This phenotype was more commonly seen in less heavily treated patients.\textsuperscript{168,169} The post-ASCT time period may provide a unique immune milieu, more suited to T-cell redirecting therapies. Total CD3\textsuperscript{+} T-cell count returns to normal 30 days after ASCT; however, Treg

| Clinical trials identifier | BsAb | Target | Open to recruitment | Primary completion date |
|---------------------------|------|--------|---------------------|-------------------------|
| NCT03287908               | AMG 701 | BCMA | September 2017 | August 2023 |
| NCT04083354               | REGN5459 | BCMA | September 2019 | October 2023 |
| NCT04557098               | Tecristamab | BCMA | September 2020 | January 2022 |
| NCT04696809               | Tecristamab | BCMA | Awaited | July 2022 |
| NCT04693359               | PF-06863135 | BCMA | Awaited | June 2022 |
| NCT04735357               | EMB-06 | BCMA | Awaited | December 2023 |
| NCT04557150               | RO7425781 | BCMA | November 2020 | July 2022 |
| NCT04586426               | Talquetamab/Tecristamab | GPRC5D/BCMA | October 2020 | November 2021 |
| NCT04634552               | Talquetamab | GPRC5D | November 2020 | September 2023 |
| NCT03275103               | Cevostamab | FcRH5 | September 2017 | August 2022 |
| NCT03173430               | Blinatumumab | CD19 | May 2017 | Closed |
| NCT03309111               | ISB 1342 | CD38 | October 2017 | February 2021 |

BCMA, B-cell maturation antigen; BsAb, bispecific antibodies; CD, cluster of differentiation; FcRH5, Fc receptor homologue 5; GPRC5D, G protein-coupled receptor class C group 5 member D.
levels remain low initially as cytotoxic CD8+ numbers recover, leading to a markedly reduced Treg:CD8+ ratio,\(^{170}\) which may be preferential to the activity of CAR-T-cell therapies and BsAbs. A pilot study of tandem ASCT followed by a combined CD19/BCMA-directed CAR-T-cell in patients with high-risk NDMM reported an ORR of 100% with short follow-up and tolerable toxicities.\(^{171}\) To date, BsAbs have only been assessed in the RR setting in MM. Incorporation into up-front treatment, where efficacy may be improved, could provide a means of increasing the proportion of patients attaining MRD-negative responses, and trials of BsAbs post-ASCT are under development.

Another potential challenge to the successful integration of BsAbs into routine MM care is loss of antigen expression. Anti-BCMA CAR-T-cell treatment has been associated with reduced BCMA expression,\(^{129}\) and subsequent BCMA-negative relapses have been seen.\(^{116}\) Approaches to overcome this issue, which may also face BsAbs, include combining immunotherapeutic agents using therapies specific to multiple MM epitopes. In the CAR-T setting, simultaneously targeting BCMA and GPRC5D prevented BCMA-mediated disease escape in a murine model.\(^{172}\) Results of a study combining teclistamab and talquetamab (NCT04586426) may provide more insight into this approach when available. BsAbs targeting other antigens are also being studied in clinical trials, e.g. the anti-CD38 BsAb ISB 1342 (NCT03309111); or are in preclinical stages, e.g. BsAbs targeting CD-138,\(^{173}\) SLAMF7\(^ {174}\) and New York oesophageal squamous cell carcinoma 1 (NY-ESO-1).\(^ {175}\) Another option under development is BsAbs designed to activate endogenous NK cells. The BCMA-CD16a-directed BsAbs AFM 26 and R07297089 have shown NK-mediated MM cell lysis \(^ {176}\) and safety in an animal model of MM respectively.\(^ {177}\) Combining T cell and NK-redirecting therapies could be a potent treatment option, although at the moment, no NK BsAbs are in clinical trials in MM.

BsAbs have great potential in the treatment of MM. Larger clinical trials with more mature data are required in both RRMM and NDMM to clarify where these agents optimally fit within the treatment paradigm, and what role they may have for high-risk or refractory patients. Combination approaches of BsAbs with checkpoint inhibitors, T-cell co-stimulation, targeting of multiple MM epitopes, and use of both T cell and NK-activating BsAbs are interesting areas requiring further study in this dynamic field.

**Author contributions**

Dawn Swan wrote and manuscript, David Routledge and Simon Harrison provided critical appraisal and review.

**Conflict of interest**

Dawn Swan: none to declare. David Routledge: Amgen: Honoraria, investigator on studies; BMS: Honoraria, Advisory Board, GSK: Investigator on studies; Janssen: Honoria; Roche/Genetec: Investigator on studies; Sandes: Honoraria, Advisory Board. Simon Harrison: AbbVie: Consultancy, Advisory Board, Investigator on studies; Celgene: Consultancy, Honoraria, Advisory Board, Research Funding, Investigator on studies; GSK: Consultancy, Research Funding, Advisory Board; Janssen Cilag: Consultancy, Honoraria, Advisory Board, Research Funding, Investigator on studies; Roche/Genetec: Consultancy, Honoraria, Advisory Board, Investigator on studies; Takeda: Consultancy, Honoraria, Advisory Board; Haematologica: Scientific Advisory board, research funding, Investigator; Sanofi: consultancy, advisory role; Eusa: consultancy, advisory role, Expert testimony; Terumo: consultancy, advisory role, Expert testimony.

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