# The Role of Chimeric Antigen Receptor T-Cell Therapy in the Era of Bispecific Antibodies

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**KEYWORDS**

• CAR T-cell therapy • Bispecific antibodies • Immunotherapeutic agents
• Multiple myeloma

**KEY POINTS**

- Chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies have led to significant advancements in the management of relapsed/refractory blood cancers with several FDA approved products for multiple myeloma, non-Hodgkin lymphoma and B-cell lymphoblastic leukemia.
- In the absence of head-to-head comparisons of CAR T-cell therapy versus bispecific antibodies, treatment selection is personalized and needs to balance the toxicity and efficacy of each product.
- The community eagerly awaits ongoing multicenter studies to determine where in the treatment paradigm T-cell engaging therapies are best utilized, and if their earlier use may enhance their curative potential.

## INTRODUCTION

T-cell redirecting therapies, which include chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies, have revolutionized the management of blood cancers. There are now several US Food and Drug Administration (FDA) approved CAR T-cell therapies for relapsed/refractory (r/r) multiple myeloma (MM), non-Hodgkin lymphoma, and B-cell lymphoblastic leukemia (B-ALL).[1–9] Despite the high response rates and durability in a subset of patients, the use of autologous CAR T-cell therapy can be challenging. This is especially the case for patients with rapidly progressive disease where a

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delay of several weeks for product manufacture is often unacceptable. Limitations in the availability of manufacturing slots and potential geographic and resourcing constraints often compound delays to accessing commercial products. Off-the-shelf bispecific antibodies, some of which were recently FDA approved, appear to have similar efficacy to CAR T-cell therapy and offer a readily accessible therapeutic option.[10–12] However, bispecific antibodies often require a continuous administration schedule and can be associated with high rates of infection. In the absence of head-to-head comparisons between CAR T-cell therapy and bispecific antibodies, clinicians will need to decide between the optimal sequencing of bispecific agents and CAR T-cell therapies.[13] Such decisions are often guided by availability, differing logistics and safety profiles. What is certain is that T-cell redirecting therapies have dramatically increased the treatment armamentarium and continue to improve outcomes for our patients. Ongoing studies of combination approaches and the use of T-cell redirecting therapies in earlier lines of treatment are eagerly awaited. An increased understanding of the predictive biomarkers and mechanisms of resistance to these novel class of agents offers exciting avenues for research and should be pursued. This review summarizes the role of CAR T-cell therapy in the era of bispecific antibodies with a particular focus on MM.

## DISCUSSION

### *Background–Chimeric Antigen Receptor T-Cell Therapy*

CAR T-cell therapy represents a pivotal advancement in the field of immunotherapy. This personalized approach involves apheresis of peripheral blood T cells which are then transferred to a Good Manufacturing Practice facility where they undergo in vitro activation and genetic modification to encode a CAR, and subsequent expansion of CAR-expressing T cells. Autologous CAR-T cells are then reinfused into a patient after they receive mandatory lymphodepleting chemotherapy. FDA approved CAR constructs are second generation, composed of an extracellular antigen-binding domain, transmembrane domain, and intracellular costimulatory and CD3 signaling domains. Each product has important differences including the antigen-binding domain, costimulatory domains (CD28 or 4-1BB), gene-transfer technique, and product manufacturing times. In addition to the logistical challenges of CAR manufacturing and administration, specific immune-mediated toxicities of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) means that sites administering CAR-T cells require a robust clinical infrastructure for the management of such complications.[14]

In addition to improving efficacy, identifying resistance mechanisms, and reducing toxicity, the development of efficient manufacturing techniques is vital, particularly for the significant number of patients who have rapid progression of disease.[15] In this regard, translational insights have led to the investigation of off-the-shelf allogeneic and inducible pluripotent stem cells derived CAR-T cells.[16]

CAR T-cell therapy is being brought forward in the treatment armamentarium. Three prospective phase 3 clinical trials were conducted to define the optimal second-line treatment for large B-cell lymphoma. Two of these studies (ZUMA-7 and TRANSFORM) demonstrated significant improvements in outcomes with CARs and led to the FDA approval of CD19 CARs in the second line.[6,9,17] The phase 3 KarMMA-3 and CARTITUDE-4 studies are asking similar questions in MM (NCT03651128; NCT04181827).[18]

### *Background–Bispecific Antibodies*

Bispecific antibodies are off-the-shelf antibody molecules with at least 2 arms, one with binding specificity for a tumor antigen and the other typically for an activation

receptor on endogenous T-cell surfaces (eg, CD3). The first FDA approved bispecific antibody was blinatumomab, which targets CD19 and is used for the treatment of r/r B-ALL.[12] Since then, there has been a dramatic advancement with a diverse family of antibody constructs, particularly in lymphoid cancers and MM. This therapeutic class is not only limited to blood cancers but is also being studied in solid tumors and noncancer indications (eg, hemophilia A).[19] After engagement of a bispecific antibody to a tumor antigen on a malignant cell, and CD3 on the T-cell, the proximity of the 2 cells leads to T-cell and immune activation, which in turn leads to tumor cell death.

Unlike blinatumomab, which has a short half-life requiring continuous infusion, novel full-length bispecific antibodies share pharmacokinetic characteristics with monoclonal antibodies and can be dosed less frequently. The FDA recently approved teclistamab (once-weekly subcutaneous administration after step-up dosing), a CD3-BCMA (B-cell maturation antigen) bispecific antibody in October 2022 for patients with r/r MM, and soon after, mosunetuzumab, the first-in-class CD3-CD20 bispecific antibody for r/r follicular lymphoma.[10,11] Both these therapies are administered until progression of disease. Although high-grade immune-mediated toxicities are uncommon, patients are usually admitted for close monitoring during initiation of therapy.

There is no doubt that bispecific antibodies have demonstrated remarkable single-agent activity. Of great curiosity is whether adjunctive pharmaceutical interventions could enhance the therapeutic efficacy of these agents. Furthermore, some bispecific antibodies in development have a trivalent design to induce greater tumor lysis such as glofitamab, a CD3-CD20 bispecific with 2 CD20 binding sites (2:1 configuration).[20] Preclinical data also demonstrate that RG6234, a novel 2:1 GPRC5D (G protein-coupled receptor, class-C, group-5, member-D) T-cell bispecific in MM, has superior T-cell activation and myeloma cell depletion.[21]

### *Bispecific Antibodies in the Context of Chimeric Antigen Receptor T-Cell Therapy*

CAR T-cell therapy is appealing given as it is a one-time treatment. However, a critical advantage of bispecific antibodies is their off-the-shelf availability, obviating any concern for long processing times and potential manufacturing failures. The lack of lymphodepleting chemotherapy, which is mandatory with CAR T-cell therapy, also avoids the adverse effects from cytotoxic chemotherapy.

Regarding safety profiles, immune-mediated toxicities of CRS and ICANS are described in both treatments. However, the pathogenesis of ICANS with bispecifics may be distinct to CAR T-cell therapy. CAR T-cells are known to traffic to the cerebrospinal fluid but IgG-like bispecific antibodies are not expected to cross the blood-brain barrier, and accordingly, neurological adverse events are less common, and typically self-resolving.[22] Treatment with bispecific antibodies also allows for the administration of small to intermediate “priming” doses prior to the full dose of the therapy, which may help mitigate toxicities, and regular dosing provides the option of dose interruptions for toxicity. Regarding CRS and ICANS, there remains concern that nonspecific immune suppression with corticosteroids may impact CAR T-cell expansion, but this is not a concern for bispecific antibodies.[23] Infection rates after bispecific antibodies in MM is significantly higher than with CAR T-cell therapy and underscores the need for comprehensive infection prophylaxis protocols—opportunistic infections including cytomegalovirus infection have also been reported.[13,24] The higher incidence of infections may relate to ongoing B-cell aplasia and hypogammaglobulinemia from continuous therapy, differences in the number of prior lines of therapy between recipients of CAR T-cell therapy and bispecific antibodies, and the potential for bispecific antibodies to activate immunosuppressive regulatory T cells.

Lenalidomide is reported to fortify the T-cell immune synapse via downregulation of immune inhibitor ligands, and the potential synergy of bispecific antibodies with lenalidomide is being tested in MM.[25,26] In addition to combination strategies, studying both classes of T-cell engaging therapies in earlier lines is ongoing. Enrichment of immunophenotypically naive T cells has shown to enhance both the persistence and efficacy of CAR T-cell manufactured products and preservation of naive T-cell subsets can be accomplished by limiting immune-suppressive therapies from multiple lines of treatment. Another obvious question remains: where in the context of therapeutic sequencing should CAR T-cell versus bispecific antibody therapies be considered? No accepted standard approach exists–decisions are often guided by availability and logistics. Nonetheless, in patients with MM who relapse after CAR T-cell therapy, we have shown that subsequent treatment with bispecific antibodies appears to maintain pronounced clinical activity.[27]

Finally, the cost of anticancer drugs continues to increase in the United States, and it is critical to partner with the biopharmaceutical industry to ensure cost-effectiveness of cellular therapies. Technological innovations have led to place-of-care manufacturing of CAR T-cell therapy which may be a fiscally prudent and sustainable model, particularly in financially constrained regions.[28]

### *T-Cell Redirecting Therapies in Multiple Myeloma*

There are a range of modern immune-based therapies for MM, some of which are in development and others are FDA approved (**Fig. 1**). The remainder of this review will summarize CAR T-cell therapies and bispecific antibodies in MM. Readers can review **Table 1** and **Table 2** which summarizes selected CAR T-cell and bispecific antibody studies in multiple myeloma.

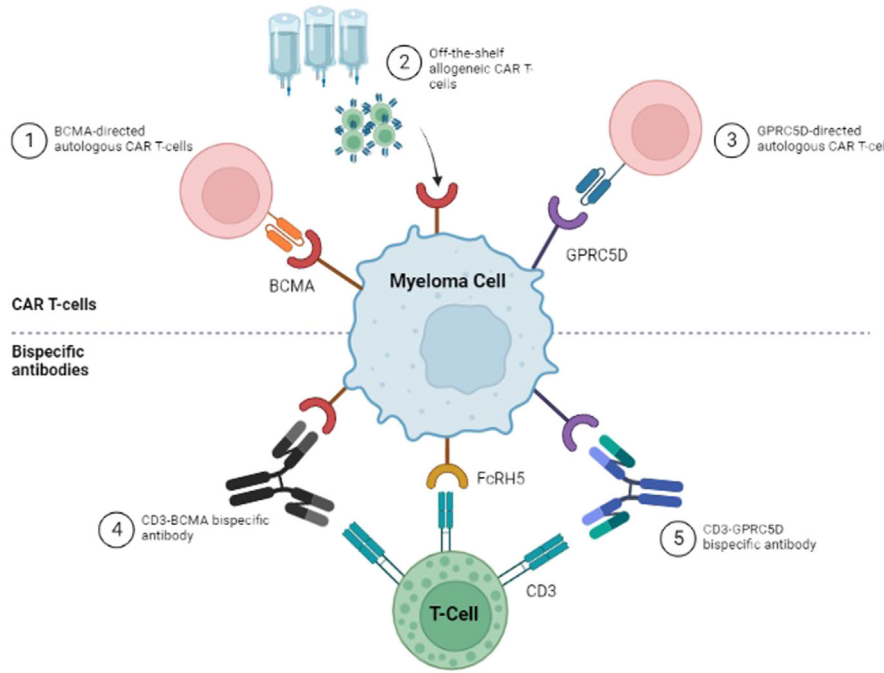


**Fig. 1.** Schematic of CAR T-cell and bispecific antibody therapy in MM.

**Table 1**
**Conceptual overview of selected chimeric antigen receptor T-cell therapy studies in multiple myeloma with available results**

| Setting | Trial ID | Report Format | Phase | Study | Drug(s) | CAR Target | N. | ORR (CR), % | DOR, mo | PFS, mo | CRS, % | Neurotoxicity, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ fourth line | NCT03361748 | Paper | II | KarMMA | Ide-cel | BCMA | 128 | 73 (33) | 10.7 | 8.8 | 84 | 18 |
| | NCT03548207 | Paper | I/II | CARTITUDE-1 | Cilta-cel | BCMA | 97 | 98 (83) | NR | NR | 95 | 21 |
| | NCT04555551 | Paper | I | - | MCARH109 | GPRC5D | 17 | 71 (35) | 7.8 | NA | 88 | 6 |
| | NCT04674813 | Abstract | I | - | CC-95266 | GPRC5D | 33 | 90 (47) | NR | NA | 64 | 6 |
| | NCT05016778 | Paper | I | POLARIS | OriCAR-017 | GPRC5D | 9 | 100 (60) | NA | NR | 100 | 0 |
| | NCT04093596 | Paper | I | UNIVERSAL | ALLO-715 | BCMA | 43 | 56 | 8.3 | NA | 56 | 14 |
| 2–4 prior lines | NCT03651128 | Paper | III | KarMMA-3 | Ide-cel vs standard regimens | BCMA | 386 | 71 (39) vs 42 (5) | 14.8 vs 9.7 | 13.3 vs 4.4 | 88 | 15 |
| 2nd line - early relapse after ASCT | NCT03601078 | Abstract | II | KarMMA-2 cohort 2A | | BCMA | 37 | 84 (46) | 15.7 | 11.4 | 83 | 22 |
| 1–3 prior lines | NCT04181827 | - | III | CARTITUDE-4 | Cilta-cel vs PVd or DPd | BCMA | - | - | - | - | - | - |
| 1st line after VRd induction - not intended for ASCT | NCT04923893 | - | III | CARTITUDE-5 | Cilta-cel vs Rd | BCMA | - | - | - | - | - | - |
| 1st line after D-VRd induction | NCT05257083 | - | III | CARTITUDE-6 | Cilta-cel vs ASCT | BCMA | - | - | - | - | - | - |

Reported abstract data refer to the time of their presentation.

*Abbreviations:* –, not reported; ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; DOR, duration of response; DPd, daratumumab-pomalidomide-dexamethasone; GPRC5D, G protein-coupled receptor, class-C, group-5, member-D; ide-cel, idecabtagene vicleucel; MM, multiple myeloma; N, number; NA, not available; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PVd, pomalidomide-bortezomib-dexamethasone; Rd, lenalidomide-dexamethasone; VRd, bortezomib-lenalidomide-dexamethasone.

**Table 2**
**Conceptual overview of selected bispecific antibody studies in multiple myeloma with available results**

| Setting | Trial ID | Report Format | Phase | Study | Drug(s) | Bispecific Target | N. | ORR (CR), % | DOR, mo | PFS, mo | CRS, % | Neurotoxicity, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ fourth line | NCT04557098 | Paper | I-II | MajesTEC-1 | Teclistamab | BCMA: CD3 | 165 | 63 (39) | 18.4 | 11.3 | 72 | 14 |
| ≥ fourth line | NCT03486067 | Abstract | I | - | Alnuctamab | BCMA: CD3 | 68[a] | 53 (23) | NR | NR | 53 | 3 |
| 1–3 prior lines | NCT04722146 | Abstract | Ib | MajesTEC-2 | Tec-Dara-Len | BCMA: CD3 | 32 | 94 (55) | NA | NA | 81 | 0 |
| RRMM | NCT03399799 | Paper | I | MonumenTAL1 | Talquetamab | GPRC5D: CD3 | 74[a] | 64–70 | 7.8–10.2 | NA | 78 | 7 |
| RRMM | NCT04649359 | Abstract | 2 | MagnetisMM-1 | Elrantamab | BCMA: CD3 | 123 | 61 (28) | NR | NR | 58 | 3 |
| RRMM | NCT04557150 | Abstract | I | - | RG6234 | GPRC5D: CD3 | 57[a] | 64 (26) | 12.5 | NA | 79 | 2 |
| RRMM | NCT03275103 | Abstract | I | - | Cevostamab | FcRH5: CD3 | 18 | 100 (64) | NA | NA | NA | NA |

Reported abstract data refer to the time of their presentation.

*Abbreviations:* –, not reported; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; Dara, daratumumab; DOR, duration of response; FcRH5, Fc receptor-homolog 5; GPRC5D, G protein-coupled receptor, class-C, group-5, member-D; len, lenalidomide; MM, multiple myeloma; N, number; NA, not available; NR, not reached; ORR, overall response rate; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

[a] Data indicated for subcutaneous route of administration.

### *B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T-Cell Therapy for Multiple Myeloma*

In the absence of modern immunotherapeutic strategies, patients with triple-class exposed MM had limited treatment options. The LocoMMotion trial prospectively enrolled patients with triple-class exposed r/r MM after greater than or equal 3 prior lines of therapy and demonstrated that only 20% of patients responded to their next line of therapy, and the MAMMOTH study reported that the median overall survival of triple-class refractory disease is only 9 months.[29,30] As such, the increasing availability of BCMA-directed CAR T-cell therapy is changing the natural history of triple-class exposed r/r MM.

BCMA, a member of the TNF superfamily, has a favorable expression pattern as a CAR target given its expression on myeloma cells, and otherwise, limited expression on nonmalignant plasma cells and small B-cell subsets.[31] Idecabtagene vicleucel (ide-cel) is the first FDA approved BCMA-directed autologous CAR T-cell therapy for triple-class exposed r/r MM after greater than 3 prior lines of therapy.[1] Ide-cel has a 4-1BB costimulatory domain and uses a lentivirus vector for CAR delivery, and the pivotal phase KarMMA trial reported a 73% response with ide-cel ($\geq$ complete response, CR 33%). But the median time from leukapheresis to product availability was 33 days and this can be challenging in patients with rapid disease progression, often necessitating bridging therapy between apheresis and CAR infusion. Among patients with a CR, the median progression-free survival was 20.2 months. Patients who received the highest target dose ($450 \times 10^6$) of CAR-positive T cells appeared to have a higher frequency and depth of response. Immune-mediated toxicities with ide-cel were mostly low grade.

A recent multicenter analysis from 11 US sites reported outcomes of standard of care ide-cel in a real-world population.[32] Of the 196 leukapheresed patients, there were 17 patients who did not proceed to cell infusion due to manufacturing failure (n = 5) or disease progression (n = 12). Despite 75% of treated patients being ineligible for the KarMMA inclusion criteria, the efficacy and safety profile of ide-cel in this real-world cohort were comparable to the KarMMA study. Prior use of BCMA-targeted therapy, high-risk cytogenetics, poor performance status, and younger patient age were associated with an inferior progression-free survival.

Ciltacabtagene autoleucel (cilta-cel) is the second FDA approved CAR T-cell therapy for the treatment of triple-class exposed patients with r/r MM after greater than 3 prior lines of therapy.[2] The median time from receipt of apheresis material to release of this product was 29 days. The updated 2-year results from CARTITUDE-1 demonstrated an extremely favorable overall response rate (ORR) of 97.9% (82.5% stringent CR), which is unprecedented in this patient population.[33] Median overall survival was not reached at 27-month follow-up with a progression-free survival of 55% at 27 months. The cilta-cel construct has 2 BCMA-targeting domains and whether this contributes to its high efficacy warrants consideration. The investigators report a high rate of second primary malignancies which is likely reflective of the heavily pretreated nature of the patient population.

### *Unique Toxicities of Chimeric Antigen Receptor T-Cell Therapy in Multiple Myeloma*

CAR-T cells are known to traffic to the cerebrospinal fluid. This is relevant not only in the context of ICANS but also because there have been reports of late-onset, progressive movement disorders after receipt of BCMA-directed CAR T-cell therapy which may relate to on-target, off-tumor effects in the central nervous system.[34] On postmortem

analysis in one such patient, BCMA was found to be expressed within the basal ganglia.[35] Similarly, there have been 2 cases of late-onset cerebellar toxicity in patients who received the highest dose level of MCARH109, a GPRC5D CAR.[36] Whether this relates to possible low-level expression of GPRC5D within the inferior olivary nucleus of the brainstem requires additional study.[36]

Real-world data have also highlighted protracted high-grade cytopenias in a subset of patients. The rate of grade greater than or equal 3 neutropenia persisting beyond 30 days was 60%, anemia 38%, and thrombocytopenia 59% after ide-cel.[32] Another retrospective analysis of patients treated with BCMA-directed CAR T-cell therapy found that approximately one-third had persistent grade greater than or equal 3 cytopenias at 4 months post CAR T-cell infusion.[37]

Finally, one of the biggest hurdles with CAR T-cell therapy is limited manufacturing slot availability. Presently, the median waitlist for commercial BCMA-directed CAR T-cell therapy in the United States is approximately 6 months, and approximately a quarter of patients die whilst waiting for treatment.[38]

### *Novel Chimeric Antigen Receptor T-Cell Therapies in Multiple Myeloma*

An effective allogeneic CAR product can overcome limitations of lengthy manufacturing times and slot availability. In this regard, Mailankody and colleagues reported interim results from the phase I UNIVERSAL trial of ALLO-715, a first-in-class "off-the-shelf" allogeneic anti-BCMA CAR T-cell therapy.[16] Patients are lymphodepleted with fludarabine, cyclophosphamide and ALLO-647 (an anti-CD52 antibody), which in turn eradicates CD52-expressing host immune cells and reduces the risk of a host-versus-graft reaction. The ALLO-715 CAR product has knockout of CD52 to allow for cell expansion and persistence in the context of ALLO-647. Interim data from the UNIVERSAL trial suggest that allogeneic CAR T-cell therapy is safe and efficacious, but longer-term data are awaited to determine durability. Importantly, no patient required bridging therapy. Part-B of the UNIVERSAL trial incorporates a gamma secretase inhibitor (nirogacestat) with ALLO-715 with the aim of preserving myeloma cell expression of BCMA to reduce antigen escape.[39]

Given a downregulation of BCMA expression has been observed in some patients who relapse post CAR T-cell therapy another strategy is to target an alternative antigen.[40] We recently reported that GPRC5D-directed CAR T-cell therapy (MCARH109) is safe and an effective novel immunotherapeutic strategy in MM. Early results of GPRC5D CARs from other groups are also promising.[41] Notably, on-target, off-tumor skin, tongue, and nail toxicities from GPRC5D CAR T-cell therapy appear to be lower than with GPRC5D bispecific antibodies, and differences in the pharmacokinetics and dosing schedules between the 2 drug classes may be contributing. Clinical studies of dual antigen targeting of both BCMA and GPRC5D are ongoing (NCT05431608; NCT05325801).

Cell manufacture with NEX-T technology is designed to shorten the manufacturing times and improve the potency and phenotypic attributes of the autologous CAR-T cells. BMS-986354, a BCMA-directed CAR T-cell therapy, is manufactured using NEX-T, and interim results of the ongoing CC-98633-MM-001 trial demonstrated an excellent ORR of 98% with this product.[42]

BCMA-directed CAR-T cells are being studied in earlier treatment lines. Interim results from the KarMMa-2 Cohort 2A study reported a favorable clinical risk–benefit profile of ide-cel in the second line for a clinically high-risk patient population.[43] CARTITUDE-5 and CARTITUDE-6 are investigating the incorporation of cilta-cel as part of frontline therapy in MM (NCT04923893; NCT05257083). The outcomes of these upfront studies of CAR T-cell therapy are eagerly awaited and could dramatically alter

the current treatment paradigm of patients with multiple myeloma. Indeed, the phase 3 KarMMa-3 trial demonstrated that ide-cel significantly prolonged progression-free survival as compared with standard regimens in triple-class exposed r/r MM.[18]

## BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

### *Teclistamab*

Teclistamab is a bispecific IgG4 antibody with dual binding sites for CD3 and BCMA. The pivotal MajesTEC-1 phase I–II clinical trial studied teclistamab in patients with triple-class exposed MM, after $\geq$ 3 prior lines of therapy and established a new standard of care for r/r MM with recent FDA approval.[10] Patients with prior exposure to BCMA-targeting therapies were excluded. Enrolled patients were treated with once-weekly subcutaneous teclistamab (preceded by 2 step-up doses), and patients required hospitalization and premedication with glucocorticoids to mitigate immune-mediated toxicities. There was substantial clinical activity with teclistamab with a 63% ORR (39% CR) and median response duration of 18.4 months. Notably, 7% of patients died from COVID-19 infection and this may relate to immune deficiencies from BCMA expression on normal plasma cells and necessitates infection prophylaxis and close monitoring of immune functions.

Correlative analyses have demonstrated that achievement of a higher clinical response with teclistamab is associated with higher naïve $CD8^+$ T cells and lower expression T-cell exhaustion markers, supporting the study of teclistamab in earlier lines where patients are expected to have a more favorable immune profile.[44] Combination strategies of teclistamab and other anti-myeloma drugs are also being explored in earlier lines and include a phase 3 randomized trial that will compare teclistamab-daratumumab-lenalidomide versus daratumumab-lenalidomide-dexamethasone in newly diagnosed MM (MajesTEC-7).[45]

### *Talquetamab*

Talquetamab is a bispecific antibody that binds to CD3 on T cells and GPRC5D on myeloma cells. The ongoing phase I MonumenTAL trial of talquetamab in r/r MM is composed of a dose-escalation and dose-expansion phase and the pivotal phase 2 portion enrolled patients with $\geq$ 3 prior lines of therapy and included those with prior exposure to CAR T-cell or bispecific antibodies.[46] Despite the high-risk characteristics of enrolled patients, the ORR was 64% to 70% and the median duration of response was 7.8 to 10.2 months. Within the subset of patients who had a prior T-cell redirecting therapy (71% prior CAR T-cell therapy, 35% prior bispecific antibody), the ORR was still promising at 63% with a median duration of response of 13 months.

Given the expression of GPRC5D on the skin and nail folds, low-grade and reversible skin- and nail-related changes were seen in some patients. The rate of grade 3 to 4 infections was less than 20% and the rate of COVID-19 infection was approximately 10%. RG6234 is another GPRC5D-CD3 bispecific with a 2:1 configuration that is also being studied.[47]

### *Cevostamab*

Cevostamab is a bispecific antibody that targets Fc receptor-homolog 5 (FcRH5) on myeloma cells and CD3 on T cells. FcRH5 is expressed across the B-cell lineage with the highest expression on plasma cells and near ubiquitous expression on myeloma cells.[48] Cevostamab has an intravenous route of administration (3-weekly cycle), and preliminary results from the G039775 phase 1 study of this agent are promising.[49] Given the crucial role of IL-6 in mediating CRS, an important study arm is

investigation of pretreatment tocilizumab (an IL-6 receptor blocking antibody) to mitigate CRS.[50] Despite higher rates of neutropenia, the rate of CRS in patients who received tocilizumab was only 39% compared with 91% in patients who did not receive tocilizumab ($P < 0.001$), without any difference in response rates. Further investigation of prophylactic tocilizumab with bispecific antibodies is appealing, especially in the setting of their outpatient initiation.

### *Elranatamab*

Elranatamab is a humanized bispecific antibody targeting BCMA on myeloma cells and CD3 on T cells. Interim results from the ongoing phase I, first-in-human MagnetisMM-1 trial of patients who received subcutaneous elranatamab monotherapy (weekly or every-other-week) have been presented.[51] Patients received a median of 5 prior lines of therapy, including prior BCMA-targeted therapies (antibody drug conjugates [15%] and CAR T-cell therapy [16%]). The ORR was 64% (38% $\geq$ CR) with 54% of patients exposed to a prior BCMA-targeted therapy achieving a response. Grade 3 and 4 infections occurred in 22% and 6% of patients, respectively.

## SUMMARY

CAR T-cell therapy and bispecific antibodies have no doubt revolutionized the treatment of blood cancers. Together, these therapies are allowing for the median overall survival of our patients to improve. Yet, many questions remain. If we are to fully harness their therapeutic potential much work needs to be done—from improving access, defining optimal sequencing and adjunctive pharmaceutical agents, minimizing toxicity, and identifying resistance mechanisms and predictive biomarkers. In closing, the biggest question remains—can novel immunotherapeutic strategies cure blood cancers such as MM? That we can now plausibly ask such questions suggests that the future is bright for MM.

## CLINICS CARE POINTS

- Envisioning a randomized controlled study that compares CAR T-cell therapy to bispecific antibodies is difficult. Treatment selection is often personalized, taking into consideration unique patient and disease characteristics, toxicity profiles, and logistics and access to therapy. It is hoped that emerging data will help identify the optimal sequencing of these agents, resistance mechanisms, and pretherapy biomarkers of response.
- Translational insights are leading to ongoing advancements in the drug development of T-cell engaging therapies. This includes the identification of novel target antigens and off-the-shelf CAR T-cell products. However, much work remains to be done to mitigate the treatment-related toxicities.
- Considering the therapeutic efficacy of CAR T-cell therapy and bispecific antibodies, should such therapies be brought more proximal in our treatment armamentarium–particularly given as earlier use may preserve naïve T cells, which are the optimal substrates of these treatments? We look forward to results of ongoing multicenter clinical trials that are asking such questions.

## DISCLOSURE

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