Chimeric Antigen Receptor T-Cell and Bispecific Antibody Therapy in Multiple Myeloma: Moving Into the Future

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DOI https://doi.org/10.1200/JCO.23.00512

ABSTRACT

Historically, the outcomes for individuals with triple-class refractory and penta-drug refractory multiple myeloma (MM) have been poor because of a dearth of effective treatment options. However, the advent of chimeric antigen receptor (CAR) T-cell and T-cell redirecting bispecific antibody (BsAb) therapies has led to unprecedented response rates and durations of response in heavily relapsed/refractory (R/R) populations. Currently, two B-cell maturation antigen (BCMA)–directed CAR T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel) as well as one BCMA/CD3 BsAb (teclistamab) have been approved for late-line (greater than four previous lines) R/R MM in the United States. The purpose of this review is to analyze the recent data for these approved therapies as well as provide an overview of other related CAR T-cell and BsAb therapies under development, including non–BCMA-targeting agents. We review efficacy and safety considerations, with particular focus on cytokine release syndrome, neurotoxicity, and infection risk. The relative merits and limitations of each class of therapy are discussed, as well as the areas of unmet need with respect to optimal sequencing and supportive care measures. We examine the factors that challenge equitable access to these novel therapies across minoritized racial, ethnic, and socioeconomic populations. Although it is evident that CAR T-cell and BsAb therapies will transform treatment paradigms in MM for years to come, significant work remains to identify the optimal utilization of these novel therapies and ensure equitable access.

Accepted June 13, 2023
Published July 20, 2023

J Clin Oncol 41:4416-4429

INTRODUCTION

The management of multiple myeloma (MM) is becoming increasingly complex as the number of therapeutic options increase. The immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs) have become mainstays of therapy for newly diagnosed disease and early lines of relapsed/refractory (R/R) disease. Although these three classes of drugs have markedly improved long-term outcomes, management of triple-class refractory disease (IMiDs, PIs, and anti-CD38 mAb) and penta-drug refractory disease (lenalidomide, pomalidomide, bortezomib, carfilzomib, and anti-CD38 mAb) has proven difficult with limited therapeutic options and short survival duration.[1-4] In this context, the US Food and Drug Administration (FDA) approved several novel drugs, including selinexor (an XPO1 inhibitor), belantamab mafodotin (a B-cell maturation antigen [BCMA] antibody drug conjugate [ADC]), and melphalan flufenamide, all with overall response rates (ORRs) of approximately 25%-30% and median progression-free survival (PFS) durations of 3-4 months.[5-7] Subsequently, both belantamab mafodotin and melphalan flufenamide were removed from the market.

Emerging into this therapeutic landscape are chimeric antigen receptor (CAR) T cells and T-cell–redirecting bispecific antibodies (BsAbs), therapies that directly harness the activity of T cells and show substantial efficacy in heavily pretreated patients. The BCMA-directed CAR T-cell product idecabtagene vicleucel (ide-cel) was approved by the FDA on March 27, 2021, with an indication for patients with R/R MM after four or more previous lines of therapy, including an IMiD, PI, and anti-CD38 mAb. On February 28, 2022, the FDA approved another BCMA-directed CAR T-cell product, ciltacabtagene autoleucel (cilta-cel), with the same indication. The anti-BCMA/CD3 BsAb, teclistamab, received approval by the FDA on October 25, 2022, again with the same indication. Of note, the phase II studies that led to the approval of these agents all enrolled patients with three or more previous lines of therapy.[8-10] In this review, we provide an overview of the approved CAR T-cell/BsAb therapies as well as many of the therapies undergoing clinical trial investigation. We examine the relative merits and challenges associated with each class of therapy and examine the factors that challenge equitable access to these novel therapies and MM-related care in general.

CONTEXT

Key Objective

To provide an overview of the mechanisms of action, efficacy, toxicity, and issues surrounding equitable access to novel chimeric antigen receptor (CAR) T-cell and bispecific antibody (BsAb) therapies in multiple myeloma (MM).

Knowledge Generated

CAR T-cell and BsAb therapies targeting B-cell maturation antigen and other novel targets are yielding unprecedented responses in patients with heavily pretreated MM. Optimal sequencing of these agents, as well as strategies to limit toxicities such as cytokine release syndrome, neurotoxicity, and infections, remains to be determined.

Relevance *(S. Lentzsch)*

The review explores the pros and cons of the currently approved CAR T and bispecific products in MM for the multidisciplinary oncology community at large, including medical, radiation, and surgical oncologists.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

MECHANISM OF ACTION

Both CAR T cells and T-cell–redirecting BsAbs harness the cytotoxic activity of T cells. Although it has long been recognized that T cells possess anti-MM activity,[11,12] there are many mechanisms underlying T-cell dysfunction in MM.[13] CAR T cells are designed to overcome some of these barriers by genetically modifying T cells such that the T cells are directed toward a specific tumor antigen (eg, BCMA) via an antigen-recognizing receptor coupled to signaling domains that lead to T-cell activation (Fig 1A). The commercially available products are derived from autologous T cells, although allogeneic CAR T cells are also under development. In brief, patients undergo leukapheresis of peripheral blood to obtain autologous T cells. Subsequently, these T cells are shipped to a central manufacturing laboratory (or, in some cases, for investigational products, are manufactured in-house) where they undergo engineering and expansion. Depending on the product and the manufacturing process, this might take anywhere from a few days to up to 8 weeks. Before receiving the finished engineered product, patients receive lymphodepleting chemotherapy (most commonly fludarabine and cyclophosphamide). Bridging chemotherapy is often administered during the manufacturing time period in an attempt to maintain disease control. CAR T-cell therapy has been referred to as a living drug as cells can expand in vivo, with variable durations of persistence.

Often referred to as off-the-shelf alternatives to CAR T-cell therapy, BsAbs and related T-cell redirecting agents take the approach of directing T cells to MM cells by simultaneously engaging both T cells and MM cells, creating an immunologic synapse (Fig 1B). Initial efforts in the field involved the bispecific T-cell engager AMG-420, composed of two linked single-chain variable fragments targeting BCMA and CD3 (Fig 1C). Although AMG-420 did show activity in a phase I first-in-human study in R/R MM (ORR of 31%; 70% at the maximum tolerated dose), this therapy was hindered by the need for a continuous IV infusion.[14] Subsequent efforts focused on extended half-life derivatives such as pavurutamab (AMG 701; Fig 1C).[15] Ultimately, the field turned to BsAbs (eg, teclistamab), which include an Fc region that provides stability and prolongs the agent's half-life permitting less frequent dosing (Fig 1C). Other variations include agents with two BCMA binding domains (eg, ABBV-383 and alnuctamab), trispecific T-cell–activating constructs that include an antialbumin domain for half-life extension (eg, HPN217) and modification of the Fc portion to minimize binding to FcγR and C1q (eg, alnuctamab; Fig 1C).

EFFICACY

The accelerated approvals of ide-cel, cilta-cel, and teclistamab were based on phase I/II studies conducted in individuals with R/R MM who had not previously received BCMA-directed therapy. As shown in Table 1, most people with MM enrolled in these studies were heavily pretreated (median of five to six previous lines) with triple-class refractory disease, while a minority had penta-drug refractory disease. In this context, the ORRs of 73% (ide-cel), 98% (cilta-cel), and 63% (teclistamab) represented new benchmarks in this population with difficult-to-treat disease.

Several other ide-cel or cilta-cel studies have reported outcomes thus far. The CARTITUDE-2 cohort A evaluated patients (n = 20) with one to three previous lines of therapy (median of two previous lines, all triple class exposed, 40% triple-class refractory).[18] The ORR was 95% with 85% achieving a complete response (CR) or better. The 6-month PFS rate was 90%. The KarMMa-2 cohort 2a enrolled participants experiencing disease progression within 18 months of frontline therapy (induction, autologous

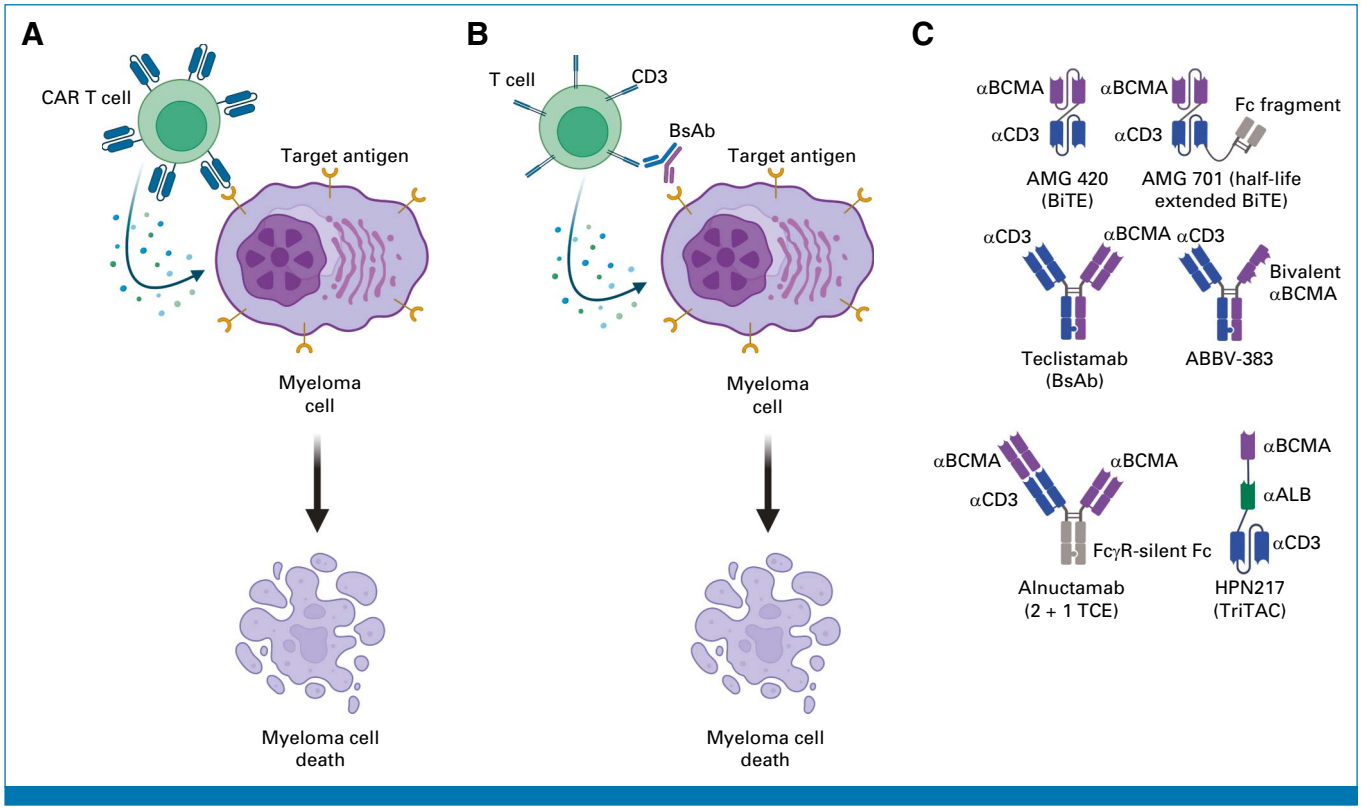

FIG 1. Mechanism of action of CAR T-cell and BsAb therapies in MM. (A) The engineered CAR T cells recognize and engage with the target antigen (eg, BCMA) on the surface of the myeloma cell, leading to activation of the CAR T cell with subsequent release of perforin, granzymes, and cytokines, leading to cytolysis of the tumor cell. (B) A BsAb simultaneously engages the target antigen (eg, BCMA) on the myeloma cell as well as CD3 on the T cell, leading to an immunologic synapse and cytolysis of the tumor cell via release of perforin, granzymes, and cytokines. (C) Examples of the designs of several types of T-cell–redirecting agents developed as anti-BCMA therapies in MM. Currently only teclistamab, a BsAb, has achieved FDA approval for the treatment of relapsed/refractory myeloma. BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; BsAb, bispecific antibody; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; MM, multiple myeloma; TCE, T-cell engager; TriTAC, trispecific T-cell–activating construct.

stem-cell transplant [ASCT], and lenalidomide-containing maintenance; n = 37). Forty-six percent of participants achieved a CR or better (the primary end point), and the median PFS was 11.4 months.[19] The CARTITUDE-2 cohort B study also evaluated a functionally high-risk population—those who relapsed within 12 months of upfront ASCT or within 12 months from the start of induction (n = 19). The ORR was 100%, with 90% achieving CR or better and a 12-month PFS rate of 90%.[20]

Thus far, the full results of two confirmatory phase III studies have been reported. The KarMMa-3 study enrolled participants with two to four previous lines of therapy, randomizing in a 2:1 manner to ide-cel or one of five standard-of-care chemotherapy regimens. This study met its primary end point of PFS, with a median PFS of 13.3 months in the ide-cel group versus 4.4 months in the standard regimen arm (hazard ratio [HR], 0.49 [95% CI, 0.38 to 0.65]; $P < .001$).[21] The CARTITUDE-4 trial enrolled patients with lenalidomide-refractory MM and one to three previous lines of therapy and randomized patients to either cilta-cel or standard of care (consisting of either daratumumab/pomalidomide/dexamethasone or pomalidomide/bortezomib/dexamethasone). This study also met its primary end point of PFS, with a median PFS not yet reached for the cilta-cel group versus 11.8 months in the standard-of-care group (HR, 0.26 [95% CI, 0.18 to 0.38]; $P < .001$).[22]

The results from real-world experiences with commercial ide-cel and cilta-cel are beginning to be reported. Hansen et al[23] reported on the experience of 11 US institutions with ide-cel. The ORR was 84% with a median PFS of 8.5 months.[23] Similarly, a report from a French registry (n = 49 patients infused with ide-cel) noted an ORR of 76% at 3 months along with a 3-month PFS rate of 82%.[24] Hansen et al[23] also reported on the experience of 12 US institutions with commercial cilta-cel. With brief follow-up (median of 5.8 months), the observed best ORR was 89% and the 6-month PFS rate was 79%.[25]

Although teclistamab represents the first BCMA-directed BsAb to obtain regulatory approval, there are multiple other BCMA-directed agents under development (Fig 1C; Table 2). Interestingly, response rates for all of these

TABLE 1. Efficacy Data for FDA-Approved BCMA-Directed CAR T-Cell and Bispecific Antibody Therapies

Therapy	N	Median Previous Lines of Therapy, No. (range)	Triple Class Refractory, %	Penta-Drug Refractory, %	High-Risk, %	ORR, %	≥CR, %	PFS	DOR	OS
Ide-cel[8]	128	6 (3-16)	84	26	35	73	33	Median 8.8 months	Median 10.7 months	Median 19.4 months
Cilta-cel[9,16,17]	97	6 (4-8)	88	42	24	98	82.5	Median 34.9 months	Median 33.9 months	63% at 3 years
Teclistamab[10]	165	5 (2-14)	78	30	26	63	39.4	Median 11.3 months	Median 18.4 months	Median 18.3 months

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DOR, duration of response; FDA, US Food and Drug Administration; ide-cel, idecabtagene vicleucel; ORR, overall response; OS, overall survival; PFS, progression-free survival.

BCMA-/T-cell–directed agents have been strikingly consistent across studies thus far (range, 50%-60%). Whether all these agents will ultimately obtain regulatory approval and whether disease refractoriness to one agent equates to refractoriness to all agents in this group remains to be determined. Multiple other BCMA-directed CAR T-cell products are under investigation (Table 2), with some using innovative manufacturing procedures (eg, CC-98633/BMS-986354[37]), heavy chain-only BCMA binding domains (eg, FHVH-T[35]), dual antigen targeting (eg, bispecific CS1-BCMA[42]) or allogeneic T-cells (eg, ALLO-715[43]). All products have been reported to have high response rates (>60%), but follow-up for many of the studies is insufficient to gauge the durability of response.

Notably, CAR T-cell and BsAb development has moved beyond targeting BCMA (Table 2). Of particular interest is the orphan G-protein-coupled receptor class C, group 5, member D (GPRC5D), which is highly expressed on plasma cells.[48] Several phase I studies of GPRC5D-directed CAR T cells have shown high response rates (71%-100%).[44-47] Likewise, the GPRC5D/CD3 BsAbs talquetamab and RG6234 have demonstrated ORRs in the 60%-70% range.[31,32] Finally, Fc receptor-like 5 (FcRH5) has also proven to be a target of interest in MM.[49] A phase I study of cevostamab, a BsAb directed against FcRH5/CD3, has shown an ORR of 57% at higher dose levels.[33] The anti-GPRC5D and FcRH5 trials included some participants with previous BCMA-directed therapy, which is significant because this population is quickly becoming an area of unmet need.

TOXICITY

In addition to typical hematologic and nonhematologic toxicities of MM therapies, CAR T-cell and bispecific therapies have important classes of toxicity, including cytokine release syndrome (CRS) and immune-effector cell–associated neurotoxicity syndrome (ICANS; Table 3). CRS, characterized by fever, hypotension, hypoxia, and respiratory distress,[51] occurs in about 90% of patients with MM receiving CAR T-cell therapy and around 70% of those receiving BsAbs (Table 3). CRS with the BsAbs appears to be generally lower in frequency and of lower grade than with CAR T-cell therapy, which may be in part due to the use of step-up dosing, wherein the BsAb is introduced at a very low dose and then escalated over several doses to reach the full planned dose. Clinical practice guidelines for managing CRS encourage early use of steroids and the interleukin-6 receptor antagonist tocilizumab.[52] Prophylactic tocilizumab 2 hours before the first dose of cevostamab was explored, resulting in 36% of patients experiencing CRS, compared with 90% from a historical comparison cohort.[53] Continued refinement of supportive care, including premedications, alternative dosing strategies, and prophylactic tocilizumab, may further reduce the incidence of this complication in patients receiving CAR T-cell and BsAb therapy.

TABLE 2. Summary of Investigational T-Cell–Directed Engagers/Antibodies and CAR T-Cell Therapies

Agent	Class	Target	N	Median Lines of Previous Treatment, No. (range)	Triple Class Refractory, %	Penta-Drug Refractory, %	Previous BCMA, %	ORR, %
Elranatamab[26]	BsAb	BCMA/CD3	123	5 (2-22)	97	43	0	61
ABBV-383[27]	BsAb	BCMA/CD3	174	5 (3-15)	80	34	0	56
Linvoseltamab[28]	BsAb	BCMA/CD3	221	5 (2-14) (RP2D)	74 (RP2D)	24 (RP2D)	0	71 (at RP2D)
HPN-217[29]	TriTAC	BCMA/CD3/ albumin	62	6 (2-19)	76	42	21	51 (≥2.15 mg)
Alnuctamab[30]	2 + 1 TCE	BCMA/CD3	68	4 (3-11)	63	28	0	53
Talquetamab[31]	BsAb	GPRC5D/CD3	232 (130 SC, 102 IV)	6 (2-17) (SC) 6 (3-20) (IV)	75 (SC) 85 (IV)	25 (SC) 35 (IV)	32 (SC) 16 (IV)	68 (SC)[a] 72 (IV)[a]
RG6234[32]	BsAb	GPRC5D/CD3	105 (54 SC, 51 IV)	4 (2-14) (SC) 5 (2-15) (IV)	73 (SC) 63 (IV)	42 (SC) 31 (IV)	20 (SC) 20 (IV)	60 (SC) 71 (IV)
Cevostamab[33]	BsAb	FcRH5/CD3	161	6 (2-18)	85	68	34	57 (132-198 mg dose level)
CT103A[34]	CAR T	BCMA	103	4 (3-23)	NR	NR	NR	95
FHVH-T[35]	CAR T	BCMA	25	6 (3-10)	NR	NR	NR	92
CART-Ddbcma[36]	CAR T	BCMA	33	5 (3-16)	77	68	NR	100
CC-98633/BMS-986354[37]	CAR T	BCMA	65	5 (3-13)	91	48	0	95
Orvacabtagene autoleucel[38]	CAR T	BCMA	62	6 (3-18)	94	48	0	92
Zevorcabtagene autoleucel[39]	CAR T	BCMA	102	4 (3-15)	23	NR	NR	93
PHE885[40]	CAR T	BCMA	50	4 (2-10)	94	62	NR	98
FasTCAR-T CG012F[41]	CAR T	CD19 and BCMA	29	5 (2-11)	NR	NR	NR	93
Bispecific CS1-BCMA[42]	CAR T	CS1 and BCMA	16	5 (2-10)	NR	NR	55	90
ALLO-715[43]	CAR T (allogeneic)	BCMA	53	5 (3-11)	NR	44	NR	64-80[b]
MCARH109[44]	CAR T	GPRC5D	17	6 (4-14)	94	NR	59	71
CC-95266/BMS-986393[45]	CAR T	GPRC5D	33	4 (3-13)	NR	24	41	86
OriCAR-017[46]	CAR T	GPRC5D	10	5.5 (4-10)	20	NR	50	100
Anti-GPRC5D[47]	CAR T	GPRC5D	33	4 (2-12)	NR	NR	27	91

Abbreviations: BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; FcRH5, Fc receptor-like 5; GPRC5D, G-protein-coupled receptor class 5, group 5, member D; IV, intravenous; NR, not reported; ORR, overall response rate; RP2D, recommended phase II dose; SC, subcutaneous; TCE, T-cell engager; TriTAC, trispecific T-cell–activating construct.

[a]At most active dose levels.

[b]At dose level 3 of the CAR T-cells and lymphodepletion with fludarabine/cyclophosphamide and ALLO-647 (39 or 60 mg).

TABLE 3. Key Adverse Events Reported in Published CAR T-Cell and Bispecific Antibody Myeloma Trials

Study	CARTITUDE-1[9]	CARTITUDE-4[22]	KarMMa[8]	KarMMa-3[21]	MCARH109 Phase I[44]	POLARIS[46]	Anti-GPRC5D CAR T Phase II[47]	MajesTEC-1[10]	MonumenTAL-1[31]	ABBV-383 Phase I[50]
Therapy	Cilta-cel	Cilta-cel	Ide-cel	Ide-cel	MCARH107	OriCAR-017	Ant-GPRC5D CAR T	Teclistamab[a]	Talquetamab	ABBV-383
Any grade 3-4 adverse events, %	94	97	99	93	100	100	100	95	86	72
Neutropenia (≥grade 3), %	95	90	89	76	100	100	100	64	43	34
Thrombocytopenia (≥grade 3), %	60	41	52	42	65	60	45	21	16	12
Infections (any grade/≥grade 3), %	58/20	62/27	69/22	58/28	18/12	NR	NR	76/45	39/7	41/23
Hypogammaglobulinemia (any grade), %	NR	42	21	NR	NR	NR	NR	75	77	14
Diarrhea (any grade), %	30	34	35	34	NR	30	9	29	22	27
Constipation (any grade), %	22	24	16	27	NR	NR	15	21	11	NR
Nausea (any grade), %	28	49	29	45	24	30	27	27	22	29
Fatigue (any grade), %	37	29	34	28	41	10	NR	28	30	30
Headache (any grade), %	NR	26	21	24	NR	20	3	24	23	16
Dysgeusia (any grade), %	NR	NR	NR	NR	12	NR	NR	NR	59	NR
Rash (any grade), %	NR	NR	NR	NR	18	NR	3	NR	36	NR
Nail-related (any grade), %	NR	NR	NR	NR	65	30	27	NR	39	NR
Cytokine release syndrome (any grade/≥grade 3), %	95/4	76/1	84/5	88/5	88/6	100/0	76/0	72/1	78/1	57/2
Neurotoxicity (any grade), %	21	21	18	15	18	0	6	15	8	2

Abbreviations: CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; GPRC5D, G-protein-coupled receptor class 5, group 5, member D; ide-cel, idecabtagene vicleucel; NR, not reported.
[a]Data for subcutaneous dosing.

ICANS can include a range of symptoms and signs, including headache, confusion, somnolence, seizures, and coma. Strategies proposed for minimizing the development of ICANS include the use of bridging therapy to reduce tumor burden, intensive sustained monitoring, and early initiation of treatment for neurotoxicity.[54] Our understanding of the impact of ICANS on patient function and quality of life (QoL) continues to evolve, particularly as delayed neurologic toxicities, such as Parkinsonism, movement disorders, cognitive impairment, cranial nerve palsies, and peripheral neuropathy, emerge as experience with CAR T-cell therapy grows.[22,44,54,55]

By nature, patients with advanced MM are severely immunocompromised and at risk for serious infections. High infection rates (including grade 3 or higher) were observed across many of the MM CAR T-cell and bispecific trials (Table 3), and grade 5 events have been reported as well.[10,16,21,31,56] Rates of grade 3 or greater infections were approximately 20% with ide-cel or cilta-cel.[8,9] The MajesTEC-1 trial reported a 45% grade 3 or higher rate of infections with teclistamab.[10] In addition, there was a high incidence of COVID-19 infections, including 12 deaths due to COVID-19.[10] Whether all BCMA-directed bispecific agents have similar risk of infection remains to be determined. Interestingly, in the talquetamab MonumenTAL-1 study, the rate of grade 3 or higher infection was only 7%,[31] perhaps suggesting that the infection risk might be lower for GPRC5D-directed therapy than with BCMA-directed therapies.

In a real-world cohort of patients receiving ide-cel, over half of the patients experienced infections within the first 100 days.[57] In this study, infections within the first 30 days tended to be bacterial and associated with cytopenias.[57] Another group reported that within the first 3 months after BCMA CAR T-cell therapy there were primarily viral infections, with 95% developing hypogammaglobulinemia.[58] Another retrospective analysis revealed high rates of infections in patients receiving BCMA BsAb therapy, with all responders experiencing severe hypogammaglobulinemia (IgG level <200 mg/dL).[59] A recent pooled analysis of 1,185 participants in 11 trials of BsAbs demonstrated high rates of serious or even fatal infection: 24.5% grade 3/4 infection, including 10% grade 3/4 pneumonia.[60] Of the reported deaths, 25% were due to infection. Opportunistic infections not typically observed in the MM population outside of the allogeneic transplant setting have been reported, including Pneumocystis jiroveci pneumonia infection and cytomegalovirus reactivation.[21,31,56,61] There have also been reports of prolonged viral infections, including parvovirus and norovirus, in patients receiving BCMA-directed bispecific agents.[62]

Rates of grade 3/4 neutropenia appeared to be slightly higher in those treated with BCMA BsAbs versus non-BCMA BsAbs. Prolonged lymphopenia and hypogammaglobulinemia have been noted after BCMA CAR T-cell therapy.[63] In the four studies reporting on hypogammaglobulinemia, the prevalence was 75%, with nearly half of the patients receiving intravenous immunoglobulin.[60] As the majority of the clinical trials and commercial use of approved products have occurred during the ongoing COVID-19 pandemic, it is also not surprising that deaths from COVID-19 have been reported.[10,31,56,64] The extent to which potential COVID-19–induced immune dysregulation, particularly T-cell dysfunction,[65-67] affects susceptibility to other infections and MM responsiveness to CAR T-cell and BsAb therapies remains to be determined. Collaborations among MM clinicians, cellular/transplant specialists, and infectious disease specialists are needed to develop best practices for prophylaxis after CAR T and BsAb therapy.

It is worth noting that the development of new classes of agents targeting a novel antigen (GPRC5D) is accompanied by a new set of toxicities. GPRC5D is an orphan receptor whose physiologic function has not yet been clearly defined.[48,68] Although GPRC5D is highly expressed on plasma cells, it is also expressed on cells within the hard keratinizing tissues and hair follicles of skin.[48,68] Studies conducted to date using either GPRC5D-directed CAR T cells or BsAbs have reported skin and nail changes, rash, and oral-related adverse events, including dysgeusia, dry mouth, and dysphagia (Table 3), which are presumably related to GPRC5D expression in these tissues.[31,32,44,45] Strategies to minimize these toxicities and improve long-term tolerability of these therapies are needed.

Beyond traditional adverse event reporting and grading, clinicians and researchers must also center their decision making about these agents from the perspectives of the lived experiences of patients who receive these therapies. This patient-centered focus would capture potential toxicities and other individual health outcomes, such as the impact of CAR T-cell therapies on patient-reported function and QoL. In addition, it could also unearth the potential barriers that limit equitable access to these therapies. Qualitative analyses of interview data collected from patients who received ide-cel or cilta-cel in clinical trials revealed overall positive patient-reported experiences, with the treatments meeting or exceeding their expectations and resulting in improvements in symptom burden and QoL.[69,70] Complementary data using quantitative health-related QoL measures demonstrated longitudinal improvement in symptoms and QoL in individuals with MM receiving cilta-cel or ide-cel.[71,72] Patient-reported outcome data were reported from a cohort in the MajesTEC-1 study and showed longitudinal improvements in global health status and reduction in pain with no change in fatigue or physical functioning.[73] Similar data of patient experience and QoL with other BsAbs under development are awaited.

ACCESS TO CARE AND EQUITY IN REAL-WORLD SETTINGS

Despite the promising data supporting the efficacy of CAR T-cell and BsAb therapies among clinical trial participants and those fortunate enough to receive these therapies in the real world, the potential to see widening disparities in MM treatment access and key health outcomes, including

survival, is of concern. Studies have shown disparities in MM treatment access on the basis of age, race/ethnicity, socioeconomic status, and residential neighborhood characteristics (eg, social vulnerability, which is considered to be the cumulative effects of poverty, housing, and transportation concerns, and large populations from minoritized racial/ethnic backgrounds).[74-77] One database study of CAR T-cell therapy recipients with lymphoma, acute lymphoblastic leukemia, and MM identified disparities in access to this therapy among Black persons, those with government-funded health insurance (Medicare or Medicaid), and median household incomes <$40,000 in US dollars per year.[78] Another study of 3,922 patients with diffuse large B-cell lymphoma also identified access barriers according to practice setting (academic *v* community-based).[79] This early demonstration of disparities among CAR T therapy recipients provides an opportunity to identify equity-driven strategies and solutions that would improve access to clinical trials evaluating these products and help guide clinician decision making to ensure equitable access to these products with the anticipated expansion in availability.

One early barrier clinicians would need to overcome would be the generalizability of early trial data, given that clinical trial populations are typically highly selected. Table 4 highlights what is known about the demographic characteristics of participants in published MM CAR T-cell and BsAb trials. Participants tended to be younger, with good performance status, and identified as non-Hispanic White. In addition, most studies excluded patients with various common comorbid conditions. Thus, clinicians are left with gaps in knowledge about the most effective treatments among those typically under-represented in clinical trials. Real-world data represent an important source of information in this setting. For example, Hansen et al[23] recently reported on the outcomes of real-world patients who received commercial ide-cel in the United States. Notably, 75% of patients would have been ineligible for the KarMMa trial because of laboratory abnormalities, previous BCMA-directed therapy, other malignancies, or other conditions. Reassuringly, the reported ORR and PFS values were similar to those of the original trial.[8,23]

Across most hematologic malignancies, older adults are underenrolled in clinical trials,[81] a finding again seen among the published CAR T and BsAb trials highlighted here (Table 4). Exclusionary comorbidities typically include congestive heart failure, recent myocardial infarction, active infection, and second malignancies within the past 3-5 years. Nevertheless, even within these enrollment criteria, an older adult may have aging-associated vulnerabilities, raising a clinician's concern about their risk of toxicity. Although early data are encouraging that older patients selected for CAR T-cell therapy in real-world practice tolerate it similarly to younger patients,[82] more widespread use of the therapy will reveal subgroups of people who may have poorer outcomes. For example, one recent study demonstrated that sarcopenia was associated with an increased risk of ICANS and longer length of hospital stay.[83] Consistently gathering additional data (including geriatric assessment)[84,85] about the baseline health of individuals enrolled in clinical trials of CAR T-cell and BsAbs will improve clinicians' insight into whether their patients are similar to those treated on trial and identify those who may be at increased risk for toxicity, allowing more informed shared decision making.

Barriers to racial equity in access to innovative therapies start during the clinical trial design phase and drug development process and persist after approval. A recent study demonstrated that only 36% of Black persons reside in US counties with available CAR T-cell trials.[86] Although geographic location as a measure of availability is critical, Black persons with MM encounter several multilevel barriers such as clinician bias and stereotyping that influence the decision to offer trials to certain groups and perceived untrustworthiness and general distrust of the health care system and research enterprise, especially among the Black population.[87-89] As mentioned above, a study of real-world patients, including those with MM, demonstrated that those who self-identified as Black race were less likely to receive CAR T-cell therapy.[78] Gormley et al[90] have suggested concrete steps to eliminating racial disparities in outcomes in MM. Among the first steps needed are multilevel interventions (eg, targeting patients, clinicians, the health care system, and community level) that address critical determinants of clinical trial enrollment for historically under-represented populations. Such interventions should target knowledge, attitudes, medical mistrust, and clinician-patient communication and include early and frequent collaboration with community representatives to ensure interventions are appropriately tailored and sustainable.

Another key step will require innovative approaches to facilitating access to CAR T cells and BsAbs after approval. Although CAR T-cell therapy is largely restricted to transplant centers at this point, BsAbs may be more easily implemented outside of tertiary care settings, although hospitalization is still required during initial treatment, as is access to tocilizumab. Areas for future exploration to improve access to therapy for rural populations could capitalize on technology such as wearable patient devices for early detection of CRS and ICANS.

SEQUENCING

The emergence of CAR T cells and BsAbs will give our patients additional therapeutic options, but how to best integrate these innovations into the therapeutic journey of the patient is not yet established. One published randomized trial has demonstrated the superiority of ide-cel over standard regimens in patients with two to four previous lines of therapy.[21] Several other comparative and indirect treatment comparisons have similarly suggested the benefit of cilta-cel over standard options.[91-93] Given that many of the emerging therapies target the same epitopes and trials excluded patients who had received therapy targeting those

TABLE 4. Patient Demographics From Published CAR T-Cell and Bispecific Antibody Myeloma Trials

Study	CARTITUDE-1 (N = 97)[9]	CARTITUDE-1 Japanese Cohort (N = 9)[80]	CARTITUDE-4 (n = 208)[22]	KarMMa (N = 140)[8]	KarMMa-3 (n = 254)[21]	MCARH109 Phase I (N = 17)	MajesTEC-1 (N = 165)[10]	MonumenTAL-1 (N = 232)[31]	ABBV-383 Phase I (N = 124)[50]
Drug	Cilta-cel	Cilta-cel	Cilta-cel	Ide-cel	Ide-cel	MCARH109	Teclistamab	Talquetamab	ABBV-383
Location	United States	Japan	Europe, North America, Asia, Australia	United States, Europe	North America, Europe, Japan	United States	United States, Europe	United States, Europe	United States
Age, years, median (range)	61 (56-68)	57 (45-71)	62 (27-78)	61 (33-78)	63 (30-81)	60 (38-76)	64 (33-84)	62-64 (33-84)	68 (35-92)
ECOG PS 0/1/2, %	40/56/4	78/11/11	55/45/<1	45/53/2	47/52/<1	NR	33/67	NR	32/57/9
Male/female, %	59/41	56/44	56/44	59/41	61/39	76/24	58/42	56/44	55/45
Race, %									
White	71	0	76	NR	68	NR	81	81	79
Black	18	0	3	NR	7	NR	13	11	16
Asian	1	100	8	NR	3	NR	2	3	1
American Indian	1	0	NR	NR	NR	NR	NR	NR	NR
Native Hawaiian/ Pacific Islander	1	0	NR	NR	NR	NR	NR	NR	NR
Other/not reported	8	0	<1	NR	22	NR	NR	4	4
Ethnicity, %									
Hispanic or Latino	6	NR	9	NR	NR	NR	NR	NR	4
Not Hispanic or Latino	88	NR	73	NR	NR	NR	NR	NR	96
Not reported	6	100	18	100	100	100	100	100	0

Abbreviations: CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ide-cel, idecabtagene vicleucel; NR, not reported.

epitopes, the role of sequential therapies targeting the same molecule is not known.

The CARTITUDE-2 cohort C study enrolled individuals with previous triple class exposure as well as prior noncellular BCMA therapy (n = 20). The ORR was 60% with a median PFS of 9.1 months, both substantially lower than observed in the BCMA-naïve cohort of CARTITUDE-1.[94] These data, in conjunction with real-world data of commercial ide-cel showing inferior outcomes in individuals previously treated with BCMA-directed therapies (median PFS of 3.2 [prior BCMA] *v* 9.0 [no prior BCMA] months; $P = .0002$),[95] suggest that sequencing of BCMA-directed therapies matters. Intriguingly, data from the MajesTEC-1 cohort C study, which enrolled participants (n = 40) with previous BCMA therapy (either ADC or CAR T), showed an ORR of 53% for teclistamab.[96] With a median follow-up period of 11.8 months, 71% of patients who had initially achieved a response were still maintaining their response.[97] For the 15 patients with previous CAR T-cell exposure, the ORR was also 53%. A pooled analysis of patients enrolled in elranatamab clinical trials who had received previous BCMA-directed therapies showed an ORR of 46% (n = 87) and a median PFS of 5.5 months.[98] For the subset of patients who had received previous BCMA CAR T-cell therapy, the ORR was 53% (n = 36) with a median PFS of 10.0 months.[98] In aggregate, these data suggest that BCMA BsAb therapy may serve as effective salvage therapy in people whose disease progressed on BCMA CAR T-cell therapy.

Whether these lower response rates/response durations are a reflection of target-specific resistance mechanisms (eg, related to BCMA expression), T-cell fitness/exhaustion, or are simply a reflection of more heavily pretreated disease, remains to be determined. Until that time, there are substantial uncertainties regarding the optimal sequencing of these BCMA-directed therapies. As discussed earlier, GPRC5D- and FcRH5-directed CAR T-cell and/or BsAb therapies are showing efficacy in patients with previous BCMA-directed therapy,[31-33,44,45] but again whether optimal sequencing should involve options within the same class (eg, BsAb to BsAb) or should involve switching classes (eg, CAR T-cell to BsAb) will need to be investigated.

PROS AND CONS

A commonly posed question to MM specialists is which patient would you recommend for BsAb therapy and which patient would you recommend for CAR T-cell therapy? Although there are a multitude of factors that should be considered, including patient preference, access to therapy, and disease-related features, for many patients, the reality is that they will likely receive both CAR T-cell and BsAb therapy at some point during their therapeutic journey. Table 5 provides a summary of the key features of both commercial and investigational products. A key advantage of CAR T-cell therapy is the current one and done approach, which permits responding patients to experience a true treatment-free interval. However, this practice might change in the future as several ongoing/planned studies are investigating consolidation/maintenance approaches post-CAR T. Likewise, although most bispecific therapies are currently being studied in a treat-until-progression manner, there is significant interest in determining whether fixed duration or response-directed duration approaches could limit treatment intensity. A common theme across recently reported CAR T-cell studies (both clinical trials and real-world studies) is the dropout of patients between time of apheresis and time of CAR T-cell administration, in part due to manufacturing failures and to disease progression/clinical decline. Thus, a key advantage of BsAb therapy over current CAR T-cell therapies is its off-the-shelf nature, permitting immediate initiation of treatment and of clear importance for patients with rapidly progressing disease. However, innovations in CAR T-cell manufacturing, such as reducing manufacturing to less than a week[37] or using off-the-shelf allogeneic products,[43] will be critical in permitting more timely administration of CAR T cells.

As discussed earlier, widespread utilization of both classes of therapies may be limited because of access and logistical issues. Currently, hospitalizations are required for both commercial CAR T-cell products as well as for the first three step-up doses of teclistamab. CAR T-cell therapy is primarily being administered in transplant centers; thus, biases or assumptions about CAR T-cell candidacy on the part of community oncologists might limit referral of potential candidates to the MM/CAR T specialists. Although outpatient administration of teclistamab could be more readily done in community infusion centers, the need for initial hospitalization, with access to personnel trained in recognizing/treating CRS/ICANS, may also prove a barrier. Prolonged cytopenias, hypogammaglobulinemia, and infection risk are attributes of both classes of therapies and will require intensive supportive care measures to ensure safety.

Finally, patient preferences will remain an important consideration in guiding patients through the newest therapies discussed here. A recent study found that most patients with R/R MM continue to prioritize response rates and overall survival.[99] However, route of administration and toxicity profile remain important considerations to others and may inform recommendations for an individual. The current dearth of data regarding efficacy and safety of CAR T-cell and BsAb therapy in minority, underserved, older, or frail patients represents a significant limitation for the clinician who is counseling their patients about these therapies.

In conclusion, the field of MM is only at the beginning of its journey with CAR T-cell and BsAb (and other T-cell–redirecting agents) therapies, but clearly unprecedented response rates are being achieved in patient populations that previously had dismal outcomes. The rate at which new data are emerging from studies involving CAR T-cell and T-cell–redirecting therapies renders any review article outdated almost as soon as it is published. With current approval status of the commercial

TABLE 5. Summary of Key Features of CAR T-Cell and Bispecific Therapies in Multiple Myeloma

	CAR T-Cell Therapies		Bispecific Therapies	
Feature	Commercial	Investigational	Commercial	Investigational
FDA-approved indication	After four or more previous lines, including an IMiD, PI, and anti-CD38 mAb (ide-cel and cilta-cel)	NA	After four or more previous lines, including an IMiD, PI, and anti-CD38 mAb (teclistamab)	NA
Hospitalization	Yes	Yes	Yes (for step-up dosing during cycle 1)	Generally, yes for initial doses
Treatment frequency	Once	Generally, once	Weekly	Every 1-3 weeks
Lymphodepletion	Yes	Yes	No	No
Manufacturing time	4-6 weeks	None (allogeneic)-approximately 4 weeks	None (off the shelf)	None (off the shelf)
Manufacturing failure	Approximately 10%	Variable	NA	NA
Wait list for commercial manufacturing slots	Yes	NA	NA	NA
Overall response rate, %	73-98	>70	63	Approximately 50-70
Median progression-free survival	8.8 -34.9 months	NR	11.3 months	NR
Cytokine release syndrome (grade all/≥3), %	Approximately 85-95/5	Approximately 40-100/<1-7	72/1	Approximately 25-85/0-2
ICANS and/or neurotoxicity (grade all/≥3), %	Approximately 20/3-12	Approximately 2-30/0-3	15/1	Approximately 2-15/0-1
Infections (grade all/≥3), %	Approximately 60-70/~20	Approximately 20-55/12-30 and NR	76/45	Approximately 35-60/ approximately 7-30
Hypogammaglobulinemia (all grade), %	21 and NR	7-24 and often NR	15	14-77 and often NR
Data on minority/underserved populations	Minimal	Minimal	Minimal	Minimal
Data on frail patients	Minimal	Minimal	Minimal	Minimal
Features under development		Novel targets Faster manufacturing Dual-targeting Allogeneic products		Trispecific Novel targets

Abbreviations: CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; FDA, US Food and Drug Administration; ICANS, immune-effector cell–associated neurotoxicity syndrome; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; mAb, monoclonal antibody; NA, not available; NR, not reported; PI, proteasome inhibitor.

agents being for patients with four or more previous lines of therapy, and with most patients being penta-drug exposed/refractory by three lines (and many being triple-class refractory after one to two lines), there are significant therapeutic challenges in accessing the commercially available CAR T-cell and BsAb therapies. However, it is anticipated that approval indications may change in the future based off the results of KarMMa-3,[21] CARTITUDE-4,[22] and ongoing phase III studies, at which point the next challenge will become incorporating these agents into earlier lines of therapy. Likewise, with the expected eventual approval of non–BCMA-targeted agents, even more questions will arise as to the optimal sequencing of these therapies and resulting changes in treatment paradigms. Preliminary data showing remarkable efficacy of combining BsAbs (ie, teclistamab + talquetamab in the RedirecTT-1 trial[100]) raise even more questions about optimal use and sequencing of BsAbs. No matter what the future brings with respect to new therapeutic options, it is critical that the patient experience be documented and that proactive efforts are made toward ensuring equitable access to all of these innovative therapies.

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SUPPORT

S.J.G.: National Cancer Institute Grant No. 5-K12-CA120780-13; PI: William Kim and National Institute on Aging Grant No. 1 R03 AG074030-01; PI: S.J.G.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00512.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Chimeric Antigen Receptor T-Cell and Bispecific Antibody Therapy in Multiple Myeloma: Moving Into the Future

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Consulting or Advisory Role: GlaxoSmithKline, Oncopeptides, Secura Bio, Takeda, Janssen Oncology, AbbVie
Research Funding: Oncopeptides (Inst), Bristol Myers Squibb/Celgene (Inst)

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Research Funding: Janssen Oncology (Inst)

No other potential conflicts of interest were reported.