Current use of CAR T cells to treat multiple myeloma

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Anti–B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapies currently approved by the US Food and Drug Administration (FDA) have dramatically improved clinical outcomes for patients with heavily pretreated multiple myeloma who have disease refractory to conventional proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies. However, despite this progress, multiple myeloma remains an incurable hematologic malignancy. In this review, we discuss practical considerations for currently FDA approved CAR T-cell therapies, including newer data evaluating those agents in earlier lines of therapy. We also discuss considerations for patients following relapse from anti-BCMA CAR T-cell therapy, which currently represents an unmet clinical need.

LEARNING OBJECTIVES

- Discuss practical considerations for CAR T-cell products currently approved by the US Food and Drug Administration and potential expanded indications for those agents
- Explore currently available research regarding challenges with therapy
- Evaluate treatment options following relapse from CAR T-cell therapy

CLINICAL CASE

A 62-year-old man was diagnosed with IgG κ multiple myeloma with cytogenetic studies notable for deletion of 17p and a t(4;14) translocation. In the first 3 years since his diagnosis, he has had progressive disease following 5 different lines of therapy, which have collectively included 2 proteasome inhibitors, 2 immunomodulatory drugs, anti-CD38 and anti-SLAMF7 monoclonal antibodies, and an autologous stem cell transplant. He was referred by his local oncologist to a major academic medical center for consideration for chimeric antigen receptor (CAR) T-cell therapy. After discussions with his medical team, he undergoes apheresis for planned treatment with commercial ciltacabtagene autoleucel (cilta-cel) after observed biochemical disease relapse.

Introduction

Although multiple myeloma (MM) remains an incurable malignancy,[1] novel T-cell redirecting therapies, including chimeric antigen receptor (CAR) T-cell and bispecific antibody (BsAb) therapies, have shown tremendous promise in heavily pretreated relapsed/refractory (RR) disease.[2-5] "While patients with high-risk disease, often defined by revised international staging system (R-ISS) III disease or by the presence of either high-risk cytogenetic abnormalities or extramedullary disease, typically have vastly inferior outcomes with systemic therapies, cur- rent prospective data sets have shown less disparate results among patients treated with CAR T-cell therapy" (Figure 1).[6,7] Despite success in the aggregate, outcomes for patients with myeloma receiving cellular therapies remain highly variable, with some patients having brief or no responses and some with years of progression-free survival (PFS) following treatment. However, given MM's current incurability, newer therapies inevitably lead to new challenges, with there now being a need to identify appropriate treatment options for patients following relapse from CAR T-cell therapy.

CAR T-cell therapy in multiple myeloma: patient and product selection

CAR T-cell products for MM currently approved by the US Food and Drug Administration (FDA) include the B-cell maturation antigen (BCMA) targeting products idecabta-

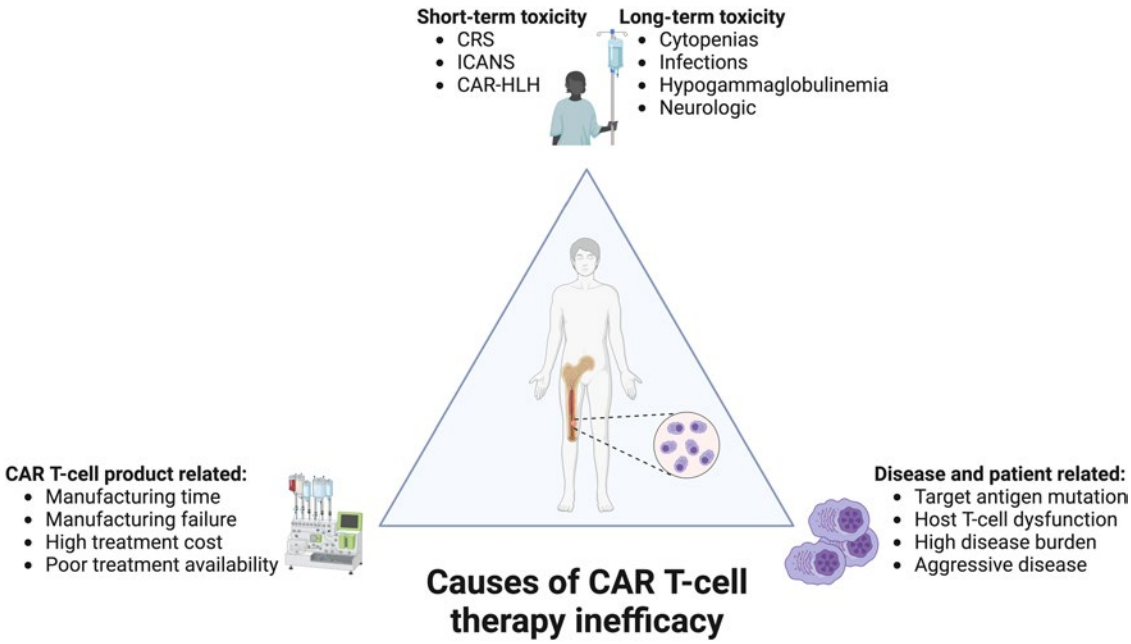

Figure 1. Causes of CAR T-cell therapy inefficacy: therapy inefficacy for patients with MM receiving CAR T-cell therapy can be due to disease- or patient-related factors, although logistical concerns relating to product manufacturing and cost/availability are also significant. Therapy-related toxicity can also represent a challenge even in patients with strong responses. CAR-HLH, Chimeric antigen receptor T cell-related hemophagocytic lymphohistiocytosis.

gene-vicleucel (ide-cel) and cilta-cel.[2,3] Both agents were approved based on results of single-arm phase 2 trials with commercial use permitted for patients with MM with at least 4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. The initial KarMMA-1 (ide-cel) and CARTITUDE-1 (cilta-cel) trials demonstrated high response rates to their respective CAR T-cell products in their heavily pretreated patient populations, with both trials having a significant percentage of patients with triple-class refractory (84% and 88%, respectively) and penta-drug refractory (26% and 42%, respectively) disease. These data indicate that CAR T-cell therapies are an appropriate treatment option for heavily pretreated patients, including "penta-refractory" patients. This population has been estimated to have a median overall survival (OS) of less than 6 months,[8] with available treatment options in this setting having poor efficacy and high toxicity.[9]

There is currently no consensus with regards to patient selection for CAR T-cell therapies from available data sets. With regards to disease status, patients with several disease features typically associated with aggressive myeloma, including extramedullary disease, high-risk cytogenetic abnormalities, and high tumor burden, were included in the KarMMa-1 and CARTITUDE-1 trials. For patient-specific factors, patients included in these trials typically had good performance status with less than 5% of patients in all trials having an Eastern Cooperative Oncology Group performance score of 2 or higher. Performance status considerations with regards to CAR T-cell therapy may be due to both tolerating lymphodepleting therapy prior to CAR T-cell infusion, which included combination therapy with fludarabine (30 mg/m^2 body surface area) and cyclophosphamide (300 mg/m^2 body surface area) in all trials and expected therapy associated toxicities. Additionally, the contribution of rapidly progressing disease to poor performance status during the time required for CAR T-cell manufacturing may make this treatment option less feasible for this population. As patient age was highly variable in all trial populations, assessments of fitness is often done clinically.

There remain no reported or pending prospective data sets comparing outcomes between available FDA-approved BCMA targeting CAR T-cell products, leaving product selection up to the discretion of individual clinicians. The patient populations for both the KarMMa-1 and CARTITUDE-1 studies were similar (Table 1) with regards to prior therapy exposure and patient fitness, although the patients included in CARTITUDE-1 were less likely to have extramedullary disease or high-risk cytogenetic abnormalities. Nevertheless, the outcomes between these 2 trials are distinct, with cilta-cel patients included in CARTITUDE-1 achieving a 94% overall response rate (ORR) with 67% reaching a complete response (CR) while ide-cel patients achieved a 73% ORR with 25% reaching CR in KarMMA-1. Safety profiles were notable for similar rates of any grade and grade 3 or 4 cytokine release syndrome (CRS) with both cilta-cel and ide-cel (95%, 4% vs 84%, 5%) and similar rates of any grade neurotoxicity (21% vs 18%) but perhaps higher rates of grade 3 or 4 neurotoxicity with cilta-cel (9% vs 3%).

With regards to real-world data sets, 1 real-world analysis of 159 commercial ide-cel–infused patients, 75% of whom would have been ineligible for KarMMa-1 based on comorbidities, showed an ORR of 84% (42% ≥ CR) compared with 76.4% (30% ≥ CR) in KarMMa-1.[10] However, a similar real-world study of commercial ide-cel outcomes in 190 KarMMa-1–eligible patients identified significantly inferior outcomes when compared to KarMMA-1 data, with an ORR of 32.2%, with these results remaining when

Table 1. Review of clinical data sets for currently FDA-approved CAR T-cell therapies

	Ide-cel (KarMMa-1)	Ide-cel (KarMMa-3)	Cilta-cel (CARTITUDE-1)	Cilta-cel (CARTITUDE-4)
Trial phase	2	3	1b/2	3
No. of patients infused (enrolled)	128 (140)	225 (254)	97 (113)	208 (176)
Median age (range),† y	61 (33–78)	63 (30–81)	Not reported	61.5 (27–78)
Median time since diagnosis (range),† y	6 (1–18)	4.1 (0.6–21.8)	5.9 (4.4–8.4)	3.0 (0.3–18.1)
Median No. of prior lines (range)†	6 (3–16)	3 (2–4)	6 (4–8)	2 (1–3)
EMD,† No. (%)	50 (39)	61 (24)	13 (13)	44 (21.2)
ECOG,† No. (%)				
0	57 (45)	120 (47)	39 (40)	114 (54.8)
1	68 (53)	133 (52)	54 (56)	93 (44.7)
≥2	3 (2)	1 (<1)	4 (4)	1 (0.5)
R-ISS†				
I	14 (11)	50 (20)	61 (63)	136 (65.4)
II	90 (70)	150 (59)	22 (23)	60 (28.8)
III	21 (16)	31 (12)	14 (14)	12 (5.8)
Unknown	3 (2)	23 (9)	0	
Cytogenetic abnormalities†				
High risk	45 (35)	107 (42)	23 (24)	123 (59.4)‡
del(17p)	23 (18)	66 (26)	19 (20)	49 (23.7)
t(4;14)	23 (18)	43 (17)	2 (2)	30 (14.5)
t(14;16)	6 (5)	8 (3)	3 (3)	3 (1.4)
Prior ASCT†	120 (94)	214 (84)	87 (90)	Not reported
Prior treatment refractory status†				
IMiD	126 (98)	224 (88)	Not grouped (highest is Len with 96, 99%)	208 (100)
PI	116 (91)	189 (74)	Not grouped (highest is V with 92, 95%)	Not grouped (highest is V with 55, 26.4%)
Anti-CD38	120 (94)	242 (95)	94 (97)	50 (24)
Triple-class refractory	108 (84)	164 (65)	85 (88)	30 (14.4)
Penta drug refractory	33 (26)	15 (6)	41 (42)	2 (1)
No. (%) requiring bridging therapy†	112 (88)	213 (84)	Not reported	All
Response rate				
MRD negative, No. (%)	33 (24)	51 (20)*	43 (38)	126 (60.6)
sCR or CR	42 (30)	98 (39)	80 (71)	152 (73.1)
≥ VGPR	68 (48)	153 (60)	92 (81)	169 (81.3)
≥ PR/ORR	85 (67)	181 (71)	95 (84)	176 (84.6)
Median PFS (95% CI),† mo	8.8 (5.6–11.6)	13.3 (11.8–16.1)	34.9 (25.2-NR)[39]	NR (Not reported)
Median OS (95% CI),† mo	19.4 (18.2-NR)	Not reported	NR (NE)	NR (NE)
Grade 3+ CRS,† No. (%)	8 (6)	11 (4)	4 (4)	2 (1.1)
Grade 3–4 heme tox,† No. (%)	114 (89)	218 (87)	96 (99)	196 (94.2)

ASCT, Autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; NE, Not estimable; NR, Not reached; PI, proteasome inhibitor; PR, partial response; R-ISS, Revised International Staging System; sCR, stringent complete response; VGPR, very good partial response.

*ORR are for all patients enrolled (and not enriched for those receiving cell infusion as reported in the manuscript).

†Values reported for only the patients who received ide-cel infusion (full data not reported) in the KarMMa-1 and CARTITUDE-1 population. Values include all enrolled patients in the KarMMa-3 and CARTITUDE-4 populations.

‡High risk in this trial included +1q in addition to del(17p), t(4;14), and t(14;16) as included in the other studies.

matching for KarMMa-1 patient characteristics.[11] With regards to cilta-cel, there is a paucity of published data; however, 1 report of a 139-patient commercial cohort observed an ORR of 80% (40% CR) with a similar toxicity profile to that observed in CARTITUDE-1.[12]

Considerations for bridging therapy and manufacturing time

One of the major logistical challenges with CAR T-cell therapy administration is managing disease relapse during the product manufacturing time to avoid complications associated with myeloma-related end-organ damage, as is present in our patient case described above. Current manufacturing times for ide-cel and cilta-cel are estimated at ~28 days. However, factoring in the time required to confirm disease relapse and coordinate the logistics for cell collection in the standard care setting likely involves a longer functional time between disease reemergence and CAR T-cell infusion. This time delay, unique to CAR T-cell therapy when compared to off-the-shelf therapies, is associated with a frequent need for bridging therapy. Over 80% of ide-cel patients (included in both KarMMA-1 and KarMMA-3) required bridging therapy during product manufacturing time, which is likely shorter in the context of a clinical trial than it would be in a standard-of-care setting.[2,13] Additionally, all currently published MM CAR T-cell trials have a notable percentage of their intention-to-treat population who did not ultimately receive their cell infusion. Specifically, 8% to 14% of enrolled patients in currently published ide-cel and cilta-cel trials dropped out prior to infusion.[14] The reasons for these dropouts are not explicitly reported in all relevant trials but are often attributed disease progression, adverse events, or cell manufacturing failure.

Off-the-shelf allogeneic CAR T-cell products have been investigated as a potential solution to issues surrounding CAR T-cell manufacturing time, as patient-specific autologous product preparation is not required. The only published clinical trial of allogeneic CAR T-cell therapy for MM evaluated the safety and feasibility of Allo-715, an allogeneic anti-BCMA CAR T-cell therapy, demonstrating a 70.8% ORR with a median duration of response of 8.3 months.[15] Of note, none of the 43 infused patients in this study required bridging therapy (Table 3). In this study, grade ≥3 adverse events were rare, including CRS (2.3%) and neurotoxicity (0%), meaning that this approach could potentially be an option for patients with rapidly progressing disease.

CLINICAL CASE (continued)

Following apheresis, the patient reports progressive fatigue and bone pain while awaiting cilta-cel delivery. On evaluation, the patient is noted to have worsening anemia, acute kidney injury, and radiographic studies demonstrating several new lytic bone lesions. He is admitted for bridging therapy with dexamethasone, cyclophosphamide, etoposide, and cisplatin, and while he has a transient partial response to therapy, he is found to have actively progressing disease just prior to cilta-cel infusion. Following infusion with cilta-cel, the patient experienced grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS) among other significant treatment-related toxicities. He ultimately recovered from these side effects after a prolonged stay in the hospital intensive care unit and achieved CR to therapy with no evidence of minimal residual disease seen following bone marrow biopsy.

Notable short- and long-term therapy toxicities

Short-term toxicities for CAR T-cell therapy are well described, and most notably include CRS and ICANS.[16] These are common short-term side effects of CAR T-cell therapy and in most of cases are associated with no long-term sequelae, although cases of CRS- and ICANS-related mortality have been reported. Both are thought to have increased incidence in patients with high pretreatment disease burden, further indicating the importance of bridging therapy in patients with evidence of rapid disease progression.[17]

While these short-term toxicities are well documented in relevant clinical trials and have a consensus with regards to management guidelines, long-term toxicities are less thoroughly described. One single-center report observed cytopenias can persist long after cell infusion, with 28% of patients with grade ≥3 cytopenias 120 days following cell infusion.[18] Long-term neurotoxicity, including parkinsonian-like movement disorders as well as neurocognitive events, has been observed in 5% of patients in 1 cohort of cilta-cel–treated patients, which, given the small number of affected patients, does not have a clear clinical management strategy.[17]

CAR T-cells in earlier lines of therapy

The recently published KarMMa-3 and CARTITUDE-4 studies evaluated the efficacy of ide-cel and cilta-cel in earlier treatment settings. KarMMa-3 recruited patients with RR MM with 2 to 4 prior lines of therapy to evaluate the potential role for ide-cel in earlier lines of therapy.[19] The study was designed as a phase 3 randomized trial (2:1 randomization favoring ide-cel) comparing ide-cel to a selection of standard therapy regimens chosen at the clinician's discretion. Non–ide-cel treatment options included daratumumab in combination with pomalidomide and dexamethasone, daratumumab in combination with bortezomib and dexamethasone, ixazomib in combination with lenalidomide and dexamethasone, carfilzomib in combination with dexamethasone, and elotuzumab in combination with pomalidomide and dexamethasone. The trial met its primary end point, demonstrating superior PFS in the ide-cel group when compared to the conventional therapy group (13.3 vs 4.4 months). However, there are some challenges with interpreting this trial as strictly favoring ide-cel over standard therapy. OS comparisons were not reported (noted as an immature data set in the published study) and a notable number of patients in the ide-cel–treated group died during the study. Deaths due to any cause were reported as marginally higher in the ide-cel group compared to the standard therapy group (30% vs 26%), with deaths related to treatment representing less than half of deaths in the ide-cel arm.

The available regimens in the standard therapy group lacked some therapy options for patients with 1 to 3 prior lines of therapy exposure. Carfilzomib-containing triplet regimens including carfilzomib in combination with dexamethasone and either lenalidomide, daratumumab, or isatuximab were not included as control. However, while these regimens showed superiority to carfilzomib in combination with dexamethasone in the RR MM setting in the phase 3 ASPIRE, CANDOR, and

Table 2. Ongoing phase 3 clinical trials of ide-cel and cilta-cel in earlier lines

	CARTITUDE-5	CARTITUDE-6
Setting	NDMM following VRd without planned ASCT	NDMM, transplant eligible, following DVRd
Product	Cilta-cel	Cilta-cel
Control arm	Rd maintenance	ASCT
Primary end point	PFS	PFS, sustained MRD-CR
Estimated enrollment	650	750
Study start date	June 2021	February 2022
Estimated primary completion date	June 2026	June 2026
NCT ID	NCT04923893	NCT05257083

DVRd, daratumumab, bortezomib, lenalidomide and dexamethasone; NDMM, newly diagnosed multiple myeloma; VRd, bortezomib, lenalidomide and dexamethasone.

IKEMA trials,[20-22] the KarMMA-3 population was nearly entirely refractory to anti-CD38-based therapy, which was not the case for patients recruited to those phase 3 studies. It should be noted that, in the standard care group, Kd was highly represented as a clinician-chosen treatment option, with clinicians for 23% of patients selecting it, indicating favor for carfilzomib's use in this setting. Furthermore, 38% of patients in the standard therapy group received daratumumab-containing regimens (daratumumab in combination with pomalidomide and dexamethasone or daratumumab in combination with bortezomib and dexamethasone) despite 94% of patients having daratumumab refractory disease. While not specific to daratumumab, prospective trials evaluating anti-CD38 monoclonal antibodies in the daratumumab refractory setting have shown 0% ORRs.[23]

CARTITUDE-4 specifically recruited patients with lenalidomide refractory disease with 1 to 3 prior lines of therapy, and patients were randomized (1:1) to either cilta-cel or physicians' selection of standard-of-care therapies, including bortezomib in combination with pomalidomide and dexamethasone, as well as daratumumab in combination with pomalidomide and dexamethasone (DPd).[13] This trial also met its primary end point, showing superior PFS in the cilta-cel group when compared to the standard therapy group (PFS not reached vs 15.9 months). Like in KarMMa-3, carfilzomib-containing triplets were notably not included in the control arm of this study, despite carfilzomib in combination with dexamethasone and daratumumab being FDA approved within 2 months of trial enrollment. This is of particular relevance when comparing the outcomes of these 2 trials to each other as patients in the cilta-cel arm included in this study had far lower carfilzomib exposure compared to bortezomib exposure (37.0% vs 97.6%) and far lower daratumumab exposure than the patients included in KarMMa-3 (24.5% vs 95%). The control arm may have had more success if the protocol had been amended to include these regimens, particularly carfilzomib in combination with dexamethasone and lenalidomide as per the ASPIRE trial. The significant prior bortezomib exposure is reflected in the observation that, for patients included in the control arm, 86.7% were given DPd by their treating clinician as opposed to bortezomib in combination with pomalidomide and dexamethasone, likely to avoid retreatment with a previously received agent. Unlike the KarMMa-3 study, deaths on study due to any cause in the CARTITUDE-4 study were not higher in the cilta-cel arm than in the control arm (18.8% vs 21.8%). However, this did not include patients who had evidence of disease progression prior to receiving cilta-cel on trial and were subsequently given cilta-cel as postprotocol therapy per trial design (with 10/20 such patients dying at the time of trial publication). Side effects related to neurotoxicity, as represented by ICANS and movement disorders, showed lower frequency than in clinical trials evaluating cilta-cel in more heavily pretreated disease. This may be due to the fact that toxicity associated with CAR T-cell therapy has been observed more frequently in patients with higher disease burden at the time of cell infusion, as is the case with our patient described above.

Overall, it is difficult to compare the relative efficacy of ide-cel and cilta-cel in these trials, as they recruited patients in different settings, which is reflected in the disparate outcomes in their respective control arms. Further, comparisons of treatment arms across these trials should be done with significant caution as the ide-cel population in KarMMA-3 had a significantly higher percentage of triple-class refractory disease when compared to the cilta-cel population in CARTITUDE-4 (65% vs 25.5%). This discrepancy is primarily due to a significantly higher daratumumab refractory population in KarMMa-3 compared to CARTITUDE-4 patients (95% vs 24.5%), a population with notable poorer treatment outcomes.[8] It should be noted, however, that a recently reported real-world data set of 143 cilta-cel patients, 71% of whom were triple-class refractory, had an ORR of 89% with median PFS not reached, albeit with a short median follow-up time of 5.8 months.[12] Both the KarMMa-3 and CARTITUDE-4 studies appropriately analyzed data via intention-to-treat analysis, but neither phase 3 study has reported OS in either group, which, when available, will further inform clinical decision-making. Additionally, there are current ongoing clinical trials evaluating cilta-cel in the frontline setting (Table 2), which has to potential to further expand the indications for CAR T-cell therapy in MM.

Therapy considerations for patients with prior exposure to anti-BCMA targeting agents

There are no fully reported prospective data sets evaluating the efficacy of ide-cel or cilta-cel in patients with prior exposure to other BCMA targeting agents, including the antibody

Table 3. Non-FDA-approved CAR T-cell therapies with complete clinical trial data available

	Allo-715	MCARH109	Xuzhou GPRC5D CAR T cell therapy	OriCAR-017
Trial phase	1	1	2	1
Target	BCMA	GPRC5D	GPRC5D	GPRC5D
Specificity	Allogeneic	Autologous	Autologous	Autologous
Patients enrolled (infused)	48 (43)	19 (17)	33 (33)	13 (10)*
Median age (range), y	64 (46–77)	60 (38–76)†	58 (39–70)	64 (58–68)†
Median prior lines (range)	5 (3–11)	6 (4–14)†	4 (2–12)	5.5 (4–10)†
Triple-class refractory, No. (%)	39 (91)	16 (94)†	Not reported	Not reported
Penta refractory, No. (%)	18 (42)	Not reported	Not reported	Not reported
Prior anti-BCMA CAR T-cell therapy, No. (%)	Excluded	8 (47)†	9 (27)	5 (50)†
Received bridging therapy, No. (%)	0	16 (94)†	Not reported	2 (80)†
ORR, No. (%)	24 (56)†	12 (71)†	30 (91)	10 (100)†
CR, No. (%)	Not reported	6 (35)†	21 (64)	6 (60)†
ORR in patients with prior anti-BCMA CAR T-cell therapy, No. (%)		7/10 (70)†	9/9 (100)	5 (100)†
Median PFS	Not reported	Not reached	Not reached	Not reached
CRS grade 3+, No. (%)	1 (2)	1 (6)	0 (0)	0 (0)
ICANS grade 3+, No. (%)	0 (0)	1 (6)	1 (3)	0 (0)
Trial ID	NCT04093596	NCT04555551	ChiCTR2100048888	NCT05016778

*Thirteen patients were screened for the trial, but 1 was excluded due to low plasma cell GPRC5D expression.

†Values listed are for only the enrolled patients receiving product infusion.

drug conjugate belantamab mafodotin, other BCMA targeting CAR T-cell products, or BCMA targeting bispecific antibody therapies. In a small subset of patients receiving anti-BCMA CAR T-cell and anti-BCMA BsAbs, single-cell genomic sequencing of myeloma cells at relapse identified BCMA biallelic loss and BCMA missense mutations at relapse, indicating that prior BCMA-directed therapy exposure may limit the efficacy of further BCMA-directed therapies, although there are no clinical data available linking these.[24-26] In 1 retrospective study of real-world ide-cel outcomes, PFS following ide-cel infusion was found to be inferior in 33 patients with prior exposure to either belantamab mafodotin or anti-BCMA BsAbs with a median PFS of 9.0 months (7.6-not reached) in the anti-BCMA therapy-naive group and 3.2 months (2.8-not reached) in the anti-BCMA therapy-exposed population ($P \leq .001$).[10] While this may be due to resistance mechanisms to anti-BCMA therapies that follow anti-BCMA therapy, it is unclear if the anti-BCMA refractory population represents a more heavily pretreated population with more aggressive disease regardless. Further data sets will be required to determine if prior BsAb therapy is disruptive to lymphocyte apheresis prior to CAR T-cell manufacturing and if this represents a cause of CAR T-cell therapy failure with clinical significance.

An early report of CARTITUDE-2 cohort C, a phase 2 study evaluating the efficacy of cilta-cel in patients with prior noncellular anti-BCMA therapy exposure, has been reported. Among 20 cilta-cel–infused patients, 7 with prior anti-BCMA BsAb and 13 with prior anti-BCMA antibody drug conjugate exposure, the ORR was 67%, compared with the 98% ORR among infused cilta-cel patients in CARTITUDE-1.[27] Notably, this patient population was more heavily pretreated, with a median of 8 prior lines of therapy compared to CARTITUDE-1's 6 median prior lines. While this data set reported worse outcomes for cilta-cel in the post-BsAb setting (ORR, 57.1%; median PFS, 5.3 months) than in the CARTITUDE-1 study, it is difficult to draw generalizable conclusions from a 7-patient data set.

Overall, these data indicate that anti-BCMA CAR T-cell therapy should remain a consideration for patients with relapse following other anti-BCMA therapies, although responses rates may be diminished. There may also be utility in assessing the genetic integrity of *TNRSF17*, the gene coding for BCMA, prior to consideration for therapy.

Response assessment and PFS prediction

Response assessments following MM treatment, classified according to International Myeloma Working Group criteria,[28] were strongly predictive of duration of response in both KarMMA-1 and CARTITUDE-1, with patients achieving a CR having drastically improved outcomes compared to those with very good partial response or partial response following infusion. Additionally, the prognostic role of minimal residual disease (MRD) negative status remains critical in this population. A recent single-center retrospective study of CAR T-cell therapy outcomes in MM identified that median PFS for MRD-positive vs MRD-negative patients was drastically different, with a median PFS of 2.9 vs 17.5 months, favoring the MRD-negative group.[29]

This indicates that, in clinical practice, discussions regarding subsequent therapy should be a priority in those not achieving MRD negativity following infusion. Additionally, this finding supports the need for further research into identifying patients most likely to have a strong response to therapy, given the high costs associated with CAR T-cell therapy.

Considerations for access and cost-effectiveness

CAR T-cell therapies are associated with considerable expense. Given the requirement for inpatient administration at specialized centers, only patients with means to travel to these institutions and those living in countries with an infrastructure for CAR T-cell therapy administration will have access to these cellular therapies. Wholesale acquisition costs for cilta-cel are currently estimated at $465,000 USD per patient with additional nonproduct costs, including inpatient and outpatient management as well as adverse event management, being estimated in 1 study to be an additional $160,933 per patient.[30] While cost-effectiveness analyses cannot be accurately performed until complete PFS and OS data are available for CARTITUDE-1 patients, this indicates that CAR T-cell therapy for RR MM will potentially be a cost-effective treatment option only for those patients who achieve multiyear remissions following therapy.[31] Treatments costs in CAR T-cell therapy nonresponders are not substantially mitigated when compared to strong responders, as opposed to other MM therapies that are administered continuously and are typically discontinued at relapse.[32]

When compared to CAR T-cell therapies for lymphoma, ide-cel and cilta-cel are not regarded as curative therapies, with patients relapsing following successful CAR T-cell therapies often proceeding to similarly expensive alternatives. Overall, this further indicates an unmet need for a robust system of identifying patients most likely to response to CAR T-cell therapy prior to product manufacturing.

Considerations for relapse

There are several data sets evaluating the efficacy of various treatment options in patients with disease relapse following previous response to anti-BCMA CAR T-cell therapies. Three currently published clinical trials evaluating the efficacy of anti-GPRC5D targeted CAR T-cell therapies included several patients with prior anti-BCMA CAR T-cell therapy exposure, with such patients in both trials having high response rates to therapy.[33-35] Overall response rates were >70% in all 3 studies, with median PFS not being reached in any and with grade ≥3 CRS being seen in <10% of patients in all studies.

A recently published retrospective multicenter study assessed 140 anti-BCMA CAR T-cell–treated patients, 79 of whom were evaluable and went on to receive subsequent antimyeloma therapy. Among these patients, there were 35 instances of salvage therapy with another T-cell redirection therapy, including either CAR T-cell or BsAb therapy, with an ORR of 91.4% for these instances.[36] Most of these agents included non-BCMA targeted T-cell redirection therapies, indicating that treatment options for anti-BCMA CAR T-cell refractory patients will be strong pending the approval of recently evaluated non-BCMA targeting T-cell redirection therapies.[5,33-35] Although not fully reported, safety and feasibility studies of CAR T-cell combination therapy and dual targeting approaches may also represent an effective treatment option, with 1 study of a BCMA/CD19 dual targeting CAR T-cell therapy showing a 93.1% ORR with a median duration of response of 37 months.[37] Other studies of dual targeting approaches are ongoing (NCT05509530, NCT05325801, NCT05431608).

BsAb therapy should be strongly considered in the post-CAR T-cell relapse setting. Preliminary retrospective data sets have evaluated teclistamab specifically in this context and demonstrated the potential for durable responses despite anti-BCMA CAR T-cell therapy exposure.[38]

Conclusions

Anti-BCMA CAR T-cell therapies represent highly effective treatment options for patients with heavily pretreated RR MM. While there remain questions with regards to patient selection, outcome heterogeneity, overall cost, patient access, and appropriate treatment timing, there is little doubt that these therapies have revolutionized clinical management of RR MM. Going forward, it will be critical to continue to evaluate new prospective studies evaluating these agents, particularly in earlier lines of therapy and in patients with prior exposure to anti-BCMA agents.

Conflict-of-interest disclosure

Ross S. Firestone: no competing financial interests to declare.
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Off-label drug use

Ross S. Firestone: There are no discussions of off label drug use in this article.
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