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CAR T-Cell therapy for Myeloma: Where are we now and what is needed to move CAR T-cells forward to earlier lines of therapy? Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy

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Abstract

Since 2021, two B-Cell Maturation Antigen (BCMA) directed chimeric antigen receptor T-cell (CAR T-cell) therapies, Idecabtagene vicleucel (ide-cel), and ciltacabtagene autoleucel (cilta-cel), have been approved by the US FDA for relapsed or refractory multiple myeloma (RRMM) after four or more prior lines of therapy including an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody. The two products have both shown unprecedented activity in RRMM, but relapses are still common, and access and safety of CAR T-cells in patients with rapidly progressing advanced disease is not ideal. Sequencing CAR T-cell therapy with other options, including the 2 recently approved BCMA directed T-cell engaging bispecific antibodies (TCE BsAbs) teclistamab and elranatamab, has become increasingly challenging due to data showing inferior outcomes from CAR T-cells after prior BCMA directed therapy. This has led to the consideration of using CAR T-cell therapy earlier in the course of disease for myeloma, when T-cells are potentially healthier and the myeloma is less aggressive. To address the question of earlier use of CAR T Cells, several trials are either ongoing or planned, and results have recently been reported for 2 randomized trials of CAR T-cells showing improved progression free survival compared to standard of care therapy in 2nd line (CARTITUDE-4) or 3rd line therapy (KarMMA-3). With the anticipation of the FDA possibly expanding approval of CAR T cells to earlier lines of myeloma therapy, the American Society for Transplantation and Cellular Therapy (ASTCT) convened a group of experts to provide a comprehensive review of the studies that led to approval of CAR T-cells in late line therapy of myeloma, discuss the recently reported and ongoing studies designed to move CAR T-cell therapy to earlier lines of therapy, and to share insights and considerations for sequencing therapy and optimization of patient selection for BCMA directed therapies in current practice.

Keywords

Chimeric antigen receptor (CAR) T-cells; Cellular therapy; relapsed/refractory multiple myeloma (RRMM); B-cell maturation antigen (BCMA); T-cell redirection therapy

INTRODUCTION

Since 2021, two B-Cell Maturation Antigen (BCMA) directed chimeric antigen receptor T-cell (CAR T-cell) therapies, Idecabtagene vicleucel (ide-cel; Bristol Myers Squibb, Princeton, NJ), and ciltacabtagene autoleucel (cilta-cel; Janssen Biotech, Inc), have been approved by the US FDA for relapsed or refractory multiple myeloma (RRMM) after four or more prior lines of therapy including an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody [1-3]. The two products have both shown unprecedented activity in RRMM, but relapses are still common in the late line setting where many patients have bulky rapidly growing high risk disease that may decrease both efficacy and safety. This has led to the consideration of using CAR T-cell therapy

earlier in the course of therapy for myeloma, when T-cells are potentially healthier and the myeloma is less aggressive and/or with lower tumor bulk. Furthermore, access to late line myeloma CAR T-cells has remained challenging due to production capacity issues (vector supply chain following the pandemic), manufacturing failures, and due to the rapid pace of disease progression in advanced myeloma. Sequencing CAR T-cell therapy with other options, including the 2 recently approved BCMA directed T-cell engaging bispecific antibodies (TCE BsAbs) teclistamab and elranatamab, has become increasingly important yet challenging due to data showing inferior outcomes for BCMA CAR T-cells after prior BCMA directed therapy [4, 5]. Talquetamab, a recently approved TCE BsAb targeting G-protein-coupled receptor class C group 5 member D (GPRC5D) with high response rates in RRMM also represents another treatment option for sequencing considerations in relation to BCMA-targeted CAR T-Cells.

To address the issues of improving access and effectiveness of CAR T-cells and the question of whether this can be improved by moving to earlier lines of therapy for myeloma, several trials are ongoing or planned in the 1st, 2nd, and 3rd line setting, and results from 2 randomized trials have recently been reported with encouraging results in the 2nd and 3rd line settings. In these trials CAR T-cells showed improved progression free survival (PFS) compared to standard of care (SOC) therapies after 1-3 prior lines of therapy in lenalidomide-refractory myeloma (cilta-cel, CARTITUDE-4) or after 2-4 prior lines of therapy in daratumumab-refractory myeloma (ide-cel, KarMMA-3)[6, 7]. Based on these results we are anticipating possible expansion of the FDA approval of CAR T cells to earlier lines of therapy for myeloma. Therefore, the American Society for Transplantation and Cellular Therapy (ASTCT) convened a group of experts to provide a comprehensive review of the studies that led to approval of CAR T-cells in late line therapy of myeloma, the recently reported studies in earlier lines of therapy pending FDA review, and the ongoing or planned studies designed to move CAR T-cell therapy to earlier lines of therapy, as well as considerations for sequencing BCMA therapies and optimization of patient selection for BCMA directed therapies in current practice (Box 1).

Box 1.	Questions addressing the role of CAR T-cells in earlier lines of therapy for myeloma
FAQ 1	What are the 2 currently approved CAR T-Cell therapies for Relapsed/Refractory Myeloma, and what studies and data led to their approval?
FAQ 2	What mitigation strategies can be utilized to try to decrease the risk of severe CRS and neurotoxicity after CAR T-cell therapy for myeloma?
FAQ 3	What other specific risks are seen with CAR T-Cell Therapy besides CRS and Neurotoxicity?
FAQ 4	What considerations will help us choose between one BCMA CAR T-cell product over another?
FAQ 5	Many patients don't fit the eligibility criteria for the trials used for approval of CAR T-cells. What is the data for CAR T-cell therapy outside of the clinical trial setting?
FAQ 6	What are some bridging strategies for effective cytoreduction to mitigate risks or keep the myeloma under control in penta-refractory patients during product manufacturing?
FAQ 7	With multiple treatment options and modalities targeting BCMA (CAR T-cells, Bispecific T-cell engagers), what are some considerations for sequencing BCMA directed therapies?
FAQ 8	Are there T-cell markers predictive for poor outcome after CAR T-cell therapy, and what are the reasons that CAR T-cells may be more effective earlier in the course of disease?

Box 1.	Questions addressing the role of CAR T-cells in earlier lines of therapy for myeloma
FAQ 9	What are the studies being done, and what data has been reported from randomized trials to support moving CAR T-cells to 2 nd or 3 rd line therapy for myeloma?
FAQ 10	What studies are being done, and what data would be needed to move CAR T-cells to frontline therapy of myeloma?
FAQ 11	Will moving CAR T-cells to earlier lines of therapy for myeloma be cost prohibitive, and will the quality of life improvement with CAR T justify a cost difference?
FAQ 12	For patients relapsing after BCMA-directed therapy, what options do we have, and what data do we have for non-BCMA T-cell redirection therapies?

Q 1: What are the 2 currently approved CAR T-Cell therapies for Relapsed/Refractory Myeloma, and what studies and data led to their approval?

Idecabtagene vicleucel (Ide-cel) was the first CAR T-Cell therapy product approved for myeloma on March 26, 2021. It was approved based on the results of the phase 2 KarMMa study, which enrolled RRMM patients who had received at least 3 prior lines of therapy including a PI, an IMiD, and an anti-CD38 antibody therapy (Table 1). For the 128 patients reported, the median number of prior lines of therapy was 6 (3-16), and 84% of patients were refractory to at least one agent in all 3 of these classes of therapy (triple class refractory), while 26% were refractory to 2 Pis, 2 IMiDs, and a CD38 antibody (penta-refractory)[1, 8, 9]. Based on the heavily pre-treated population studied in this trial, the current FDA label for ide-cel requires at least 4 prior lines of therapy, although outcomes in this trial were similar when comparing those with 3 vs 4 or more prior lines of therapy [8, 9]. The overall response rate (ORR) was 73% across all doses and 81% at the final target dose of 450×10^6 CAR T-cells, while the very good partial response (VGPR) or better rate was 52% overall and 65% at the 450×10^6 cell dose. The complete response (CR) or better rate was 33% in all dose groups and 39% at the 450×10^6 dose [1]. High response rates were observed across high-risk subgroups including those with high tumor burden, high risk cytogenetics, presence of extramedullary disease (EMD), or penta-refractory status [1, 8, 10]. The majority of those achieving a CR also achieved minimal residual disease (MRD) negative status by next generation sequencing (all that were evaluable). The median progression-free survival (PFS) was 8.8 months overall and 12.2 months in the target dose group of 450×10^6 T-cells, and the median overall survival (OS) was 24.8 months, which was unprecedented in this heavily refractory patient population [8, 10]. Duration of response (DOR) was dependent on depth of response at 21.5 months for those achieving at least CR, 10.4 months for those achieving VGPR, and 4.5 months for those with PR [10]. Toxicity included cytokine release syndrome (CRS) in 84% (grade 3-4 in only 5%) and neurotoxicity in 18% (grade 3-4 only 4%), referred to as Immune effector cell associated neurotoxicity syndrome (ICANS).

Ciltacabtagene autoleucel (cilta-cel) was the second CAR T-Cell therapy product approved for myeloma on February 28, 2022. It was approved based on the results of the phase 1b/2 CARTITUDE-1 study, which enrolled RRMM patients who had received at least 3 prior lines of therapy including a PI, an IMiD, and an anti-CD38 antibody therapy (though the label requires 4 prior lines of therapy)(Table 1)[11, 12]. The cilta-cel CAR construct uses a 4-1BB costimulatory domain similar to ide-cel, but cilta-cel has two BCMA-binding

domains compared to one for ide-cel [12]. Dosing for cilta-cel was also different at 0.75×10^6 CAR T-Cells per kg body weight rather than flat dosing. For the 97 patients reported, the median number of prior lines of therapy was 6 (3-18), and 21.9% had high disease burden ($\geq 60\%$ plasma cells), 13.4% had EMD (vs 39% in KarMMa). The ORR was 97.9% with 82.5% achieving a stringent CR (sCR) at a median follow up of 27.7 months [11, 12]. MRD negative CR was seen in 44.3%. Median PFS was 34.9 mo and median OS was not yet reached, but 27 month OS was 70% [13]. PFS and OS were shorter in patients with high-risk cytogenetics, ISS stage III, high tumor burden, and EMD. Toxicity included CRS in 95% (grade 3-5 in only 5%) with a median time to onset of CRS of 7 days (compared to 1 day for ide-cel) and neurotoxicity in 21% (grade 3-5 in 10%). However, neurotoxicity from cilta-cel included not only classical ICANS (16.5%) but also atypical neurotoxicity manifestations in 12.4% including parkinsonism in 6% of patients, as well as small numbers with cranial nerve palsies (most commonly CN VII), ataxia, and peripheral sensorimotor neuropathy, with median time to onset 27 days (range 11-108 with one late occurrence at day 914) and median time to resolution 70 days (range 2-159)[11, 14].

Q2: What mitigation strategies can be utilized to try to decrease the risk of severe CRS and neurotoxicity after CAR T-cell therapy for myeloma?

The impressive anti-tumor potency of BCMA CAR T-cells in RRMM has resulted in unprecedented clinical responses in heavily treated patients. However, there are immunologic toxicities associated with CAR T-cell expansion such as CRS and ICANS, which require close monitoring and rapid intervention. The rates and severity of CRS and ICANS depend on CAR product type, disease burden and patient comorbidities. CRS results from a cascade of cytokine signaling triggered by synchronous activation of CAR T-cells encountering malignant plasma cells. The driver cytokine that is implicated for CRS is interleukin-6 (IL-6), leading to a wide range of clinical symptoms ranging from mild flu-like symptoms to severe multi-organ dysfunction. In the pivotal studies that led to the approval of ide-cel and cilta-cel, the rates of grade 3 and higher CRS were low at 5% and 4% respectively with only 1 grade 5 CRS event reported with both ide-cel and cilta-cel in each of the 2 registration studies (Table 1) [1, 12].

Validated models to predict CRS and ICANS are lacking. Several studies have reported associations between clinical, biological and product related characteristics with CRS and ICANS severity. High tumor burden at baseline as well as high CAR T-cell expansion and persistence have been shown to be associated with severe CRS. These along with grade ≥ 2 CRS are associated with severe ICANS. Presence of preexisting neurologic comorbidity and cyclophosphamide and fludarabine lymphodepletion have also been identified as independent predictors of ICANS severity [15, 16].

Several strategies have been used to mitigate CRS and ICANS (Summarized in Table 2). Prophylactic administration of tocilizumab in diffuse large B cell lymphoma showed that it was effective at preventing severe CRS, however ICANS rates were increased [17]. Prophylactic corticosteroids, and more recently, the interleukin 1 receptor antagonist anakinra have also been used in lymphoma CAR T, but it is unclear how these strategies may impact disease response in myeloma [18-20]. The best timing of intervention for CRS

and ICANS is unknown, though data from multiple studies done in B-cell malignancies suggest benefit with early interventions. Enhanced bridging to reduce tumor burden prior to CAR-T infusion and performing neuroimaging and neurology consultation in patients with preexisting neurologic disease are other preventative strategies. Monitoring patients for CRS and ICANS with early and more aggressive supportive care and treatment including hospitalization for $\geq$ grade 2 ICANS are some of the monitoring and management strategies. Patients who do not respond to steroids and tocilizumab should be considered for other cytokine-targeting therapies like anakinra to decrease the duration of their side effects and prevent worsening of severity [21].

Neurotoxicity events, including ICANS, have variable clinical presentation with a highly variable course. The etiology of CAR T-cell related neurotoxicities is not clearly understood. They can occur concurrent with CRS or days after resolution of CRS. In some cases, neurotoxicity can occur >4 weeks after treatment (which prompted the FDA label prohibiting patients from driving for 2 months after infusion)[22]. The rates of grade 3 and higher ICANS for ide-cel and cilta-cel were very low at 3% and 2%, respectively. However, cilta-cel has also been associated with a risk for delayed atypical neurotoxicity as well, referred to as movement and neurocognitive treatment emergent adverse events (MNTs), comprised of a cluster of movement, cognitive and personality changes similar to parkinsonism[14]. MNTs were observed after cilta-cel at a median of 27 days in about 5% of the patients [14]. Risk factors for MNTs were similar to those for CRS and determined to be high tumor burden, grade 2+ CRS, any grade ICANS, or high CAR T-cell expansion/persistence [14]. Therefore, mitigation strategies have been implemented in subsequent trials of cilta-cel to try to prevent or minimize MNTs. Strategies include using more aggressive cytoreductive bridging therapy to reduce baseline tumor burden, early and aggressive treatment of CRS and ICANS, and extended monitoring for neurotoxicity beyond 100 days, which appears to have reduced rates of neurocognitive MNTs to 1% or lower with these precautions in the CARTITUDE-2 and CARTITUDE-4 studies, though facial nerve palsy was still seen in 1 patient in CARTITUDE-2 and in 16 (9.1%) in CARTITUDE-4 [14, 23-25].

Q3: What other specific risks are seen with CAR T-Cell Therapy besides CRS and neurotoxicity? Cytopenias, recently termed Immune Cell Associated Hematotoxicity (ICAHT):

Hematopoietic recovery following CAR T-cells is often delayed and is clinically consequential in the form of increased risk of infections, increased risk of life-threatening hemorrhage, increased resource utilization, and overall deterioration of quality of life [26]. In a study including investigational BCMA-directed CAR T-cell therapy, grade 2 or higher cytopenias in all cell lines were common, and normalization of levels took over 6 months on average [27, 28]. Furthermore, grade 3 or higher CRS or ICANS were significantly correlated with lack of count recovery at 1 month [28]. In real world data analyses of patients treated with ide-cel, cytopenias of grade 3 or higher were seen beyond 1 month in about 65% of patients, including neutropenia in 60%, anemia in 38%, and thrombocytopenia in 59% [29, 30]. At day 90, persistence of grade ≥ 3 cytopenias was associated with higher plasma cell burden in the marrow at baseline [30]. Cytopenias can result in a significant

increase in morbidity as well as fatalities related to limited transfusion capacities in some countries reported in global studies of cilta-cel [31].

In cases of severe or prolonged cytopenias requiring frequent transfusions and/or refractory to growth factor support, a stem cell boost (SCB) using autologous cryopreserved CD34⁺ peripheral blood stem cells (PBSC) without conditioning chemotherapy may be considered since PBSC are often available for myeloma patients. SCB demonstrated efficacy with effective hematopoietic recovery in 4 of 7 patients given allogeneic PBSC after CD19 CAR T for acute lymphoblastic leukemia (ALL) in 1 study, in 7 of 9 evaluable patients given either autologous or allogeneic PBSC after CD19 CAR T for lymphoma or ALL in other study, and in 18 of 23 given frozen autologous PBSC after BCMA CAR T for myeloma [32-34].

Immune effector cell associated HLH-like syndrome (IEC-HS): Hemophagocytic lymphohistiocytosis (HLH)-like hyperinflammatory response is now recognized as a common toxicity after CAR T-cell therapy, most commonly with CD22-directed CAR T-cells but also with BCMA and CD19 CAR T; however, standard clinical parameter based HLH diagnostic criteria has major overlap with CRS [35-37]. A more discriminatory criteria for the entity now called IEC-HS, along with expert created management guidelines, were recently created to allow for uniform recognition and appropriate interventions [38]. With BCMA-directed CAR T-cell specifically, depending on diagnostic criteria applied, HLH-like hyperinflammatory response has been reported in up to 22% of patients, which is a relatively high proportion for this potentially life-threatening toxicity [36]. High-dose steroids and anakinra have been commonly used for treatment while fatalities have been reported [37, 39]. Earlier recognition, timely intervention and development of treatment strategies is critical to ensure increased safety of CAR T-cells in patients undergoing treatment in the earlier course of their disease (See Table 2 for interventions).

Hypogammaglobulinemia: BCMA directed CAR T-cell therapy not only depletes malignant plasma cells but also normal plasma cells, which can lead to plasma cell aplasia, severe hypogammaglobulinemia with immunoglobulin G (IgG) level <400 mg/dL, and increased risk of infections. Infection risks are greatest within the first few months, but the hypogammaglobulinemia may persist for many years. There is no clear consensus or prospective data to guide us on post-CAR T prophylaxis with intravenous immunoglobulin (IVIG) therapy, but for those whose IgG level drops below 400 mg/dL after BCMA CAR T, many experts recommend starting prophylactic IVIG therapy (0.4 g/kg monthly), even in the absence of severe or recurrent infections during the first few months post-CAR T [40]. This is in contrast to recommendations for non-CAR T therapy of myeloma, where most guidelines recommend IVIG only in the setting of both IgG <400 AND frequent/severe infections, mainly due to the less complete plasma cell depletion with standard myeloma therapies compared to the more profound immune dysfunction seen after BCMA CAR T-cell therapy (plasma cell aplasia often combined with T-cell and B-cell deficiencies similar to common variable immune deficiency, plus sometimes compounded by prolonged neutropenia) [40-45].

It has also been proposed that patients with IgG <400 that have not experienced significant infections by 3 months post CAR T could be considered for a trial of withdrawing IVIG replacement with close monitoring [40, 46]. Nevertheless, even if many can be taken off IVIG in the absence of infections, one must weigh the risks and benefits for a particular patient, including presence or absence of other risk factors for infection like delayed CD4 recovery or prolonged neutropenia.

Q4: What considerations will help us choose between one BCMA CAR T-cell product over another?

Although both ide-cel and cilta-cel target the same antigen with a similar mechanism of action and have been studied in heavily pretreated triple class exposed RRMM patients after a median of 6 prior lines, there are several important differences including CAR T construct, cell doses, and the patient populations studied in the two pivotal clinical trials KarMMA and CARTITUDE-1 (Table 1). These characteristics include a higher incidence of EMD in KarMMA (39% vs 13%), higher stage disease in KarMMA (86% stage 2-3 vs 75%), and higher number with high risk cytogenetics in KarMMA (35% vs 24%). However, there were fewer penta-refractory patients in KarMMA (26% vs 42%). Although a matching-adjusted indirect comparison of efficacy outcomes for cilta-cel in CARTITUDE-1 vs ide-cel in KarMMA has been published showing a higher ORR, CR rate, DOR, and PFS for cilta-cel compared to ide-cel, this comparison did not include patient level data for KarMMA and should be interpreted with caution [47]. In the absence of a randomized controlled trial or at least a real world head-to-head comparison, it is difficult to state whether one CAR T product is superior in efficacy to the other; nevertheless, potentially due to different binding domains (murine scFv for ide-cel and 2 camelid VH binding domains for cilta-cel) and differences in cell dose, there are notable differences in kinetics of CRS (median onset day 1 for ide-cel and day 7 for cilta-cel), which means that cilta-cel is more likely to be suitable for outpatient administration while ide-cel is more likely to require admission within a few days of the infusion if given outpatient.

If given a choice, many patients would prefer to receive a product with the highest response rate and the longest remissions reported to date for triple class exposed RRMM (ORR 97.9% and median PFS 34.9 mo for cilta-cel in CARTITUDE-1). Therefore, if they have disease that can be controlled while waiting on a collection slot and manufacturing (indolent relapse or an effective bridging therapy option), then cilta-cel may be a preferred choice when possible. However, the potential tradeoff of the extremely high efficacy with cilta-cel is a higher rate of atypical neurotoxicity, including the risk of cranial nerve palsy or parkinsonism, which is further increased for those with myeloma that is not adequately cytoreduced. In addition, early reports of real world data with cilta-cel suggest a high rate of manufacture failures which must also be considered (further discussed below).

In general, both products are often well tolerated and less toxic compared to high dose chemotherapy in myeloma and can be given to patients even in their 80s with careful monitoring. However, one factor that can be used to help determine candidacy for one product over the other (other than availability of a production slot) is the patient's comorbidities. For example, if the patient has baseline neurologic disease (seizure disorder,

significant peripheral neuropathy, or early symptoms of parkinsonism), then they will likely be more suitable for ide-cel over cilta-cel due the very low risk of atypical neurotoxicity with ide-cel, or if they have severe baseline neurologic issues then they may be more suited for a BsAb with even lower risks. Also, if they have bulky disease that is expected to be difficult to cytoreduce due to lack of good options remaining to bridge them to CAR T, that may place them at increased risk for proceeding to either CAR T but especially cilta-cel. We would recommend avoiding cilta-cel in high tumor burden patients without good cyto reduction options and avoid either CAR T-cell product for those with rapidly progressive disease without a plan for significant pre-CAR T cyto reduction.

Q5: Many patients don't fit the eligibility criteria for the trials used for approval of CAR T-cells. What is the data for CAR T-cell therapy outside of the clinical trial setting?

We now have experience from real world data published from the US Myeloma CAR T Consortium database of 196 patients that completed ide-cel leukapheresis at 11 centers across the US [29]. One hundred and fifty-nine of the patients received the ide-cel infusion, with 17 patients not proceeding to CAR-T due to manufacturing failure (n=5) or progression/death (n=12), while the remaining were pending infusion at last follow-up. One of the most notable findings from the study was that 75% of the patients receiving ide-cel in the real world would not have been eligible for the KarMMa study due to significant comorbidities. It is also notable that the efficacy and safety results were very similar to results of the KarMMa study despite the real-world patients being sicker and more frail. The real-world ORR was 84% with 42% CR and median PFS was 8.8 months with OS 19.4 months. Rates of CRS (84% with 5% grade 3+) and ICANS (18% with 3% grade 3+) were also almost identical to KarMMa. The Center for International Blood and Marrow Transplant Research (CIBMTR) infrastructure is also being utilized to assess outcomes from long term follow up protocols enrolling 1000 ide-cel and 1250 cilta-cel recipients to fulfill the regulatory requirements upon FDA approval of these products. Analysis of these large real world studies is ongoing and aims to help optimize utilization of these CAR T-cell products.

Another analysis from the US Myeloma CAR T Consortium evaluated the subgroup of 28 patients with renal impairment defined as creatinine clearance <50 mL/min or on dialysis (n=1) [48]. Although the patients benefited from ide-cel without excess risk of CRS or ICANS, they tended to have a longer hospital stay and higher rates of grade 3+ cytopenias at day 30, but the cytopenias were no longer different than patients without renal impairment by day 90. Adjustment of the fludarabine lymphodepletion dose is very important in renal impairment and was done routinely as SOC with 74% of patients having >20% dose reduction. ORR was 96% with 58% CR rate and PFS 6.5 months, confirming safety and efficacy in this common myeloma population that has been excluded from most trials.

The US Multiple Myeloma CAR T consortium also recently presented the first real world safety and efficacy analysis of cilta-cel [49]. Of the 153 patients who underwent apheresis, 143 received cilta-cel. In this cohort, 57% of patients would have been ineligible for the CARTITUDE-1 trial. Despite this, safety and efficacy was comparable to the clinical trial cohort. Amongst infused patients, ORR was 89% and CR rate was 56%. Incidence and

severity of CRS (80%, grade 3: 5%) and ICANS (18%, grade 3: 6%) was similar to the trial cohort. Delayed neurotoxicity was seen in 12% of patients, most common being 7th cranial nerve palsy (6%). Parkinsonism like syndrome MNT was seen in 1% of patients. Median PFS was not reached at a median follow up of 6 months, and 6 mo PFS was estimated at 79%.

Q6: What are some bridging strategies for effective cytoreduction to mitigate risks or keep the myeloma under control in penta-refractory patients during product manufacturing?

The current process of manufacturing CAR T-cells in RRMM uses the patient's autologous T-cells, a process that takes roughly 5-10 weeks for BCMA CAR T. This results in about 5-30% of patients never receiving the intended CAR T-cell infusion (9% in the real-world ide-cel CAR T Consortium data set), partly due to rapid disease progression during manufacturing and less commonly due to failure of the CAR T-cells to adequately expand [29]. Hence bridging therapy is recommended for the majority of patients except in those with slowly progressive disease with indolent biochemical progression. In the KarMMa trial, 88% of the patients received bridging therapy with only a 5% response, but options were limited to therapies the patient had already received (and likely had failed), which is not applicable to the real world. In the CARTITUDE-1 trial, 75% of the patients received bridging therapy with reduction of tumor in 34% of the patients. Bridging therapy should be started soon after leukapheresis when needed, but most recommend a 2-week washout period prior to leukapheresis (after holding therapy) when able and another 2-week washout prior to lymphodepletion (after bridging therapy) to avoid issues with T-cell dysfunction and cytopenias [50, 51].

There are limited data on the choice of bridging therapies that can be used effectively, but BCMA-targeted agents prior to planned BCMA CAR T therapy should be used with caution as the recent prospective data from the CARTITUDE-2 cohort as well as real world retrospective data for ide-cel from the US Myeloma CAR T Consortium showed relatively sub-optimal outcomes in patients with prior BCMA therapy exposure [4, 5, 52]. Nevertheless, it is noted that out of the 5 patients that had previously received a different BCMA CAR T-cell therapy, all 5 responded to ide-cel in the CAR T Consortium report, while most of the detrimental effect was seen with prior BCMA-directed T-cell engaging bispecific antibodies (TCE BsAbs) and antibody drug conjugates (ADC). It is unclear if the same detrimental effect would be seen if patients going into BCMA CAR T are still responding to bridging with BCMA-directed BsAbs, because most were likely refractory to BCMA therapy in the reported data, and we have no data yet on using BsAbs as bridging therapy. It is also unclear if a TCE BsAb against a different target like talquetamab targeting GPRC5D may be a more useful bridging strategy to get to BCMA CAR T, though it is suspected that if any TCE BsAb is used as bridging it should be given after T cell collection or with a washout period to avoid collecting exhausted T-cells as a source of CAR T manufacturing.

Other options for bridging therapy include selinexor based combinations, alkylator therapy combinations including adding cyclophosphamide to the current regimen, or inpatient infusional chemotherapy (KD-PACE, DCEP, etc)[53, 54]. One may also use novel

combinations of agents the patient has already received but not previously in combination together [55]. However, bendamustine should be avoided prior to leukapheresis whenever possible due to its lymphodepleting effect and risk of CAR T production failure [56, 57]. In patients with rapidly progressing disease and no good standard options, infusional multi-agent combination chemotherapy may help debulk the disease and also mitigate subsequent CAR T toxicities like CRS and ICANS due to better cytoreduction (KD-PACE for fit patients, DCEP or similar for those with cardiac history or not as fit).

We now also have further information on outcomes after various bridging therapies from the US Myeloma CAR T Consortium presented at ASCO 2023 showing that those not needing bridging therapy have the best outcomes after ide-cel (likely due to more indolent disease), and bridging with alkylator therapy was associated with inferior PFS and OS, likely due to more aggressive disease characteristics in patients requiring alkylator therapy but unclear if there are other effects [58]. Therefore, alkylators should be used with caution, and in general when using conventional chemotherapies, the risk of cytopenias and possible infections should be considered as well. Agents that can enhance T-cell fitness (including IMiDs) should be explored further for use prior to leukapheresis as well as bridging, and one trial already exploring this is the KarMMa-2 Cohort 3 trial of priming with lenalidomide prior to collection and after infusion of ide-cel in patients not in CR at 3 months out from Auto SCT and at high risk for early relapse ([NCT03601078](#)).

Q7: With multiple treatment options and modalities targeting BCMA (CAR T-cells, Bispecific T-cell engagers), what are some considerations for sequencing BCMA directed therapies?

FDA approved products targeting BCMA currently include 2 CAR T-cells (ide-cel and cilta-cel) and 2 T-cell engaging (TCE) BsAbs (teclistamab and elranatamab), all of which currently require triple class exposure and 4 prior lines of therapy. Although the previously approved BCMA ADC belantamab mafodotin is now only available through compassionate use, it is anticipated that the list of products targeting BCMA will continue to grow in the coming months, and with that comes complexity of decision-making in terms of how to pick one over the other without head-to-head trials. In general, TCE BsAbs have an advantage over CAR T-cell products, because they are “off-the-shelf” and immediately available, while the currently approved autologous CAR T-cell products require procuring an apheresis slot at best 2 weeks later and waiting several weeks to manufacture [59]. CAR T-cells also have a risk of manufacturing failure between 5 and 20%, depending on the product [49, 60]. As a result, patients in need of immediate therapy due to rapidly progressive disease will be routed towards off-the-shelf products like TCE BsAbs while those that have controllable or less-explosive relapses will be able to wait a month for CAR T-cells. That being said, allogeneic CAR T-cell products are currently under investigation and would not have the same time limitation as autologous products once available. For those that have options for successful bridging therapy and can get a slot for CAR T-cell production, the “one-and-done” infusion of CAR T-cells offers the advantage over long term ongoing injections needed with TCE BsAbs. Both require either one week in the hospital or very intensive outpatient monitoring for CRS and ICANS for 1-2 weeks, though the severity

of these side effects is often lesser with BsAbs compared to CAR T, especially less risk of severe neurotoxicity.

An increasingly important question is what to do for the patient who is currently receiving a TCE BsAb with a meaningful response. Should we continue to maintain them on a long-term therapy or use it as a bridge to receive CAR T-cell therapy? While data on moving to CAR T in the setting of ongoing response to BCMA directed BsAbs is limited, data showing that relapsed disease after prior BCMA directed bispecific therapy is associated with inferior PFS following ide-cel or cilta-cel CAR T [4, 5, 52]. Therefore saving CAR T for after progression on BCMA BsAbs may not be the best option, though patients can often still respond to other BCMA directed therapies after post-CAR T relapse (either a different CAR T or BsAbs) when CAR T is their first BCMA directed therapy [61, 62].

As noted, one unique advantage of CAR T-cell therapy is the one-time administration which is in stark contrast to TCE BsAbs that need to be administered repeatedly and perhaps in perpetuity. This therapy-free interval may be quite important for many patients with myeloma, as many have never really had a treatment free period since diagnosis. A counter argument in favor of BsAbs is that they do not require lymphodepleting chemotherapy. In myeloma, where patients are already immunocompromised, lymphodepletion with fludarabine and cyclophosphamide can easily add to the immune suppression and cytopenias, often requires the need for toxic bridging therapy while waiting on production, and can add increased risk of second malignancies, so patients that are more frail or with pancytopenia may be better suited to BsAbs. BsAbs also do not require close proximity to the referral center for 2 months and the avoidance of driving for 2 months like CAR T-cells. Age is typically not a deciding factor on BCMA CAR T as much as physiologic fitness, as we routinely give CAR T-cells and BsAbs to myeloma patients in their 80s and see much less toxicity with BCMA CAR T compared to autologous stem cell transplant [60, 63, 64]. However, for those that are on the more frail side, BsAbs may be a good choice due to the less severe toxicity.

The phase I/II Majestic-1 study that led to FDA approval of teclistamab on October 25, 2022 showed a 63% ORR and median PFS of 11.3 months in a patient population similar to the KarMMa and CARTITUDE-1 studies [65]. The phase II MagnetisMM-3 trial that led to FDA approval of elranatamab on August 14, 2023 showed a 61% ORR, 35% $\geq$ CR rate, 51% PFS at 15 mo and median PFS not reached at 14.7 mo follow-up [66]. The ORR for elranatamab in a subgroup with prior BCMA therapy was 33%. Both of these BCMA-CD3 TCE BsAbs are approved for triple class exposed RRMM patients after 4 prior lines of therapy (same indication as both CAR T). Although the response rates are slightly lower for both BsAbs than for CAR T-cells, they are still drastically higher than for any other non-T-cell redirecting therapy in late line RRMM (like selinexor), and one could argue that the PFS of 11-15 months for BsAbs is very similar to ide-cel (12.2 months at the 450×10^6 target dose and 8.8 months for all doses) and therefore may be of equal or higher value for some patients despite having to continue injections until progression. However, the median PFS for cilta-cel in CARTITUDE-1 was 34.9 mo, so without a head-to-head trial cilta-cel appears to be the most durable option available [11]. Furthermore, response rates for BsAbs were noted to be lower in patients with EMD, stage III R-ISS, and at least 60%

marrow replacement by plasma cells, so those patients may be better suited to aggressive cytoreductive bridging therapy and CAR T when possible.

In the meanwhile, ongoing research is being done through the US MM immunotherapy consortium (formerly US MM CAR T consortium) and other collaborative efforts to help determine the real-world answers to these questions on BCMA therapy sequencing with both CAR T and BsAbs. We need more real-world data in specific sub-populations of RRMM, such as patients with renal impairment, baseline cytopenias, heavy tumor burden, or diminished performance status. Correlative research is also being done to interrogate the pattern of expression of BCMA post BCMA targeting therapy. We know that it is rare to lose BCMA expression after CAR T through biallelic deletions; however, emerging data shows that despite ongoing expression of BCMA on the MM cells in patients relapsing after TCE BsAb therapy, it is common to develop BCMA gene mutations that affect the extracellular BsAb-binding domain of BCMA, which then renders the BCMA unrecognizable by some TCE BsAbs but not others [67, 68]? This has led to the question of whether or not we should use a TCE BsAb targeting a completely different antigen, like the anti-GPRC5D Talquetamab, if needing to bridge to CAR T with a TCE BsAb, or should we save this different target for post-BCMA progression.

Q8: Are there T-cell markers predictive for poor outcome after CAR T-cell therapy, and what are the reasons that CAR T-cells may be more effective earlier in the course of disease?

Despite high response rates, there are many potential reasons for disease progression after CAR T including factors related to the tumor, the tumor microenvironment, and intrinsic to the CAR T-cells themselves [69-71]. The ability of the CAR T-cell to expand and persist is thought to have a direct impact on outcomes [72]. Early studies in B-cell malignancies showed that persistence of central memory T-cells positively impacted outcome and that the constitution of the cell product influenced the presence of these cells post infusion, with naïve and stem cell like memory T-cell quantity related to expansion [73]. The frequency of CD8⁺CD45RO⁻CD27⁺T-cells (naïve or memory like) in the premanufacturing leukapheresis product was then identified as the main factor correlated with disease response after CD19 directed CAR T-cells in a CLL cohort [74]. Further studies have expanded this theory to the BCMA space and showed increased antigen-responsive cytotoxicity of the manufactured product in myeloma patients with higher CD8⁺CD45RO⁻CD27⁺T-cells and higher CD4/CD8 ratio at time of leukapheresis [75]. In addition, the frequency of CD8⁺CD45RO⁻CD27⁺ T-cells and the CD4/CD8 ratio decreased over the disease course and at relapse [76]. Although it is unclear if CAR T-cell expansion or persistence is necessary for durable responses in BCMA CAR T-cell therapy of myeloma, recent data for ide-cel support the importance of T-cell phenotype, because PFS ≥18 months was associated with a higher percentage of naïve and early memory (less exhausted, less senescent, more proliferative) T-cells in the apheresis material (CD4⁺CD28⁺CD27⁺ and CD8⁺CCR7⁺CD45RA⁺CD57⁻) and improved functional T-cell phenotype (interferon-γ secretion upon BCMA stimulation) in the drug product compared to those with less durable response [77].

Prior therapies may directly impact T-cell fitness, and T-cells from multiply relapsed patients may be more susceptible to activation-induced cell death [70]. Percentages of naïve T-cells decrease over time with myeloma from diagnosis to relapse and further decrease after treatment with daratumumab, while central memory T-cells are higher after daratumumab exposure [78]. Hence the timing of leukapheresis may drastically change the composition of T-cells in the product. Changes in the T-cell compartment associated with myeloma progression can also include elevation of regulatory T-cells over Th17 T-cells and expression of exhaustion markers such as PD-1, TIM3, LAG3, and TIGIT, which are associated with decreased proliferation and decreased effector function, thus adding to the hypothesis that collection of T-cells earlier in the disease course may positively impact outcomes [79]. Furthermore, patients who received early IMiD maintenance after anti-BCMA/CD19 CAR T-cells had T-cell re-expansion and late onset clinical responses, so manipulation of the product pre or post infusion may also impact outcomes [80]. Remaining questions include whether or not there are T-cell markers of exhaustion or memory that can help predict better response to T-cell therapy or predict those not suitable for generation of a durable CAR T-cell clone. These answers may eventually help guide our decision-making regarding CAR T vs TCE BsAbs.

Q9: What are the studies being done, and what data has been reported from randomized trials to support moving CAR T-cells to 2nd or 3rd line therapy for myeloma?

Two exploratory phase II studies have reported favorable outcomes for CAR T-cells in 2nd line myeloma treatment. The KarMMa-2 cohort 2a phase II study ([NCT03601078](#)) evaluated ide-cel after early relapse within 18 mo from frontline Auto SCT, and the CARTITUDE-2 cohort A phase II study ([NCT04133636](#)) evaluated cilta-cel after 1-3 prior lines of therapy. Ide-cel given as 2nd line therapy in KarMMa-2 showed an ORR of 83.8%, 45.9% CR rate, 85% MRD negative rate at 6 mo, and median PFS of 11.4 mo, while cilta-cel in CARTITUDE-2 cohort A after 1-3 prior lines showed an ORR of 95%, 90% CR rate and 75% 12 mo PFS with median not yet reached [81, 82]. However, these studies are only a proof of concept and were not randomized to prove superior PFS.

Fortunately, we now have results from 2 separate randomized studies of myeloma CAR T in earlier line settings for both ide-cel and cilta-cel (Table 3), and approval in the earlier line setting is now pending FDA review (after triple class exposure for ide-cel without regard for lines of therapy, and after at least 1 prior line following exposure to a PI and refractory to Len for cilta-cel) [6, 7, 83]. The randomized phase III KarMMa-3 study ([NCT03651128](#)) enrolled triple class exposed RRMM patients after 2-4 prior lines of therapy and randomized 2:1 to ide-cel CAR T vs investigators choice of 1 of 5 SOC regimens with either daratumumab/pomalidomide/dexamethasone (Dara/Pom/dex), Dara/bortezomib/dex (Dara/Vel/dex), ixazomib/lenalidomide/dex (Ixa/Len/dex), elotuzumab/Pom/dex (Elo/Pom/dex), or carfilzomib/dex [7]. 66% were triple class refractory, and 95% were dara refractory. Primary endpoint was PFS, and out of 386 pts enrolled, 254 were assigned to ide-cel and 132 to SOC with 88.5% of the ide-cel group receiving CAR T. At a median of 18.6 mo follow up, median PFS was more than tripled at 13.3 months for ide-cel vs 4.4 months for SOC (HR 0.49; 95% CI 0.38-0.65; P<0.001). ORR was 71% for ide-cel vs 42% for SOC with a CR rate of 39% vs 5%, while OS data was not yet mature. CRS and ICANS rates

were similar to KarMMa with 88% CRS, 5% grade 3+ CRS, 15% ICANS and only 3% grade 3+ ICANS with no parkinsonism or cranial nerve palsies seen.

CARTITUDE-4 ([NCT04181827](#)) is a randomized phase III trial that enrolled lenalidomide-refractory RRMM patients after 1-3 prior lines of therapy and compared cilta-cel vs investigators choice of SOC regimen with either Pom/Vel/dex or Dara/Pom/dex [6, 83]. This was a much earlier population as only 23% were CD38 refractory (compared to 95% in KarMMa-3), 14% were triple class refractory (compared to 66% in KarMMa-3) and 73% had received only 1-2 prior lines of therapy (vs median 3 prior lines in KarMMa-3). 419 pts were randomized to cilta-cel (n=208) or the SOC arm (n=211). The primary endpoint was PFS in the intent-to-treat randomized population. There were no manufacturing failures, and 176 (85 %) of the cilta-cel group received CAR T. At a median of 15.9 mo follow up, median PFS was not reached for cilta-cel vs 11.8 mo for SOC (HR 0.26; 95% CI 0.18-0.38; P<0.001). Intent-to-treat PFS at 12 mo was 76% for cilta-cel and 49% for SOC. ORR was 85% for cilta-cel vs 67% for SOC. CR rate was 73% vs 22% and MRD negative rate (at 10^{-5}) was 61% vs 16%. In the 176 that received cilta-cel, ORR was 99%, CR rate was 86%, and MRD negative rate was 88% (vs 33% for SOC), while OS data was not yet mature. Out of 176 that received cilta-cel, CRS was seen in 76%, but only 2 (1%) had grade 3-4. Only 4.5% had ICANS (all grade 1 or 2) but 1 developed parkinsonism, 9.1% developed cranial nerve palsies (mostly CN VII), and 2.8% developed CAR T-related peripheral neuropathy for a total of 17% (30/176) non-ICANS neurotoxicity (despite mitigation strategies).

The significantly improved CR rates in KarMMa-3 and CARTITUDE-4 have already translated into a significant PFS advantage compared to SOC options in early line myeloma therapy, so our opinion is that it is likely CAR T-cell therapy will move up to 2nd line for cilta-cel and ide-cel based on the PFS advantage, though we await FDA review of all the data. Although we don't yet have mature OS data for either study, the large number of treatment options for subsequent relapses will likely make OS data less useful for early line myeloma therapy trials. Furthermore, it is noted that many of our patients are currently receiving quadruplet induction therapy and triplet 2nd line therapy, and they are often triple class refractory after 1-2 lines and penta-refractory after 2-3 lines, so waiting until 5th line for CAR T is no longer practical in the current era of myeloma therapy [84]. Another argument for moving CAR T up is the high treatment attrition rate in RRMM with only 13 to 35% of pts receiving 4 or more lines of therapy [85]. However, we don't yet know if any of these patients are going to be "cured" with earlier line CAR T-cell therapy, and it is also noted that a small percentage of patients may end up trading a chronic controllable problem like myeloma into a potentially irreversible and debilitating neurologic problem like parkinsonism or cranial nerve palsy, so the decision to use CAR T early must not be taken lightly, and patients must be thoroughly counseled on the risks and optimized for minimal risk with cytoreduction and early aggressive treatment of CRS/ICANS, especially for cilta-cel.

Q10: What studies are being done, and what data would be needed to move CAR T-cells to frontline therapy of myeloma?

Myeloma is currently an incurable disease with a finite number of types and classes of treatments, but the hope is that by using T-cell redirection therapy in the proper setting or combination, we may start to see more long-term remissions, especially if used earlier in the course of therapy when T-cells are more functional and patients are healthier. However, one must be fully cognizant of side effects, temporary or permanent, that patients are exposed to in order to potentially achieve a more durable remission. For later lines of MM therapy it is often possible to prove that a therapeutic intervention is effective (and safe) using a single arm or randomized phase 2 trial showing that it meets a certain threshold needed for regulatory approval. However, with the highly effective and well tolerated combination therapies available for frontline therapy of myeloma, it becomes imperative to design confirmatory phase 3 trials with CAR T vs a SOC arm in the frontline setting. This is how the recent phase 3 randomized DETERMINATION trial has secured the current role of auto SCT in the frontline therapy setting based on a readout of PFS with auto SCT consolidation showing a 21 mo increase in median PFS compared to non-transplant therapy (67.5 vs 46.2 mo) [86].

To address the role of frontline cilta-cel CAR T-cell therapy in transplant-eligible myeloma, the European Myeloma Network (EMN) has designed the international phase III randomized CARTITUDE-6 study (EMN28, [NCT05257083](#)) to directly compare cilta-cel CAR T-cell therapy versus auto SCT as consolidation after Dara-Vel/Len/dex (D-VRd) quadruplet induction therapy in newly diagnosed myeloma with a plan to finish enrollment by 2026 [87]. This trial has dual primary endpoints of PFS and rate of sustained MRD negative CR over ≥ 12 months with both endpoints needing to be met to prove benefit. Loss of MRD negativity over the first 2-3 years will be used as an earlier readout, and PFS will be used as a later readout since PFS is expected to take several years to read out, and these will both be more informative than an OS readout, which would likely take over a decade to read out as myeloma patients are living on average 8-10 years now [86]. For those that are not eligible or not wanting to consider auto SCT, the randomized phase III CARTITUDE-5 study ([NCT04923893](#)) is being done to compare standard VRd induction therapy followed by len/dex maintenance vs VRd followed by cilta-cel CAR T as consolidation. No data are available yet for these highly anticipated frontline CAR T-cell studies [88].

In the meanwhile, in order to explore the role of moving ide-cel to frontline therapy, the KarMMa-2 Cohort 3 study ([NCT03601078](#)) is being done with ide-cel CAR T as consolidation post auto SCT for those not in CR at 3 months out from SCT and therefore at high risk for early relapse. In this study lenalidomide is also being used to “prime” the T-cells prior to leukapheresis and starting 1 mo post CAR T-cell infusion to try to improve the long-term persistence of the CAR T-cells. A similar trial run by BMT/CTN (BMTCTN 1902, [NCT 05032820](#)) is also underway to evaluate ide-cel CAR T in those with functional high risk due to suboptimal response despite auto SCT plus at least 6 months of maintenance lenalidomide prior to CAR T-cell therapy. Since these are not randomized trials, it is not certain what PFS will be acceptable in this setting, but this data will be useful as a proof of concept with comparison to historic controls. However, the randomized

KarMMA-9 trial (CA089-1043) is now under development and will compare ide-cel CAR T + lenalidomide vs lenalidomide maintenance alone in those without achieving a CR at day 100 after frontline auto SCT.

Q 11: Will moving CAR T-cells to earlier lines of therapy for Myeloma be cost prohibitive, and will the quality-of-life improvement with CAR T justify a cost difference?

Another question that will arise from moving up very expensive CAR T-cells to 1st or 2nd line therapy of MM, is whether the cost will be worth it if CAR T offers only 1-2 years longer PFS. Although the initial price of CAR T is high (list price \$419,500 for ide-cel and \$465,000 for cilta-cel, not counting supportive care and hospital stay), it is fortunately a one-and-done infusion while standard myeloma therapy may cost similar amounts over a 2-year period. For example, each SOC non-CAR T myeloma therapy typically costs between \$150,000 (lenalidomide) and \$200,000 per year (carfilzomib, dara, etc), and when those are combined into 3-4 drug combinations for relapse, the cost can easily surmount the price of a CAR T-cell infusion in the first 1-2 years [89, 90]. Therefore, CAR T for relapsed disease after 1-2 prior lines of therapy is likely to at least break even financially compared to SOC. However, frontline patients receive a relatively short duration of combination induction therapy (3-6 months) +/- a relatively inexpensive auto SCT (~\$109,856) and then are typically maintained on a single drug maintenance therapy (sometimes doublet) for 3-6 years until relapse, so the PFS for frontline CAR T would have to be at least a few years to make up the difference financially [91]. Even if approved as earlier line therapy, acquisition price could be a significant barrier to receiving CAR T-cells for many patients that are under-insured, not only in the US but especially in lower and middle income countries [92, 93].

Nevertheless, even if the cost of CAR T ended up being higher and front-loaded, one could argue that the patient reported quality of life improvements seen with CAR T and the ability to be off therapy for a number of years or at least several months allows patients to have a significantly better experience and feeling of “normalcy” [94-97]. The patient reported outcomes from KarMMA-3 showed significant improvements in fatigue, pain, physical functioning, global health status, and quality of life measurements compared to SOC [94]. The improved quality of life measurements seen are despite having more side effects in the first 1-2 months compared to SOC therapy, and it is likely that this difference will be even more striking when comparing frontline CAR T with high dose melphalan and auto SCT, though we only have one report addressing this and more data is needed in myeloma [98].

Q 12: For patients relapsing after BCMA-directed therapy, what options do we have, and what data do we have for non-BCMA T-cell redirection therapies?

Fortunately, myeloma that relapses after BCMA-directed CAR T-cell therapy may still respond to other BCMA-directed therapy including a different CAR T or BCMA-directed TCE BsAbs as the cells usually still express BCMA and the relapse is likely due to loss of persistence of the CAR T-cells (even though the reverse is not necessarily the case with inferior outcomes from CAR T after failing BCMA BsAbs) [99-101]. However, it is important to have treatment options for these patients after failure of BCMA targeted therapy (especially after failing more than one BCMA-directed therapy). The 2 non-BCMA

targets most rigorously studied for T-cell redirection therapy so far are GPRC5D (CAR T-cells under development and 1 TCE BsAb recently approved) and Fc receptor-like 5 (FcRH5, aka 5cRL5/IRTA2/CD307), a surface protein expressed selectively on B-cells and plasma cells [102, 103]. Both GPRC5D and FcRH5 are over-expressed on myeloma cells and have limited expression in normal tissues. Currently most of these promising therapies are given only in clinical trials, but talquetamab (anti-GPRC5D BsAb) was just approved by the FDA on August 10, 2023.

In an ideal world, a patient relapsing a few years after BCMA CAR T would then be able to receive a GPRC5D-directed CAR T, which would allow them to have maximum time off therapy. We now have preliminary data regarding activity of GPRC5D-specific CAR T-cell therapy in 2 separate phase I trials. One was recently published in NEJM (MCARH109), and one is an ongoing phase 1 CAR T-cell trial run by BMS with preliminary data presented at ASH 2022 (BMS-986393, CC-95266)([NCT04674813](#)) [104, 105]. The NEJM study published by MSKCC reported on 17 patients, including 10 of which had received prior BCMA therapies [104]. Responses were observed in 71% of the entire cohort and 7 of the 10 with prior BCMA. At the 450×10^6 cell dose 1 patient experienced grade 4 CRS, and 2 patients developed a grade 3 cerebellar disorder, while no cerebellar disorder or any ICANS or high grade CRS occurred at 25 to 150×10^6 cells. In the BMS study of GPRC5D-directed CAR T-cells, 17 patients were reported with 7 (41%) having received prior BCMA therapy (all but 1 prior BCMA CAR T)[105]. Responses were seen in 86% with 4 of 6 responding after prior BCMA therapy. CRS was seen in 65% with median onset day 3, and ICANS was seen in 12% (both grade 1). On-target, off-tumor toxicity was seen but all grade 1 with 18% skin changes, 12% nail changes, and 12% dysgeusia. The rate of cerebellar toxicity appears low but is still being assessed with further follow up and dose expansion cohorts.

For patients that relapse after BCMA CAR T (and/or anti-BCMA TCE BsAb) and are not a candidate for an alternative CAR T-cell product or clinical trial, we now have one FDA approved option (talquetamab) that is a first-in-class off-the-shelf TCE BsAb targeting GPRC5D/CD3 [106]. Out of 232 patients (with a median of 6 prior lines of therapy) in the phase II registration trial MonumenTAL-1, dysgeusia was a dose limiting side effect seen in 57-63% of pts. CRS was seen in 77-80% (all but 1 were grade 1-2), and skin-related events (rash) were seen in 67-70% (all grade 1-2 except 1 grade 3). ORR was 64-70%, and DOR was 7.8 to 10.2 months, depending on dose, as both a weekly and biweekly subcutaneous option were tested and approved.

Cevostamab (anti-FcRH5xCD3 BsAb) is another therapy that has significant activity in prior BCMA exposed patients. It was studied in the phase 1 GO39775 ([NCT03275103](#)) trial of 16 patients, 4 of whom were refractory to BCMA therapy [107]. The ORR was 94% with 7 in stringent CR, 3 in CR, 5 in VGPR and 1 in PR. At data cut-off 13 of the responding 16 patients remained in remission. Cevostamab, like other BsAbs, was associated with increased risk of infections, but treatment duration was fixed at 17 months to avoid long term exposure.

Studies are ongoing to use BsAbs in fixed duration to decrease the infection risk and in combinations of 2 BsAbs or in combinations with IMiDs or other therapies to try to achieve

more durable remissions in both the early line (MonumenTAL-6, Majestec-7, Majestec-4/EMN30) and late line setting (RedirecTT-1, MM22-947). The phase 1b RedirecTT-1 trial ([NCT04586426](#)) was the first to report preliminary results of dual combination anti-BCMA + anti-GPRC5D BsAb therapy with teclistamab + talquetamab in triple class exposed RRMM at ASCO 2023 [108]. For the first 63 pts reported, median prior lines of therapy was 5, 78% were triple class refractory, 43% had bone-independent EMD, and at 14.4 mo follow up, 81% had CRS with only 3% grade 3 and only 1 pt with ICANS. At the recommended phase II dose, ORR was 92% (12/13) overall and 83% (5/6) for pts with EMD with a CR rate of 31% overall and 33% in EMD. Median PFS has not been reached. These results give us hope for having more options in the not-so-distant future for late stage post-CAR T relapsed RRMM patients, and other ongoing studies may result in even better responses when combining immunotherapy modalities.

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Highlights

- BCMA-directed chimeric antigen receptor (CAR) T-cells have been shown to be highly effective in treating relapsed/refractory multiple myeloma (RRMM).
- Two BCMA-directed CAR T-cell products have been FDA approved, but both currently require 4 prior lines of therapy, where finding effective bridging therapy can be difficult.
- BCMA CAR T Cells were superior to standard of care therapy options in two randomized phase 3 trials, where they led to prolonged progression free survival in second line and third line therapy of multiple myeloma.
- We review implications for clinical practice with earlier use of BCMA CAR T-Cells for treatment of multiple myeloma.

TABLE 1:

Results of KarMMa and CARTITUDE-1 trials

	KarMMa [1, 8, 101]	CARTITUDE-1 [2, 11, 131]
Study Design		
CAR T-Cell Therapy given	Ide-Cel	Cilta-Cel
CAR T-Cell Dose	150-450x10 ⁶ cells	0.75x10 ⁶ cells/kg
Baseline Characteristics		
No of pts (infused)	128	97
Median Prior Lines	6 (3-16)	6 (3-18)
R-ISS III (%)	21 (16)	14 (14)
R-ISS II-III (%)	111 (86)	73 (75)
High risk FISH (non-1q)	45 (35)	23 (24)
Add 1q	45 (35)	NR
Extramedullary Disease	50 (39)	13 (13)
African American/Black	6/100 (6)	17 (17.5)
Triple Class Refractory (%)	108 (84)	85 (88)
Penta-Refractory (%)	33 (26)	41 (42)
Efficacy		
ORR (%)	94 (73)	94 (97.9)
ORR at 450x10 ⁶ cell dose (%)	44 (81)	N/A
≥ CR (%)	42 (33)	80 (83)
≥ VGPR (%)	68 (53)	92 (95)
Median PFS, months	8.8	34.9
Median PFS for 450x10 ⁶ cell dose, mo	12.1	N/A
Median OS, months	24.8	Not Reached, 70% at 27 mo
Safety		
CRS any grade (%)	107 (84)	92 (95)
CRS grade ≥ 3 (%)	7 (5)	4 (4)
Median day of CRS onset (range)	1 (1-12)	7 (5-8)
Neurotoxicity any grade (%)	23 (18)	21 (21)
ICANS grade ≥ 3 (%)	5 (4)	10 (10)
Non-ICANS Neurotoxicity (%)	0 (0)	12 (12.4)

Abbreviations: N/A indicates not applicable; NR, not reported

TABLE 2:**BCMA CAR T-Cell Toxicities, Risk Factors, and Mitigation Strategies**

Toxicity	Risk Factors	Mitigation/Treatment Strategies
CRS	- High tumor burden - Rapidly progressive disease (inadequate bridging therapy)	- Effective pre-CAR T cyto-reduction/bridging to minimize tumor burden - If rapidly progressing, EMD, >50% marrow, R-ISS III - May use combo of novel agents either with unused drug or in new combo if available [55] - For penta-refractory consider Selinexor combo or infusional chemo (KD-PACE, DCEP) [53, 54] - Prior non-CAR T BCMA therapy may decrease PFS, but unclear if BCMA or GPRC5D TCE BsAb may be used safely as bridging [4] - Alkylator bridging may be assoc. with lower PFS/OS [58] - Avoid bendamustine prior to apheresis due to risk of manufacturing failure [57] - Low grade CRS: - Ide-cel: Supportive care, tocilizumab if persistent grade 1 CRS or early onset with high tumor burden - Cilta-cel: Early tocilizumab +/- corticosteroids - Higher grade CRS (2+):[109] - Early tocilizumab +/- corticosteroids - Prophylactic dex 10 mg days 0, 1, & 2 effective in preventing in CD19 CAR but not studied in BCMA [18]
ICANS	- High grade CRS - High tumor burden - Poorly understood	- Early Corticosteroids - Anakinra if refractory to steroids [21, 109] - Neuro consult, EEG, MRI, seizure prophylaxis if severe [110] - Mitigation strategies: - Prophylactic steroids used in CD19 CAR with high tumor burden but not studied in BCMA [18] - Prophylactic anakinra appears effective in CD19 CAR but not studied in BCMA [19]
Non-ICANS Neurotoxicity	- Cilta-cel (rare with ide-cel) - Previous high grade CRS - Previous ICANS - High tumor burden	- Effective pre-CAR T cyto-reduction/bridging to minimize tumor burden [14] - Baseline Neuro Imaging/consult for those at risk - Early/aggressive treatment of CRS/ICANS, especially cilta-cel - Avoid cilta-cel in pre-existing neurologic disorder (severe neuropathy, baseline Parkinson's symptoms, etc)
MAS/HLH (IEC-HS)	- High tumor burden - Severe CRS - Baseline inflammation - Poorly understood	- Early Recognition & timely intervention [38] - Anakinra if HLH suspected, rapidly rising ferritin, or if severe CRS not responding rapidly to steroids/IL-6 therapy [111] - Ruxolitinib if refractory to anakinra/steroids [112] - Etoposide or Cytosan if refractory to above
Severe, refractory, or prolonged	- Pre-existing cytopenias - High tumor burden	- Growth factor and transfusion support [27] - filgrastim (long acting if persistent or refractory)

Toxicity	Risk Factors	Mitigation/Treatment Strategies
cytopenias (ICAHT)	High grade CRS/ ICANS	– thrombopoietin receptor agonists • Antibimicrobial prophylaxis • Marrow biopsy to rule out relapse or MDS • Stem cell boost if persistent (if frozen PBSC available) [32, 33]

MAS, macrophage activation syndrome; HLH, hemophagocytic lymphohistiocytosis; IEC-HS, immune effector cell associated HLH-like syndrome; ICAHT, immune effector cell associated hematotoxicity; IL-6, interleukin-6; PBSC, peripheral blood stem cells; MDS, myelodysplastic syndrome

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TABLE 3:

Results of Randomized KarMMA-3 and CARTITUDE-4 trials of Early Line CAR T

	KarMMA-3 [7]		CARTITUDE-4 [6, 83]	
	Ide-Cel	SOC	Cilta-Cel	SOC
Study Design				
Inclusion Criteria	2-4 prior lines including PI + IMiD + Dara		1-3 prior lines, Len refractory	
Lymphodepleting Chemo	Flu 30 mg/m ² + Cy 300 mg/m ² x3d		Flu 30 mg/m ² + Cy 300 mg/m ² x3d	
Therapy given	CAR T	Choice: DPd, DVd, IRd, Kd, or EPd	CAR T	Choice: DPd or PVd
CAR T-Cell Dose, median (range)	445x10 ⁶ (175-529x10 ⁶)	N/A	0.71x10 ⁶ /kg	N/A
Baseline Characteristics				
No of pts Randomized	254	132	208	211
Completed Apheresis (%)	249 (98)	N/A	208	N/A
Manufacturing Failure (%)	3 (1)	N/A	0 (0)	N/A
No Infused/Treated (%)	225 (89)	126 (95)	176 (85)	208 (99)
Median time from apheresis to infusion, days (range)	49 (34-117)	N/A	44 (25-127)	N/A
Median Age (range) years	63 (30-81)	63 (42-83)	61.5 (27-78)	61 (35-80)
Age ≥ 65 (%)	104 (41)	54 (41)	NR	NR
Age ≥ 75 (%)	12 (5)	9 (7)	NR	NR
Male sex (%)	156 (61)	79 (60)	116 (56)	124 (59)
White race (%)	172 (68)	78 (59)	157 (76)	157 (75)
Black race (%)	18 (7)	18 (14)	6 (3)	7 (3)
R-ISS II (%)	150 (59)	82 (62)	60 (29)	65 (31)
R-ISS III (%)	31 (12)	14 (11)	12 (6)	14 (7)
ECOG 0-1 (%)	153 (99)	128 (97)	207 (99.5)	210 (99.5)
High risk FISH (non-1q) (%)	107 (42)	61 (46)	73/207 (35)	69/210 (33)
Add 1q (gain or amp) (%)	125 (49)	51 (39)	89/207 (43)	107/210 (63)
Extramedullary Disease (%)	61 (24)	32 (24)	44 (21)	35 (17)
High Tumor Burden (%)	71 (28)	34 (26)	42/206 (20)	43/208 (21)
Median Prior Lines (range)	3 (2-4)	3 (2-4)	2 (1-3)	2 (1-3)
Refractory to anti-CD38 Ab	242 (95)	123 (93)	50 (24)	46 (22)
Triple Class Refractory (%)	164 (65)	89 (67)	30 (14)	33 (16)
Penta-Refractory (%)	15 (6)	5 (4)	2 (1)	1 (0.5)
Efficacy (intent-to-treat)				
ORR (%)	181 (71)	55 (42)	176 (85)	142 (67)
≥ CR (%)	98 (39)	7 (5)	152 (73)	46 (22)
≥ VGPR (%)	153 (60)	20 (16)	169 (81)	96 (46)
MRD Negative 10 ⁻⁵ (%)	51/254 (20)	1 (1)	126/144 (88)	33/101 (33)
ORR for infused pts (%)	NR	NR	175/176 (99.4)	N/A

	KarMMa-3 [7]		CARITUDE-4 [6, 83]	
Progressive Disease as best response (%)	24 (9)	10 (8)	17 (8)	6 (3)
Median DOR, months	14.8	9.7	Not Reached; 85% at 12 mo	Not Reached; 63% at 12 mo
Median PFS, months	13.3	4.4	Not Reached; 76% at 12 mo	11.8 49% at 12 mo
Median OS, months	Not reached	Not reached	Not Reached, 84% at 12 mo	Not Reached, 84% at 12 mo
Safety (for treated pts only)	N=225	N=126	N=176	N=176
Infections Any Grade	146 (58)	68 (54)	129/208 (62)	148/208 (71)
Infections Grade 3-5	72 (28)	26 (20)	56/208 (27)	51/208 (25)
CRS any grade (%)	197 (88)	N/A	134/176 (76)	N/A
CRS grade ≥ 3 (%)	11 (5)	N/A	2 (1)	N/A
Median days to CRS (range)	1 (1-14)	N/A	8 (1-23)	N/A
Neurotoxicity any grade (%)	34 (15)	N/A	(4.5)	N/A
ICANS grade ≥ 3 (%)	7 (3)	N/A	0 (0)	N/A
Non-ICANS Neurotoxicity (%)	0 (0)	N/A	30 (17%) 1 Parkinsons, 18 CN Palsy, 5 PN	N/A

Abbreviations: N/A indicates not applicable; NR, not reported; Flu, fludarabine; Cy, cyclophosphamide; DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab + bortezomib + dexamethasone; IRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; EPd, elotuzumab + pomalidomide + dexamethasone; PVd, pomalidomide + bortezomib + dexamethasone; CN, cranial nerve; PN, peripheral neuropathy