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From Trials to Practice: A 2025 Review of Idecabtagene Vicleucel and Ciltacabtagene Autoleucel Efficacy Across Clinical Studies and Real-World Evidence

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ABSTRACT

B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapies have revolutionized the approach and management of relapsed/refractory multiple myeloma (RRMM), and as of 2025, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) are the only BCMA-targeted CAR T-cell therapies approved by the FDA. Exceptional responses were demonstrated for heavily pretreated patients in the KarMMa-1 trial, reporting a 73% overall response rate (ORR) and 98% in the CARTITUDE-1 trial. Furthermore, both therapies show a significant improvement in progression-free survival (PFS) compared to standard regimens when administered in earlier lines. Current real-world evidence confirms their effectiveness and manageable safety in a more diverse patient population, including those who would have been ineligible for clinical trials. Key toxicities include cytokine release syndrome (CRS) and neurotoxicity, with emerging concerns regarding delayed neurotoxicities, second primary malignancies, and IEC-enterocolitis. This review provides a detailed analysis of recent clinical trial data, the reported outcomes of real-world published evidence, and the changing role of these therapies within the myeloma treatment paradigm, including challenges, gaps in knowledge, potential barriers to accessibility, and future directions aimed at optimizing the efficacy and safety of CAR T-cell therapy for MM patients.

1 | Introduction

1.1 | Multiple Myeloma Overview

Multiple myeloma (MM) is a hematologic malignancy of plasma cells characterized by malignant clonal expansion in the bone marrow. However, clonal plasma cells can also be found in other extramedullary sites and peripheral blood [1]. This malignant proliferation leads to the production of monoclonal immunoglobulins, also known as monoclonal protein or M-protein, with IgG as the most frequent isoform [2, 3]. In 2022, MM represented 1.8% of all cancers in the USA and was responsible for 10% to 15% of the hematologic malignancies [4].

The MM diagnosis criteria have been established by the International Myeloma Working Group (IMWG) [5]. It is crucial to stratify the risk based on cytogenetic and tumor burden to determine prognosis and guide treatment strategies. The Revised International Staging System (R-ISS) incorporates cytogenetic abnormalities to enhance prognostic accuracy and

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facilitate therapeutic decision-making [6]. The Mayo Clinic M-Smart MM risk stratification defines high-risk multiple myeloma as having at least one of the following cytogenetic characteristics: t(4;14), t(14;16), t(14;20), del(17p), p53 mutation, gain(1q), and del(1p) [7, 8]. Furthermore, it introduces the concepts of "double-hit" and "triple-hit" multiple myeloma, where their presence is associated with significantly poorer prognosis [9, 10].

Significant advances in MM treatment have been achieved in the last 10 years, including proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), monoclonal antibodies (mAbs), and the discovery of new MM targets such as B-cell maturation antigen (BCMA). However, the disease remains incurable, and relapse of the disease is expected with subsequent decreased duration of response after each line of therapy [11, 12]. The discovery and recent approval of novel therapies, including Bispecific T-cell engagers (BiTEs or TCEs) and BCMA-targeted chimeric antigen receptor (CAR) T-cells, have opened new opportunities in MM treatment [7, 11].

1.2 | Mechanism of Action of BCMA CAR T Therapy in Multiple Myeloma

BCMA, a transmembrane protein, is a tumor necrosis factor superfamily member 17 receptor (TNFRSF 17) or CD256. This protein was discovered to be present in B-cells, especially in late B-cell stages, plasmablasts, and plasma cells [13, 14]. BCMA expression is increased significantly in malignant plasma cells compared to normal and is a key component for the survival of plasma cells in MM. BCMA activation by the proliferation-inducing ligand (APRIL) and B cell–activating factor (BAFF), which are two natural ligands for BCMA, promotes plasma cell growth and survival via NFκB and MAPK8/JNK, among others, which upregulates the production of antiapoptotic proteins such as BCL-XL and BCL-2 [13, 15]. It is well known that MM cells overexpress BCMA, which plays a key role in MM pathogenesis. As a result, BCMA has become a major therapeutic anti-tumor target of CAR T-cell therapy in MM [16, 17].

Ide-cel and Cilta-cel are part of the second generation of BCMA CAR T for MM and were approved by the U.S. Food and Drug Administration (FDA) to start their clinical trial phase on December 18, 2017 and June 29, 2018, respectively [18–20]. Ide-cel utilizes a murine anti-BCMA single-chain variable fragment (scFv), a CD8a-derived hinge, and a transmembrane region. The CAR construct also includes a CD3-zeta signaling domain and a 4-1BB costimulatory domain, which enhance T-cell activation and cytotoxicity [21–23]. Conversely, cilta-cel features two different camelid variable heavy-chain-only domains that confer high avidity and specificity for BCMA. This dual-targeting approach is designed to improve binding affinity and reduce the likelihood of antigen escape [21–25].

Multiple mechanisms of resistance to CAR T-cells in MM have been identified, comprising three main mechanisms: (1) Antigen Escape through genomic instability [26–29], (2) Immunosuppressive tumor environments, and (3) T-cell exhaustion [26, 30–34].

1.3 | Introduction to CAR T-Cell Therapy in Multiple Myeloma

Currently, there are two FDA-approved CAR T-cell therapies: idecabtagene vicleucel (also known as ide-cel; Abecma; or bb2121), approved on March 26, 2021, under the pivotal KarMMa-1 trial (ClinicalTrials.gov identifier NCT03361748), and ciltacabtagene autoleucel (cilta-cel; Carvykti; JNJ-68284528), approved on February 28, 2022, under the CARTITUDE-1 trial (NCT03548207) [35–37].

Upon FDA approval of idecabtagene vicleucel in March 2021 and ciltacabtagene autoleucel in February 2022, patients had to receive at least four or more prior lines of therapy (LOT) before they were eligible for CAR T-cell therapy. However, on April 4, 2024, the FDA approved ide-cel for the treatment of RRMM after two or more prior LOT, becoming a new option for triple-class exposed patients based on results from the KarMMa-3 trial (NCT03651128), and on April 5, 2024, based on the CARTITUDE-4 trial (NCT04181827), Cilta-cel received FDA approval for patients who have received at least one prior LOT, becoming the first BCMA CAR-T approved as a second line of therapy in RRMM [38–41].

The production process of ide-cel and cilta-cel begins with collecting the patient's peripheral T-cells via leukapheresis. After collection, unwanted cells are removed, and T-cells are enriched. Next, a viral vector is used to transduce the specific gene into the T-cells to express BCMA-specific CAR on the T-cells' surface. The T-cells then move on to the Expansion phase, where they are stimulated with growth factors to produce multiple copies of these new genetically modified T-cells. Once the CAR T-cell dose is achieved, the patient undergoes lymphodepletion (LD), typically with cyclophosphamide and fludarabine, followed by the CAR T-cell product administration as a one-time infusion [13, 24, 42].

The infusion process of the product is currently performed at an authorized CAR T Center in the USA due to the potential adverse effects, such as cytokine release syndrome (CRS), immune effector cell-associated neurologic syndrome (ICANS), immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), late neurologic symptoms, among others [43]. Clinical data have demonstrated that cilta-cel administration in an outpatient setting yields comparable outcomes to inpatient administration, representing a viable strategy for appropriately selected patients in centers with a dedicated institutional structure for close monitoring of potential adverse effects [44–46].

2 | Patient Selection and Pre-Treatment Considerations

2.1 | Eligibility and Recommendations Prior to CAR T Therapy

Patients with RRMM are treated as soon as possible after progressive disease (PD) is confirmed, mainly in the setting of rapid progression that can lead to clinical deterioration. For this reason, patients should be referred promptly for CAR

T-cell therapy evaluation since access to manufacturing slots is limited and manufacturing time can vary between 3 and 6 weeks. A prompt referral can also help the discussion of salvage therapy considerations to optimize the leukapheresis phase [43, 47, 48].

Current recommendations for patient selection by the International Myeloma Working Group Immunotherapy Committee indicate that there is no absolute contraindication due to age, high-risk cytogenetic features, extramedullary disease (EMD), and advanced-stage disease for CAR T therapy, and patients with these characteristics may still benefit from evaluation and treatment and should not be excluded. However, frailty and other physiologic characteristics should be considered on a case-by-case [43, 49, 50].

Before undergoing leukapheresis, some of the considerations are the drug's half-life and its effect on the number and quality of T cells, and, when clinically possible, a 14-day washout period should be considered to optimize the T cell collection [43, 49–51]. Additionally, lymphotoxic agents such as fludarabine, melphalan, bendamustine, and high-dose cyclophosphamide should be avoided whenever possible [51–53].

Patients move to bridging therapy after the leukapheresis phase is completed, and generally, MM treatment is resumed during the CAR T manufacturing process. Patients with high-burden disease or those who show rapidly progressing disease are at increased risk of more severe CRS, ICANS, IEC-HS, and late neurological symptoms, and should be placed on a regimen to which they are not refractory [43].

If the patient has no rapidly progressing disease and a low disease burden, minimum therapy to limit disease progression needs to be considered. However, it is always important to avoid lymphotoxic drugs whenever possible in case T cells recollection is required since the risk for manufacturing failure in clinical practice is still unknown [43, 54].

3 | Efficacy of CAR-T in Clinical Trials

3.1 | IDE-CEL

The phase 2 trial KarMMa-1 (NCT03361748) (Table 1) (Figure 1) enrolled 140 patients with RRMM who had at least 3 prior lines of therapy (LOT) that included a PI, an IMiD, and an anti-CD38 mAb, from which 128 received treatment with ide-cel at 3 different target doses: 150×10^6, 300×10^6, and 450×10^6 CAR T-cells [35]. The median age for patients was 61 years. Thirty-five percent had high-risk cytogenetic abnormalities; 51% had high-burden disease, 39% had EMD, and 26% were penta-refractory (refractory to two IMiD drugs, two PI, and one anti-CD38 mAb) [35].

The ORR was 73% (95% CI: 66 to 81, $p<0.001$) for patients who achieved a partial response (PR) or higher. Among this group, 33% of the patients showed a stringent complete response (sCR) or complete response (CR). The median time to best response was 2.8 months (range 1.0 to 11.8) [35]. The median PFS (mPFS) was 8.8 months (95% CI: 5.6 to 11.6); however, patients treated with 450×10^6 CAR T-cells had a PFS of 12.2 months. The median overall survival (mOS) was 19.4 months (95% CI: 18.2 to Not estimated [NE]) [35].

In the sub-analysis of the KarMMa-1 trial of Japanese patients, the ide-cel target dose used was 450×10^6 CAR T-cells. Results demonstrated an ORR of 89%, 56% achieved sCR, and 33% achieved a VGPR. All patients who were evaluated for Minimal residual disease (MRD) were MRD-negative, and 4 out of 5 patients who achieved sCR or CR had EMD that resolved [35, 55]. The PFS at 12 months was higher in the Japanese population than in the non-Japanese population (75% and 52%, respectively). This is likely due to baseline characteristics of the Japanese population that included a lower tumor burden, lower ECOG, fewer prior LOT, and higher median lymphocyte count, among others, compared with the non-Japanese population [35, 55].

The phase 3 KarMMa-3 trial (Table 1) (NCT03651128) enrolled 386 patients with RRMM who had received between two and four prior LOT. Patients were randomized to receive ide-cel or one of the five standard regimens within the trial, in a 2:1 ratio. The dose range for ide-cel was 150×10^6 to 450×10^6 CAR-positive T cells. The primary endpoint was to evaluate PFS [40].

The median age was 63 years, 24% had EMD, and 28% had a high tumor burden. Forty-two percent had high-risk cytogenetic abnormalities in the ide-cel group and 46% in the standard regimen arm [40].

The mPFS in the ide-cel group was 13.3 months (95% CI: 11.8 to 16.1) and 4.4 months (95% CI: 3.4 to 5.9) in the standard-regimen group, representing a 51% risk reduction in disease progression or death with ide-cel (hazard ratio [HR] 0.49, 95% CI: 0.38–0.64, $p<0.0001$). The PFS among ide-cel and standard-regimen groups at 6 and 12 months was notoriously higher in the ide-cel group (73% and 55% vs. 40% and 30%, respectively) [40].

The PFS subgroup analysis of Ide-cel versus standard regimens showed a mPFS of 11.9 months (95% CI: 8.0 to 14.5) and 4.2 months (95% CI: 2.4 to 5.7) in high-risk cytogenetic patients [40]. Furthermore, in the ide-cel group, patients with R-ISS I or II had better mPFS than those with R-ISS III (14.7 months; 95% CI: 12.7 to 17.3, and 5.2 months; CI 1.8 to 7.2, respectively). This mPFS was also superior to R-ISS I or II versus R-ISS III in the standard regimens group (4.4 months; 95% CI: 3.2 to 5.9, and 3.0 months; 95% CI: 0.8 to 6.1, respectively) [40].

An even higher mPFS was noted in the non-white population of 20.3 months (95% CI: 11.1 to 24) with ide-cel versus 6.9 months (95% CI: 3.4 to 20.7) in the standard-regimen group, being Hispanic or Latino, the group with the higher mPFS (22.6 months; 95% CI: 1.3 to NE for ide-cel, and 6.0; 95% CI: 1.0 to NE, respectively) [40]. However, it is important to consider that the sample size was significantly lower in this group.

For secondary endpoints, the ORR in the ide-cel group was 71% (95% CI: 66 to 77). Among this group, 36% achieved sCR and 3% CR. In the standard-regimen group, the ORR was 42% (95% CI: 33 to 50), with only 5% of the patients achieving a CR or better, with a difference in the ORR of 30% ($p<0.0001$) among groups [40]. The median duration of response (mDOR) for ide-cel and

TABLE 1 | Summary data for key clinical trials of FDA-approved CAR-T therapies for RRMM.

Trial	KarMMa-1	CARTITUDE-1	CARTIFAN-1	KarMMa-3 (Ide-cel cohort/SOC cohort)	CARTITUDE-4 (cilta-cel cohort/SOC cohort)
Prior LOT criteria	> 3	> 3	> 3	2–4	1–3
Number of patients treated	128	97	48	225/126	176/208
Baseline Characteristics					
Median age (range)	61 (33–78)	61.0 (56–68)[f]	61.0 (30–72)	63 (30–81)/63 (43–83)	61.5 (27–78)/61.0 (35–80)
Median prior lines (range)	6 (3–16)	6.0 (4–8)[f]	4 (3–9)	3 (2–4)/3 (2–4)	2 (1–3)/2 (1–3)
Extramedullary diseased	39%	13%	10.4%	24%/24%	21.2%/16.6%
R-ISS stage II/III (%)	86%	37%[a]	56.3%[a]	71%/73%	34.6%[a]/37.4%[a]
High-risk cytogenetics	35%	24%	43.8%	42%/46%	59.4%/62.9%
Triple-refractory disease[b]	84%	88%	18.8%	65%/67%	14.4%/15.6%
Penta-refractory disease[c]	26%	42%	Not Reported	6%/4%	1.0%/0.5%
Efficacy					
ORR	73%	97%	89%	71%/42%	84%/67%
CR or better	33%	67%	77%	39%/6%	73.1%/21.8%
VGPR	20%	26%	12.5%	22%/10%	8.2%/23.7%
PR	21%	4%	0%	11%/27%	3.4%/21.8%
MRD Negative (10–5)[d]	26%	93%[e]	97.5%	20%/1%	60.6%/15.6%
Median Time to First Response (range-months)	1.0 (0.5–8.8)	1.0 (0.9–1.0)[f]	1.0 (0.9–5.2)	2.9 (0.5–13.0)/2.1 (0.9–9.4)	2.1 (0.9–11.1)/1.2 (0.6–10.7)
Median Time to Best Response (months)	2.8 (1.0 to 11.8)	2.6 (1.0–6.1)	3.3 (0.9–15.1)	Not reported	6.4 (1.1–18.6)/3.1 (0.8–20.6)
mDOR (months)	10.7 (overall)	NE (15.9–NE)	NE (17.2–NE)	14.8/9.7 (5.4–16.3)	Not reported
Median PFS (months)	8.8 (overall)	NR (16.8–NE)	NR	13.3/4.4 (3.4–5.9)	NR (22.83–NE)/11.8 (9.7–13.8)
Median OS (months)	19.4	NR	NR	Immature Data	Immature Data

Abbreviations: CR, Complete Response; IQR, Interquartile Range; mDOR, median Duration of Response; MRD, Minimal Residual Disease; NE, Not estimable; NR, not reached; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; PR, Partial Response; SOC, standard of care; VGPR, Very Good Partial Response.

[a]Data is for the International Staging System (ISS) stage.

[b]Triple-class refractory was defined as MM refractory to an immunomodulatory (IMiD) drug, a proteasome inhibitor (PI), and an anti-CD38 antibody.

[c]Penta-class refractory was defined as MM refractory to 2 IMiDs, 2 PIs, and an anti-CD38 antibody.

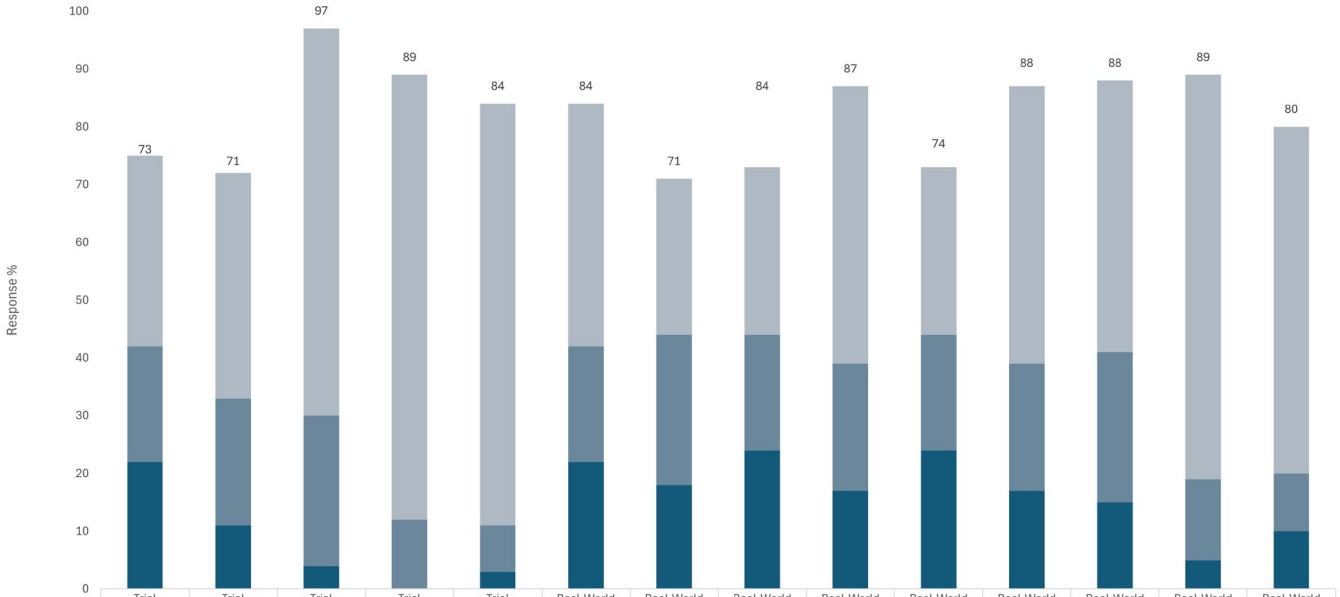
[d]The percentage reported corresponds to the number of patients who were tested for MDR. Not all the patients were tested, and the results need to be interpreted accordingly.

[e]Only 57 patients were evaluable for MRD rate at 10^{-5}, from which 53/57 resulted negative.

[f]Data reported as median (IQR).

standard regimen was 14.8 months (95% CI: 12.0 to 18.6) and 9.7 months (95% CI: 5.4 to 16.3), respectively, and 20 months (95% CI: 15.8 to 24.3) for patients who achieved CR or sCR [40].

A sub-analysis of the KarMMa trials (KarMMa-1, KarMMa-2 cohort-1, and KarMMa-3) assessed the impact of specific genomic features on the PFS. Deletion of 14q was associated with a shorter



	Trial KarMMa-1	Trial KarMMa-3	Trial CARTITUDE-1	Trial CARTIFAN-1	Trial CARTITUDE-4	Real-World Hansen et al.	Real-World Sidana et al. (CIBMTR)	Real-World Kalariya et al. <65y vs >65y	Real-World	Real-World Ferreri et al. Prior BCMA-TT vs No prior BCMA-TT	Real-World	Real-World Ferment et al.	Real-World Sidana et al. (Cilta-cel)	Real-World Gaballa et al.
sCR or CR (%)	33	39	67	77	73	42	27	29	48	29	48	47	70	60
VGPR (%)	20	22	26	12	8	20	26	20	22	20	22	26	14	10
PR (%)	22	11	4	0	3	22	18	24	17	24	17	15	5	10
ORR (%)	73	71	97	89	84	84	71	84	87	74	88	88	89	80

FIGURE 1 | Comparative efficacy among trials and real-world outcomes.

mPFS of 4.0 months, and deletion of 1p31.2 was associated with an even shorter mPFS of 2.3 months [35, 56]. Nonetheless, no patient with 1p loss achieved an overall response better than a partial response (PR). Furthermore, biallelic p53 inactivation showed a stronger association with shorter PFS in the aggregate dataset compared to the KarMMa cohort alone [56].

3.2 | CILTA-CEL

The CARTITUDE-1 trial (NCT03548207) (Table 1) was a phase 1b/2 multicenter study conducted primarily in the USA that enrolled 113 patients with RRMM who had received three or more prior LOT or were double-refractory to a PI and an IMiD drug and had received a PI, IMiD, and an anti-CD38 mAb. Phase 1b's aim was to confirm the recommended dose for Phase 2, and Phase 2 aimed to evaluate the clinical activity. Of the 113 enrolled patients, 97 received treatment as a one-time cilta-cel infusion at a target dose of 0.75×10^6 CAR-positive viable T cells/Kg [36]. The median age for patients was 61 years old, with a median prior LOT of 6.0 (4.0 to 8.0). Twenty-four percent had a high-risk cytogenetic profile; 88% were triple refractory, and 42% were penta-refractory [36].

The ORR was 97% (95% CI: 91.2 to 99.4), among which 67% of the patients achieved sCR. From the sCR group, 94% ($n = 33/35$) of the patients evaluated for MRD status were MRD-negative. The median time to achieve best response was 2.6 months (1.0 to 6.1) [36]. In October 2024, the final results of CARTITUDE-1 showed a median follow-up (MFU) of 33.4 months (1.5 to 45.2), demonstrating an ORR of 98%, mDOR of 33.9 months (95% CI: 25.5 to NE), mPFS of 34.9 months (25.2 to NE), and an estimated PFS of 47.5% at 36 months, being higher in the group who achieved CR or better with 66.8% and 59.8% at 30 and 36 months, respectively. The mPFS was not reached in the MRD subgroups [57]. The Japanese cohort of the CARTITUDE-1 also reported equitable results [58].

The CARTIFAN-1, a phase II trial (NCT03758417) (Table 1), evaluated cilta-cel in the Chinese population that enrolled 64 patients with RRMM, from which 48 received treatment as a one-time cilta-cel infusion. Patients who had received at least three prior LOT were eligible. However, a prior anti-CD38 mAb was not required compared with the pivotal CARTITUDE-1 [36, 59]. The median age was 61 years, number of prior LOT 4 (3 to 9), and 10.4% had EMD. Forty-three percent of the patients had high-risk cytogenetic disease. The ORR was 89.6% (95% CI: 77.3 to 96.5); among this, 77.1% achieved CR or better. The PFS at 12 and 18 months were 77.0% (95% CI: 62.3 to 86.5) and 66.8% (95% CI: 49.4 to 79.4), respectively. The OS at 18 months was 78.7%. The mDOR, mPFS, and the mOS were not reached [59].

CARTITUDE-4, an open-label phase 3 trial (NCT04181827) (Table 1), enrolled 419 patients with RRMM who had 1 to 3 prior LOTs and were lenalidomide-refractory. Patients were assigned to receive a single cilta-cel infusion administered after the physician's standard of care (SOC) chemotherapy choice [41]. Of the enrolled patients, 176 received cilta-cel infusion, and 208 received SOC therapy. The primary endpoint was to evaluate PFS [41].

The mPFS was not reached in the cilta-cel group at the MFU of 15.9 months (range 0.1 to 27.3). The mPFS was 11.8 months (95% CI: 9.7 to 13.8) in the SOC group, indicating a 74% lower risk of disease progression or death in the cilta-cel group compared to those receiving SOC therapy (HR, 0.26; 95% CI: 0.18

TABLE 2 | Summary of adverse events reported in FDA-approved CAR-T therapies for RRMM.

Adverse event (AE)	Grade	KarMMa-1	CARTITUDE-1	CARTIFAN-1	KarMMa-3 (Ide-cel cohort/SOC cohort)	CARTITUDE-4 (Cilta-cel cohort/SOC cohort)
CRS	Any	84%	95%	97.9%	88%/N/A	76.1%/N/A
	Grade ≥ 3	5%	4%	35.4%	5%/N/A	1.1%/N/A
ICANS	Any	18%	21%	4.2%	15%/N/A	20.5%/N/A
	Grade ≥ 3	3%	9%	0%	3%/N/A	2.8%/N/A
Neutropenia	Any	91%	96%	97.9%	78%/44%	89.9%/85.1
	Grade ≥ 3	89%	95%	97.9%	76%/40%	89.9%/82.2%
Anemia	Any	70%	81%	100%	66%/36%	54.3%/26.0%
	Grade ≥ 3	60%	68%	52.1%	51%/18%	35.6%/14.4%
Lymphopenia	Any	27%	53%	95.8%	29%/20%	22.1%/13.9%
	Grade ≥ 3	27%	50%	91.7%	28%/18%	20.7%/12.0%
Thrombocytopenia	Any	63%	79%	87.5%	54%/29%	54.3%/31.2%
	Grade ≥ 3	52%	60%	54.2%	42%/17%	41.3%/18.8%
Infections	Any	69%	58%	85.4%	58%/54%	62.0%/71.2%
	Grade ≥ 3	22%	20%	37.5%	24%/18%	26.9%/24.5%
SPM		Not Reported[a]	22%	Not Reported	6%/4%	4.3%/6.7%

Abbreviations: CRS, Cytokine Release Syndrome; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome; N/A, Not Applicable; SPM, Second Primary Malignancies.
[a]SPM was reported as 12.5% in the 18-month post hoc analysis.

to 0.38; $p < 0.001$). In the intention-to-treat (ITT) analysis, the 12-month PFS was 75.9% (69.4 to 81.1) and 48.6% (41.5 to 55.3), respectively (HR, 0.26; 95% CI: 0.18 to 0.38; $p < 0.001$) [41]. In the subgroup analysis, cilta-cel showed similar results for all groups compared to SOC therapy, including ISS stage III and high-risk cytogenetic patients.

For secondary endpoints, cilta-cel showed an ORR of 85.6%, from which 73.1% of the patients achieved CR or better compared with 67.3% ORR in the SOC group, with only 21.8% achieving CR or better (OR, 10.3; 95% CI: 6.5 to 16.4; $p < 0.0001$). The estimated OS at 12 months was 84.1% in the cilta-cel group and 83.6% in the SOC group [41]. In addition, the MRD analysis showed that cilta-cel significantly increased MRD negativity rates more than threefold compared to SOC therapy in the ITT population [60]. Patients who achieved a CR with MRD-negative status at 12 months had a mPFS exceeding 3 years, irrespective of the treatment received [60].

4 | Safety of CAR-T in Clinical Trials

4.1 | IDE-CEL

Table 2 summarizes relevant adverse effects (AE) reported by pivotal clinical trials. Adverse effects were graded using the Common Terminology Criteria for Adverse Events (CTCAE), and CRS according to published criteria by Lee et al. [61, 62]. In the KarMMa-1, 84% of patients experienced any grade of CRS, most commonly Grade 1 (48%) and Grade 2 (30%) [35]. The median time to onset was 1 day (range 1 to 12) with a median duration of 5 days (1 to 63) [35]. Neurotoxic effects were observed in 18% of the patients, with no grade 4 or 5 neurotoxicities observed. The median time to any neurotoxic effect was 2 days (1 to 10), and the median duration was 3 days (1 to 26). The most commonly reported hematological toxicities were neutropenia, anemia, and thrombocytopenia [35]. The time to recovery for neutropenia and thrombocytopenia grade 3/4 was 1.9 months (1.2 to 5.6) and 2.1 months (1.2 to 13.8), respectively. Most adverse events occurred within the first 8 weeks after infusion, except hypogammaglobulinemia and infections that were reported beyond this period [35]. Forty-four patients (34%) died during the study, with 27 deaths attributed to disease progression. Four patients died from ide-cel-related adverse events (CRS, gastrointestinal bleeding, bronchopulmonary Aspergillosis, and cytomegalovirus pneumonia) [35]. In the 18-month post hoc analysis, eight patients (12.9%) developed second primary malignancies (SPM) after ide-cel infusion. The reported malignancies were myelodysplastic syndrome (MDS), Bowen disease, breast cancer, malignant melanoma, adenocarcinoma of the colon, basal cell carcinoma, and bladder cancer [63].

For the KarMMa-3 trial, in the ide-cel group, 88% of patients experienced any grade of CRS, and neurotoxic events were observed in 15% of the patients [40]. Hematologic toxicities were reported in 90% of the patients in the ide-cel group and 71% in the standard-regimen group. The most common of these were neutropenia, anemia, and thrombocytopenia, with a median

time to recovery of 1.7 months (95% CI: 1.5 to 1.9) for neutropenia and 1.9 months (95% CI: 1.5 to 2.1) for thrombocytopenia. Other frequent adverse events reported for the ide-cel and standard-regimen groups were gastrointestinal (73% vs. 52%, respectively) and infections of any grade (58% vs. 54%, respectively) [40]. The most frequently observed infections were upper respiratory tract infections (12% vs. 7%) and pneumonia (10% vs. 7%, respectively) [40]. A total of 109 patients (28%) died; among this, 30% were in the ide-cel group and 26% in the standard regimen group. The incidence of any SPM was 6% and 4%, respectively, with two deaths in total (leukemia and pancreatic adenocarcinoma) in the ide-cel group; additionally, solid tumors were the most common type of SPM [40]. The most common cause of death was attributed to disease progression in both groups (17% vs. 17%, respectively), and 6% due to treatment-related AEs for both groups. Other causes of death for the ide-cel group included hemothorax ($n=1$), respiratory failure ($n=1$), cardiac failure ($n=1$), sepsis ($n=1$), and cerebral hemorrhage ($n=1$). For the standard regimens group, these included death ($n=2$) and euthanasia ($n=1$) [40].

4.2 | CILTA-CEL

In CARTITUDE-1, 95% of the patients developed any grade of CRS, from which 90% of the reported cases were grade 1 and 2 (Table 2). The median time to onset was 7 days (range 5 to 8), and the median duration was 4 days (3 to 6) [36]. Neurotoxicity occurred in 21% of the patients, with ICANS representing 17% [36]. The median time to onset was 8 days (6 to 8) with a median duration of 4 days. Hematologic adverse events were the most frequent grade 3–4 events [36]. Infections were observed in 58%, of which 20% were grade 3–4 [36]. The most common observed infections were upper respiratory infections, with pneumonia being the most common within the grade 3–4 infection group [36]. In the 2-year follow-up, a total of 20 SPM were observed in 16 patients, with MDS, acute myeloid leukemia (AML), melanoma, and squamous cell carcinoma among the reported [37]. None of the cases were determined to be related to cilta-cel use [37]. Additionally, 30 deaths were reported; 14 patients died due to progressive disease and six due to AEs related to treatment (Sepsis, CRS/HLH, Neurotoxicity, among others) [37]. CARTIFAN-1 showed similar results compared with CARTITUDE-1 except for neurotoxicities that were observed to be lower (4.2% vs. 21%, respectively) [59].

In the CARTITUDE-4 trial (Table 2), within the cilta-cel arm, any grade of CRS was reported in 76.1% of the patients; among these, only two patients (1.1%) developed CRS grade 3 or 4 [41]. Neurotoxicity occurred in 20.5% of the patients, with ICANS representing 4.5% of the cases [41]. When comparing adverse effects between cilta-cel and standard regimen group, hematologic adverse events were the most frequent grade 3–4 events, including neutropenia (89.9% vs. 82.2%), anemia (35.6% vs. 14.4%), and lymphopenia (35.6% vs. 14.4%) [41]. Serious adverse effects (SAEs) were observed in 44.2% vs. 38.9%, respectively [41]. Among the SAEs, infections were the most frequently reported (24% vs. 24.1%), with respiratory infections being the most common [41]. Furthermore, SPM, including cutaneous noninvasive malignancies, hematologic malignancies (AML, MDS, and one case of peripheral T-cell lymphoma), and noncutaneous invasive malignancies, were observed in both groups (4.3% vs. 6.7%, respectively) [41]. During the study, death was observed in 39 (18.8%) patients in the cilta-cel arm, from which only 4.8% of the deaths were attributed to be treatment-emergent [41]. In the standard regimen group, 46 (22.1%) deaths were reported, with only 2.4% attributed to treatment-emergent adverse events [41].

5 | Real-World Data Insights and Special Populations

Real-world outcomes (RWOs) are crucial for understanding the possible generalizability of CAR T-cell therapies due to the higher volume of patients and a more diverse population, many of whom are ineligible for pivotal trials, helping to bridge the gap between clinical trials and practical application.

In the pivotal trials, patients with creatinine clearance <30 mL/min for ide-cel and <40 mL/min for cilta-cel, secondary amyloidosis, active plasma cell leukemia, and secondary central nervous system (CNS) involvement were excluded, among others [35, 36].

Table 3 shows summarized baseline characteristics and efficacy data from multiple real-world studies. Table 4 summarizes relevant adverse events from real-world studies.

5.1 | Ide-Cel Real-World Reported Outcomes

A multicenter retrospective study from the Myeloma CAR T consortium (Table 3) included 159 patients with RRMM who received ide-cel as SOC, from which 75% of the patients would not have been eligible for participation in the KarMMa trial [64]. No significant differences in the safety profile of SOC ide-cel were observed compared to the phase 2 KarMMa trial [35, 64]. The observed best ORR was 84%, from which CR or better was achieved in 42% of the patients with a mDOR of 8.6 months [64]. The mPFS was 8.5 months (95% CI: 6.5 to not reached [NR]), and the mOS was 12.5 months (95% CI: 11.3 to NR), demonstrating comparable safety and efficacy of SOC ide-cel despite most patients not meeting trial eligibility criteria [35, 64]. Of note, inferior PFS was observed in patients with prior exposure to BCMA-targeted therapy (HR, 2.81; 95% CI: 1.44 to 5.51; $p=0.003$), high-risk cytogenetics (HR, 2.31; 95% CI: 1.34 to 3.97; $p=0.003$), ECOG PS 2 to 4 at LD (HR, 2.19; 95% CI: 1.16 to 4.14; $p=0.016$), and younger age (HR, 0.97; 95% CI: 0.95 to 1.00; $p=0.043$) [64].

Another large retrospective study using data from The Center for International Blood and Marrow Transplant Research (CIBMTR) (Table 3) included 603 patients, among which 26% were 70 years or older, had plasma cell leukemia, or had a prior BCMA therapy exposure who received SOC ide-cel treatment for RRMM. The results were comparable to those in the KarMMa-1 trial, with an ORR of 71% vs. 73%; CR rate of 27% vs. 27%; and VGPR rate of 53% vs. 52%, respectively [35, 65]. Any grade of CRS and neurotoxicities were observed in 81% and 27% of the patients, respectively, of which grade 3 or higher was observed only in 3% and 4%, respectively [65]. Similar results were observed in the KarMMa-1 trial (84%/5%

TABLE 3 | Summary of comparative characteristics and efficacy in real-world outcomes of FDA-approved CAR T-Cell therapies in RRMM.

Variable	Hansen et al.	Sidana et al.	Kalariya et al. (< 65/≥ 65 years)	Ferreri et al. Prior/ No Prior BCMA-TT	Ferment et al.	Sidana et al.	Gaballa et al. (CNS-MM)
Baseline characteristics							
CAR-T Type	Ide-cel	Ide-cel	Ide-cel	Ide-cel	Ide-cel	Cilta-cel	Ide-cel/cilta-cel
Number of patients treated (N)	159	603	81/75	50/153	159	236	10
Median age (range)	64 (36–83)	65 (29–86)	58 (42–64)/69 (65–83)	66 (43–79)/63 (36–83)	61 (34–82)[a]	64 (30–84)	58 (36–71)
Median prior lines of therapy (range)	7 (4–18)	7 (4–21)	6 (4–16)/6 (4–18)	9 (4–18)/6 (4–19)	4 (2–12)	6 (2–18)	6 (4–10)
Extramedullary diseased	48%	17%	51.9%/41.3%	50%/56%	17%	26%	100%
R-ISS stage II/III (%)	82%	52%[b]	78.6%/79.4%	89%/76%	Not reported	72%	40%
High-risk cytogenetics	35%	23%	33.8%/39.4%	36%/31%	42%	39%	40%
Triple-refractory disease[c]	84%	Not reported	95.1%/84%	90%/82%	79%	69%	80%
Penta-refractory disease[d]	44%	36%	46.9%/32%	62%/37%	28%	30%	70%
Efficacy							
ORR	84%	71%	84%/86.7%	74%/88%	88%	89%	80%
CR or better	42%	27%	54.3%/56%	29%/48%	47%	70%	60%
VGPR	20%	53%	16.1%/17.3%	20%/22%	26%	14%	10%
PR	22%	Not reported	13.6%/13.3%	24%/17%	15%	5%	10%
MRD Negative (10–5)	72%	Not reported	Not reported	Not reported	79%[e]	95%[f]	40%
Median PFS (months)	8.5 (6.5–NR)	NR[g]	7.4/9.1	3.2/9.0	12.5 (8.8–16.3)	NR[h]	6.3
Median OS (months)	12.5 (11.3–NR)	NR[g]	24.2/26.5	12.5–NR	20.8 (9.4–NR)	NR[h]	13.3

Abbreviations: CR, Complete Response; IQR, Interquartile Range; MRD, Minimal Residual Disease; NR, not reached; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression-Free Survival; PR, Partial Response; SOC, standard of care; VGPR, Very Good Partial Response.

[a]Data reported as median (IQR).

[b]Data is for International Staging System (ISS) stage.

[c]Triple-class refractory was defined as MM refractory to an immunomodulatory (IMiD) drug, a proteasome inhibitor (PI), and an anti-CD38 antibody.

[d]Penta-class refractory was defined as MM refractory to 2 IMiDs, 2 PIs, and an anti-CD38 antibody.

[e]Evaluated only in 47/159 patients (30%), of whom 37/47 (79%) achieved MRD negativity.

[f]MRD reported in 98 patients with CR or better, of whom 93/98 were MRD negative.

[g]No median reported for PFS and OS. PFS and OS at 6 months reported as 62% (95% CI: 58%–66%) and 82% (95% CI: 79%–85%), respectively.

[h]mPFS and mOS were not reached, with a reported PFS and OS at 12 months of 68% and 82%, respectively.

TABLE 4 | Summary of key Adverse Events reported from Real-World Cohorts Treated with Cilta-cel and Ide-cel.

Variable	Grade	Hansen et al.	Sidana et al.	Kalariya et al. (<65/>65 years)	Ferreri et al. Prior/No prior BCMA-TT)	Ferment et al.	Sidana et al.	Gaballa et al.
CRS	Any	82%	81%	81.5%/88.0%	80%/86%	90%	75%	80%
	Grade ≥ 3	3%	3%	2.4%/1.2%	2%/3.3%	2%	5%	0%
ICANS	Any	NR[a]	NR[b]	13.6%/25.3%	17%/22%	NR[c]	14%	30%
	Grade ≥ 3	NR[a]	NR[b]	4.9/4.0%	8.5%/6.9%	NR[c]	4.4%	10%
DNT	Any	—	—	—	—	—	10%	20%
Neutropenia	Grade ≥ 3	88%	—[d]	8.8%[e, f]/11.3%[e, f]	76%/78%	25%[e]	80%[e]	30%[e]
Anemia	Grade ≥ 3	51%	NR	8.7%[e, f]/11.3%[e, f]	38%/35%	7%[e]	37%[e]	20%[e]
Thrombocytopenia	Grade ≥ 3	68%	—[d]	23.2%[e, f]/24.2%[e, f]	64/57%	21%[e]	53%[e]	40%[e]
Infections	Any	34%	42%[g]	17.2%/24%	34%/39%	34%[h]	47%[h]	50%
SPM		NR	4.5%	NR	NR	NR	8.5%	NR

Abbreviations: BCMA-TT, B-cell maturation antigen-targeted therapy; CRS, cytokine release syndrome; DNT, Delayed Neurotoxicities (Includes 7th CN palsy, diplopia, parkinsonism, PRES, dysautonomia, polyneuropathy); ICANS, immune effector cell-associated neurologic syndrome; NR, Not reported.
[a]Report as grouped neurotoxicities by the author. Any/Grade ≥ 3: 18%/3%.
[b]Report as grouped neurotoxicities by the author. Any/Grade ≥ 3: 27%/4%.
[c]Report as grouped neurotoxicities by the author. Any/Grade ≥ 3: 13%/4%.
[d]No grading reported for Neutropenia and Thrombocytopenia. Reported incidence by the author was 13%/25%, respectively.
[e]Reported as toxicity within the first 90 days post CAR T.
[f]16.3%/21.6% and 18%/12.3% at 30 and 60 days, respectively.
[g]Only clinically significant infections were reported.
[h]Sidana et al. reported 46% Grade ≥ 3 infections. Ferment et al. reported 26% Grade ≥ 3 infections.

and 18%/3%, respectively). This indicates that safety and efficacy are comparable in real-world settings, despite including a significant proportion of patients who would not have been eligible for the KarMMa trial [35, 65].

Results about older and frail patients treated with ide-cel were not well-established, and a multicenter retrospective study focused on this population included 156 patients treated with commercial ide-cel. Of this cohort, 66.7% were considered frail, 26% had an ECOG ≥ 2, and 75 patients were 65 years old or older (Table 3) [66]. CRS and ICANS were observed in 84.6% and 23.8% of cases, respectively, with only 1.9% and 4.5% being Grade ≥ 3 [66]. The ORR in 65 years old or older was 86.7%, among which 56% achieved CR or better [66]. When comparing groups (< 65 years old vs. 65 years or older), the mPFS and mOS were higher in the older population (7.4/9.1 months vs. 24.2/26.5 months, respectively) [66]. Such difference could be related to the fact that patients in the < 65-year-old group had a higher percentage of frail patients compared with the older group (53.5% vs. 33.3%, respectively) [66]. Death was observed in 73 patients, of which 75% were myeloma-related. Infections were the most common cause of nonrelapse death and only one case was attributed to CRS/ICANS [66]. Of note, this study also reported one deceased patient due to Lewy-body dementia in the 65 or older group [66]. These results show equal safety and efficacy of ide-cel in older populations despite significant differences in frailty and geriatric characteristics such as comorbidities, polypharmacy, and organ dysfunction. Importantly, these differences did not result in a poorer overall outcome in the multivariate analysis [35, 66].

In the phase 2 KarMMa trial, prior exposure to an anti-BCMA targeted therapy (BCMA-TT) was an exclusion criterion, and the availability of data addressing this scenario remains limited [35, 67]. A multicenter retrospective study compared patients with prior BCMA-TT, including antibody-drug conjugate (ADC), bispecific, and CAR T, versus patients without prior BCMA-TT exposure who received SOC ide-cel. The incidence of CRS, ICANS, infections, and other adverse hematologic toxicities was comparable among both groups [67]. A lower ORR was observed in the prior BCMA-TT group (74% vs. 88%; $p = 0.021$), among which all patients with prior CAR-T responded to therapy; however, the number of patients with prior CAR-T exposure was low ($n = 5$), and the timing to ide-cel infusion from the prior BCMA CAR-T needs to be also considered [67]. In the multivariate analysis, the prior BCMA-TT group showed an inferior mDOR (7.4 vs. 9.6 months; $p = 0.03$) and inferior mOS (3.2 vs. 9.0 months; $p = 0.0002$), compared with the no prior BCMA-TT group. Further, it was found that patients with prior BCMA-TT had an inferior PFS (HR, 2.91; 95% CI: 1.68–5.04; $p < 0.0001$) and inferior OS (HR, 3.44; 95% CI: 1.45–8.14; $p = 0.005$) [67]. These findings remark that despite having a suboptimal response and DOR, treatment with ide-cel in prior BCMA-TT and heavily pretreated patients still shows a significant clinical response [67].

The multicenter retrospective study from the French national DESCAR-T registry (Table 3) included 159 patients infused with SOC ide-cel. Safety and efficacy were also comparable with trials and other multicenter studies despite having a more diverse patient population, including prior BCMA-TT exposure [68]. Furthermore, the ORR observed with ide-cel compares

favorably with those reported for other BCMA-TT in this scenario. Cohort C of the prospective CARTITUDE-2 trial included 20 patients infused with cilta-cel after prior exposure to a non-cellular BCMA-TT. Cilta-cel treatment resulted in an ORR of 60%, mDOR of 11.5 months, and mPFS of 9.1 months [69].

5.2 | Cilta-Cel Real-World Reported Outcomes

The largest multicenter retrospective study to date, reporting RWOs in patients with RRMM treated with cilta-cel as SOC (Table 3), included 236 patients, of which 54% of the patients would have been ineligible for the CARTITUDE-1 trial [70]. The most common AEs were CRS (75%) and ICANS (14%), from which Grade ≥3 occurred in 5% and 4% of patients, respectively, which is consistent with the reported findings in the CARTITUDE 1 trial (4% and 9%, respectively) [36, 70]. Delayed neurotoxicity (DNT) was reported in 10% of patients, including seventh cranial nerve palsy (CNP), parkinsonism, diplopia, posterior reversible encephalopathy syndrome (PRES), dysautonomia, and polyneuropathy [70]. Other SAEs included infections, hematologic toxicities including Grade ≥3 neutropenia, anemia, and thrombocytopenia, and 8.5% of the infused patients were observed to develop SPM [70].

The ORR was 89%, of which 70% achieved CR or better [70]. Patients with prior BCMA-TT exposure had an inferior best ORR compared with those with no prior exposure (92% vs. 70%; $p<0.001$, respectively) [70]. In the multivariate analysis, prior BCMA-TT was associated with a lower likelihood of achieving ORR (OR 0.19; 95% CI: 0.06 to 0.54; $p=0.002$) and CR or better (OR 0.20; 95% CI: 0.07 to 0.54; $p=0.002$) [70]. Other statistically significant associated characteristics with a lower likelihood of achieving ORR were higher baseline ferritin levels, White race, and male sex [70]. Furthermore, patients with penta-refractory disease ($p=0.005$), high-risk cytogenetics ($p=0.05$), presence of EMD ($p=0.03$), and a poor performance status (ECOG ≥2) at LD ($p=0.002$) also showed lower odds of achieving CR or better in the multivariable analysis [70].

The mPFS was not reached, and the estimated 12-month PFS was 68% (95% CI: 62 to 74) [70]. It is important to notice that in the prior BCMA-TT, patients who received cilta-cel infusion ≥6 months after their last exposure had a significantly higher ORR compared to those with an interval of <6 months (94% vs. 54%; $p=0.03$). This group also had a higher mPFS (16.8 vs. 6.2 months), although this difference was not statistically significant ($p=0.29$) [70]. Similarly, no statistically significant difference was found in the OS [70]. High baseline ferritin levels (HR 2.99, 95% CI: 1.86 to 4.80; $p<0.001$), high-risk cytogenetics (HR 1.90, 95% CI: 1.20 to 3.02; $p=0.006$), and EMD (HR 1.96, 95% CI: 1.19 to 3.23; $p=0.009$) were independently associated with inferior PFS and OS (HR 3.5, $p=\leq 0.001$; HR 2.57, $p=0.005$; HR 1.88, $p=0.04$; respectively) [70].

Patients with MM and CNS involvement have historically had a poor prognosis and limited treatment options [71, 72]. One multicenter retrospective study evaluated outcomes in a small cohort (10 patients) of RRMM patients with CNS involvement (brain/cranial nerve and/or spinal cord/leptomeningeal involvement) treated with SOC cilta-cel or ide-cel (Tables 3 and 4) [73]. CRS occurred in 80% of patients, and ICANS was observed in 30% [73]. Only 10% had grade 3 ICANS, with no grade 4 reported [73]. The ORR was 80%, with 60% of patients achieving CR or better [73]. Notably, CNS response by day 90 achieved 100% [73]. The PFS at 6 months was 62.5%, and the OS at 6 and 12 months was 87.5% and 75%, respectively [73]. Despite being a small cohort due to the low frequency of CNS involvement in MM patients, results show promising data regarding comparable safety and efficacy with the KarMMa and CARTITUDE-1 trials in which patients with CNS involvement were not eligible [35, 36, 73].

In a post-commercial CAR T-cell analysis of the FDA Adverse Events Reporting System (FAERS) database, the incidence of SPMs was included [74]. In the cilta-cel group, SPMs were reported in 24 patients, of which 4 cases were T cell malignancies (two anaplastic large T-cell lymphomas, one peripheral T-cell lymphoma, and one enteropathy-associated T-cell lymphoma), 3 cases were AML, and 8 cases were MDS [74]. In the Ide-cel group, 15 patients were reported with SPMs, of which MDS comprised 5 cases, followed by AML ($n=3$). No T-cell malignancies were reported in the ide-cel group [74]. Cilta-cel showed a higher reporting odds ratio (ROR) for MDS (ROR = 6.7, 95% CI: 3.3 to 13.5) compared with ide-cel (ROR = 2.8, 95% CI: 1.2 to 6.7) [74]. Of note, multiple analyses of cases have been made to investigate transgene insertion post-CAR T. However, no clear evidence of this relationship has been found [75, 76].

Pivotal trials classified diarrhea and colitis as general gastrointestinal adverse effects [35, 36, 40, 41]. However, a new toxicity was later identified in case reports of patients' gut-infiltrating CAR T-cells who developed T-cell lymphomas [77]. A retrospective multicenter study from the US Multiple Myeloma Immunotherapy Consortium introduced the concept of immune effector cell (IEC)–associated enterocolitis [78].

This study meticulously analyzed 14 patients with an overall incidence of 1.2% [78]. IEC-enterocolitis was more frequently noted with cilta-cel (2.2%) compared to ide-cel (0.2%) [78]. The median time to onset was 92 days (22 to 210) post-infusion and typically occurred after resolution of other toxicities like CRS and ICANS [78]. Symptoms were manifested as non-bloody diarrhea in all cases except one. Interestingly, pathologic analyses from gut biopsies showed significant inflammation with features resembling graft-versus-host disease [78]. Treatment outcomes were poor, with low response to corticosteroids (40%), second-line agents (50% in refractory cases), and a 36% mortality rate from complications, including sepsis and bowel perforation [78]. This highlights the need for rapid recognition of IEC-enterocolitis and more effective toxicity management strategies.

6 | Challenges, Gaps in Knowledge, and Future Directions

6.1 | Challenges and Gaps in Knowledge

Although ide-cel and cilta-cel are available, several challenges delay access to these therapeutic options [79]. The limited number of authorized CAR T-cell centers in the US creates a significant access barrier for MM patients, particularly those in

rural areas who face long travel distances [48]. Furthermore, the complex, weeks-long CAR T-cell manufacturing process is a critical limitation for patients with rapidly progressive disease [80]. Another important aspect is the financial toxicity, particularly with insurance coverage, which also impacts patient access [81, 82].

Beyond access and financial barriers, RWO studies provide new insights, yet the long-term durability of response for patients ineligible for pivotal trials is still being evaluated [80, 83]. Furthermore, the resistance mechanisms are not fully understood yet, and the optimal sequencing with other anti-myeloma regimens requires further investigation [26–34]. In addition, investigating the dynamics of CAR T-cell expansion and its relation with toxicities is needed to develop appropriate risk stratification and strategies to minimize the risk of the development of SPMs, delayed toxicities, and IEC-enterocolitis [75].

6.2 | Future Directions

Most recently, the 5-year follow-up results from the CARTITUDE-1 were presented at the American Society of Clinical Oncology (ASCO) meeting. The results demonstrated a 5-year PFS of 33% with no need for additional treatments, and a mOS of 60.7 months (95% CI: 41.9 to NE), respectively [84]. These results show an impactful achievement in heavily pretreated patients.

The KarMMa-4 phase 1 (NCT04196491) is the first ongoing trial exploring ide-cel in patients with high-risk newly diagnosed multiple myeloma (NDMM). This trial includes patients who have received three cycles of standard induction therapy (triplet or quadruplet) prior to leukapheresis and ide-cel infusion and to follow with lenalidomide-based maintenance therapy [85, 86].

The phase 2 CARTITUDE-2 trial (NCT04133636), which includes multiple cohorts, has shown promising results in earlier lines of therapy. Specifically, in cohort A, cilta-cel demonstrated high response rates with an ORR of 95%, and 90% of patients achieved CR or better [87].

CARTITUDE-5 (NCT04923893) is an ongoing randomized phase 3 clinical trial enrolling patients with NDMM not planned for ASCT. CARTITUDE-6 (NCT05257083) is a randomized phase 3 clinical trial currently enrolling patients with NDMM who are eligible for ASCT, becoming the first randomized trial to compare CART therapy to ASCT in NDMM [88, 89]. Additionally, the emergence of new CART options, such as the G protein-coupled receptor class C group 5 member D (GPRC5D) in the QUINTESSENTIAL trial, represents a promising therapy for the future [90].

7 | Conclusion and Implications for Clinical Practice

These findings demonstrate the effectiveness and safety of ide-cel and cilta-cel in a real-world setting, including patients with diverse clinical characteristics, with some of them showing a slightly better ORR compared to trials with a comparable safety profile, highlighting the importance of continued monitoring for long-term complications such as SPM and the need for strategies to mitigate delayed toxicities and non-relapse mortality.

Author Contributions

Hector Garcia Pleitez: designed the scope of the review, supervised the project, performed the primary literature search, synthesized the data, created the visualizations, and wrote the first draft of the manuscript. **Sakditad Saowapa**, **Andrea Ortiz Maldonado**, **Chanakarn Kanitthamniyom**, and **Diego Olavarria Bernal:** assisted in the literature search, contributed to the visualizations, and the critical revision of the manuscript. **Lukman Tijani:** supervised the project, contributed to the conceptualization, and performed the final critical review and editing. All authors have read and approved the final version of the manuscript.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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