

2025 Update of Cellular Immunotherapy for Plasma Cell Disorders

Plazma Hücre Hastalıklarında Hücresel İmmünoterapinin 2025 Güncellemesi

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Abstract

Despite progression-free survival in multiple myeloma (MM) patients extending to 17 years due to contemporary quadruplet induction therapies, there remains a necessity for novel products in the treatment of high-risk patients. BCMA, GPRC5D, FcRH5, SLAMF7, and TACI are the principal chimeric antigen receptor T (CAR-T) cell target molecules, with dual-target treatments under development to enhance treatment efficacy. Ide-cel and cilta-cel are CAR-T cells directed against BCMA, having received approval from the U.S. Food and Drug Administration for relapsed/refractory MM based on the phase 2 KarMMa and CARTITUDE trials, respectively. Research is currently being conducted on the administration of these products in newly diagnosed patients and for maintenance therapy. Additional anti-BCMA targeted medicines, including LCAR-B38M, completely humanized CAR-T (FHVH-T), P-BCMA-ALLO-1, ALLO-715, and anti-BCMA CAR-NK, provide promising treatment options. Moreover, the anti-CD19 Fast-CAR, designed to shorten production time, and PHE885, which possesses in vivo proliferation capability, are regarded as very efficacious. Arlo-cel, developed for the significant target GPRC5D, has demonstrated efficacy compared to conventional treatments. The development of academic CAR-T products such as ARI0002h, HBI0101, eque-cel, zavorcel, anito-cel, and Sleeping Beauty (utilizing a non-viral vector) have importance due to their accessibility and cost-effectiveness. Real-world data have demonstrated comparable efficacy and safety outcomes in both academic and commercial CAR-T research. CAR-T cell studies are also being undertaken for smoldering MM and amyloid light-chain (AL) amyloidosis. CAR-PRISMM and CAR-HiRiSMM are regarded as extremely effective and safe therapies for patients with high-risk smoldering MM. NXC-201, which targets BCMA, has been developed for AL amyloidosis. Notwithstanding these promising outcomes, numerous difficulties still confront CAR-T therapy. These factors may be related to the tumor, the patient, and/or the CAR-T product. To overcome these issues, new strategies are being implemented, including combination therapy and the incorporation of gamma-secretase inhibitors. In conclusion, CAR-T treatments have evolved into an effective therapy modality and are anticipated to be utilized in earlier treatment phases in the future. The CRISPR gene editing method contributes to future perspectives.

Öz

Güncel quadruplet indüksiyon rejimleri sayesinde multipl miyelom (MM) hastalarında progresyonsuz sağkalımın 17 yıla kadar uzadığı bildirilmesine rağmen yüksek riskli hasta popülasyonunda halen yenilikçi tedavi modalitelerine belirgin bir gereksinim bulunmaktadır. BCMA, GPRC5D, FcRH5, SLAMF7 ve TACI, kimerik antijen reseptörü T hücreleri (CAR-T) tedavilerinde başlıca hedef antijenler olup, etkinliği artırmaya yönelik çift hedefli CAR-T yaklaşımları aktif olarak geliştirilmektedir. BCMA'yı hedefleyen ide-cel ve cilta-cel, sırasıyla faz II KarMMa ve CARTITUDE çalışmaları temelinde relaps/refrakter MM için ABD Gıda ve İlaç Dairesi onayı almıştır. Güncel klinik araştırmalar, bu ürünlerin yeni tanı alan hastalarda ve idame tedavisi bağlamında kullanım potansiyelini değerlendirmeye odaklanmaktadır. Buna ek olarak, LCAR-B38M, tamamen insanlaştırılmış CAR-T yapıları (FHVH-T), P-BCMA-ALLO-1, ALLO-715 gibi allojeneik CAR-T uygulamaları ve anti-BCMA CAR-NK hücreleri, umut vadeden yeni nesil tedavi stratejileri olarak öne çıkmaktadır. Üretim süresini kısaltmayı hedefleyen anti-CD19 Fast-CAR ile in vivo proliferasyon kapasitesine sahip PHE885, yüksek terapötik etkinlik potansiyeli nedeniyle özellikle dikkat çekmektedir. GPRC5D'yi hedefleyen arlo-cel, konvansiyonel tedavilere kıyasla anlamlı klinik etkinlik göstermiştir. ARI0002h, HBI0101, eque-cel, zavorcel, anito-cel ve viral olmayan vektör kullanan Sleeping Beauty gibi akademik CAR-T ürünlerinin geliştirilmesi, erişilebilirlik ve maliyet etkinliği açısından kritik öneme sahiptir. Gerçek yaşam verileri, akademik ve ticari CAR-T uygulamaları arasında etkinlik ve güvenilirlik açısından karşılaştırılabilir sonuçlar elde edildiği ortaya koymaktadır. CAR-T hücre tedavileri ayrıca smoldering MM ve hafif zincir (AL) amiloidozu için de geliştirilmektedir. CAR-PRISMM ve CAR-HiRiSMM, yüksek riskli smoldering MM hastalarında yüksek etkinlik ve kabul edilebilir güvenlilik profili ile dikkat çekmektedir. BCMA'yı hedefleyen NXC-201, AL amiloidozu için özel olarak geliştirilmiştir. Bu olumlu gelişmelere karşın, CAR-T tedavilerinde tümöre, hastaya ve ürünün kendisine bağlı çok sayıda sınırlayıcı faktör hala mevcuttur. Bu engelleri aşmak amacıyla kombinasyon stratejileri ve gama-sekretaz inhibitörlerinin entegrasyonu gibi yenilikçi yaklaşımlar gündeme gelmiştir. Sonuç olarak, CAR-T hücre tedavileri etkili bir tedavi modalitesi haline gelmiş olup, gelecekte daha erken tedavi



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Abstract

Keywords: Myeloma and other plasma cell dyscrasias, Neoplasia, Antigen recognition by T lymphocytes, Immunology, Molecular hematology

Öz

basamaklarında konumlandırılması beklenmektedir. CRISPR tabanlı gen düzenleme teknolojileri, CAR-T alanında geleceğe yönelik stratejilere önemli katkılar sunmaktadır.

Anahtar Sözcükler: Multipl miyelom ve diğer plazma hücre diskrazileri, Neoplazi, T lenfositleri tarafından antijen tanınması, İmmünoloji, Moleküler hematoloji

Introduction

The lifespan of patients with multiple myeloma (MM) has improved dramatically both among newly diagnosed and relapsed/refractory MM (RRMM) patients. The introduction of quadruplet regimens to induction treatment has increased the estimated progression-free survival (PFS) of these patients to 17.1 years [1,2,3]. For RRMM patients, antibody-drug conjugates, bispecific-trispecific T-cell engagers (BITEs), and chimeric antigen receptor T (CAR-T) cells are novel treatments achieving very successful outcomes even among patients who are refractory to proteasome inhibitors (PIs), immunomodulating drugs (IMiDs), or anti-CD38 monoclonal antibodies [4]. While overall response rates (ORRs) of up to 30% were previously considered successful, RRMM patients are now able to obtain minimum ORRs of 60% with these novel agents following at least four lines of therapy (LoTs) [5].

CAR-T cells have been genetically modified to recognize myeloma-specific targets such as B-cell maturation antigen (BCMA), CD38, CD138, CD44v6, CD19, kappa light chain, FcRH5, SLAMF7, integrin β 7, NKG2D, semaphorin-4A, and G protein-coupled receptor, class C, group 5, member D (GPC5D). These receptors contain CD3 ζ -activating transmembrane intracellular costimulatory domains, a hinge region, and an extracellular single-chain variable fragment (scFv). There are currently five generations of CAR-T cells [6]. All currently approved CAR-T cells belong to the second generation of CAR-T products. There are also emerging new CAR-T cells from the third generation, also known as T-cells redirected for universal cytokine-mediated killing, which differ in their capacity to generate cytokines.

CAR-T cell-mediated cellular immunotherapy consists of three steps. First, T-cells are collected from the patient following lymphopheresis. These cells are transfected with a specific vector to expand for 1-3 weeks under ex vivo good manufacturing practice conditions. After quality checks, the CAR-T products are infused into the patient following bridging and then lymphodepletion therapy [4]. The first successful CAR-T product reported in MM targets BCMA, and GPC5D-targeting or dual-targeting CAR-T products were subsequently developed. The historical evolution of CAR-T trials is summarized in Figure 1.

Current CAR-T Therapies in Multiple Myeloma

Anti-BCMA CAR-T Products

Idecabtagene Vicleucel (Ide-Cel) (Abecma)

The first anti-MM CAR-T cell targeting BCMA contained a murine scFv plus a 4-1BB costimulatory domain. Among 24 RRMM patients following a median of 7.5 LoTs, the ORR and the complete response (CR) rate were respectively 81% and 13% [7]. Subsequently, another CAR-T product named ide-cel, which includes a murine scFv with a 4-1BB costimulatory domain, was developed. The first phase 1 study with ide-cel was conducted with 33 RRMM patients with an ORR of 85% [8]. The subsequent phase 2 study, KarMMa, resulted in an ORR of 73%, leading to U.S. Food and Drug Administration (FDA) approval on March 26, 2021 [9]. The KarMMa-2 study, conducted with 128 RRMM patients, resulted in an ORR of 81% and a CR rate of 39%. The median PFS and overall survival (OS) rates were 12.1 and 19.4 months, respectively. Cytokine release syndrome (CRS) and neurotoxicity were observed among 84% and 18% of these patients, respectively [10]. To address high-risk patients, those relapsing within 18 months after induction therapy (KarMMa-2a study) or not achieving very good partial response (VGPR) after autologous stem cell transplant (ASCT) (KarMMa-2c) were included in subsequent studies, resulting in an ORR of 83.8% and PFS of 11.4 months (KarMMa-2a) and ORR of 87.1% and 36-month PFS of 76.8% (KarMMa-2c) [11]. Following the approval of ide-cel, open-label phase 3 global studies were initiated, including the KarMMa-3 study. This study was conducted with 386 RRMM patients after 2-4 LoTs. Ide-cel demonstrated a significant PFS advantage compared to the standard of care (SOC). Rates of disease progression and death were also 51% lower compared to the SOC. The ORR was 42% with 39% of patients achieving CR [12]. Subsequently, the phase 1 KarMMa-4 study was designed for high-risk newly diagnosed MM (NDMM) patients; the results are not yet published yet [11]. The KarMMa-7 study is ongoing to investigate the efficacy and tolerability of ide-cel in combination with other agents [13]. The phase 3 KarMMa-9 trial (NCT06045806) is a maintenance trial investigating the efficacy and safety of ide-cel plus lenalidomide versus lenalidomide as maintenance therapy among NDMM patients achieving only VGPR or partial response (PR) following ASCT. When these studies are completed, CAR-T therapies may find their place among previously established treatment approaches.

Ciltacabtagene Autoleucl (Cilta-Cel) (Carvykti)

The second available CAR-T product was originally manufactured in China and sold to Janssen to be named ciltacabtagene autoleucl (cilta-cel). The first relevant study was the phase 1b CARTITUDE-1 study in which 97 RRMM patients following a median of 6 LoTs achieved an ORR of 97.9%, stringent CR (sCR) of 82.5%, and median 36-month PFS and OS of 34.9 months and 63%, respectively [14]. Based on this study, cilta-cel was approved by the FDA on February 28, 2022 [15]. Approval was expanded in 2024 to RRMM patients following one or more prior line with a PI plus IMiD and lenalidomide refractoriness. Subsequently, the CARTITUDE-2 study involving patients after 1-3 LoTs was reported to result in an ORR of 88.9% following a median of 0.9 months [16]. Similarly to the KarMMa-3 study, a comparison against the SOC was planned in the CARTITUDE-4 study. Among 419 RRMM patients after 1-3 LoTs, an ORR of 85% versus 67% and 12-month PFS of 75.9% versus 48.6% were obtained, reflecting significantly better outcomes in the cilta-cel arm [17]. More recently, the phase 3 CARTITUDE-5 study was planned among NDMM transplant-ineligible patients to investigate the role of cilta-cel after frontline bortezomib, lenalidomide, and dexamethasone (VRD) therapy, comparing it against VRD and lenalidomide maintenance. The results have not yet been published (NCT04923893). CARTITUDE-6, another phase 3 trial, is comparing the efficacy of induction treatment with daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) followed by ASCT, DVRd consolidation, and maintenance

treatment with lenalidomide against induction treatment with DVRd followed by a single infusion of cilta-cel and subsequent maintenance treatment with lenalidomide. This study has not yet reached its endpoint and does not yet have published results (NCT05257083).

Efficacy and adverse events reported by the KarMMa-3 and CARTITUDE-4 studies are illustrated in Figure 2. To compare the specificities of these two major commercially available anti-BCMA CAR-T products, Table 1 was prepared. In addition, early and advanced phase studies, either completed or ongoing and designed to target myeloma, are summarized in Tables 2, 3, and 4.

Other Anti-BCMA Agents

LCAR-B38M is another anti-BCMA CAR-T cell produced in China. In the LEGEND-2 study, its efficacy was investigated in 57 RRMM patients and highly successful results of 88% ORR and 74% CR were reported. The median PFS and OS rates were 18 and 55.8 months, respectively [18]. The 5-year follow-up results included 5-year unmaintained PFS of 21.0% and OS of 49.1%, suggesting the possibility of a cure in MM [18].

Fully humanized (FH) CAR-T products are also now being developed to mitigate immunogenicity. As an example, FHVH-T, administered to 25 RRMM patients, resulted in a median PFS of 65 weeks and ORR of 92% [19]. Another FH CAR-T product is equecabtagene autoleucl (CT103A), approved in China and used after 4 LoTs. The FUMANBA-1 study of eque-cel and the

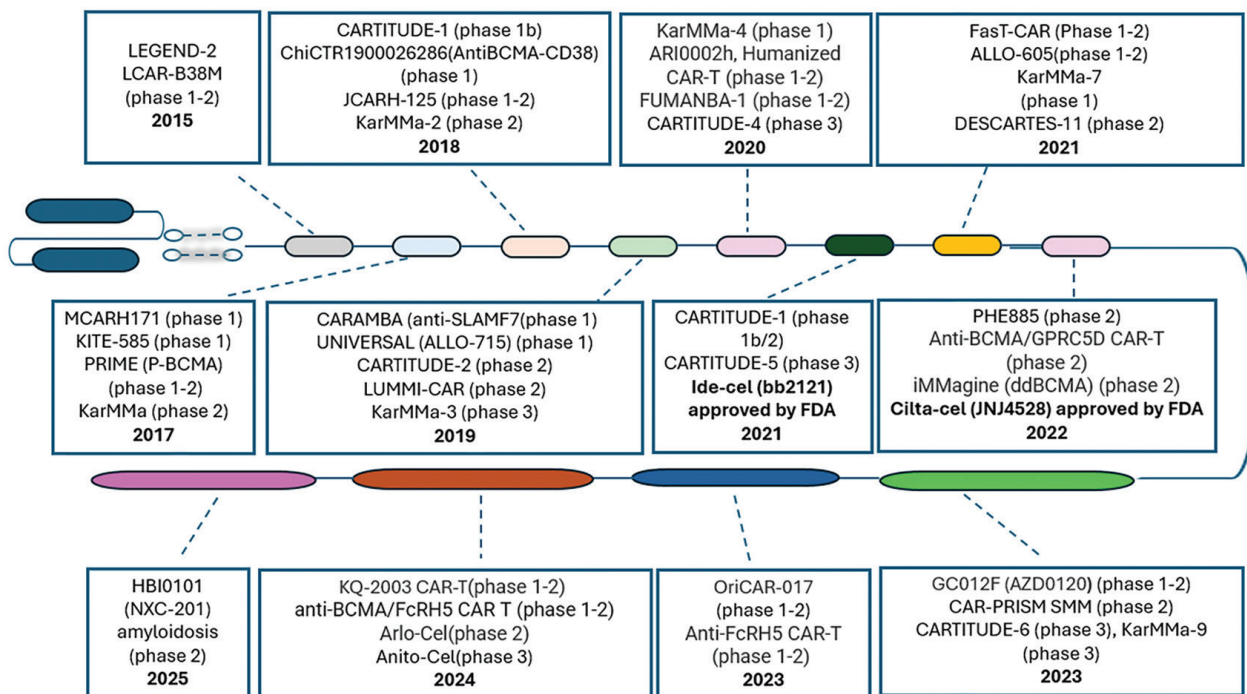


Figure 1. The historical evolution of CAR-T products and related trials.

BCMA: B-cell maturation antigen; CAR-T: chimeric antigen receptor T cell; FDA: US Food and Drug Administration.

Comparison of KarMMA-3 and CARTITUDE-4 trials

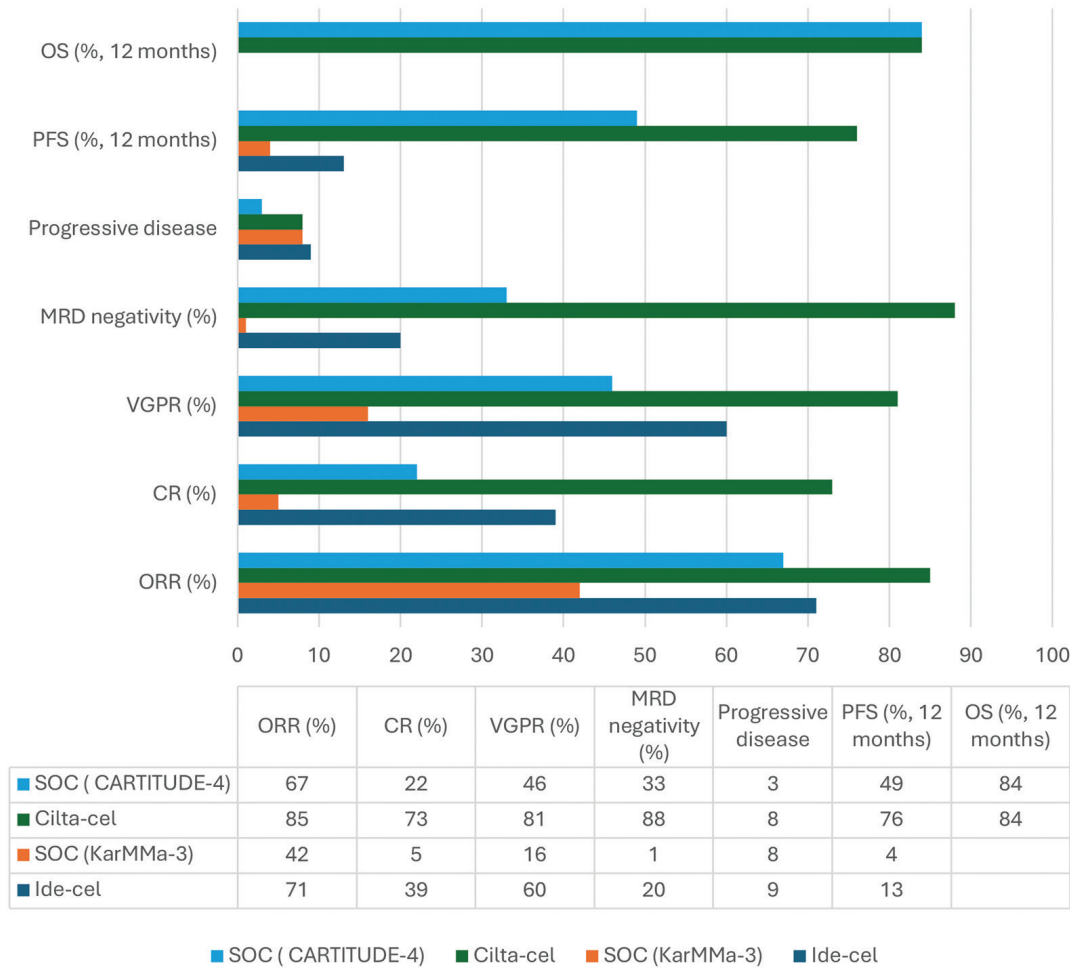


Figure 2. Comparison of efficacy and toxicity between the KarMMA-3 and CARTITUDE-4 studies.

OS: Overall survival; PFS: progression-free survival; MRD: minimal residual disease; VGPR: very good partial response; CR: complete response; ORR: overall response rate; SOC: standard of care; cilta-cel: ciltacabtagene autoleucel; ide-cel: idecabtagene vicleucel.

LUMMICAR-1 study of zevor-cel have presented academic products that will be discussed in the following sections [20].

PHE885 is a novel FH CAR-T product that uses the T charge platform to enable in vivo CAR-T expansion following the in vitro phase. The production time is less than 2 days and the ORR was found to be 98% in a trial including 46 RRMM patients (NCT04318327).

Another novel anti-BCMA technology developed to increase cell surface stability and reduce immunogenicity is the ddBCMA CAR-T product anitocabtagene autoleucel, with the synthetic D-domain increasing the stability and cytotoxicity of the product, resulting in an ORR of 100% and CR/sCR rate of 71% in 33 RRMM patients [21,22].

Finally, to reduce immunogenicity and T-cell exhaustion, allogeneic CAR-T and CAR-NK cells acting against BCMA have

been investigated. There are multiple advantages to such products, including off-the-shelf availability, younger donors, and lower costs. In Arm A of the UNIVERSAL study, the ALLO-715 CAR-T product was administered to 43 RRMM patients and an ORR of 55.8% was observed [22]. In the phase 1 P-BCMA-ALLO1 study, the piggyBac system, which has a non-viral transposon, was designed for RRMM patients (NCT04960579).

Following another innovative approach, anti-BCMA CAR-NK (FT576) derived from induced pluripotent stem cells has shown sustainable antitumor activity in mouse models [22]. A phase 1 clinical trial investigating its combination with daratumumab is ongoing (NCT05182073). Early-phase anti-BCMA studies are presented in Table 2 [23].

Table 1. Comparisons of cilta-cel and ide-cel in terms of structure, efficacy, toxicity, response rates, and adverse events.

Comparisons	Cilta-cel	Ide-cel
FDA approval date	February 2022	March 2021
Target antigen	BCMA	BCMA
Vector system	Lentivirus	Lentivirus
Antigen binding region (scFv)	Bivalent scFv (dual epitope)	Monovalent scFv (single epitope)
Epitope affinity	Very high	Moderate
Costimulatory domain	4-1BB (CD137)	4-1BB (CD137)
Intracellular signaling domain	CD3 ζ	CD3 ζ
Cytotoxicity	Higher	Lower
In vivo persistence	12 months	6 months
Response rate	Deeper and more durable	Effective but lower
Overall response rate CARTITUDE-1 vs. KarMMa CARTITUDE-4 vs. KarMMa-3	97% 84.6%	74.5% 71%
Overall survival (median, months) CARTITUDE-1 vs. KarMMa CARTITUDE-4 vs. KarMMa-3	62.9% (36 months) 76.4% (30 months)	28.2 41.1
Progression-free survival (median, months) CARTITUDE-1 vs. KarMMa CARTITUDE-4 vs. KarMMa-3	34.9 76% (12 months)	8.9 13.3 months
Cytokine release syndrome CARTITUDE-1 vs. KarMMa CARTITUDE-4 vs. KarMMa-3	89.6% (grade ≥ 3 CRS: 3%) 78% (grade ≥ 3 CRS: 3%)	84.7% (grade ≥ 3 CRS: 5.5%) 88% (grade ≥ 3 CRS: 5%)
ICAN/neurotoxicity CARTITUDE-1 vs. KarMMa CARTITUDE-4 vs. KarMMa-3	20.6% (grade ≥ 3 neurotoxicity: 5%) 20% (4.5% ICAN, 0.6% delayed parkinsonism, 9.1% cranial nerve paralysis, 2.8% peripheral neuropathy)	38.7% (grade ≥ 3 neurotoxicity: 3%) 15% (grade ≥ 3 neurotoxicity: 3%, early-onset ICAN)
KarMMa: ≥ 3 lines, KarMMa-3: 2-4 lines, CARTITUDE-1: ≥ 3 lines, CARTITUDE-3: 1-3 lines		
FDA: U.S. Food and Drug Administration; scFv: single-chain variable fragment; BCMA: B-cell maturation antigen; CRS: cytokine release syndrome; ICAN: immune effector cell-associated neurotoxicity; cilta-cel: ciltacabtagene autoleucel; ide-cel: idecabtagene vicleucel.		

CAR-T Products for Alternative Myeloma Targets

G Protein Receptor Coupled 5 D (GPCR5D)

GPCR5D is another highly specific MM target molecule with proven efficacy with bispecific monoclonal antibodies targeting GPCR5D. Approaches targeting this antigen are still under development. MCRH109 is the first CAR-T product to be developed against GPCR5D, humanized, and modified with a lentiviral vector containing the 4-1BB costimulatory domain. Among 17 RRMM patients following 4 or more LoTs, the ORR was 71% [24]. In a series of 10 patients, another anti-GPCR5D molecule, OriCAR-017, achieved 100% ORR [25]. In addition, dual-affinity CAR-T cells recognizing both GPCR5D and BCMA have been developed to obtain an ORR of 86% among 21 RRMM patients [26].

One of the ongoing phase 3 studies is exploring arlo-cel, developed against GPCR5D. The QUINTESSENTIAL-2 (NCT06615479) study is comparing arlo-cel versus the relevant SOC and the primary

endpoints are PFS and minimal residual disease (MRD) negativity. The results have not yet been published [27].

Fc Receptor-Homolog 5 (FcRH5)

FcRH5 is a member of the immunoglobulin superfamily expressed on malignant plasma cells three times more frequently than normal plasma cells. Discussions about the use of CAR-T products against this target are still premature. However, dual-target CAR-T studies are being conducted in murine xenograft models targeting both BCMA and FcRH5, obtaining stronger cytotoxicity, better cytokine-secreting capacity, and longer median survival compared to monospecific CAR-T products [28].

Other Targets

The expression of CD19 on mature MM cells is associated with poor prognosis [29]. GC012F is a BCMA-CD19 bispecific CAR-T product developed with FastCAR-T technology. Among 29 RRMM patients, the ORR/SCR rates were very high, as expected, reported as 93.1% and 82.8%, respectively [30].

Another target is CS1 (SLAMF7), which is also expressed predominantly on plasma cells. In a study investigating the efficacy of murine-derived CS1-BCMA bispecific CAR-T cell therapy, the ORR was found to be 81% among 16 RRMM patients [31].

TACI is a receptor belonging to the TNFR superfamily. It is also overexpressed on plasma cells. These two receptors have two ligands called B-cell activating factor and a proliferation-inducing ligand (APRIL). The AUTO2 study, conducted with APRIL, resulted in an ORR of 45.5%, lower than that obtained with major CAR-T products [32]. Trimeric APRIL-targeting CAR-T (TRIPRIL) cells are currently being investigated (NCT05020444).

Finally, CD38 and CD138 are worthy of note. The CD38-BCMA bispecific CAR-T cell named BM38 was administered to 23 RRMM patients to obtain an ORR of 87% [33]. In *in vitro* experiments, the combination of CAR-T cells with low affinity for CD138 and high affinity for CD38 was shown to be highly effective [34]. The use of non-viral vectors such as the Sleeping Beauty transposon vector has also facilitated stable gene integration [35].

Academic CAR-T Products

The numbers of CAR-T treatments are increasing gradually, but the manufacturing capacity of the pharmaceutical industry does not meet the current need. To increase access to CAR-T products, academic CAR-T manufacturing has been attempted as a solution. ARI0002h (cesnicabtagene autoleucel) is one of the first academic point-of-care BCMA-directed CAR-T cells. This construct is an autologous CAR-T cell with costimulatory domain 4-1BB and a humanized scFv that targets BCMA, manufactured at the University of Barcelona. In a study including 60 RRMM patients, the ORR was 95% (CR: 58%) in the first 3 months. Median PFS was 15.8 months, while median OS was not reached after a median follow-up period of 23.1 months. The CRS rate was 90%, but only 5% of these cases were of grade 3-4. Mild immune effector cell-associated neurotoxicity (ICAN) was reported for only 2 patients [36]. This product is currently approved and reimbursed in Spain.

HBI0101, another academic BCMA-targeting CAR-T therapy for MM, was produced in Israel. According to phase 1b/2 clinical trial results, the ORR was 90% (CR: 56%) with MRD negativity of 70% within a median follow-up period of 12.3 months. CRS of any grade was reported in 96% of patients (grade 3: 14%) and the neurotoxicity rate was 6% [37].

China has two academic CAR-T products: zevor-cel and eque-cel. Zevor-cel is a FH anti-BCMA CAR-T cell product currently being evaluated with phase I/II data in the LUMMICAR-1 study (NCT03975907). The outcomes to date are quite successful, including an ORR of 100%. Eque-cel is also a FH anti-BCMA CAR-T cell product. Its efficacy was examined in the FUMANBA-2 study (NCT05181501), demonstrating an ORR of 100%.

Anito-cel, initially an academic CAR-T product and previously known as CART-ddBCMA, is an anti-BCMA CAR-T product developed using an alternative method incorporating a novel synthetic D-domain. This approach enhances the efficacy of CAR-T cells. The iMMagine-1 study reported an ORR of 100% (NCT05396885). The results of these studies are summarized in Table 2.

At the Würzburg University Clinic, a highly effective and economical CAR-T product known as SLAMF7 has been produced using non-viral Sleeping Beauty transposon-based mRNA/minicircle DNA technology, and its efficacy is being evaluated in the CARAMBA study (phase I/IIA; Eudract: 2019-001264-30). At Case Western Reserve University, a novel academic CAR-T product that bypasses *in vitro* expansion is being developed. This novel technology alleviates the need for and costs of good manufacturing practice facilities while reducing the manufacturing time to a week and reducing the costs to highly affordable levels [38].

Real-World Data

Clinical trial design mandates eligibility and exclusion criteria to harmonize efficacy and toxicity. The meticulous selection of patients increases the probability of a favorable outcome, underscoring the need for real-world data. For example, real-world data on ide-cel indicate that 75% of patients were not eligible to participate in the KarMMa study. Even among such patients, however, the 84% ORR (\geq CR: 42%) and median PFS and OS of 8.5 and 12.5 months are highly acceptable. High-risk cytogenetics, younger age, hyperferritinemia, and BCMA-based bispecific administration before CAR-T therapy were found to impair the outcome. Severe CRS and neurotoxicity were observed at rates of 82.3% and 18.6%, respectively, demonstrating safety similar to that of the clinical trial [39]. Since cilta-cel studies started later, real-world data have not yet been finalized. However, early analyses show that 57% of real-world patients were not eligible for the CARTITUDE-1 study. The ORR was 84% with a \geq CR rate of 53%, and median PFS and OR have not been reached yet. The percentages of severe CRS and neurotoxicity were 80.5% and 18.6%, respectively, in line with previous safety results [40]. In a study presenting a single center's experience with 87 RRMM patients after a median of 5 LoTs with CAR-T cells (both ide-cel and cilta-cel), the median PFS was found to be 17.5 months. No information about side effects was provided in this report [41]. In another study of a single-center, real-world experience with ide-cel, 16 triple-class-refractory patients were evaluated. After a median of 6 LoTs, the ORR was found to be 69% ($>$ CR 50%), the CRS rate was 94%, and the ICAN rate was 6%; the ORR was lower than previously reported values [41]. In another study involving real-world data comparing ide-cel (n=162) and cilta-cel (n=42), cilta-cel was found to be superior in terms of ORR (93% vs. 79%; $p<0.001$). The 10-month PFS and OS rates for

these products were 82% versus 47% ($p < 0.001$) and 90% versus 77% ($p = 0.06$), respectively. CRS and ICAN rates were similar [42]. Real-world data from the Myeloma CAR-T Consortium, CIBMTR, and Hansen et al. [40,45] are presented in Figure 3 [43], where they are compared with pivotal data on ide-cel and cilta-cel [44]. Cilta-cel is generally accepted as a more effective product while ide-cel is less toxic. Table 1 summarizes the features of these two commercially available CAR-T products.

Despite the demonstrated efficacy of approved CAR-T treatments, survival rates remain inferior among patients presenting with extramedullary disease (EMD) compared to patients without EMD. In a study presenting international multicenter real-world CAR-T data, 29% of patients in the ide-cel group and 48% in the cilta-cel group had EMD. The presence of EMD significantly shortened PFS in this study ($p = 0.01$), without a significant effect on OS ($p = 0.11$) [42].

CAR-T Therapies for Smoldering Myeloma

Smoldering MM (SMM) is an asymptomatic plasma cell disorder. The risk of progression from SMM to MM increases up to 70% in the presence of the 2/20/20 criteria [42,46]. Whether these high-risk SMM patients should be treated is still a topic of debate [47]. Daratumumab monotherapy was recently approved for the treatment of high-risk SMM. To improve efficacy, the CAR-PRISMM study was designed. The main goal is to test the safety and effectiveness of cilta-cel in high-risk SMM. In the 6-month median follow-up period, an ORR of 100% with 50% CR was achieved among 6 patients. While CRS was observed in all patients, they were all low-grade cases without any neurological abnormalities excluding Bell's palsy [48].

Another ongoing study of high-risk SMM is CAR-HiRisMM (NCT06574126). This study is administering cilta-cel to high-risk SMM patients following DVRd. It is planned to monitor MRD for up to 5 years. While traditional treatments in SMM are still a topic of debate, more research is needed for CAR-T therapies to come to the forefront.

CAR-T Therapies for Amyloid Light-Chain Amyloidosis

Amyloid light-chain (AL) amyloidosis is a clonal plasma cell disorder and approximately only 20% of patients are suitable for transplantation. Treatment with daratumumab and bortezomib has become the SOC. Nevertheless, in patients not responding to treatment, poor tolerance of IMiDs, the cardiotoxicity of carfilzomib, and the limitation of venetoclax to t(11;14) reduce the treatment options, increasing the demand for CAR-T therapy [49]. NEXICART-2 (NCT06097832) is a single-arm, multi-phase 1b/2 dose escalation and expansion trial of the BCMA-targeting CAR-T NXC-201 in relapsed/refractory AL amyloidosis. Although 40 patients with relapsed/refractory AL amyloidosis were screened for this study, only 7 were able to enroll. The median

follow-up period was 97 days, with treatment resulting in the normalization of all hematological parameters of AL amyloidosis. The ORR was 100% without any relapses. CRS was observed in 5 patients with no neurotoxicity. Renal organ response with a decrease in albuminuria was observed in 1 of 7 patients, and the New York Heart Association heart failure score regressed from class II to I in another patient.

Challenges and Strategies for Overcoming Them

The efficacy of CAR-T treatments is impressive but long-term success is not always possible. Loss of CAR-T cell persistency, immune system exhaustion, target antigen loss, shedding of BCMA into the circulation, and immunosuppressive factors constitute the mechanisms of resistance. In addition, challenges involving tumor penetrance, high tumor burden, and CAR-T product-related factors may develop [50,51].

The MyCARE model is able to predict the risk of early relapse following CAR-T treatment. This score includes the presence of EMD or plasma cell leukemia, IMiD refractoriness, and ferritin level at the time of lymphodepletion. The model calculates the 5-month relapse rate as 7% in the absence of all four risk factors and 53% in the presence of all four [52].

Antigen loss was also found to be an important parameter. In the KarMMA study, BCMA loss was observed in only 4% of patients, and subsequent studies have identified biallelic deletions and other mutations as causative factors [53]. For CAR-T cells to function, a certain threshold level of BCMA expression is required. To address this problem, BCMA-independent targets and dual-target products have been developed. The cleavage of BCMA by gamma-secretases, detaching it from the cell surface, increases the amount of soluble BCMA. In a study in which the oral gamma-secretase inhibitor JSMD194 was used concurrently with CAR-T therapy, antigen binding capacity increased by approximately 20 times and the ORR was 100% [54]. Gamma-secretase inhibitors are approved for the treatment of Alzheimer's disease [55].

T-cell fitness and the tumor microenvironment are two examples of relevant host factors. The CD4/CD8T cell ratio decreases following several LoTs, which has an adverse effect on cells' ability to proliferate and survive [56]. Having a high tumor burden and receiving multiple LoTs negatively affect T-cell performance [14]. The immunomodulatory effects of BITEs and radiotherapy positively influence CAR-T treatment outcomes [57,58]. Tumor microenvironment-related factors include less CAR-T cells trafficking to tumor sites, such as in cases of EMD, resulting in a shorter duration of response. The enhancement of CAR-T cells in immunosuppressive environments may be possible with the production of CAR-NK cells expressing NKG2D, adding the granulocyte-macrophage colony stimulating factor inhibitor lenzilumab or other similar products [59,60,61].

Table 2. Early phase clinical trial results of anti-BCMA CAR-T products, adapted from Swan et al. [23].

Trial	CAR-T	Study design	Patients, n	Follow-up, months	ORR, %	CR, %	OS, months	PFS, months	CRS/CRS ≥grade 3, %	Neurotoxicity/neurotoxicity ≥grade 3, %	
Anti-BCMA											
NCT02215967 Phase 1	Murine scFv (11D5-3) CD28 costimulatory domain Retroviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 0.3x10 ³ -9x10 ⁶	24 RRMM		81	63 ≥VGPR			94/38	-/25	
NCT02658929 Phase 1	CRB (bb2121/ide-cel) 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 50-800x10 ⁶	33 RRMM	11.3	85	45	34.2	11.8	76/7	44/3	
NCT03361748 Phase 2 KarMMa	CRB (bb2121/ide-cel) 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 150-450x10 ⁶	137 RRMM		74.5	34.3	28.2	8.9	84.7/5.5	38.7/3	
NCT03601078 Phase 2 KarMMa-2	Bb2121/ide-cel 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 150-450x10 ⁶	37 Arm 2a RRMM	21.5	83.8	45.9	NR 84.7% (2 years)	11.4	81.1/2.7	21.6	
NCT03274219 Phase 1	CRB402 (bb21217) Murine scFv (11D5-3) 4-1BB Lentiviral vector Phosphoinositide 3 kinase inhibitor added to enrich memory-like T-cells	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 150-450x10 ⁶	72 RRMM	9	69	28		11	75/4	15/4	
NCT03502577 Phase 1	CRB402 (bb21217) Murine scFv (11D5-3) 4-1BB Lentiviral vector Phosphoinositide 3 kinase inhibitor	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² CAR-T 50-450x10 ⁶ Gamma-secretase inhibitor (crenigacestat) 25 mg, thrice weekly for 3 weeks for up to 9 doses	18 RRMM	36	89	44	42	11	94/11	39/11	
NCT03090659 Phase 1/2 Legend-2	LCAR-B38M 2 camelid variable heavy chain only domains 4-1BB costimulatory domain Lentiviral vector	Fludarabine 25 mg/m ² Cyclophosphamide 250 mg/m ² D (-5 to -3), or cyclophosphamide 300 mg/ m ² CAR-T 0.07-2.1x10 ⁶ /kg	74 RRMM	47.8	87.8	73	NR	18	91.9/9.5	1	
NCT03548207 Phase 1b CARITUDE-1	JNJ-4528 (cilta-cel) 2 camelid variable heavy chain only domains 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 0.75x10 ⁶ /kg	97 RRMM	12.4	97	78	62.9 (36 months)	34.9	89.6/3	20.6/5	

Table 2. Continued.

Trial	CAR-T	Study design	Patients, n	Follow-up, months	ORR, %	CR, %	OS, months	PFS, months	CRS/CRS ≥grade 3, %	Neurotoxicity/neurotoxicity ≥grade 3, %
NCT04133636 Phase 1 CARTITUDE-2 Cohort A Cohort B Cohort C	JNJ-4528 (cilta-cel) 2 camelid variable heavy chain only domains 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 0.75x10 ⁶ /kg	20 RMMM 19 ER 20 Anti-BCMA	11.3	95 100 60	80 74 35	9.1	95/10 84/5 60/0	30/5 26/5 20/10	
Fully human anti-BCMA										
NCT0318861 Phase 1	KITE-583 Human anti-BCMA scFv CD28 costimulatory domain	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T: 30-1000x10 ⁶ /kg	14 RMMM	12	33	0	12.2	21.4/0	21	
NCT04318327 Phase 1	PHE885 T-charge platform enables in vivo CAR-T expansion and manufacturing in <2 days Human anti-BCMA scFv 4-1BB costimulatory domain Lentiviral vector	Fludarabine and cyclophosphamide regimens not stated CAR-T 5-14.3x10 ⁶	46 RMMM	4.9	98 (n=10)	50 (n=4)		96/11	22/7	
NCT03070327 Phase 1	MCArH171 Human scFv 4-1BB costimulatory domain, tEGFR safety switch Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3), or cyclophosphamide 3 g/m ² CAR-T 72-818x10 ⁶ /kg	11 RMMM		64			60/20	10/0	
NCT03430011 Phase 1/2 EVOLVE	JCARH125 (orva-cel) Human scFv 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 50-600x10 ⁶ /kg	44 RMMM	5.9	91	39	NR	-/2	-/4	
ChiCTR1800018137 Phase 1/2 FUMANBA-1 study	CT103A Human scFv 4-1BB costimulatory domain Lentiviral vector	Fludarabine 25 mg/m ² Cyclophosphamide 20 mg/kg for 3 days CAR-T 1-6x10 ⁶	103 RMMM	394 days	96	74		95/3	2	
NCT03602612 Phase 1	FHVH33-CD8BBZ Human heavy chain variable domain (FHVH33) 4-1BB costimulatory domain Gamma retroviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3)	25 RMMM		92	52 (SCR)	78 weeks	96/25	-/8	

Table 2. Continued.

Trial	CAR-T	Study design	Patients, n	Follow-up, months	ORR, %	CR, %	OS, months	PFS, months	CRS/CRS \geq grade 3, %	Neurotoxicity/neurotoxicity \geq grade 3, %
NCT03716856 NCT03302403 NCT03380039 Phase 1	CT053 Human scFv (25C2) 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 50x10 ⁶ to 18x10 ⁶ /kg	24 RRMM		88	79			63/0	0/4
NCT03975907 Phase 2 LUMMICAR	CT053 (zevor-cell) Human scFv (25C2) 4-1BB costimulatory domain Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 1x10 ⁶ /kg (n=3), 1.5x10 ⁶ /kg (n=11) CAR-T 1-3-6x10 ⁶ /kg	14 RRMM	13.6	100	92.9	NR 85% (1 year)		92.9/0	0
ChiCTR1800018137	CT103A (median persistence: 307.5 days)	CAR-T 1-3-6x10 ⁶ /kg	18 RRMM		100	72.2			70.6	0
Other anti-BCMA techniques										
NCT03288493 Phase 1/2 PRIME/POSEIDA	P-BCMA 101 Non-viral piggyBac DNA mod system using transposons and rimiducid	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 0.75-15x10 ⁶ /kg	43 RRMM		57				17/1	1/0
NCT04093596 Phase 1 UNIVERSAL	ALLO-715 Second-gen scFv with TALEN knockout of T cell receptor alpha constant and CD52 with rituximab safety switch	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 40-480x10 ⁶ /kg	53 RRMM		80 (FCA 60) 63.6 (FCA 39)	20 (FCA 60) 27.3 (FCA 39)			52/2	11/0
NCT05396885 Phase 2 iMMagine-1	ddBCMA, anitocbtagene autofeucel synthetic antigen-binding domain with reduced immunogenicity and improved CAR stability	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T: 115x10 ⁶ /kg	58 RRMM		95	62			84/2	9/2 (ICAN)
NCT04115749 Phase I	ddBCMA	CAR-T 100 or 300x10 ⁶ /kg	13 RRMM	12.6	100	75 (CR/sCR)			92/7	15
ChiCTR- OPC-16009113 Phase I	BRD05 murine anti-BCMA scFv CD3 ζ and CD28 domains	CAR-T 5.4-25x10 ⁶ /kg	28 RRMM		87	73				

BCMA: B-cell maturation antigen; CAR-T: chimeric antigen receptor T cell; ORR: overall response rate; CR: complete response; OS: overall survival; PFS: progression-free survival; CRS: cytokine release syndrome; scFv: single-chain variable fragment; ddBCMA: D-domain B cell maturation antigen; RRMM: relapsed/refractory multiple myeloma; ER: early relapse; FCA: fludarabine, cyclophosphamide, ALLO-647; VGPR: very good partial response; NR: not reached; sCR: stringent complete response; ICAN: immune effector cell-associated neurotoxicity.

Table 3. Early phase clinical trial results of non-BCMA and dual-target CAR-T products, adapted from Swan et al. [23].

Trial	CAR-T	Study design	Patients, n	Follow-up, months	ORR, %	CR, (%)	OS, months	PFS, months	CRS/CRS ≥grade 3, %	Neurotoxicity/ neurotoxicity ≥grade 3, %
Dual targets										
ChiCTR1800018143 Phase I	BCMA/CD38 Bispecific CAR-T cells Lentivirus	Fludarabine 25 mg/m ² Cyclophosphamide 250 mg/m ² D (-5 to -3) CAR-T 0.5-4x10 ⁶ /kg	28 RMMM	9	87	52 (sCR)	NR 75% (1 year)	17.2	87/21	0
ChiCTR1900026286 Phase I	BCMA/CD38 Hela cells	Fludarabine 25 mg/m ² Cyclophosphamide 250 mg/m ² D (-4 to -2) CAR-T 2.1x10 ⁶ /kg (range: 0.5-10.0x10 ⁶ /kg)	16 RMMM	11.5	88	%81	NR 75% (1 year)	NR 68.8% (1 year)	75/31.3	
ChiCTR1800017051 Phase II	Combined humanized anti-BCMA and anti-CD38 CAR-T cells	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-4 to -2) CAR-T 2.1x10 ⁶ /kg	22 RMMM	24	90.9	54.5	NR 56.6% (2 years)	NR 48.7% (2 years)	100/27.3	13.6/0
ChiCTR-OIC-17011272 Phase II	Combined humanized anti-BCMA and anti-CD19 CAR-T cells	Fludarabine 30 mg/m ² D (-5 to -3) Cyclophosphamide 750 mg/m ² D (-5) CAR-T 1x10 ⁶ /kg	21 RMMM	179 days	95	56			90/4	
ChiCTR-OIC-17011272 Phase II	Combined humanized anti-BCMA and anti-CD19 CAR-T cells Lentiviral vector	Fludarabine 30 mg/m ² D (-5 to -3) Cyclophosphamide 750 mg/m ² D (-5) CAR-T 1x10 ⁶ /kg	62 RMMM	21.3	92	60	NR 84% (2 year)	18.3	95/10	11
NCT03455972	Combined humanized anti-BCMA and anti-CD19 CAR-T cells after ASCT Lentiviral vector	Induction: PADx4 Mobilization: Cyclophosphamide 3 g/m ² Conditioning: Busulfan 2.4 mg/kg D (-8 to -5) CAR-T 1-5x10 ⁷ /kg Maintenance: Lenalidomide	43 NDMM, HR	63.4	100	89.2	NR 85.3 (5 years)	NR 59.2 (5 years)	100	0
NCT02546167 Phase I	Combined humanized anti-BCMA and anti-CD19 CAR-T cells (huCART19)	Arm A: CAR-T 5x10 ⁶ /kg Arm B: CAR-T 5x10 ⁸ /kg + lenalidomide/pomalidomide maintenance	Arm A: 10 RMMM Arm B: 20 NDMM, HR	Arm B: 248-966	23	6	NR	NR	90 (Arm B)	3 (Arm B)
NCT04935580 Phase I	Combined anti-BCMA and anti-CD19 FastCAR-T cells (GC012F)	Several induction regimens Fludarabine 30 mg/m ² D (-5 to -3) Cyclophosphamide 750 mg/m ² D (-5) CAR-T 1x10 ⁵ /kg, 2x10 ⁵ /kg, 3x10 ⁵ /kg	13 NDMM, HR	5.3	95	69 (sCR)			23/0	0

Table 3. Continued.

Trial	CAR-T	Study design	Patients, n	Follow-up, months	ORR, %	CR, (%)	OS, months	PFS, months	CRS/CRS ≥grade 3, %	Neurotoxicity/neurotoxicity ≥grade 3, %
NCT04662099 Phase 1	BCMA/CS1 (7A8D5 clone) Bispecific CAR-T cells	Fludarabine 30 mg/m ² Cyclophosphamide 250 mg/m ² D (-5 to -3) CAR-T 0.75x10 ⁶ , 1.5x10 ⁶ , 3.0x10 ⁶ /kg	16 RRMM	290 days	100	31 (sCR)	NR 83.9% (1 year)	NR 55.2% (1 year)	38	0
Other targets										
NCT02135406 Phase 1	CTL019 (tisa-cel, Kymriah, Novartis) CD19 scFv (FMC63) 4-1BB costimulatory domain Lentiviral vector	Salvage melphalan ASCT followed CAR-T 1.1-6x10 ⁸	10 RRMM			80 (≥PR)			10/0	
NCT04555551 Phase 1	MCARH109 GPRC5D scFv Lentiviral vector	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 25-450x10 ⁶ /kg	17 RRMM	10.1	71	35			41/0	0
NCT03287804 Phase 1/2	AUTO2 truncated form of APRIL recognizes BCMA and TACI OX40 costimulatory domain Gamma retroviral vector RQR8 safety switch	Fludarabine 30 mg/m ² Cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 15-350x10 ⁵ /kg	11 RRMM	43		0	12.5	5	45/0	0
NCT02203825 Phase 1	Human NKG2D gamma retroviral vector	No lymphodepletion CAR-T 1x10 ⁶ -3x10 ⁷	5 RRMM (7 patients had AML)		0		4.7		0	0

BCMA: B-cell maturation antigen; CAR-T: chimeric antigen receptor T cell; ORR: overall response rate; CR: complete response; OS: overall survival; PFS: progression-free survival; CRS: cytokine release syndrome; scFv: single-chain variable fragment; ASCT: autologous stem cell transplant; RRMM: relapsed/refractory multiple myeloma; NDMM: newly diagnosed multiple myeloma; HR: high risk; AML: acute myeloid leukemia; NR: not reached; sCR: stringent complete response; PR: partial response.

Table 4. Description of ongoing clinical studies for all anti-multiple myeloma targets, adapted from Sheykhhasan et al. [4].

Trial	CAR-T	Study design	
NCT04196491 Phase 1 KarMMa-4	Bb2121/ide-cel 4-1BB costimulatory domain Lentiviral vector	4 cycles standard induction (KRd ±Dara, VRd ±Dara, CyBorD, fludarabine 30 mg/m ² , cyclophosphamide 300 mg/m ²), lymphodepletion and ide-cel CAR-T 150-800x10 ⁶	HR NDMM
NCT04855136 Phase 1/2 KarMMa-7	Bb2121/ide-cel 4-1BB costimulatory domain Lentiviral vector	Tolerability and efficacy of ide-cel in combination with other therapies in RRMM cohort A) CC-220 ± low-dose dexamethasone B) BMS986405 C) DPd/PVd CAR-T 150-450x10 ⁶	RRMM
NCT03448978 Descartes-08 Phase I/II	CD8 ⁺ , mRNA	Fludarabine, cyclophosphamide CAR-T	RRMM
NCT04436029 Descartes-11 Phase II	Earlier employment, CD8 ⁺ , mRNA		NDMM
NCT05182073 Phase I	FT576 BCMA CAR-NK	FT576 CAR-T 1-3x10 ⁶ /kg + daratumumab, fludarabine, and cyclophosphamide	RRMM
NCT03464916 Phase 1	CAR2 Anti-CD38 A2 CAR-T	Dose escalation of CAR2	RRMM
NCT03672318 Phase 1	ATLCAR anti-CD138 CAR-T	Fludarabine 30 mg/m ² , cyclophosphamide 300 mg/m ² D (-5 to -3) CAR-T 1x10 ⁶ -2x10 ⁸	RRMM
NCT03958656 Phase 1 CARAMBA	Sleeping Beauty gene transfer SLAMF7	Fludarabine 30 mg/m ² , cyclophosphamide 300 mg/m ² D (-5 to -3)	RRMM

BCMA: B-cell maturation antigen; CAR-T: chimeric antigen receptor T cell; ide-cel: idecabtagene vicleucel; RRMM: relapsed/refractory multiple myeloma; NDMM: newly diagnosed multiple myeloma; HR: high risk.

FH or synthetic binding domains aim to reduce immunogenicity. The CD28 costimulatory region activates more slowly compared to 4-1BB, but its persistence is longer [62]. The addition of a PI3K inhibitor to ide-cel can increase memory-like T-cells in an ex vivo environment [8]. The development of CAR-T enhancers is among the most recent advancements in this area. CAR-T cells can selectively activate the interleukin (IL)-2 signaling pathway in the presence of an immunomodulatory ligand. Thus, IL-2-related toxicities decrease while T cell activation and antitumor activities are enhanced [63]. Faster production may also increase the effectiveness of CAR-T cells. For example, FasT-CAR was developed based on this need. The vein-to-vein time, which can reach up to 6 weeks, has been reduced to less than 2 days with this new technology [64]. Allogeneic CAR-T and CAR-NK technologies are alternative options to serve this purpose as they are off-the-shelf products. In addition, recent studies have shown that adding selinexor to CAR-NK therapies with downregulation of HLA-E positively contributed to the outcomes [65].

Finally, a breakthrough has occurred in China in the form of early results showing the feasibility of in vivo CAR-T transduction and expansion, allowing for the bypassing of ex vivo apheresis and expansion procedures and speeding up access. ESO-T01 (NCT06691685) is a CAR-T cell produced in a similar manner, featuring a nanobody target, lentiviral vector, BCMA targeting,

and humanized in vivo proliferation capability. It has been administered to 4 patients with published results. Especially due to its in vivo tumor homing capability and success in infiltration, it appears promising, particularly for EMD patients [66]. A phase 1 study (inMMycAR) recently presented at the American Society of Hematology's 2025 session as publication number LBA-1 offers another in vivo CAR-T approach demonstrating MRD negativity within 3 months among 3 patients (NCT07075185) [67].

Conclusion and Future Perspectives

Following the highly successful results for RRMM, CAR-T cells are now moving to the frontline of MM treatment. However, investigations are still needed to improve the efficacy, shorten the vein-to-vein time, and decrease toxicity and costs while increasing access. Recent developments have begun to highlight ionizable lipid nanoparticle technology (L829-tLNP) and in vivo T cell engineering [68,69]. Finally, the possibility of editing normal T-cells with the CRISPR-Cas9 gene editing system and in vivo CAR-T production may enhance access to and the success of CAR-T therapies in the near future [70].

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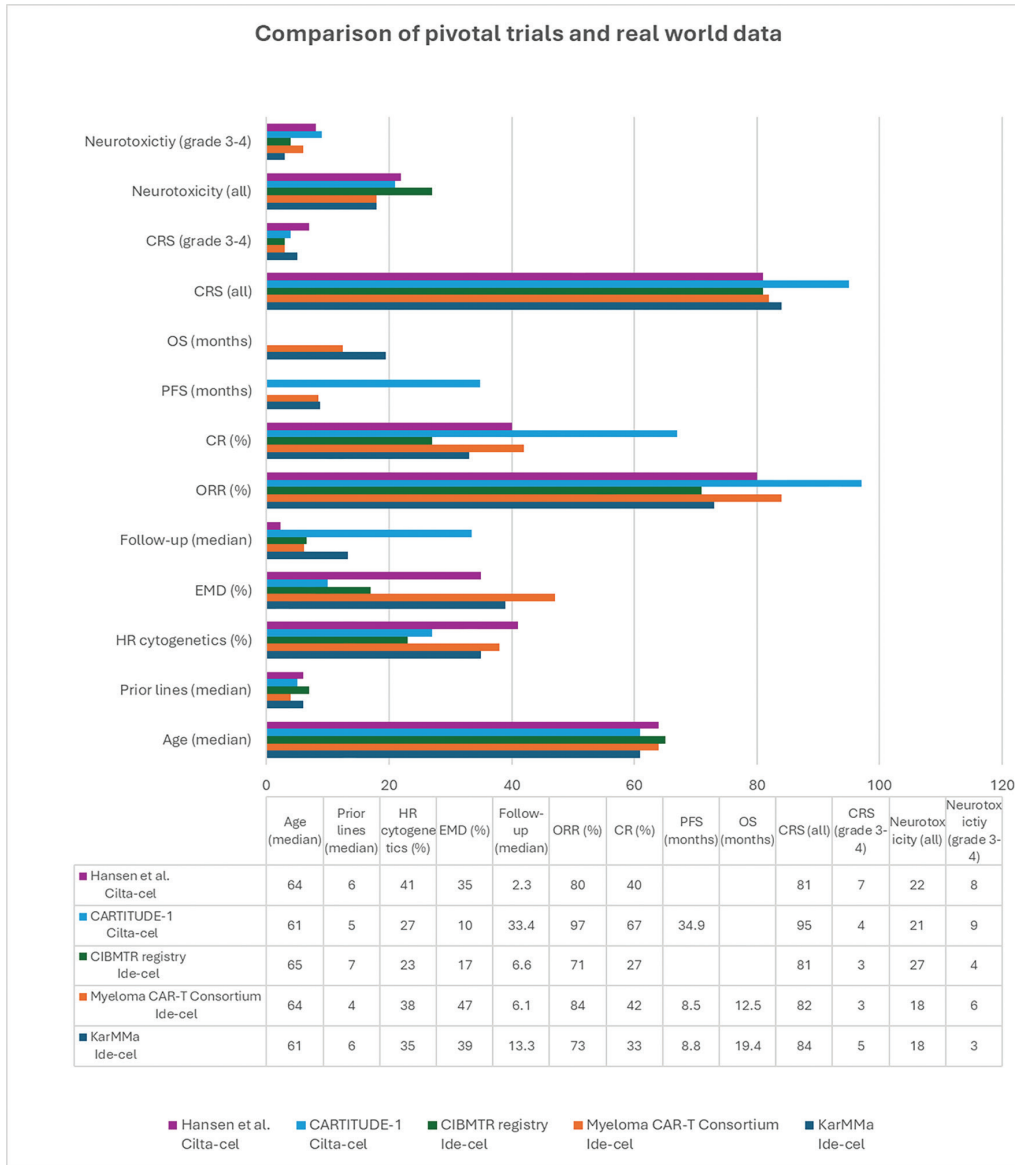


Figure 3. Comparison of clinical trial and real-world data adapted from the CAR-T Consortium, CIBMTR, and Hansen et al. [40,44,45,71,72].

CRS: Cytokine release syndrome; OS: overall survival; CR: complete response; HR: high risk; EMD: extramedullary disease; ORR: overall response rate; PFS: progression-free survival; cilta-cel: ciltacabtagene autoleucel; ide-cel: idecabtagene vicleucel.

Footnotes

Authorship Contributions

Concept: M.B.; Design: M.B.; Data Collection or Processing: E.V.; Analysis or Interpretation: M.B., E.V.; Literature Search: M.B., E.V.; Writing: E.V.

Conflict of Interest: Meral Beksac reports advisory board or speaker bureau participation with BMS, Janssen, Menarini, Pfizer, Abdi Ibrahim, Onko, Regeneron, Takeda, and GSK. These affiliations have no relevance to or involvement with the present manuscript. The remaining author also declares no conflict of interest.

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