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CAR-T cells for the treatment of relapsed/refractory multiple myeloma in 2022: efficacy and toxicity

Minireview

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Chimeric antigen receptor (CAR)-T cells are a new treatment modality in various hematological malignancies, including relapsed/refractory multiple myeloma (RRMM). RRMM patients have a poor prognosis, and their treatment options are limited. Currently available data from clinical trials on CAR-T cell therapy have demonstrated efficacy and manageable toxicity in RRMM. The CAR-T cells in RRMM mostly focus on already known cellular targets, such as B-cell maturation antigen (BCMA). CAR-T cells focusing on other targets have been analyzed in various clinical trials as well. Cytokine release syndrome (CRS), specific neurotoxicity, and hematological toxicity are the main adverse events (AE); according to the clinical trials, they are mostly mild with a low incidence of grade 3 or higher toxicities. The autologous CAR-T cell therapy against BCMA (ide-cel and cilta-cel) shows the best efficacy with an overall response rate and a median progression-free survival in RRMM. Both ide-cel and cilta-cel have already been approved by the FDA. Currently, the main controversies in the routine use of CAR-T cells are high treatment costs and unknown long-term efficacy. In this review, we summarize the current overview of CAR-T cell therapies in RRMM in 2021 with various targets for CAR-T cells and their efficacy, safety, and possible limitations. Future prospective clinical trials are needed to clarify the optimal role of CAR-T cells in MM therapy.

Key words: multiple myeloma, CAR-T cells, chimeric antigen receptor, B-cell maturation antigen

Multiple myeloma (MM) is a hematological malignancy characterized by clonal plasma cell proliferation [1]. In Europe, MM incidence is 4.5–6/100,000 with a median age at diagnosis between 63 and 70 years [2]. So far, a standard therapy for relapsed/refractory multiple myeloma (RRMM) patients is mostly immunomodulatory drugs (IMIDs) or proteasome inhibitors (PI) combined with anti-CD38 monoclonal antibody (i.e., daratumumab, isatuximab). This treatment is highly effective in achieving response, but patients still relapse [3]. The patients who are refractory to all these modalities are called triple-refractory or penta-refractory in case of refracterity to 2 IMIDs, 2 PI, and anti-CD38 monoclonal antibody [4]. Searching for a new treatment approach for such advanced MM patients became a relevant clinical issue. CAR-T cell therapy represents a relatively novel promising immunotherapeutic method showing clinical potential in other hematological malignancies, such as acute lymphoblastic leukemia and diffuse large B cell lymphoma [5, 6]. Several CAR-T products have already been developed for the treatment of MM [7, 8]. Currently, some of these products are already approved [9]. However, there are some issues that have to be overcome before CAR-T cells are generally clinically used, such as toxicity and long-term outcomes. In this review, we describe recent clinical and preclinical findings about CAR-T cell therapy aimed against MM.

CAR-T cells

CAR-T cells are genetically modified T cells containing antigen-specific extracellular domain linked to a transmembrane component, followed by the intracellular costimulatory domain and the CD3ζ part of the T-cell receptor (TCR) complex [10]. There are four generations of CAR-T cells (Figure 1) [11]. The CAR-T cells of the first generation have

only the CD3ζ part as an intracellular domain [12]. However, these CAR-T cells could not produce enough interleukin 2 (IL-2) to kill tumor cells [13]. In the second generation of CAR-T cells, cytokine receptors and co-stimulatory receptors are present, such as CD28, OX-40, or 4-1BB, which can improve cytotoxicity and proliferation as well as *in vivo* survival [14–16]. In the third generation of CAR-T cells, multiple signaling domains, such as CD3ζ-CD28-OX40, or CD3ζ-CD28-41BB, are present. They can potentiate cytokine production [17]. The fourth generation is typical by adding interleukin-12 to the base of the construct used in the second generation. These CAR-T cells are known as T-cell-redirected for universal cytokine-mediated killing (TRUCKs). They are able to activate the innate immune cells to eliminate antigen-negative tumor cells [18].

The CD3ζ part leads to T-cell activation, while the costimulatory molecules, such as CD28, 4-1BB, and OX-40, enhance the T-cell response. Moreover, costimulatory molecules can modify the phenotype of the CAR-T cells, such as memory phenotype or effector T-cell phenotype [16, 17].

The CAR-T cells have an antigen-specific part, which is variable and adjustable for a specific target and has HLA independent function, making the CAR-T cell therapy applicable in various hemato-oncologic diseases regardless of HLA typing [19–21].

Autologous CAR-T cells' production time is another key limitation mostly for adjustment of manufacturing processes for each patient individually. The time interval between clinical decision to use CAR-T cell therapy for an individual patient takes a least 3 weeks but often more [22].

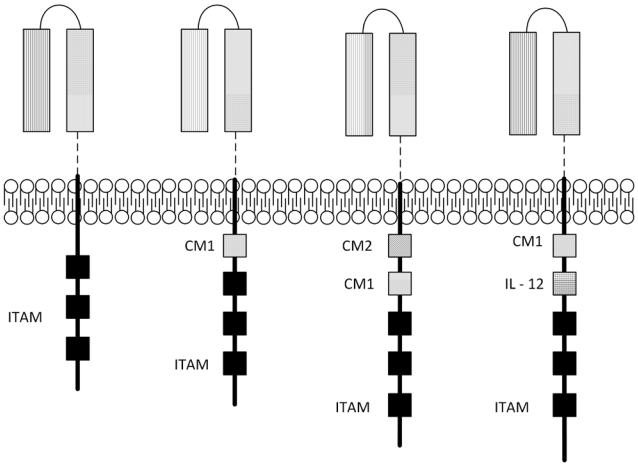

Figure 1. Four generations of CARs. The single chain is connected with immunoreceptor tyrosin-based motifs (ITAMs) in the first generation. In the second and third generations, the costimulatory molecules (CM) are added. In the fourth generation, interleukin-12 (IL-12) is connected with the signal transduction region.

Targets for CAR-T cell therapy in MM

B-cell maturation antigen (BCMA). BCMA is currently considered to be the most convincing and the best-known target for CAR-T cells therapy in the field of MM so far [23]. BCMA is widely expressed on the surface of plasma blasts and mature plasma cells (PC), playing important role in proliferation, maturation, terminal differentiation, and survival [23]. A BCMA-targeted CAR-T cell therapy shows promising results in heavily pretreated RRMM patients and has been described in most trials until now [19]. Ide-cel and cilta-cel are the most relevant drugs concerning BCMA-targeted CAR-T cell therapy. Both of these therapies have been approved by the FDA. Both ide-cel and cilta-cel will be compared in the following section.

Ide-cel (idecabtagene vicleucel). The first treatment results using BCMA-targeted CAR-T cells ide-cel were presented in the first-in-humans phase I CRB-401 trial [24]. In this trial, 62 patients were enrolled, and efficacy and safety data were reported. The patients were divided into cohorts covering dose-escalation and dose-expansion. After lymphodepletion with fludarabine (30 mg/m^2/day) and cyclophosphamide (300 mg/m^2/day), patients received ide-cel at target doses of 50, 150, 450, or 800×10^6 CAR-T cells in the dose-escalation phase, and 150 to 450×10^6 CAR-T cells in the dose-expansion phase. The median age was 61 years. Out of all patients, 45% received >6 prior regimens of treatment, 90% were daratumumab-exposed, and 77% were daratumumab-refractory. The overall response rate (ORR) was achieved by 47 patients (76%), and 24 (39%) of them achieved complete response (CR). Fifteen patients who reached CR or better response were assessed for minimal residual disease (MRD) and were MRD-negative at the level of 10^{-5} [24].

Median overall survival (OS) was 34.2 months. Median progression-free survival (PFS) was 8.8 months. Median follow up for all patients was 9.0 months.

The most frequent adverse events (AE) were neutropenia (92%), cytokine release syndrome (CRS) (76%), anemia (76%), and thrombocytopenia (74%). The incidence and severity of CRS events were CAR-T cells dose-dependent. Most CRS events were of grade 1 or 2 (51 patients); only 4 patients had grade 3 CRS. The neurotoxicity, which is a typical AE for CAR-T cells next to CRS, manifesting itself by a wide range of symptoms such as delirium, language or behavioral disturbance, headache, tremor, etc., was observed in 44% of patients and was mostly grade 1 or 2 (1 patient had grade 3 and 1 patient grade 4 [24, 25].

For further clinical output, the KarMMa phase II study was initiated to evaluate the potential of ide-cel in a larger group of triple refractory patients who have already been exposed to immunomodulatory drugs (IMiD), a proteasome inhibitor, and a CD38 antibody [26]. In this trial, 128 patients received CAR-T and 88% of them received previous bridging therapy. Out of all patients, 84% were triple refractory and 26% had even penta-refractory disease. The patients had a median of 6 lines of previous therapy. In total, 73% of patients responded to the therapy. CR or better response was achieved by 33% of patients. MRD-negative CR was achieved in 26% of patients.

The patients with a stage 3 disease according to R-ISS had a worse response in comparison to those with R-ISS stage 1 or 2. With a median follow-up of 13.3 months, the median PFS was 8.8 months. The median of PFS was also affected by the dose of CAR-T cells and depth of response. The patients who received 450×10^6 CAR-T cells had a median PFS of 12.1 months, and patients who achieved at least CR experienced median of PFS 20.2 months. Median OS was 19.4 months. Durable CAR-T persistence was observed for up to 1 year and CAR-T were detected at 1, 3, 6, 9, and 12 months in 99%, 75%, 59%, 37%, and 46%, respectively [26].

The main AE was hematologic toxicity including cytopenia (97%) following CRS (84%) which was mainly grade 1 or 2, only 9 patients had higher grades CRS in total. The median time to onset of CRS was 1 day. Neurotoxicity developed in 18% of patients, mostly grades 1–2 [26].

The multicenter, randomized, open-label phase 3 trial KarMMa-3 compares ide-cel with standard regimens including IMiDs, proteasome inhibitors, and CD38 antibody in RRMM patients. This trial is anticipated to randomize approximately 381 patients who received 2–4 prior lines of treatment and thus is aiming to examine the effect of ide-cel in an earlier line of treatment [27].

The possibility of the earlier use of ide-cel in RRMM patients in R-ISS stage III is discussed in a multicenter, open-label, phase 1 trial with single arm KarMMA-4. The patients should receive 4 cycles of induction therapy prior to obtaining ide-cel [28].

In an ongoing phase 1/2 of KarMMa-7-exploratory, open-label, multicenter trial – ide-cel is combined with other drugs in specific arms of this trial. It concerns patients who received either ≥3 or 1–3 prior regimens depending on the treatment arm. In arm A, there is ide-cel with iberdomide (cereblon E3 ligase modulator, IMiD) and dexamethasone as maintenance therapy. In arm B, there is ide-cel and BMS-986405, a gamma-secretase inhibitor that blocks the shedding of surface BCMA to enhance the antitumor activity of ide-cel, as concurrent therapy. In arm C, there is ide-cel with daratumumab, pomalidomide, and dexamethasone as maintenance therapy [29].

bb21217 is a BCMA-directed CAR-T cell therapy, which uses the same molecule as ide-cel but a PI3K inhibitor (bb007) is added. CRB-402, a multi-center phase 1 trial of bb21217 concerns mostly triple-refractory patients. In total, 72 patients received bb21217, 12 at 150, 14 at 300, and 46 at 450×10^6 CAR-T cells. Patients had a median of 6 lines of prior therapy. A median follow-up was 9.0 months. ORR was 69% and 58% of patients reached VGPR or better response; 28% achieved sCR/CR. CRS developed in 75% of patients and was mostly grades 1–2. Neurotoxicity was observed in 15% of patients. Fifteen patients with CR or better response were evaluated for MRD and 14 of them by NGS (93% were MRD-negative at the level of 10^{-5} by NGS. Patients with higher levels of less differentiated memory like $CD8^+$ CAR-T cells had a significantly longer duration of response (DOR) (27.2 months) in comparison to those with lower levels of $CD8^+$ CAR-T cells than median values (DOR 9.4 months) [30].

Cilta-cel (ciltacabtagene autoleucel). The results of treatment with cilta-cel were presented in phase Ib and in phase II of the CARTITUDE-1 trial. [31]. The trial included 97 MM patients with a median of 6 previous treatment lines; 87% of these patients were triple-refractory and 42% were penta-refractory. The median age at diagnosis was 61 years. Patients underwent three-day lymphodepletion with cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 with subsequent single infusion of cilta-cel at a target dose of 0.75×10^6 cells/kg [31].

ORR was 97.9%, sCR was achieved in 80.4% of patients, VGPR in 94.8%. The median DOR was 21.8 months. Moreover, out of 61 patients evaluable for MRD assessment, 91.8% achieved MRD-negativity at the level of 10^{-5} [31]. This MRD negativity was sustained for ≥6 months in 44.3% of patients and ≥12 months in 18% of patients.

The 18-month PFS and OS rates were 66% and 80.9%, respectively [31]. Eighteen-month PFS rates in patients who achieved sustained MRD for ≥6 months and ≥12 months were 96.3 and 100%, respectively. CAR-T were observed in 36% of patients at 3 months of follow-up. The response to cilta-cel was independent of CAR-T expansion and persistence [32].

The most common hematologic AEs were neutropenia (94.8%), anemia (68%), leukopenia (60.8%), and thrombocytopenia (59.8%) [31]. Nonhematologic AEs included CRS and specific neurotoxicity. CRS occurred in 94.8% of patients and was predominantly mild (95%). Approximately 21% of patients had neurotoxicity; 10% of grade ≥3. There were 6 deaths due to treatment-related AEs (sepsis, CRS, lung abscess, respiratory failure, and neurotoxicity) [31].

To compare patients' outcomes of cilta-cel vs. real-world-clinical-practice (RWCP), the LocoMMotion trial was done. There were 246 patients enrolled in this trial. More than 90 treatment regimens were used. The most frequently used regimens were carfilzomib and dexamethasone (13.8%), pomalidomide, cyclophosphamide and dexamethasone (12.6%), and pomalidomide and dexamethasone (11.0%). Adjusted comparisons versus CARTITUDE-1 trial shows improved ORR, CR, PFS, and OS for cilta-cel compared to those patients of RWCP: ORR (RR=4.43 vs. 3.00), CR (RR=568.92 vs. 169.8), PFS (HR=0.15 vs. 0.17), OS (HR=0.38 vs. 0.31), all comparisons with $p<0.001$. RR = response-rate ratio derived from the adjusted odds ratios [33].

There are more trials concerning cilta-cel and further investigations are ongoing in earlier lines of therapy. The phase 2, multicohort CARTITUDE-2 trial, is evaluating the safety and efficacy of cilta-cel in patients with MM in the various setting of the disease. There were 18 patients enrolled, all received 1 prior line of therapy. The median age of the patients was 57 years. The median follow-up was 4.7 months. 14 patients underwent prior ASCT, and 15 were

refractory to their prior therapy. ORR was 88.9%. CR was achieved by 27.8% of patients, and 66.7% achieved at least VGPR. Of 9 patients who were MRD-evaluated, all of them (100%) reached MRD negativity at the level of 10^{-5} [34].

Cilta-cel is also being evaluated in an ongoing phase 3 trial CARTITUDE-4, where it is compared to pomalidomide, bortezomib, and dexamethasone; or daratumumab, pomalidomide, and dexamethasone in patients with relapsed and lenalidomide-refractory MM [https://clinicaltrials.gov/ct2/show/NCT04181827].

There is also a possibility of using cilta-cel in patients with newly diagnosed MM. The purpose of the upcoming CARTITUDE-5 trial is to compare the efficacy of bortezomib, lenalidomide, and dexamethasone (VRd) induction followed by a single administration of cilta-cel vs. VRd induction followed by lenalidomide and dexamethasone maintenance in patients with newly diagnosed MM for whom ASCT is not planned as initial therapy [https://clinicaltrials.gov/ct2/show/NCT04923893].

Table 1 summarizes the comparison of 2 main anti-BCMA CAR-T – ide-cel and cilta-cel.

Other BCMA-specific CAR-T cells. Orva-cel (orvacaptagene autoleucel) is a BCMA-directed CAR-T product with a fully human binder. This product is currently evaluated in phase I/II of the EVOLVE trial. Over 100 patients were treated in this trial with a median of 6 prior lines of therapy, 92% of them were penta-refractory. The median age of patients was 61 years. The study reported results of 51 patients who received doses of 300, 450, and 600×10^6 CAR T-cells; ORR was 91%. CR was reached in 39% of patients. After a median follow-up of 5.9 months, the median PFS was not reached. CRS of grade ≥3 was observed in 2% of patients and neurotoxicity of grade ≥3 in 4% of patients. There was also durable persistence of CAR-T cells where 69% of patients had detectable CAR T-cells after 6 months after infusion [35].

A clinical trial of LCAR-B38M CAR-T cells conducted in The Second Affiliated Hospital of Xi'an Jiaotong University in China presents results of bispecific CAR-T cell construct derived from Lama *Glama sp.* heavy chain, which targets 2 distinct BCMA epitopes antibodies [36, 37]. This option provides a higher affinity toward BCMA. Unlike other CAR-T cell constructs, in this case, the scFv domain is not present. The trial reported data from 57 patients, all treated at 1 center, with a median of 3 prior treatment lines. In total, ORR was found in 88% of patients, 74% of patients achieved CR and 68% of patients achieved MRD negative CR assessed by bone marrow eight-color flow cytometry. At a median of follow-up of 25 months, the median PFS was 19.9 months for all patients. Patients with CR had median PFS of 28.2 months. The median OS was 36.1 months [37].

A meta-analysis of 22 trials concerning anti-BCMA CAR-T cells was done and demonstrated that the pooled ORR was 85.2%, pooled CRR 47%, and pooled rate of MRD negativity reached up to 97% [38]. The median PFS was 14 months and the median OS was 24 months [38]. The PFS and CRR of patients with extramedullary disease (EMD) were significantly shorter than those without EMD [40]. The data from meta-analysis also showed that a higher dose of CAR-T cells might be in correlation with severe CRS and thus it is not necessary to increase the dose to enhance the therapeutic effect [38]. Not all patients could be examined by NGS or new generation flow for MRD detection at the 10^{-5} or 10^{-6} sensitivity level, which led to the inclusion of only 7 trials in MRD negativity analysis [40]. More sensitive techniques for evaluating MRD are being developed [39].

Table 1. Comparison of ide-cel to cilta-cel (KarMMa phase II and CARTITUDE-1 phase IB/II).

	Orva-cel (EVOLVE phase I/II)	LCAR-B38M (bispecific CAR T)
Dose of CAR-T	$300\text{-}600\times10^6$	Not stated
Number of patients	51	57
Median of prior therapies	6	3
Penta-refracterity (%)	92	Not stated
ORR (%)	91	88
CR (%)	39	74
Median PFS	Not reached	19.9 months
Median OS	34.2 months	36.1 months
CRS (grade ≥3) (%)	2	7
Median time to CRS onset (days)	Not stated	9
Neurotoxicity (all grades) (%)	Not stated	1 patient
Neurotoxicity (grade ≥3) (%)	4	0

Abbreviations: CR-complete response; ORR-overall response rate; OS-overall survival; PFS-progression-free survival; CRS-cytokine release syndrome

Other targets of CAR-T cells

CD138-specific CAR-T cells. Malignant PC express on their surface also CD138 [40]. It can be also aimed by CAR-T cells since CD138 was proven to be an effective target in the preclinical trial [41]. There is a clinical report of 5 patients treated with chemotherapy and autologous stem cell transplantation (ASCT). The patients obtained an average dose of 0.756×10^7 cells/kg of CD138 CAR-T cells. The CAR-T cells were detectable at high levels in the peripheral blood of all patients for at least 4 weeks after infusion. Four patients responded to therapy and MM regression lasted for 3–7 months while the other patients progressed. No CR was achieved in this trial. Only mild adverse events were observed, including fever grade 3 and nausea with vomiting of grade 2 [42].

CD38-specific CAR-T cells. CD38 is a glycoprotein found on the surface of immune cells, such as B and T cells, PC, natural killer (NK) cells [43]. A higher density of CD38 on malignant PC surface, when compared to other cell types, explains the high efficiency of nowadays widely used anti-CD38 antibodies [43, 44]. Bispecific CAR-T cells against CD38 and BCMA are presented in the clinical trial of 26 CD38 naïve patients [45]. The construct of CAR T-cells

was composed of an anti-BCMA scFv and an anti-CD38 scFv connected together by using 4-1BB-containing second-generation formats of CAR-T cells [45]. All patients received lymphodepleting chemotherapy of cyclophosphamide (250 mg/m^2, day –5 to –3) and fludarabine (25 mg/m^2, day –5 to –3) [45]. In total, 20 patients (77%) responded to the treatment including 12 (46%) with sCR, 4 (15%) with VGPR and 4 (15%) with PR [45]. All responders achieved MRD-negativity on the level of $\leq 10^{-4}$ nucleated cells. The median follow-up was 9 months [45]. Hematologic toxicity was the most common AE, including neutropenia in 96% of patients, leukopenia in 87% anemia in 43%, and thrombocytopenia in 61% [45]. CRS occurred in 87% of patients and was mostly grade 1–2 (65%), neurotoxicity was not observed [45].

GPRC5D-specific CAR-T cells. G protein-coupled receptor, class C group 5 member D (GPRC5D), is expressed on CD138$^+$ MM cells [46]. A phase I first-in-human dose-escalation trial MCARH109, the first GPRC5D aimed CAR-T cell therapy, reports the results of safety and efficacy of this product. Twelve patients received MCARH109 treatment. The median age was 59 years, and the median of prior lines of therapy was 8. All patients were triple-refractory and 92% were penta-refractory. Fifty % of patients received prior BCMA CAR-T therapy; 83% of patients responded to therapy. Moreover, 16.6% of patients had sCR, 24.9 had VGPR. All 6 patients who were exposed to prior BCMA CAR-T therapy had a response including those with sCR. With a median follow-up of 13 weeks, 75% of patients are progression-free and followed without additional therapy. CRS of grade 1–3 occurred in 92% of patients with only 1 case of grade 3. There were no reports of neurotoxicity so far [47].

CD19-specific CAR-T cells. MM cells can also express low levels of CD19 on their surface [48]. One proof-of-concept pilot trial evaluated the efficacy of CD19-specific CAR-T cells. Twelve patients were enrolled and 10 received CD19 CAR-T cell therapy (CTL019) after previous ASCT. Out of all patients, 6 achieved VGPR, 2 achieved PR, and 2 patients progressed. Only minor adverse events (AE) were detected, such as CRS of grade 1 [49].

SLAMF7-specific CAR-T cells. The antigen signaling lymphocytic activation molecule (SLAM) family member 7 (SLAMF7) is an immunomodulatory receptor, which was identified on the surface of NK cells [50]. It is expressed on immune cells like T cells, B cells, and PC [51], as well as on aberrant PC and their precursors [52]. That enables using of CAR-T cells aimed against SLAMF7. CARAMBA is the first ongoing in-human clinical trial phase I/IIA that investigates the efficacy, safety, and feasibility of autologous SLAMF7 CAR T-cells [53]. The allogeneic 'of the shelf' engineered CAR T-cells (UCARTCS1) gaining FDA approval for the clinical trial (MELANI-01) were prepared with the TCRα constant (TRAC) gene using transcription activator-like effector nucleases (TALEN) to minimize the risk of GvHD. CAR-T cells were manufactured from T-lymphocytes of

Table 2. Comparison of the other BCMA-directed CAR-T cell products.

	ide-cel (KarMMa, phaseIII)	cilta-cel (CARTITUDE-1, phase IB/II)
Antigen-binding domain	scFv (murine)-monospecific	Bispecific fragments of llama heavy-chain antibodies - bi-epitope BCMA enables high avidity binding
Vector	Lentiviral	Lentiviral
Lymphodepletion	Fludarabine/Cyclophosphamide	Fludarabine/Cyclophosphamide
Dose of CAR-T	$150–450\times10^6$	Median dose: 0.7×10^6/kg
Number of patients	128	97
Bridging therapy (%)	88	65
Median of prior therapies	6	6
Triple-refracterity (%)	84	88
Penta-refracterity (%)	26	42
Extramedullary disease (%)	39	13
PR (%)	73	97
CR (%)	33	67
Median PFS	8.8 months	Not reached; 18-months PFS rate 66%
Median OS	34.2 months	Not reached; 18-months OS rate 80.9%
CRS (all grades) (%)	84	94.8
CRS (grade ≥3) (%)	5	4
Median time to CRS onset (days)	1	7
Neurotoxicity (all grades) (%)	18	21
Neurotoxicity (grade ≥3) (%)	3	10
Hematologic toxicity (%)	97	94.8
CAR-T persistence 6 months (%)	59	42

Abbreviations: CR-complete response; ORR-overall response rate; OS-overall survival; PFS-progression-free survival; CRS-cytokine release syndrome

healthy donors [54]. A novel anti-SLAMF7/BCMA bispecific CAR-T cell product is under preclinical development. These CAR-T cells showed superior CAR expression and function in comparison to T cells expressing individual CARs [55].

Allogeneic CAR-T cells

Autologous type of CAR-T cells has their own limitations, such as the process of product manufacturing and the long time between the isolation of CAR-T cells from the patient and their application during the progression of the disease [56].

Allogeneic CAR-T cells may overcome these limitations. However, there is a risk of GvHD using these allogeneic CAR-T cells. To prevent GvHD, the TALEN- and CRISPR-gene-editing were used to enable allogeneic CAR-T cells to be safer and less inducing GVHD [54, 57]. BCMA-targeted allogeneic CAR-T cell product has already shown some results in the trials mentioned above [54]. By incorporating a CD20 mimotope-based switch-off into the CAR construct, which mimics the structure of CD20, rituximab could be used to eliminate the CAR-T in case of AE. In the current investigational trials, there are included i) a non-viral piggyBac system, ii) Cas-CLOVER™ gene editing system including CRISPR guide-RNA, and iii) a nano-particle delivery system carrying the gene for an anti-BCMA CAR with a fully human binding domain. Rimiducid, a tacrolimus analog, can be used for safety switch activation [58].

A second major challenge of allogeneic CAR-T cell therapy is *in vivo* persistence of CAR-T cells [59]. Repeated administration of allogeneic CAR-T cells requires repeated patient immunosuppression. That forms an idea of creating CAR-T cells that can resist lymphodepleting agents. To do this, αβ TCR-deficient CAR-T cells were made resistant to multiple purine nucleotide analogs by deletion of the deoxycytidine kinase gene and showed the capability of efficient tumor cell killing in the presence of lymphodepleting agents [60].

Safety of CAR-T cells in MM therapy

The most common side effect in patients treated with CAR-T cells is CRS. CRS is a potentially life-threatening complication, which was observed mostly after the administration of CAR-T cells into the patients [61]. It occurs when large numbers of T-cells and B-cells are activated and produce inflammatory cytokines, such as IFNγ, IL-6, TNFα, and IL-10 [62]. In the case of CAR-T cells, the CRS symptoms' onset occurs days after the infusion of CAR-T cells [26, 31, 61]. The main mediator responsible for symptoms is IL-6 together with IL-1, both inducers of inducible nitric oxide synthase produced by macrophages [61, 62]. This enzyme enables the production of nitric oxide, which causes vasodilatation and hypotension which are features of CRS [62]. The high levels of IL-6 initiate a proinflammatory signaling cascade [61]. The symptoms are various and can be manifested as fever, which is most common, but also other symptoms, such as rash, gastrointestinal symptoms (vomiting, diarrhea), cardiovascular symptoms (tachycardia or hypotension) [61]. Potentially life-threatening can be cardiac dysfunction, adult respiratory distress syndrome, hepatic or renal failure, disseminated intravascular coagulopathy, and neurologic toxicity [61]. Severe CRS of grade 3–4 requires an intensive care approach, based on vital function support and monitoring. Tocilizumab (monoclonal antibody aiming receptor for IL-6) in combination with steroids is used for the treatment of severe forms of CRS [61]. Tocilizumab prevents IL-6 to interact with its receptors and thus inhibits cascades responsible for inflammatory symptoms [61].

It is predictable that IL-6 levels rise transiently following administration of tocilizumab due to the blockage of the receptor when tocilizumab cannot cross the hematoencephalic barrier. Thus, the elevation of IL-6 within the CNS may even be transiently aggravated by tocilizumab therapy [61]. Therefore, high grades of CRS (grades 3–4) with neurologic symptoms are treated with corticosteroids [61]. It has been tested on mice xenografts that Anakinra (IL-1 receptor antagonist) can also damper the severity of CRS [62].

In association with CRS, neurotoxicity is often AE [63]. Along with CRS, neurotoxicity seems to be caused by antigen recognition of the synthetic CAR receptor. For prevention of these specific forms of toxicity, an alternative receptor (T cell antigen coupler-TAC) has been developed. The TAC can effectively co-opt the endogenous TCR and induce antitumor response and less toxicity, which was preclinically confirmed [63].

The neurotoxicity consists of a wide range of symptoms including language disturbance, delirium, headache, tremor, behavioral disturbances, peripheral neuropathy, visual changes, etc. [64]. Acute cerebral edema is probably the most serious and potentially life-threatening complication which was described after treatment with CAR-T cells against CD-19 [64]. Very delayed symptoms, such as progressive movement disorder with features of Parkinsonism approximately 3 months after infusion of CAR-T, were described also [65].

Tocilizumab or corticosteroids can be used for the management of neurotoxicity as described above [64].

In clinical trials with CAR-T cells, other non-specific AEs, such as thrombocytopenia, anemia, or neutropenia appeared. These AEs can be managed by G-CSF or blood transfusions [31].

Limitations of CAR T-cell therapy

The exposure of BCMA-positive tumor cells to BCMA-directed CAR-T cells leads to the selection of those tumor cells with lower expression of BCMA and therefore to resistance against CAR-T cells [66]. One of the possible explanations for BCMA antigen escape is the process called trogocytosis-BCMA can be transferred from tumors to T cells causing T-cell fratricide [67]. Or it can be shed in the blood circu-

Table 3. Comparison of the other CAR-T cell products.

	CD38/BCMA (bispecific)	GPRC5D (MCARH109, phase I)
Lymphodepletion	Fludarabine/Cyclophosphamide	Not stated
Number of patients	26	12
Median of prior therapies	4	8
Triple-refracterity (%)	Not stated	100
Penta-refracterity (%)	Not stated	92
Extramedullary disease (%)	Not stated	50
ORR (%)	77	83
CR (%)	46	16.6
Median PFS	17.2 months	Not stated
Median OS	Not reached	Not state
CRS (grade ≥3) (%)	17	1 patient
Median time to CRS onset (days)	9	Not stated
Neurotoxicity (all grades) (%)	0	0
Neurotoxicity (grade ≥3) (%)	0	0

Abbreviations: CR-complete response; ORR-overall response rate; OS-overall survival; PFS-progression-free survival; CRS-cytokine release syndrome

lation which is mediated by γ-secretase [68]. The molecular BCMA aberration was described in a study using longitudinal single-cell transcriptomic analysis. [69]. The resistance to bb2121 in a patient was associated with biallelic loss of BCMA leading to BCMA inactivation [69]. The therapeutic strategies to overcome resistance to BCMA-targeted CAR-T cells include the usage of non-BCMA-targeted CAR-T cells, such as anti-SLAMF7, anti-GPRC5D, anti-CD38 as well as dual-targeted CAR-T cells as mentioned above [70].

Some patients, especially those with more comorbidities, can be more sensitive to toxicity related to CAR-T cell therapy. For this population of patients, BCMA-specific Ab-drug conjugates (ABDs) can provide an alternative solution [71]. The drug belantamab mafadotin releases the cytotoxic agent auristatin F and helps with eliminating tumor cells through cellular toxicity. It is administered every 3 weeks and the most common AE is corneal toxicity (occurring in 70% of patients. This immunotherapy is also one of the options for patients who relapsed after CAR-T cell therapy [71].

Bridging therapy was described in a trial of 75 patients with large B-cell lymphoma as the therapy between the leukapheresis and the start of lymphodepleting therapy for CAR-T therapy [72]. Both pharmacological and radiotherapy bridging were used [72]. Retreatment with previously used modalities can be a useful approach in this setting [73].

The therapy with CAR-T cells should be administrated in specialized centers – with the ability of highly specified intensive hematology care units. While clinical trials show specific adverse events, such as CRS and neurotoxicity to be generally mild and manageable, in some cases, they can escalate into life-threatening conditions requiring swift and intensive treatment, similarly to patients after an allogenic stem cell transplant.

There is a need for a technical construct of CAR-T cells, which lowers the rates of specific adverse events. The alternative receptor (TAC) has been developed to overcome these issues but so far it was tested in preclinical trials [63]. Another strategy is the incorporation of switches that can cause apoptosis, such as constructs where inducible caspase 9 is added. Dimerization of inducible caspase 9 results in apoptosis and CAR-T-specific depletion [74]. This, together with the introduction of allo- CAR-T cells could lead to more widespread use of the CAR-T technology. Advances in manufacturing and widespread use may affect the current great costs of CAR-T cells therapy.

In order to minimize the immunogenicity of the CAR binding domain, human or humanized scFv are more used instead of murine sequences [75]. Immunogenicity can be also reduced by the incorporation of heavy-binding domains, which simplify the structure of the CAR antigen-binding domain without the presence of a light-chain domain [76].

T-cells expressing single-chain bispecific CAR are able to prevent antigen escape [75]. One clinical trial investigated dual-target CAR-T consisting of 2 different target-specific scFv co-expressing 2 full-length BCMA and CD38 receptors [77]. The results especially AEs were compared with tandem CAR consisting of the expression of 2 different CARs on the surface of the same T cell. Higher CRS of grade > 3 was noted compared with tandem CAR [70, 77].

In conclusion, despite great progress in the field of RRMM treatment, triple- or even penta-refractory RRMM remains incurable with a survival median of several months [78]. CAR-T cells brought a new option for MM treatment when even heavily pretreated patients achieved MRD-negative status lasting for months or even years [24, 26, 30].

The CAR-T cell therapy in the MM field came a long way since the first BCMA-targeted CAR was developed. Currently available data from clinical trials on CAR-T cell therapy have demonstrated high efficacy and manageable toxicity in RRMM. BCMA sustains the most favorable target for the CAR-T cell field in MM The autologous CAR-T cell therapy against BCMA (ide-cel and cilta-cel) shows the best efficacy

with median ORR and median PFS in RRMM. Simpler structures and multi-target CAR-T cells may improve efficacy and safety even more.

While some limitations of CAR-T cells were described, the advantage of this treatment is the potential to finetune their design.

Future directions are multifocal with increasing the quality of CAR products in terms of T-cell persistence, as well as the optimal timing of CAR-T therapy in the MM treatment sequence with earlier CAR-T cell placing. It is questionable whether earlier administration of CAR-T cells to MM patients who are not triple refractory so far would improve their overall prognosis. There are currently ongoing clinical trials mentioned above, which are engaged in the earlier administration of CAR-T. The selection of patients who may most benefit from CAR-T and the optimal timing of their administration in the therapeutic schedule still require more clinical investigations. Another challenge is the cost-effectiveness of future commercial products. It is probable that in time the cost will be reduced as the whole process of production of CAR T-cells will become more familiar.

Although the novel drugs in the treatment of MM brought significant improvement, these agents are eliminated from the body over the time. That worsens the conditions of responses. In contrast, the CAR-T cells have the potential, if induced properly, to last for a much longer time in the body as long as the targeted tumor antigen exists. That enables a sustainable therapeutic effect. And if the efficacy is long-standing enough, in the near future there will be patients with lasting remission and MM will become a much more manageable disease.

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