Cellular therapy for multiple myeloma: what's now and what's next

Paula Rodriguez-Otero and Jesús F. San-Miguel

Clínica Universidad de Navarra, Centro de Investigación Médica Aplicada, Instituto de Investigación Sanitaria de Navarra, Centro de Investigación Biomédica en Red Cáncer, Pamplona, Spain

Despite significant improvement in the treatment of multiple myeloma (MM), a cure remains elusive, and patients failing proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies remain a challenge due to a lack of standard of care treatment and a dismal survival rate. The development of T-cell redirecting therapies, including bispecific T-cell engagers and chimeric antigen receptor (CAR) T cells, have transformed the outcome of triple-class exposed relapsed and refractory MM (RRMM). B-cell maturation antigen (BCMA) has proven to be an important target in MM, and BCMA-directed CAR T cells have shown unprecedented efficacy with a prolonged duration of response in a population with advanced RRMM, leading to the approval of 2 different BCMA CAR T-cell products. Still, and in contrast to prior experience in the field of CD19-directed CARs, no plateau has been seen in the survival curves, and relapses continue to occur. Therefore, further improvement is needed. Early use in the course of the disease as well as of next-generation CARs may further augment the efficacy of these therapies. In this review we address current state-of-the-art approved BCMA-directed CAR T-cell therapy in RRMM, as well as potential future developments focused on optimizing patient care and novel CAR designs.

LEARNING OBJECTIVES
- Summarize the current evidence regarding BCMA-directed CAR T cells for RRMM, focusing on approved constructs
- Discuss potential limitations of current CAR T-cell therapy in myeloma
- Describe potential strategies for improving current results, with a focus on the clinical perspective

CLINICAL CASE

A 56-year-old male was diagnosed in September 2019 with immunoglobulin A lambda multiple myeloma (MM). At diagnosis he presented with diffuse osteolytic lesions and a revised International Staging System (R-ISS) 3 status (high lactose dehydrogenase + t(4;14)). He received frontline treatment with daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (D-VRD) in the context of a randomized clinical trial. He completed 4 planned induction cycles followed by autologous stem cell transplant and 2 additional consolidation cycles. He achieved a very good partial response after consolidation and started maintenance treatment with daratumumab plus lenalidomide in June 2020. Unfortunately, 1 month later he progressed with the presence of a lumbar plasmacytoma. As of this moment, he has been transferred to our department to be considered for a B-cell maturation antigen (BCMA)

chimeric antigen receptor (CAR) T-cell clinical trial enrolling patients with early relapse after frontline treatment.

Introduction

The treatment landscape of MM has significantly evolved in recent years, leading to unprecedented survival rates.[1] Nevertheless, this improvement has not been uniform, and there are still patient populations with high-risk features who have not benefited enough from recently approved combinations and require innovative strategies to overcome their dismal prognosis. These populations are, among others, patients with extramedullary disease, a high number of circulating plasma cells, high-risk cytogenetic abnormalities (Cas), particularly double-hit myeloma, and patients who relapse early after optimized frontline therapy.[2-4] Regarding the latter, patients with R-ISS 3 status at diagnosis who fail to achieve undetectable minimal residual

disease (MRD) after frontline treatment are at a high risk of an early relapse with a median progression-free survival (PFS) of only 14 months and a median overall survival (OS) of fewer than 2 years.[5] In addition, patients who have failed proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies have very poor outcomes and limited treatment options.[6] Therefore, we need new treatments with novel mechanisms of action able to rescue difficult-to-treat populations and improve patient survival.

BCMA CAR T cells approved: what is now

In this scenario CAR T-cell therapy has shown unprecedented response rates in heavily pretreated patients, leading to the approval of 2 BCMA-directed CAR T-cell products (ABECMA™ and CARVIKTY™) for the treatment of triple-class exposed relapsed/refractory (RR) MM who have received at least 4 prior lines of treatment. In this review we discuss the current state-of-the-art of approved CAR T-cell therapy in RRMM and future developments, with a focus on the clinical perspective (Figure 1).

Idecabtagene vicleucel (ide-cel, bb2121, ABECMA™) was the first cellular therapy approved for the treatment of RRMM. Ide-cel

is a second-generation CAR with a 4-1BB costimulatory domain approved for the treatment of RRMM based on the data of the phase 2 single-arm pivotal KarMMa trial.[7] Overall, 128 patients were infused with 2 different doses of ide-cel 150, 300, and 450×10^{6} CAR T+ cells. The median number of prior lines was 6 (3-18), and 84% of patients were triple-class refractory. All patients received standard lymphodepleting chemotherapy with fludarabine and cyclophosphamide. The overall response rate (ORR) was 73% among all treated patients and 81% in those receiving the higher-dose level (450×10^{6}), with 33% and 39% of complete responses (CR), respectively. Responses were rapid, with a median time to first response of 1.0 month (range, 0.5-8.8 months). Median PFS was 8.8 months in the overall population and was longer in patients receiving the target dose (median PFS, 12.1 months) and in those achieving CR or better (median PFS, 20.2 months; 95% CI, 12.3-NE [not evaluable]). Median OS was 24.8 months (95% CI, 19.9-31.2). Safety overall was manageable, with cytokine release syndrome (CRS) reported in 84% of patients across the 3 doses and 96% at the target dose. The majority of events were grade 1 or 2 with a CRS grade higher than or equal to 3 in fewer than 6% of patients, with a median time to onset of 1 day (range, 1-12). Neurological complications were less common, were reported in
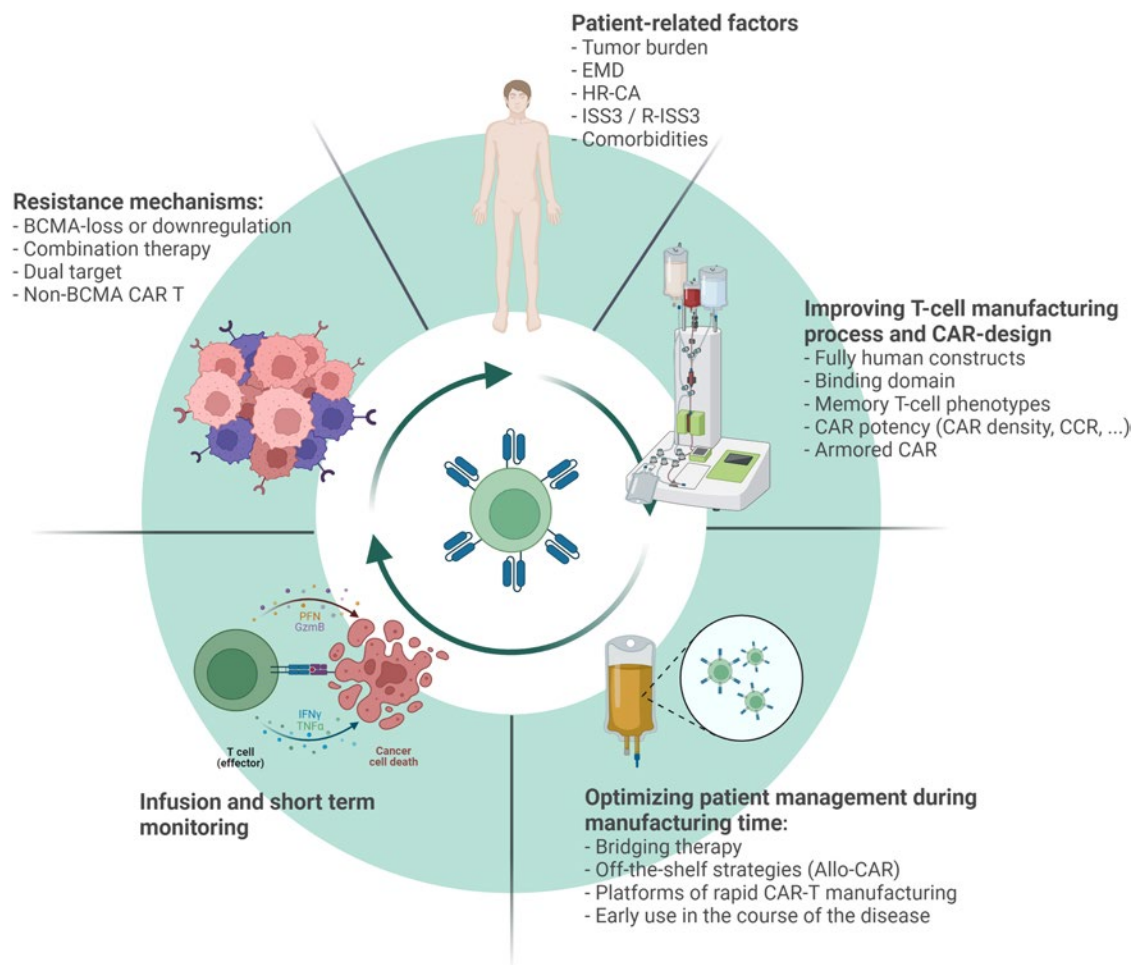
Figure 1. Several strategies are being evaluated to improve the current clinical efficacy of CAR T-cell therapy in the context of RRMM. These strategies can be divided into patient-related factors, aspects related to the manufacturing process and CAR design, patient management during bridging time and infusion, and finally, understanding the mechanisms of resistance and CAR failure. CCR, chimeric costimulatory receptor; EMD, extramedullary disease; HR-CA, high-risk cytogenetic abnormalities.

18% of patients, and were mostly grade 1 to 2. On the other hand, cytopenias were frequent and not dose related, with a median time to recovery from grade 3 or higher neutropenia and thrombocytopenia of 2 and 3 months, respectively (Table 1).[7]

Ciltacabtagene autoleucel (cilta-cel; former LCAR-B38M, CARVIKTY™), another second-generation CAR T cell containing 2 BCMA-binding domains, was investigated in the CARTITUDE-1 study (and previously evaluated in the LEGEND-2 phase 1 study). Overall, 97 patients were infused with a median number of 6 prior lines and 87.6% were triple class refractory. The ORR was 97.9% with 82.5% of patients achieving a stringent CR (sCR). With a median follow-up of 2 years, outstanding survival rates have been reported, with a 2-year PFS of 60.5% (95% CI, 48.5-70.4) and 71.0%

(95% CI, 57.6-80.9) in sCR patients. Two-year OS was 71.0% (95% CI, 57.6-80.9). Regarding safety, cytopenias and CRS were the most frequent treatment-related adverse events reported. Any grade of neutropenia was present in 96% of patients, with 95% having grade 3 or higher. The incidence of CRS was 95%, mostly grade 1 to 2, with a median time to onset of 7 days (range, 1-12). Neurological events were reported in 20 patients. Among these, 16 presented immune-effector cell–associated neurotoxicity syndrome (ICANS), and 12 patients presented with other neurotoxicities. Of these, 5 experienced a movement and neurocognitive disorder with a median time to onset of 27.0 days (IQR 16.0-73.0) (Table 1).[8]

Other BCMA-directed CARs are under development, and the status of those studies are summarized in Table 2.

Table 1. Safety and efficacy data of the 2 FDA- and EMA-approved CARs

	Idecabtagene vicleucel KarMMa trial[1-3]	Ciltacabtagene autoleucel CARTITUDE 1 trial
Number of patients infused, n	128 (140 apheresed)	97 (120 apheresed)
Phase	2	1b/2
Target/costimulation	BCMA/4-1BB	BCMA/4-1BB *2 BCMA-targeting heavy-chain antibody
scFv	Chimeric mouse	Chimeric llama
Specificity	Autologous	Autologous
Follow-up, median (range)	13.3 mo (0.2-21.2)	21.7 mo (not reported)
Prior lines, median (range)	6 (3 to 16)	6 (3-18)
Triple-class refractory, n (%)	108 (84)	85 (87.6)
Penta-exposed, n (%)	77 (60)	81 (83.5)
Bridging therapy, n (%)	112 (88)	73 (75)
Response to bridging therapy, n (%)	5/112 (4)	33/73 (45)
EMD, n (%)	50 (39)	13 (13)
CAR T-cell dose	150, 300, 450×10^6 CAR+T	0.75×10^6 CAR T+/kg
LD chemotherapy	Fludarabine 30mg/m^2×3 d Cyclo 300mg/m^2×3 d	Fludarabine 30mg/m^2×3 d Cyclo 300mg/m^2×3 d
ORR, n (%)	94 (73) At 450×10^6 (n=54): 44 (81%)	95 (97.9)
CR or sCR, n (%)	42 (33) At 450×10^6 (n=54): 21 (39)	82.5% (sCR)
Time to first response, median (range)	1.0 mo (0.5-8.8)	1.0 mo (IQR 0.9-1.0)
MRD in CR, n (%)	33/42 MRD neg (10^{-5})	61 evaluable 92% MRD negative (10^{-5})
DOR, median (95% CI)	10.7 mo (9.0-11.3)	Not reported
PFS, median (95% CI)	8.8 mo (5.6-11.6) At 450×10^6: 12.1 mo (8.8-12.3)	NR (16.8-NE) 2-y PFS: 60.5% (48.5-70.4)
PFS in high-risk, median (95% CI)		PFS at 2y, % (95% CI)
ISS 3/R-ISS 3	4.9 mo (1.8-8.2)^a	NE (NE-NE)
High-risk CA	8.2 mo (4.8-11.9)	48.4% (25.1-68.4)
Plasmacytomas	7.9 mo (5.1-10.9)	47.4% (24.4-67.3)
OS, median (95% CI)	24.8 mo (19.9-31.2)	NR (27.2-NE)
CRS, n (%)		
Overall	107 (84)	92 (95)
Grade 3–4	7 (5)	4 (4)
Time to CRS onset, median (range)	1 d (1-12)	7 d (5-8)
Duration of CRS, median (range)	5 d (1-63)	4 d (3-6)

Table 1. Safety and efficacy data of the 2 FDA- and EMA-approved CARs (*Continued*)

	Idecabtagene vicleucel KarMMa trial[1-3]	Ciltacabtagene autoleucel CARTITUDE 1 trial
Neurotoxicity, n (%)		
Overall	23 (18)	20 (21)[b]
Grade 3-4	4 (3)	9 (9)
Time to neurotoxicity onset, median (range)	2 d (1-10)	8 d (6-8) for ICANs Other: CAR-T cell neurotoxicites: 26.5 d (11–108)[b]
Grade 3-4 neutropenia, n (%)	114 (89)	92 (95)
Time to recovery, median (range)	1.9 mo (1.2-5.6)	Not reported
Grade 3-4 thrombocytopenia, n (%)	67 (52)	58 (60)
Time to recovery, median (range)	2.1 mo (1.2-13.8)	Not reported
Infections, n (%)	88 (69)	56 (58)
Grade 3-4 infections, n (%)	28 (22)	19 (20)
Death, n (%)	44 (34)	14
Reference	(1) Munshi et al[9] (2) Anderson et al.[34] (3) Oriol et al.[35]	(4) Berdeja et al[8] (5) Martin et al.[36] (6) Jakubowiak et al[11]

Data from the KarMMa and CARTITUDE-1 pivotal trials with ide-cel and cilta-cel, respectively, are summarized.

[a]PFS in R-ISS 3.

[b]ICANS occurred in 16 (17%) patients. Other neurotoxicities occurred in 12 patients, with a median time to onset of 27 days. Five patients had a cluster of movement and neurocognitive treatment–emergent adverse events.

EMA: European Medicines Agency; EMD, extramedullary disease; FDA: US Food and Drug Administration.

What is next and how to improve current results

Despite the impressive clinical results obtained thus far and given the short follow-up in some studies, no plateau has yet been seen in the survival curves, and relapses continue to occur. Therefore, further improvement is needed, and several points remain to be discussed.

Improving patient selection

Patient selection is a critical aspect of CAR T-cell therapy. Indeed, it is of particular relevance if we consider the present and future availability of other off-the-shelf BCMA-directed therapies. Although high and deep responses are achieved with both approved therapies, outcomes in selected high-risk populations remain inferior compared to standard-risk patients. In the KarMMa trial, patients with extramedullary disease, high-risk CAs, and R-ISS 3 showed lower CR rates and shorter PFS compared to patients without high-risk disease (Table 1).[9,10] Likewise, in the CARTITUDE-1 trial, patients with high-risk CAs, ISS 3, and the presence of plasmacytomas showed a lower PFS at 2 years compared to the intention-to-treat population, suggesting that further improvement is needed to abrogate the adverse outcome of patients with high-risk features even in the context of potent therapies such as CAR T cell (Table 1).[11]

On top of this, data from the different studies suggest that the achievement of deep responses (CR or MRD negativity) is of utmost importance in the context of "one-shot" CAR T-cell therapy and is associated with prolonged duration of response (DoR) and PFS.[8,9] Therefore, understanding the patient characteristics associated with a higher likelihood of achieving CR is of great importance. A recent analysis of the KarMMa trial showed that the presence of high tumor burden (soluble BCMA) and high inflammation (D-dimer, ferritin) along with the myeloma subtype (immunoglobulin G heavy chain) had a negative asso-

ciation with CR/sCR achievement, whereas a high vector copy number in the drug product showed a positive correlation with the CR/sCR rate.[12] These factors suggest that optimal and timely patient selection may be relevant for CAR T-cell outcomes since it is not an off-the-shelf therapy, and rapidly progressive patients with high-risk features or limited bridging options may be difficult to manage given the manufacturing time. In fact, between 10% and 20% of the patients who underwent apheresis in the different trials did not reach infusion due to complications during the manufacturing time or disease progression.

In this regard, adequate selection of bridging therapy is of utmost importance to maintain the patient's condition during manufacturing. Whenever possible, agents to which the patient has not been previously exposed should be prioritized. In this sense, and although the data are limited, BCMA-targeted agents are probably not the best option during the bridging period. Indeed, patients with prior BCMA treatment were excluded from the pivotal CAR T studies, and limited data are therefore available. Recent evidence from the cohort C of the CARTITUDE-2 trial that enrolled patients previously treated with BCMA-antibody drug conjugates (BCMA-ADC) and BCMA biespecific antibodies (BCMA-BsAb) showed that responses to cilta-cel were inferior to that of the CARTITUDE-1 trial (ORR: 62% in the BCMA-ADC and 57% in the BCMA-BsAb groups, respectively). Factors related to response were a shorter duration of prior BCMA treatment and a longer median time between last BCMA treatment and apheresis, suggesting a potential negative impact of prior BCMA treatment in outcome with CAR T-cell therapies.[13] On the other hand, in the recently reported real-world experience, 22% of patients had prior anti-BCMA therapy, and the ORR was consistent with that of the KarMMa trial.[14] Even so, both the downregulation of BCMA expression and the biallelic loss of the BCMA locus have

Table 2. Main reported clinical trials of BCMA-directed CAR T cells in RRMM

	BB21217 CRB-402 (n=72)	Orva-cel EVOLVE (n=62)	CT053 LUMMICAR (n=18)	CT103A FUMANBA-1 (n=79)	C-CAR088 (n=23)	P-BCMA-101 PRIME (n=53)	ALLO-715 UNIVERSAL (n=43)	ARI-002h (n=30)
Phase	1	1	1b/2	1/2	1	1/2	1	1
Follow-up, median (range)	23 (9-46)	9.5 mo	6 mo (2-11)	25.3 mo (4.1-36.7)	6.2 mo (0.7-16.1)	NA	4 mo	13 mo (7-13)
Target/costimulation	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB
scFv	Mouse	Mouse	Human	Human	Human	Mouse	Human	Human
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Autologous
CAR T-cell dose	150-450M	300-600M	1.5-3.0×10^8 cells	1.0×10^6/kg	1.0-6.0×10^6/kg	51-1178×10^6	40-480×10^6	3×10^6/kg
Population								
Age, median (range)	62 (33-76)	61 (33-77)	62 (36-78)	56 (39-70)	60 (45-74)	60 (42-74)	64 (46-77)	61 (36-74)
Prior lines, median (range)	6 (3-17)	6 (3-18)	5 (3-11)	5 (3-13)	4 (2-12)	8 (2-18)	5 (3-11)	4 (2-10)
Triple-class refractory, n (%)	50 (69)	58 (94)	85%	13 (16.5)	NR	60%	NR	61%
Penta-refractory, n (%)	NR	30 (48)	50%	NR	NR	NR	42%	NR
Efficacy							At 320×10^6	
ORR, n (%)	69%	92%	94%	75 (94.9)	22 (95.7)	50%-75%	71%	100%
CR, n (%)	36%	36%	27.8%	58.2%	43.5%	NR	25%	60%
PFS (mo), median (95% CI)	12.8 mo (7.3-18.6)	9.3 mo (300M)	NR	25.3 mo (3.0-NE)	6 mo PFS: 65.1%	NR	NR	15.8 mo (12.9-NE)
CRS								
All grade, n (%)	54 (75)	55 (89)	15/18 (83.3)	72 (92.4)	21 (91.3)	17%	24 (56)	87%
Grade 3-4, n (%)	3 (2 grade 5)	2 (3)	0 (0)	2 (2.5)	1 (4.3)	0%	1 (2)	0 (0)
Onset (d), median (range)	2 d (1-20)	2 (1-4)	2 (DL0) & 1 (DL1)	6 (1-12)	6 (1-11)	NR	NR	NR
Duration (d), median (range)	4 d	4 (1-10)	4 (DL0) & 3 (DL1)	5 (1-30)	5 (2-9)	NR	NR	4 (1-12)
Tocilizumab/steroids %/%	53/17	76/52	≈30/20	20/34.7	26/9	7/6	23/14	76/12
ICANS								
All grade, n (%)	11 (15)	8 (13)	2 (DL0) & 1 (DL1)	1 (1.3)	1 (4,3)	4%	6 (14)	0
Grade 3-4, n (%)	3 (4)	2 (3)	1 patient	0	0 (0)	4%	0 (0)	0
Onset (d), median (range)	7 d (2-24)	4 (1-6)	NR	10	8	NR	NR	—
Duration (d), median (range)	2 d	4 (1-10)	NR	1	1	NR	NR	—
Status	Not further developed	Not further developed	Ongoing	Ongoing	Ongoing	Not further developed	Ongoing	Ongoing
Reference	Raje et al[127]	Mailankody et al.[37]	Chen et al.[38]	Chunrui et al.[39]	Gan An, et al.[40]	Costello et al.[41]	Mailankody et al.[42]	de Larrea et al[24]
Identification	NCT03274219	NCT03430011	NCT03915184	NCT05066646	NCT05066646	NCT03288493	NCT04093596	NCT04309981

Data of safety and efficacy are shown.
NR, not reached.

been reported after anti-BCMA treatment, with the potential to limit BCMA CAR T-cell efficacy.[15-17]

Additionally, strategies to shorten vein-to-vein time are being developed, such as platforms for rapid CAR T-cell manufacturing or universal off-the-shelf allogeneic CAR. ALLO-715 is an allogeneic BCMA-targeting CAR T cell. It is manufactured with a knockout of the T-cell receptor alpha constant and CD52 to minimize the risk of graft-versus-host disease and to allow profound T-cell depletion using an anti-CD52 antibody to improve engraftment of the CAR T cells, respectively.[18] The UNIVERSAL phase 1 study tested ALLO-715 in 43 RRMM patients using escalating doses and different lympho-depleting regimens. The best clinical results were obtained with 320×10^6 cells in combination with fludarabine, cyclophosphamide, and anti-CD52 antibody (ALLO-647). In this cohort, 24 patients were infused. The ORR was 71%, and the median DoR was 8.3 months.[19] Potential immunogenicity and short persistence are the main challenges when using allogenic CAR T cells, and other cellular platforms are under investigation, such as natural killer CAR or γδ T cells.[18]

Treating patients in earlier lines of therapy with less refractory disease may help overcome some of the aforementioned problems. Therefore, different studies are indeed evaluating the feasibility and efficacy of this therapy in the context of early relapse or frontline disease. In cohort A from the phase 2 CARTITUDE-2 study, patients with 1 to 3 prior lines and lenalidomide-refractory disease were included and treated with cilta-cel. The median number of prior lines was 2 (range, 1-3). Interestingly, 40% of the patients were already triple-class refractory. Nineteen out of 20 patients responded (95%), and 85% achieved at least CR. The median PFS has not yet been reached, with a PFS at 12 months of 84% (95% CI, 59.1-94.7). Safety was comparable to that of the CARTITUDE-1 trial without new safety signals.[20] Likewise, in cohort B of the same study, patients with early relapse (within the first 12 months) after frontline therapy with a proteasome inhibitor and immunomodulatory drugs were included. A total of 19 patients were infused. The ORR was 95%, and 79% of patients achieved at least CR, with a 12-month PFS of 84% (95% CI, 57.9-94.5) and a safety profile comparable to that of the CARTITUDE-1 trial.[21] Altogether, these results suggest that CAR T-cell therapy in earlier lines of therapy is safe and may yield high and deep responses in different unmet-need populations. Still, its efficacy needs to be confirmed in the context of large phase 3 studies both in early relapse (KarMMa-3, NCT03651128; CARTITUDE-4, NCT04181827) and the frontline setting (BMTCTN1902, NCT05032820; CARTITUDE-5, NCT04923893; CARTITUDE-6, NCT04181827) (Table 3).

CLINICAL CASE (Continued)

Our patient underwent apheresis after the completion of screening tests and received bridging therapy, with progressive disease as the best response. The bridging period was complicated with acute kidney failure and several infectious complications. After recovery, he received standard fludarabine-cyclophosphamide conditioning before CAR T-cell infusion, which was performed in October 2020. He did not develop CRS or ICANs but did have grade 4 cytopenia requiring transfusion support, granulocyte colony-stimulating factor, erythropoietin-stimulating agents, and thrombopoietin

analogues. After CAR T-cell treatment, the patient achieved a stringent CR with MRD negativity (10^{-6}) as well as a complete metabolic response (Deauville 3), using an F-fluorodeoxyglucose emission tomography/computed tomography scan, that continues today. His cytopenia improved by month 12, and the patient no longer requires transfusions or medication.

Improving the T-cell manufacturing process

Several studies across different CAR T-cell products have shown a positive correlation between the depth and DoR and CAR T-cell expansion or persistence.[9,17] Therefore, significant effort has been fostered to optimize the final CAR T-cell product. One relevant aspect to consider is the immunogenicity of approved animal-derived constructs. Indeed, in the KarMMa trial, patients with antidrug antibodies (ADAs) increased over time, from 21% (21 of 102) at month 3 to 65% (34 of 52) at month 12.[9] Although these antibodies did not seem to influence CAR concentration or response, only patients without negative ADAs responded to CAR T-cell reinfusion, suggesting the potential role of these ADAs in CAR T-cell persistence or activity. Humanized or fully human constructs may be a way to overcome the negative impact of immunogenicity in CAR T-cell outcomes. Preliminary data from several phase 1 and 2 trials have shown encouraging clinical efficacy with high ORRs and deep and durable responses.[22,23] Moreover, in 1 academic study evaluating ARI-002h, a humanized BCMA CAR T, patients with an ongoing response and the absence of significant toxicity to the first infusion were eligible for a reinfusion. Sixteen out of 30 patients received a second infusion, and 5 patients showed an improved response, suggesting an adequate expansion of the CAR T-cell product.[24,25] Alternatively, the use of non–scFv-based CARs, such as engineered binding scaffolds, receptors, or natural ligands, might additionally serve to mitigate immunogenic reactions.[26]

Higher levels of memory T-cell phenotypes have been associated with better clinical outcomes, and several strategies, such as CD4/CD8 in a 1:1 ratio, may yield a higher proportion of these populations in the final product. An interesting approach was evaluated in the phase 1 CRB-402 study. In this trial, ide-cel was cultured with a PI3K inhibitor (bb007), resulting in a different CAR T-cell product (bb21217) enriched with T cells having a memory-like phenotype and a superior proliferative capacity upon adoptive transfer. Overall, 72 patients with a median of 6 prior lines were infused. The ORR was 69%, with 36% of the patients achieving a CR or better. The median DoR was 23.8 months and was not reached by patients in CR. Importantly, the persistence of CAR T cells was prolonged, with detectable CAR T cells in some patients up to 24 months.[27]

One limitation of targeted immunotherapies is the potential heterogeneity of antigen expression among tumor cells and the loss or downregulation of antigen after exposure.[18] Simultaneously targeting different antigens could overcome this barrier, and several trials are evaluating this possibility. GC012F is a dual BCMA/CD19-targeted CAR T manufactured in 24 to 36 hours on the FASTCAR® platform. Sixteen patients with RRMM and a median of 5 prior lines of therapy were infused with GC012F (dose range: 100 000-300 000 CAR T cells per kilogram). The ORR was 94%, with 56.3% of patients achieving CR or better. The median DoR was not reached at 7.3 months of median follow-up.[28]

Likewise, other targets are being explored (Table 4). GPR5D (G protein–coupled receptor 5 family D)-directed CAR T cells are

Table 3. Summary of ongoing studies evaluating CAR T cell therapy in earlier lines of therapy or in combinations with standard of care treatment

| Trial	Study population	Study design	CAR name	ScFv origin	Phase	n	Antigen	Cell source	End point	Dose	Status
FUMANBA-2 (NCT05181501)	NDMM high-risk	VRD/PAD/PCD×3-ASCT (if eligible) >> CT103A	CT103A	Human	1	20	BCMA	Autologous	MRD negativity 2-year PFS	$1×10^6$/kg	Not yet enrolling
NCT04287660	NDMM	BiRD + BCMA CAR T cell	NA	NA	3	20	BCMA	Autologous	ORR at 4 weeks	$2–3×10^7$/kg	Recruiting
CARTITUDE-5 NCT04923893	NDMM not intended for ASCT	A: VRD×8 + Rd B: VRD (6+2) + cilta-cel	Cilta-cel	Llama	3 randomized	650	BCMA	Autologous	PFS	$0.75×10^6$/kg	Recruiting
NCT04935580	NDMM-TE high-risk	2 cycles induction + CAR T + Len maintenance	GC012F	Human	1/2	20	BCMA-CD19	Autologous	Safety ORR, PFS, MRD	$3×10^5$/kg	Recruiting
CARTITUDE-6 NCT05257083	NDMM TE	A: DVRD×4 + ASCT +2×DVRD + Len B: DVRD×6 + cilta-cel + Len (2y)	Cilta-cel	Llama	3 randomized	750	BCMA	Autologous	PFS	$0.75×10^6$/kg	Not yet enrolling
KarMMa-4 NCT04196491	NDMM high-risk (R-ISS 3)	Standard induction×3 cycles + Ide-cel	Ide-cel	Murine	1	13	BCMA	Autologous	Safety	$450×10^6$	Active Not recruiting
CARTITUDE-2 NCT04133636	Multicohort	Cohort A: 1–3 prior lines Len-ref Cohort B: early relapse after frontline treatment Cohort C: relapse after BCMA Cohort F: NDMM after front-line Cohort E: NDMM-Tx not planned (high-risk)	Cilta-cel	Llama	2	157	BCMA	Autologous	MRD negativity at 1 year	$0.75×10^6$/kg	Recruiting
KarMMa-2 NCT03601078	Multicohort	2a + b: R-ISS 3 + early relapse 2c: suboptimal response to ASCT	Ide-cel	Murine	2	181	BCMA	Autologous	ORR	$150–450×10^6$	Recruiting
KarMMa-7 NCT04855136	1–3 PL + Len R ≥3 PL RRMM	(A): Ide-cel + iberdomide maintenance (B): Ide-cel + gamma secretase inhibitor	Ide-cel	Murine	2	181	BCMA	Autologous	ORR	$150–450×10^6$	Recruiting
KarMMa-3 NCT03651128	2–4 prior lines Len-ref & anti-CD38 exposed	A: DVd/DPd/ EloPd/Ixa-Rd/Kd B: Ide-cel	Ide-cel	Murine	3 Randomized	381	BCMA	Autologous	PFS	$450×10^6$	Recruiting
CARTITUDE-4 NCT04181827	1–3 prior lines Len refractory	A: PVd or DPd B: cilta-cel	Cilta-cel	Llama	3 randomized	419	BCMA	Autologous	PFS	$0.75×10^6$/kg	Active Not recruiting
BMTCTN1902 NCT05032820	NDMM post-ASCT	Ide-cel + Len maintenance	Ide-cel	Murine	2	40	BCMA	Autologous	ORR	$450×10^6$	Recruiting

ASCT, autologous stem cell transplantation; BiRD, bortezomib, claritromicine, lenalidomide, dexamethasone; DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; EloPd, elotuzumab, pomalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; IxaRd, izaxomib, lenalidomide, dexamethasone; Len, lenalidomide; Len-ref, lenalidomide refractory; NA, not available; NDMM, newly diagnosed multiple myeloma; NDMM-TE, newly diagnosed transplant eligible; PAD, bortezomib, adryamicine, dexamethasone; PCD, bortezomib, cyclophosphamide, dexamethasone; Pvd, pomalidomide, bortezomib, dexamethasone; Rd, lenalidomide-dexamethasone; Tx, transplant.

Table 4. Clinical trials in multiple myeloma evaluating non–BCMA-directed CAR T-cell constructs

Trial	Sponsor	CAR name	ScFv origin	Phase	n	Antigen	Costimulatory domain	Cell source	Transfer method	Dose	Efficacy
NCT04499339	European Union & CARAMBA	CARAMBA	Murine	1	38	SLAMF7	NR	Autologous	Sleeping beauty	NA	NR
NCT02135406	University of Pennsylvania	CTL019	Murine	1	10	CD19	4-1BB	Autologous	Lentiviral	$1.1\text{-}6\times10^8$	VGPR: 6; PR: 2; PD: 2
NCT01886976	Chinese PLA General Hospital	CART-138	Murine	1/2	5	CD138	4-1BB	Autologous	Retroviral	$0.44\text{-}1.51\times10^7$	SD: 4; PD: 1
NCT00881920	Baylor College of Medicine	κ.CARTs	Murine	1	7	κ light chain	CD28	Autologous	Retroviral	2.0×10^8	4 SD
NCT03958656	National Cancer Institute	NA	NA	1	42	SLAMF7	CD28 or 4-1BB/CD3z + inducible caspase 9 (IC9) cell suicide	Autologous	NA	$0.3\text{-}12.0\times10^6$	NA
NCT04142619	Cellectis S.A.	UCARTCS1	NA	1	18	SLAMF7 (TALEN-targeted gene editing TCR and SLAMF7)	4-1BB	Allogeneic	NA	NA	NA
NCT02203825	Celyad	NKG2D-CAR	Human	1	12	NKG2D ligands	DAP10	Autologous	Retroviral	$1\text{-}3\times10^7$	NA
NCT03464916	Sorrento Therapeutics	CAR2 anti-CD38 A2	NA	1	72	CD38	NA	Autologous	NA	NA	NA
EU-CART	EU Horizon 2020 Program	NA	NA	1	NA	CD44v6 (+HSV-TK suicide gene)	CD28	Autologous	Retroviral	NA	NA
NCT01716364	Peter MacCallum Cancer Centre, Australia	LeY	NA	1	6	Lewis Y	CD28	Autologous	Retroviral	NA	NA
NCT05016778	Zhejiang University	GPR5D-CAR T	NA	1	15	GPRC5d	NA	Autologous	NA	1.0, 3.0, or 6.0×10^6/kg	NA
NCT05219721	Tongji Hospital	CAR-GPR5D	Human	1	18	GPRC5d	4-1BB	Autologous	NA	0.5, 1.0, and 2.0×10^6/kg	NA
NCT04555551	Memorial Sloan Kettering Cancer Center	MCARH109	Human	1	17	GPRC5d	4-1BB	Autologous	Lentiviral	25, 50, 150, 450×10^6	ORR 69% CR 25%

NA, not available; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
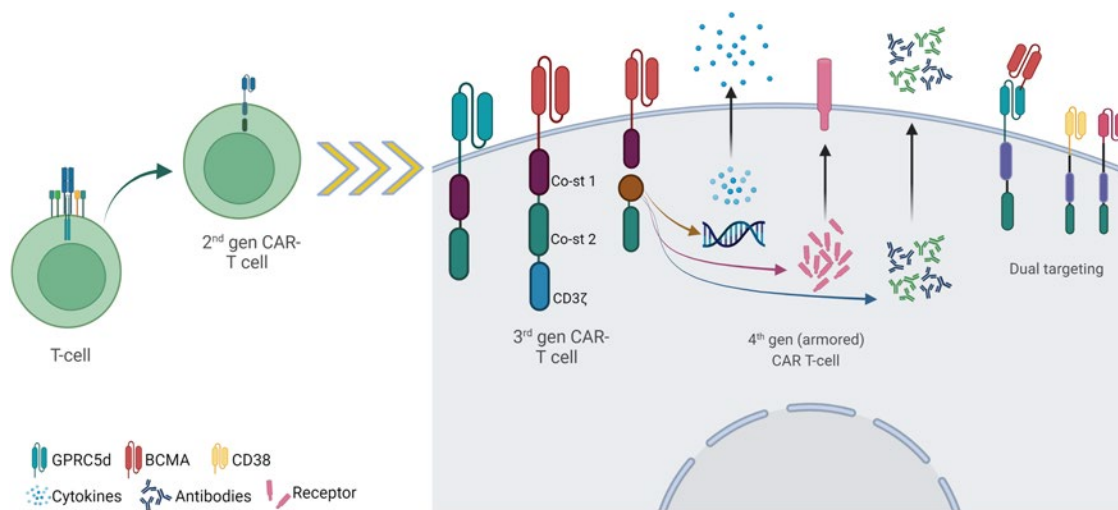
Figure 2. Possibilities for the future development of CAR T-cell therapy. Depicted are some of the novel new-generation CAR T constructs, including third-generation CARs incorporating 2 different costimulatory domains; fourth-generation CARs (also named "armored" CARs) incorporating transducible genes codifying for cytokines, antibodies, or receptors (among others); and novel target (non-BCMA) and dual targeting strategies, including tandem CAR and dual CAR.

also under investigation. In a first-in-human study of MCARH109, 17 patients were infused. Four doses were tested (25, 50, 150, and 450×10^{6} CAR+T cells). Fifty-nine percent of the patients had prior BCMA therapy, including 47% with prior CAR T-cell treatment. The ORR was 60% and 80% in patients with prior BCMA therapy. Data are still preliminary since the median follow-up was only 18 weeks.[29]

In addition, different strategies aiming to improve CAR potency and sensitivity are under evaluation, and the possibilities are endless. Therefore, the fine-tuning of CAR density in the T cell,[30] the co-infusion of CAR and chimeric costimulatory receptors,[31] the use of HLA-independent T-cell receptors instead of CAR,[32] armored CAR T, or a combination with gamma-secretase inhibitors to increase BCMA density in the tumor cell are potential venues to improve.[33] Clinical data, however, are still scanty (Figure 2).

Conclusions

In conclusion, BCMA-directed CAR T-cell therapies have demonstrated impressive clinical results in the context of advanced triple-class exposed RRMM, leading to the approval of 2 CARs. New modalities are in development to overcome some of the current limitations of CAR T-cell therapy, aiming to improve outcomes, shorten vein-to-vein time, and reduce toxicity. The further use of BCMA-directed CAR T-cell treatment in earlier lines of therapy is sure to improve outcomes and, hopefully, find the way to curing MM patients.

Conflict-of-interest disclosure

Paula Rodriguez-Otero: honoraria: Abbvie, Amgen, Bristol Myers Squibb/Celgene, GSK, Janssen, Kite Pharma, Oncopeptides, Pfizer, Sanofi; consultancy: Celgene, GSK, Janssen, Pfizer.

Jesús F. San-Miguel: honoraria: Abbvie, Amgen, Bristol Myers Squibb, Celgene, Janssen, MSD, Novartis, Sanofi, Roche, Takeda.

Off-label drug use

Paula Rodriguez-Otero: nothing to disclose.
Jesús F. San-Miguel: nothing to disclose.

Correspondence

Paula Rodríguez-Otero, Clinica Universidad de Navarra, Av de PIO XII, 36, 31008 Pamplona, Spain; e-mail: paurodriguez@unav.es.

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