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CAR-T cell therapy in Multiple Myeloma: current status and future challenges

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The treatment of multiple myeloma has changed dramatically in recent years, with huge strides forward made in the field. Chimeric antigen receptor T-cell therapy targeting the B cell maturation antigen (BCMA) is now widely approved in relapsed refractory patients and is moving into earlier treatment lines. In this review, we discuss the evidence underpinning current regulatory approvals and consider mechanisms through which CAR-T cell efficacy could be improved. These include tackling BCMA-loss, harnessing the immunosuppressive tumour microenvironment, manufacturing concerns including the potential role of other cellular sources, safety issues such as cytokine release syndrome and neurotoxicity, and optimal patient selection.

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BACKGROUND

Multiple myeloma (MM) is the second most common haematological malignancy of adults in the Western world [1]. Well-characterised manifestations of this malignancy, involving proliferation of clonal plasma cells, include anaemia, renal impairment, bone disease and immunoparesis [2, 3]. Median overall survival (OS) has more than doubled in recent years following incorporation of proteosome inhibitors (PIs), immunomodulatory agents (IMiDs) and monoclonal antibodies into standard-of-care treatment pathways [4]. However, patients with adverse cytogenetics, extra-medullary myeloma, or high-risk disease by the Revised International Staging System (R-ISS) have far less favourable outcomes, and the majority of patients eventually develop treatment-resistant disease [5–7]. Prior to the advent of T-cell engagers and cellular therapies, triple-class refractory patients, who are refractory to a PI, IMiD and CD38-directed monoclonal antibody, have had reported survival rates of less than 1 year, and penta-refractory patients (refractory to 2 IMiDs, 2 PIs and a monoclonal antibody) usually survive less than half that [8]. Given this significant unmet need, development of novel therapies has remained a priority in MM.

Chimeric antigen receptors are engineered T-cell receptors designed to recognise a specific tumour antigen without the need for antigen presentation by major histocompatibility class (MCH) molecules. The most common CAR-T construct comprises an extra-cellular antigen-recognition domain connected by a transmembrane domain to a co-stimulatory molecule, and then to the T-cell activating CD3-zeta domain [9]. The optimal tumour antigen should be consistently expressed in high concentrations by MM cells, but not expressed by the normal haematopoietic counterpoint or other tissues. The antigen most closely meeting these criteria is B-cell maturation antigen (BCMA), which is expressed by MM cells, late memory B-cells, plasmablasts and mature plasma cells, but not haematopoietic stem cells or non-haematopoietic cells [10]. BCMA has thus been at the forefront of CAR-T cell development in MM, with 2 products receiving regulatory approval in recent years.

BCMA-DIRECTED CAR-T CELLS: APPROVED PRODUCTS

US National Cancer Institute

The US National Cancer Institute (NCI) performed the first-in-human study of a BCMA-targeting CAR-T with a murine single chain variable fragment (scFv) and a CD28 co-stimulatory domain. Twenty-four RRMM patients with a median 7.5 prior lines of therapy received lymphodepleting chemotherapy followed by 0.3×10^3–9×10^6 CAR-T cells/kg. Of the 16 patients who received the highest dose, overall response rate (ORR) was 81% with complete remission (CR) achieved by 13% [11, 12].

Idecabtagene vicleucel

Idecabtagene vicleucel (Ide-cel, previously bb2121) uses the same murine scFv as the NCI product alongside a 4-1BB co-stimulatory domain. A phase 1 study, initially in 33 RRMM patients showed promising results which led to development of the phase 2 KarMMa study [13], in which 128 triple class-exposed patients, who had received at least 3 prior lines of therapy, were infused $150–450 \times 10^6$ CAR-T cells. In the 54 patients who received the highest CAR-T cell dose, ORR was 81%, ≥CR rate 39%, median PFS 12.1 months and OS was 19.4 months. Of patients in CR/stringent CR (sCR), 76% were measurable residual disease (MRD) negative to a level of 10^{-5} by next generation sequencing (NGS) and 59% of those had sustained MRD negativity after 12 months. Cytokine release syndrome (CRS) occurred in 84% and neurotoxicity in 18% [14–16]. Based on these results, the US Food and Drug Administration (FDA) granted approval for the use of Ide-cel in patients with RRMM after 4 or more prior lines of therapy, in March 2021.

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The phase 2 KarMMa-2 study assessed Ide-cel in RRMM in a number of different cohorts. Cohort 2a enroled patients with progressive disease within 18 months of induction therapy, autologous stem cell transplantation (ASCT) and lenalidomide maintenance. Thirty-nine patients were enroled, of which 37 were successfully infused 150–450 × 10^6 CAR-Ts. With a median follow-up of 21.5 months, ORR was 83.8%, CR rate was 45.9%, and 11 of 13 evaluable patients were MRD negative to a level of 10^{-5} at 6 months. Median PFS was 11.4 months and median OS was not reached. CRS occurred in 81% and neurotoxicity in 22% [17]. Cohort 2c assessed Ide-cel in patients with less than a very good partial remission (VGPR) after ASCT. With a median follow-up of 39.4 months, ORR was 87.1%, CR rate 77.4%, and median PFS and OS have not been reached in the 31 patients who received Ide-cel. After 36 months, 64.3% of evaluable patients were MRD negative. Fifty-eight percent had CRS and 7% developed neurotoxicity [18].

The phase 3 KarMMA-3 study compared Ide-cel with standard of care regimens in triple-class exposed (TCE) RRMM after 2-4 prior regimens. Three hundred and eighty-six patients were enroled, 254 randomised to the Ide-cel arm, of which 225 received the investigational product. After a median follow-up of 30.9 months, median PFS was significantly improved in the Ide-cel cohort (13.8 vs. 4.4 months) with a 51% reduced risk of PD or death. ORR, CR and MRD negativity were all also significantly in favour of Ide-cel (ORR 71% vs 42%, CR 44% vs. 5%). CRS occurred in 88% of treated patients and neurotoxicity in 15% [19]. Following these results, the FDA broadened the indication for Ide-cel to TCE RRMM after ≥2 prior lines. A more recent analysis of results failed to demonstrate a benefit in OS (median OS 41.4 vs. 37.9 months; HR 1.01, 95% CI 0.73–1.40). This is likely partly explained by the cross-over design, as 56% of patients in the standard of care arm received subsequent Ide-cel. After adjustment for cross-over, there was a trend to improvement seen with Ide-cel, however this did not meet statistical significance [20]. Results from the phase 1 KarMMa-4 (NCT04196491) study of frontline Ide-cel in high-risk MM are awaited.

LCAR-B38M

LCAR-B38M is an anti-BCMA CAR-T which incorporates 2 camelid (derived from llama) variable heavy-chain-only domains, which are highly specific for BCMA, conferring high avidity binding. The phase 1/2 LEGEND-2 study was conducted in 4 sites in China. Of 57 patients treated in 1 site, reported ORR was 88%, with a CR rate of 74% and PFS of 20 months. 82% of patients developed CRS [21, 22]. At 5 years follow-up, 74 patients had been treated, with an ORR of 88%, CR rate 73% and an MRD negative CR rate of 67%. Median PFS was 18 months and OS was 55.8 months in this heavily pre-treated cohort [23].

Ciltacabtagene autoleucel

Ciltacabtagene autoleucel (Cilta-cel, previously JNJ-4528) utilizes the same BCMA binding domain as the LCAR-B38M construct. In the phase 1b CARTITUDE-1 study, patients were administered 0.75 ×10^6 CAR-T cells/kg following lymphodepletion. Ninety-seven RRMM patients, of whom 87% were triple-refractory and 42% were penta-refractory received Cilta-cel, with an ORR of 98% and sCR of 80% reported. Ninety-two percent of evaluable patients were MRD negative to a level of 10^{-5}. The US prescribing information from the FDA reports the development of CRS in 95% of patients receiving Cilta-cel in CARTITUDE-1 (Grade ≥3 in 4%), neurotoxicity in 23% (Grade ≥3 in 3%), including movement and neurocognitive treatment-emergent adverse events (MNTs) in 6% [24]. FDA approval in RRMM after 4 or more prior lines of therapy was granted in February 2021 [25–27]. Updated results after 33 months follow-up reported an impressive median PFS of 34.9 months with an estimated 63% OS at 36 months [28].

In cohort A of the phase 1 CARTITUDE-2 study, 20 patients with lenalidomide-refractory MM, after 1-3 prior lines of therapy, were infused 0.75 ×10^6 Cilta-cel CAR-T cells. After a median follow-up of nearly 30 months, ORR and rate of ≥CR were 95% and 80% respectively, with 24-month PFS and OS of 75%. CRS occurred in 95%, neurotoxicity in 30%, ICANS in 15%, and there have been no reported MNTs to date. In cohort B, 19 patients with early relapse after frontline therapy (within 12 months of ASCT, or 12 months from commencement of a non-transplant-containing regimen), have been treated. After a median follow-up of 28 months, ORR and CR were 100% and 74% respectively, with a 24-month PFS of 73% and OS of 84%. CRS was reported in 84%, neurotoxicity in 32% and MNTs in 5% [29]. Cohort C enroled 20 triple class-exposed RRMM patients. All patients had received prior non-cellular BCMA-directed treatment (bispecific antibodies in 40%, BCMA-antibody drug conjugates in 65%) and the majority had refractory disease to such therapies. After a median follow-up of 11 months, ORR was 95% with a median PFS of 9.1 months. CRS occurred in 60%, ICANS in 20% and no patients had MNTs [30].

The phase 3 CARTITUDE-4 study in lenalidomide-refractory RRMM after 1-3 lines of therapy compared Cilta-cel with pomalidomide, bortezomib and dexamethasone, or daratumumab, pomalidomide and dexamethasone. Four hundred and nineteen patients were enroled, 208 were randomised to Cilta-cel, of which, 176 received a CAR-T infusion. Twenty-six percent of each cohort had triple-exposed RRMM. After a median 16 months follow-up, ORR, ≥CR rate and MRD negativity were significantly higher in the Cilta-cel arm (ORR 85% vs. 67%, ≥CR rate 73% vs. 22%, MRD negative status 61% vs. 16%). Median PFS has not been reached in the Cilta-cel arm versus 11.8 months in the standard of care cohort, with a 12-month PFS of 76% in the Cilta-cel arm and 49% in the control. Seventy-six percent of Cilta-cel-treated patients developed CRS, 4.5% had ICANS and 9% had cranial nerve (CN) palsy [31]. The FDA subsequently expanded approval for Cilta-cel to include patients with lenalidomide-refractory disease after 1-3 prior lines. Updated results were presented at the International Myeloma Society Annual meeting, 2024, reporting an OS benefit in the Cilta-cel arm (30 month OS 76.4% vs. 63.8%; HR 0.55, 95% CI 0.39–0.79) [32]. The phase 3 CARTITUDE-5 and CARTITUDE-6 studies in newly diagnosed MM (transplant-ineligible or transplant-eligible respectively) are ongoing [33].

At the time of writing, Cilta-cel appears to be the more efficacious of the two approved agents, with fairly similar toxicity profiles reported. Choice of drug will likely be significantly impacted by availability at a local level. BCMA-directed CAR-T studies are summarised in Table 1, and Table 2 summarises the adverse events reported within the CARTITUDE and KarMMa studies to date.

MEANS OF IMPROVING CAR-T CELL EFFICACY

Despite the dramatic responses produced by CAR-T cell therapy in RRMM, the majority of patients will eventually progress. The reasons for this are multifactorial, including loss of BCMA expression, high levels of sBCMA, the immunosuppressive MM microenvironment, timing of CAR-T administration within the treatment pathway, suboptimal CAR-T cell function and manufacturing issues [34]. Potential approaches to improve CAR-T outcomes are summarised in Fig. 1.

Reducing CAR-T immunogenicity: Fully human BCMA-binding domains

Demonstration of T-cell reactivity against the murine BCMA-binding scFv used in Ide-cel has generated interest in producing fully human BCMA CAR-Ts in order to reduce anti-CAR-T immune responses and improve persistence [35].

A number of fully humanized anti-BCMA CAR-Ts have been designed. These include CT053 (zevorcabtagene-autoleucel, Zevor-cel), which has a human BCMA-directed scFv. In the phase 1 Lummicar 1 study, 14 RRMM patients received CT053, with an

Table 1. BCMA CAR-T studies in Multiple Myeloma.

Study	CAR-T	Study design	Patients	Outcomes
Anti-BCMA				
NCT02215967 Phase 1 First in human NIH study	Murine scFv (11D5-3) CD28 co-stimulatory domain Retroviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.3×10^3 -9×10^6 CAR-Ts (9×10^6 dose expansion)	$N = 24$, $n = 16$ at the highest dose RRMM, median 7.5 prior lines	At highest dose, ORR 81% ≥VGPR 63% CRS 94% (≥ Grade 3 38%), ≥ Grade 3 neurotoxicity 25%
NCT02658929 Phase 1	CRB (bb2121/Ide-cel) 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 50-800 $\times 10^6$ CAR-Ts (150-450 $\times 10^6$ dose expansion)	$N = 33$ $N = 62$ (dose escalation $n = 21$, dose expansion $n = 41$), 45% >6 prior lines, 90% daratumumab-exposed	In the dose expansion phase: ORR 76%, ≥CR 65% For all patients, median PFS 8.8 months, median OS 34.2 months CRS 76% (≥ Grade 3 7%), neurotoxicity 44% (≥ Grade 3 3%)
NCT03361748 Phase 2 KarMMa	CRB (bb2121/Ide-cel) 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 150-450 $\times 10^6$ CAR-T	$N = 128$ ≥ 3 Prior lines of therapy including PI/IMiD/anti-CD38, refractory to last agent	ORR 73%, ≥CR 33% Of patients in sCR/CR, 76% MRD negative 10^{-5}, 59% of which had sustained MRD negativity after 12 months Median PFS 8.8 months CRS 84% (≥ Grade 3 5%), neurotoxicity 18% (14% grade 1-2)
NCT03601078 Phase 2 KarMMa-2	Bb2121/Ide-cel 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 150-450 $\times 10^6$ CAR-T	Cohort 1) RRMM ≥3 prior lines of therapy, Cohort 2b) PD < 18 months post start of therapy not including ASCT Cohort 2a) PD < 18 months post ASCT $N = 37$, 86% double class-refractory Cohort 2c) inadequate response post ASCT $N = 31$	Not reported ORR 84%, 11/13 (85%) MRD negative at 6 months Median PFS 11.4 months, median OS not reached CRS 84% grade 3 3%), neurotoxicity 22% (all Grade 1/2) ORR 87%, ≥CR 77%, median PFS and OS not reached 9/14 (64%) MRD negative at 36 months CRS 58% (all Grade 1/2), neurotoxicity 7%
NCT035651128 Phase 3 KarMMa-3	Bb2121/Ide-cel 4-1BB co-stimulatory domain Lentiviral vector	Ide-cel versus standard of care (DPd, DVd, Rd, Kd, EPd)	$N = 386$ (254 randomised to the Ide-cel arm, of which 225 treated) Triple-exposed patients after 2-4 prior lines Median 3 prior lines, 66% triple class refractory	ORR Ide-cel vs. SOC 71% vs 42%, ≥CR 39% vs 5% Median PFS 13.3 vs 4.4 months (HR 0.49, $p < 0.0001$) CRS 88% (≥ Grade 3 4%), neurotoxicity 15% (≥ Grade 3 3%)
NCT04196491 Phase 1 KarMMa-4	Bb2121/Ide-cel 4-1BB co-stimulatory 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	HR NDMM (R-ISS stage III)	Not reported
NCT04855136 Phase 1/2 KarMMa-7	Bb2121/Ide-cel 4-1BB co-stimulatory domain Lentiviral vector	Tolerability and efficacy of Ide-cel in combination with other therapies in RRMM Cohort A) CC-220 ±low dose dex, B) BMS-986405, C) DPd/PVd		Not reported

Table 1. continued

Study	CAR-T	Study design	Patients	Outcomes
NCT03274219 Phase 1	CRB402 (bb21217) Murine scFv (11D5-3) 4-1BB Lentiviral vector Phosphoinositide 3 kinase inhibitor added during ex vivo culture to enrich memory-like T cells	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 150–450 × 10^6 CAR-T	$N = 72$ ≥ 3 Prior lines of therapy including PI/IMiD/±anti-CD38, refractory to last agent, median 6 prior lines, 68% triple refractory	ORR 69%, ≥sCR/CR 28%, ≥VGPR 58%, median DOR 17 months (11-35) CRS 75% (71% grade 1-2), Neurotoxicity 15% (11% grade 1-2)
NCT03502577 Phase 1	CRB402 (bb21217) Murine scFv (11D5-3) 4-1BB Lentiviral vector Phosphoinositide 3 kinase inhibitor	Gamma secretase inhibitor (GSI) JSMD194 'run in', Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2, 5-45 ×10^7 CAR-T cells with JSMD194 thrice weekly for 3 weeks	N = 18 RRMM, median 10 prior lines of therapy, 67% penta-refractory, 39% prior- BCMA targeted therapy	ORR 89%, ≥CR 44%, ≥VGPR 78%, median PFS 11 months (2 months in BCMA-exposed) CRS 95% (83% grade 1-2), 66% ICANS
NCT03090659 Phase 1/2 Legend-2	LCAR-B38M 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2 days -5 to -3, or cyclophosphamide 300 mg/m^2 0.07-2.1 ×10^6/kg CAR-T	≥ 3 Prior lines of therapy including bortezomib N = 17 (3 sites) median 4 prior lines N = 57 (4th site) median 3 prior lines	ORR 88%, sCR 82%, median PFS 12 months CRS 59% (grade 1-2), 35% (grade 3), no neurotoxicity ORR 88%, ≥CR 74%, median PFS 20 months CRS 82% (grade 1-2), 7% (grade 3) 5 year follow-up of overall cohort: ORR 89%, ≥CR 67%, median PFS 18 months
NCT03548207 Phase 1b CARTITUDE-1	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75 × 10^6/kg CAR-T	$N = 97$ ≥ 3 Prior lines of therapy, PI/IMiD/anti-CD38 Median 6 prior lines, 87.6% triple-refractory, 42.3% penta-refractory	ORR 98%, sCR 83% Of 61 patients evaluable for MRD, 91.8% MRD negative to 10^{-5} 27 month PFS 55% and OS 70%, median PFS and OS not estimable CRS 94.8% (≥Grade 3 3%) neurotoxicity 20.6% (≥Grade 3 9.3%), 8.2% ICANS, MNTs 5% (< 1% following risk reduction strategies)
NCT04133636 Phase 1 CARTITUDE-2 COHORT A	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75 × 10^6/kg CAR-T	$N = 20$ PD after 1-3 prior lines of therapy including PI/IMiD, lenalidomide-refractory Median 2 prior lines of therapy, 40% triple-refractory, 95% refractory to last line	ORR 95%, ≥CR 80% 24 month PFS and OS 75% Sustained MRD negativity to 10^{-5} After 6 months (40%) and 12 months (35%) CRS 95% (≥Grade 3 10%), neurotoxicity 30% (≥Grade 3 5%), ICANS 15% (all Grade 1/2), no MNTs
NCT04133636 Phase 1 CARTITUDE-2 COHORT B	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75 × 10^6/kg CAR-T	Early relapse following frontline therapy including PI/IMiD (< 12 months from ASCT or start of non-ASCT containing treatment) $N = 19$	ORR 100%, ≥CR 74% 24 month PFS 74% and OS 82% Sustained MRD negativity to 10^{-5} After 6 months (53%) and 12 months (37%) CRS 84% (≥Grade 3 5%), neurotoxicity 26% (≥Grade 3 5%), ICANS 15% (all Grade 1/2), MNTs 5% (≥Grade 3 5%, $n = 1$)

Table 1. continued

Study	CAR-T	Study design	Patients	Outcomes
NCT04133636 Phase 1 CARTITUDE-2 COHORT C	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75×10^6/kg CAR-T	$N = 20$ PD post PI/IMiD/CD38 monoclonal antibody/non-cellular anti-BCMA immunotherapy 13 patients had received anti-BCMA drug conjugate, 7 prior BCMA bispecific antibody treatment, 80% refractory to prior anti-BCMA therapy	ORR 60%, 35% MRD negative at a median 11.3 months follow-up Median PFS 9.1 months CRS 60% (all Grade 1/2), ICANS 20% (≥Grade 3 10%), no MNTs
NCT04181827 Phase 3 CARTITUDE-4	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Cilta-cel vs. PVd/DPd Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75×10^6/kg CAR-T	$N = 419$ (208 randomised to Cilta-cel, of which 176 treated) 1-3 prior lines of treatment, lenalidomide-refractory.	ORR Cilta-cel vs SOC 85% vs 67%, ≥CR 73% vs 22%, MRD negativity 61% vs 16% 12 month PFS 76% vs 49% CRS 76% (≥Grade 3 1%), ICANS 5% (all Grade 1/2), 9% cranial nerve palsy, 3% peripheral neuropathy, 1 patient MNT (grade 1)
NCT04923893 Phase 3 CARTITUDE-5	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75×10^6/kg CAR-T	NDMM, not eligible for transplant VRd and Cilta-cel vs. VRd and Rd maintenance	Not reported
NCT05257083 Phase 3 CARTITUDE-6	JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 0.75×10^6/kg CAR-T	NDMM D-RVd and Cilta-cel vs. D-VRd and ASCT	Not reported
Fully human anti-BCMA				
NCT03318861 Phase 1	KITE-583 Human anti-BCMA scFv CD28 co-stimulatory domain	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 3×10^7- 1×10^9 CAR-T	$N = 14$ ≥3 prior lines of therapy including PI/IMiD median 5 prior lines	Best response is PR in 1 patient Limited expansion CRS 21%, neurotoxicity 21%
NCT04318327 Phase 1	PHE885 T-charge platform enables in vivo CAR-T expansion and manufacture <2 days Human anti-BCMA scFv 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine and cyclophosphamide-regimen not stated, 5-14.3 $\times 10^6$ CAR-T	$N = 46$ ≥ 2 Prior lines of therapy, IMiD/PI/anti-CD38 Median 4 prior lines, 96% triple class-refractory	4 evaluable after 3 months 2 sCR, 1 PR, 1 PD CRS 100% (all grade 1-2), 33% neurotoxicity ORR 98%, 60% of evaluable patients ($n = 10$) MRD negative CRS 96% (≥Grade 3 11%), ICANS 22% (≥Grade 3 7%)
NCT03070327 Phase 1	MCARH171 Human scFv 4-1BB co-stimulatory domain tEGFR safety switch Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3, or cyclophosphamide 3 g/m^2 72-818 $\times 10^6$ CAR-T	$N = 11$ Triple class-exposed RRMM Median 6 prior lines	ORR 64%, 100% at highest dose AEs evaluable in 10 patients CRS 60% (≥Grade 3 20%) Grade 2 neurotoxicity 10% ($n = 1$)
NCT03430011 Phase 1/2 EVOLVE	JCARH125 (Orva-cel) Human scFv 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 50–600 $\times 10^6$ CAR-T	$N = 44$ at higher doses ≥ 3 Prior lines of therapy including PI/IMiD/anti-CD38 median 6 prior lines, 92% penta-exposed	ORR 91%, sCR/CR 39% ≥ Grade 3 CRS 2%, ≥ Grade 3 neurotoxicity 4% (total numbers not reported)

Table 1. continued

Study	CAR-T	Study design	Patients	Outcomes
ChiCTR1800018137 Phase 1/2 FUMANBA-1 study	CT103A Human scFv 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 25 mg/m^2, cyclophosphamide 20 mg/kg for 3 days 1-6 × 10^6 CAR-T	$N = 103$ ≥ 3 Prior lines of therapy including PI/IMiD, refractory to last line, median 4 prior lines, 18.3% prior CAR-T	ORR 96%, ≥CR 74% 12-month PFS 79% 95% ($n = 101$ evaluable) MRD negative to 10^{-5} 95% CRS (≥ Grade 3 3%), ICANS in 2 patients (both grade 2)
NCT03602612 Phase 1	FHVH33-CD8BBZ Human heavy chain variable domain (FHVH33) 4-1BB co-stimulatory domain Gamma retroviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3	$N = 25$ RRMM, median 6 prior lines	ORR 92%, sCR 52% Median PFS 78 weeks CRS 96% (Grade 3 25%) Grade 3 neurotoxicity 8%
NCT03716856 NCT03302403 NCT03380039 Phase 1	CT053 Human scFv (25C2) 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 50–180 × 10^6 CAR-T	$N = 24$ ≥ 2 Prior lines of therapy Median 5 prior lines, 42% extramedullary disease	ORR 88%, ≥CR 79% CRS 63% (all Grade 1/2), 1 patient had grade 3 neurotoxicity
NCT03975907 Phase 1 Lummicar Study 1	CT053 (Zevor-cel) Human scFv (25C2) 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 1 × 10^8 CAR-T ($n = 3$), 1.5 × 10^8 CAR-T ($n = 11$)	$N = 14$ ≥ 3 Prior lines of therapy, including PI/IMiD Median 6 prior lines	ORR 100%, sCR 79% (100% of patients in sCR were MRD negative to 10^{-5}) 12 month PFS 86% CRS 93% (all Grade 1/2)

ORR and ≥CR after 38 months follow-up of 100% and 79% respectively, and a median PFS of 25 months [36].

JCARH125 (Orva-cel, orvacabtagene-autoleucel; no longer under development), was investigated in the phase 1/2 EVOLVE clinical study. Fourty-four RRMM patients received 300–600 × 10^6 CAR-Ts. ORR and ≥CR were 91% and 39%, respectively [37, 38].

Eighteen RRMM patients were infused with escalating doses of the fully human anti-BCMA CAR-T CT103A in a phase 1 study. After a median 41 months, ORR was 100% and 78% achieved ≥CR. At data cut-off, 7 patients remained in MRD negative sCR. Median PFS and OS were 23 and 42 months respectively. Median CAR-T persistence was 419 days, with transgenes detectable in 39% at the time of reporting [39]. In comparison, the majority of patients treated with Cilta-cel in CARTITUDE-1 did not have demonstrable CAR-T transgene persistence at 6 months [25]. In the phase 1b/2 FUMANBA-1 study, 103 RRMM patients with prior PI and IMiD treatment received CT103A (now called Equecabtagene Autoleucel, Eque-cel) at a dose of 1 × 10^6 cells. After a median follow-up of 14 months, ORR was 96%, ≥CR 74%, and 12-month PFS was 79%. A small number of patients with prior BCMA CAR-T treatment achieved sCR (5 of 89 patients). Eque-cel could still be detected in 40% after 24 months, with anti-drug antibodies identified in 19% of evaluable samples [40]. Eighty-eight patients within FUMANBA-1 were MRD negative, which was sustained over 6 months in 78% and over 12 months in 74% of evaluable patients [41]. This agent has been granted orphan drug designation by the FDA and appears promising. Longer follow-up will be required to determine whether improved CAR-T persistence translates to longer remission duration.

Studies of human BCMA CAR-Ts are shown in Table 1.

APPROACHES TO BCMA LOSS

Reversible or partial loss: Enhance BCMA expression

Evidence of reversible or partial loss of BCMA expression has been identified in a small number of patients following BCMA-directed CAR-T cell therapy. In one study of 18 patients, 12 demonstrated decreased BCMA expression which subsequently recovered [42]. BCMA is cleaved from the MM cell surface by gamma-secretases leading to reduced cellular expression and increased levels of serum BCMA, a known adverse prognostic feature [43, 44]. High levels of circulating soluble BCMA (sBCMA) impair binding of anti-BCMA antibodies to MM cells in vitro, in addition to the impact of reduced target antigen density on the cell surface [45]. Additional mechanisms which may lead to partial BCMA loss include trogocytosis, in which the target antigen is transferred to the CAR-T cells themselves, leading to CAR-T fratricide alongside impaired MM killing, and potential epigenetic mechanisms observed in other haematological malignancies [46, 47].

Inhibition of gamma-secretase was shown to enhance MM cell BCMA expression and reduce sBCMA in vitro [48]. A phase 1 study of CRB402 (bb21217), the Ide-cel CAR-T construct treated with a phosphoinositide-3-kinase inhibitor during ex vivo culture to enrich for memory-like T cells, incorporated JSMD194, a gamma-secretase inhibitor (GSI), pre- and post-CART-T infusion in 18 RRMM patients. Reported ORR was 89% with 44% achieving ≥CR. In comparison, CRB402 without GSI in 72 RRMM patients achieved an ORR of 69% and ≥CR rate of 28% [49–52]. This possible increase in efficacy came at the expense of high levels of severe ICANS (grade ≥3 in 50%), frequent electrolyte disturbance and grade 3 diarrhoea in 17% [52]. Despite initial interest, bb21217 is no longer being pursued. Recent work has shown that BCMA is degraded by the ubiquitin proteosome system, and that in vitro treatment with a proteosome inhibitor increases surface BCMA expression and improves BCMA CAR-T efficacy, providing a rationale for combining PIs and BCMA-CAR-Ts in future studies [53].

Table 2. Comparison of adverse events associated with Ciltacabtagene autoleucel and Idecabtagene vicleucel.

	Ciltacabtagene autoleucel	Idecabtagene vicleucel
CRS	Overall CRS rate across CARTITUDE-1 and CARTITUDE-4: all grades 84% (≥G3 4%). Median time to onset 7 days (1–23 days). Median duration 4 days (1–97 days).	Overall CRS rate across KarMMa and KarMMa-3: all grades 89% (≥G3 7%, G5 0.9%). Median time to onset 1 day (1–27). Median duration 5 days (1–63 days).
Neurotoxicity	Overall neurotoxicity across CARTITUDE-1 and CARTITUDE-4: all grades 24% (≥G3 7%). Median time to onset 10 days (1–101 days). Median duration 23 days (1-544 days). ICANS in 13%, PN 7%, CNS palsy 7%, parkinsonism 3%, immune mediated myelitis in 0.4% Overall ICANS rate across CARTITUDE-1 and CARTITUDE-4: all grades 13% (≥G3 2%). Median time to onset 8 days (1-28 days). Median duration 6 days (1-1229 days). Overall Parkinsonism/MNT rate across CARTITUDE-1 and CARTITUDE-4: all grades 3 (≥G3 2%). Median time to onset 56 days (14–914 days). Median duration 243.5 days (62–720 days). Overall PN rate across CARTITUDE-1 and CARTITUDE-4: all grades 7% (≥G3 1%). Median time to onset 57 days (1–914 days). Median duration 149.5 days (1–692 days). Overall rate of CNS palsies across CARTITUDE-1 and CARTITUDE-4: all grades 7% (≥G3 1%). Median time to onset 21 days (17–101 days). Median duration 70 days (1–262 days). VII nerve most commonly affected.	Overall neurotoxicity across KarMMa and KarMMa-3: all grades 40% (≥G3 4.6%). Median time to onset 2 days (1–148 days). Median duration 8 days (1–72 days). No parkinsonism reported in the KarMMa trials, cases reported elsewhere. Categories of neurotoxicity not reported.
HLH/MAS	Overall HLH/MAS rate across CARTITUDE-1 and CARTITUDE-4: 1%. Median onset 10 days (8–99 days).	Overall HLH/MAS across KarMMa and KarMMa-3: 2.9% (G5 in 3 patients). Median onset 6.5 days (4-10 days).
Infection	Overall infection rate across CARTITUDE-1 and CARTITUDE-4: all grades 57% (≥G3 24%). ≥G3 viral 6%, bacterial 5%, fungal 1%, unspecified pathogen12%. 5% G5 events, 2.5% Covid-19.	Overall infection rate across KarMMa and KarMMa-3: 61% (≥G3 21%). ≥G3 viral 7%, bacterial 4.3%, fungal 1.4%, unspecified pathogen 12%. 4.3% G5 events, 0.9% fungal, 0.9% viral, 0.3% bacterial, 2.3% unspecified pathogen.
Hypogammaglobulinaemia	Hypogammaglobulinaemia (IgG <0.5 g/L) across CARTITUDE-1 and CARTITUDE-4: 94%. 56% received IVIg.	Hypogammaglobulinaemia (IgG <0.5 g/L) across KarMMa and KarMMa-3: 45%. 41% received IVIg.
Cytopenias	Prolonged ≥G3 cytopenias not resolved by 30 days across CARTITUDE-1 and CARTITUDE-4: 62%. Prolonged ≥G3 Thrombocytopenia 33%, neutropenia 27%, lymphopenia 24%, anaemia 2%.	Prolonged ≥G3 neutropenia not resolved by 30 days across KarMMa and KarMMa-3: 40%. Prolonged ≥G3 thrombocytopenia: 42%.
SPMs	Overall rate of Myeloid neoplasms across CARTITUDE-1 and CARTITUDE-4: 5% (9 cases of MDS, 3 AML, 1 MDS/AML). Median time to onset 447 days (56–870 days).	Overall rate of Myeloid neoplasms in KarMMa-3: 2.2% (4 cases of MDS, 1 AML)

Complete BCMA loss: Target other tumour epitopes

Complete BCMA loss may also occur in patients following BCMA CAR-T therapy. Homozygous gene deletion or heterozygous deletion and mutation have been identified by a number of authors in a small proportion of refractory patients [54–56]. Heterozygous BCMA gene deletion is found in approximately 20% of patients prior to BCMA-directed therapy [55]. These patients may therefore be at higher risk of selective expansion of BCMA-negative MM cells, in response to BCMA CAR-T cell therapy [57]. Patients with complete BCMA loss will not respond to BCMA-directed approaches, and consideration of other target antigens may be required. There are numerous clinical and pre-clinical trials ongoing assessing a variety of antigens, such as CD38, CD138, SLAMF7, GPRC5D, NKG2D, APRIL, CD44v6 and FcHR5.

G protein-coupled receptor class C group 5 member D (GPRC5D) is one of the more promising targets, with efficacy already demonstrated by the bispecific antibody talquetamab [58]. The phase 1 MCARH109 study enroled 17 patients, almost half of whom had received prior BCMA CAR-T cell therapy. ORR was 71%, ≥CR 35% and median duration of response was 7.8 months [59]. The phase 1 POLARIS study administered OriCAR-017 to 10 patients, with 50% prior BCMA CAR-T exposure. ORR was 100%, with 60% attaining a sCR [60]. The phase 1, BMS-986393 study enroled 33 patients, with 39% having received a BCMA CAR-T. ORR was 90%, with ≥CR in 47% [61]. As with the GPRC5D bispecific antibodies, on-target, off-tumour adverse events were common across these studies, including dysgeusia, nail disorders and dysphagia. The majority were mild and resolved without intervention [62]. Fc receptor-like 5 (FcHR5), a membrane protein that regulates B-cell receptor signalling [63] has shown encouraging results when targeted by the bispecific antibody, cevostamab [64]. Pre-clinical work has demonstrated efficacy of FcRH5 CAR-Ts in murine MM models, including those lacking BCMA expression [65, 66], however there are no clinical trials available at the time of writing.

Clinical studies of non-BCMA CAR-Ts in MM are shown in Table 3.

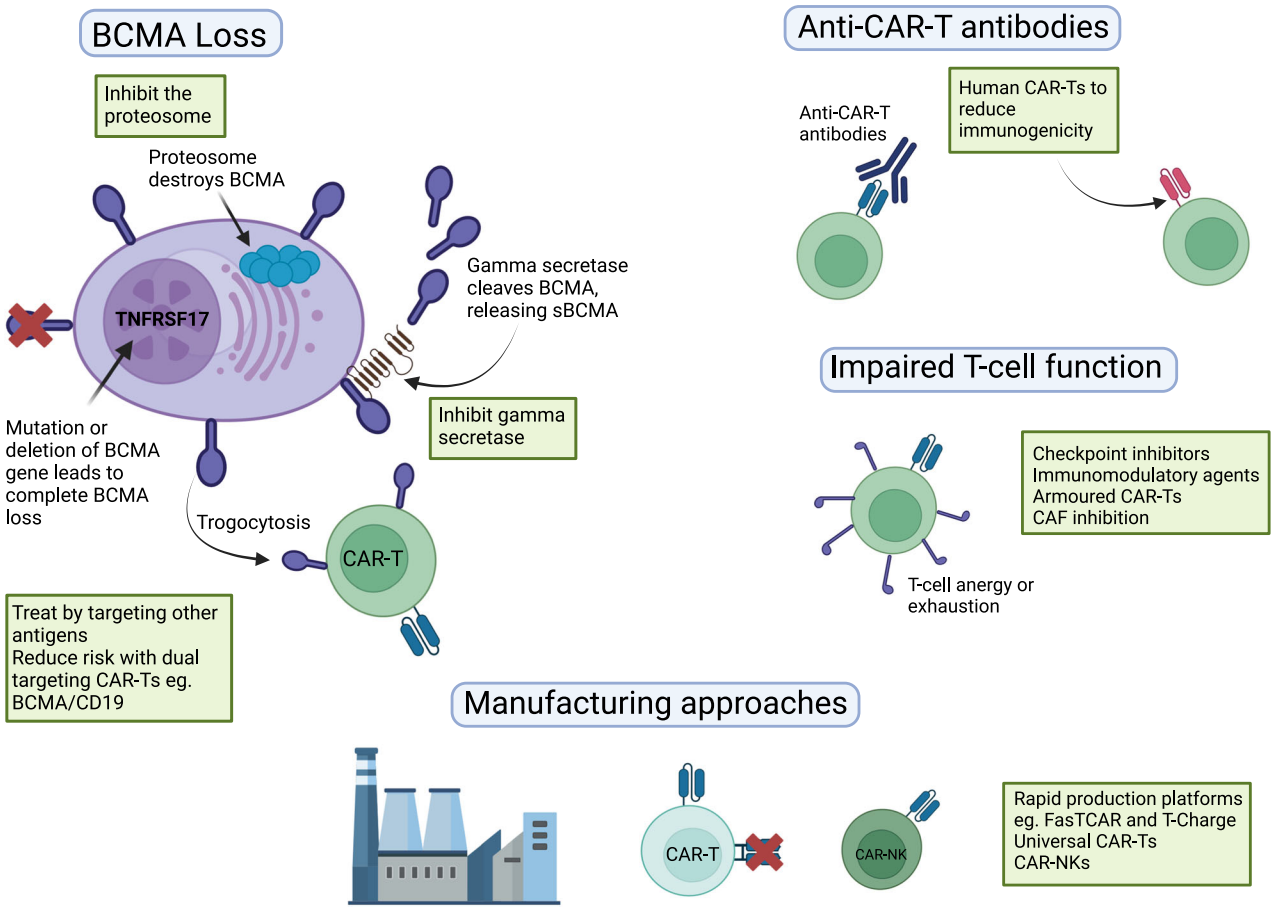

Fig. 1 Approach to improving CAR-T efficacy in Multiple Myeloma.

REDUCING THE LIKELIHOOD FOR BCMA LOSS: DUAL ANTIGEN TARGETING

Targeting multiple tumour epitopes may be achieved by administering multiple CAR-T products or through use of bispecific CAR-T cells. This approach may improve specificity and reduce the selective pressure that promotes BCMA downregulation or loss.

Only a very small proportion of myeloma plasma cells express CD19, with some groups suggesting these may represent so-called myeloma stem cells [67, 68]. Despite expression in only 0.05% of the dominant plasma cell population, administration of CD19-directed CAR-T cell therapy alone has demonstrated efficacy in MM, providing a rationale for combined approaches with BCMA [69]. GC012F, a BCMA/CD19 dual-targeting CAR-T was tested in escalating doses in 22 newly diagnosed high-risk MM patients in a phase 1 study. After a median follow-up of nearly 14 months, ORR was 100%, sCR 96% and 100% attained MRD negativity to a sensitivity of 10^{-6}. CRS occurred in only 27%, with no ICANS reported [70]. One group gave a combination of BCMA and CD19-directed CAR-Ts to 62 of 69 enroled participants. After a median follow-up of 21 months, ORR was 92%, ≥CR occurred in 60%, and 77% of assessed patients were MRD negative. Median PFS was 18 months, with CRS and neurotoxicity in 95% and 11% respectively [71]. Another study administered sequential anti-CD19 and BCMA CAR-T cell therapy with lenalidomide maintenance following ASCT in 10 high-risk NDMM patients. Seventy percent of the cohort have remained MRD negative after 2 years with this strategy [72].

APRIL (a proliferation-inducing ligand) recognises both BMCA and TACI (transmembrane activator, and calcium-modulator and cyclophilin ligand interactor), another MM epitope. AUTO2 is a CAR-T cell construct incorporating a truncated form of APRIL as it's antigen-binding domain, enabling dual-targeting of BCMA and TACI. In a phase 1 study, ORR in 11 patients was 43% [73]. Similarly, a bispecific BCMA/CD38 CAR-T cell construct was tested in 16 RRMM patients in a single-centre phase 1 study (ChiCTR1900026286). ORR was 87.5%, 81% achieved sCR, and 12 month PFS and OS were 69% and 75% respectively [74]. Other bispecific CAR-Ts are under pre-clinical development, including a BCMA/CD24 CAR-T [75] and a CAR-T directed against BCMA and MICA (human MHC class 1-related chain gene A), which is upregulated by MM cells as a means of immune-evasion [76].

There are numerous methods of generating CAR-T products with specificity for more than one tumour associated antigen, with advantages and disadvantages unique to each. Additional information may be found in some excellent reviews on this rapidly developing area [77, 78]. A combination approach utilising CAR-Ts and/or bispecific antibodies to target multiple tumour epitopes may provide a highly efficacious future model of therapy. Studies of dual-targeting BCMA CAR-Ts are shown in Table 3.

TARGETING THE TME

One of the hallmarks of MM is the tumour-permissive microenvironment (TME). A complex interplay between MM cells, immune cells and bone marrow stromal cells leads to progressive immunoparesis, protecting and facilitating MM growth and survival. Peripheral blood and bone marrow samples were analysed from 11 and 6 Ide-cel-treated patients, respectively. Durable responses have been observed in patients with upregulation of genes expressing pro-inflammatory cytokines, Nuclear factor kappa B (NFKB) signalling genes and anti-apoptotic genes

Table 3. CAR-T studies with dual BCMA targets or non-BCMA targets.

Study	Target antigen(s)	CAR-T	Study design	Patients	Outcomes
NCT02135406 Phase 1	CD19	CTL019 (Tisa-cel, Kymriah, Novartis) CD19 scFv (FMC63) 4-1BB co-stimulatory domain Lentiviral vector	Salvage melphalan ASCT followed by 1.1-6 × 10^8 CTL019 CAR-T	$N = 10$ median 6 prior lines, 100% previous ASCT	≥PR 80% at D100 20% had longer PFS after ASCT/CTL019 than initial ASCT CRS 10% (grade 1)
ChicTR-01C-17011272 Phase 2	BCMA/CD19	Humanized CD19 scFv 4-1BB co-stimulatory domain Lentiviral vector BCMA scFv 4-1BB co-stimulatory domain Lentiviral vector	Fludarabine 30 mg/m^2 for 3 days, cyclophosphamide 750 mg/m^2 for 1 day 1 ×10^6 each CAR-T product	$N = 62$ RRMM	ORR 92%, ≥CR 60%, MRD negative 77%, median DOR 20.3 months, median PFS 18.3 months CRS 95% (Grade 3 10%), 11% neurotoxicity (≥ Grade 3 3%)
NCT04935580 Phase 1/2	BCMA/CD19	GC012F CAR-T FasT CAR-T Platform	Standard lymphodepleting chemotherapy following induction chemotherapy 1-3 ×10^5 CAR-T cells	$N = 22$ High risk NDMM	ORR 100%, sCR 96%, 100% MRD negativity to 10^{-5} Median PFS not reached at 13.6 months CRS 27% (all Grade 1/2), no ICANS
NCT04555551 Phase 1	GPRC5D	MCARH109 GPRC5D scFv Lentiviral vector	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 25-450 ×10^6 CAR-T	$N = 17$ ≥ 3 Prior lines of therapy, including PI/IMiD/CD38 Median 6 prior lines, 100% penta-exposed, 94% triple class-refractory, 47% prior BCMA CAR-T	ORR 71% MTD identified at 150 ×10^6 CAR-T cells. Patients who received 25 – 150 ×10^6 CAR-T cells had CRS in 41% (all Grade 1/2) and no ICANS Grade 1 nail changes (65%), rash (18%) and dysgeusia (12%)
NCT03287804 Phase 1/2	BCMA/TACI	AUTO2 Truncated form of APRIL recognises BCMA and TACI OX40 co-stimulatory domain Gamma retroviral vector RQR8 safety switch	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 15-350 ×10^6 CAR-T	$N = 11$ ≥ 3 Prior lines of therapy Median 5 prior lines of therapy $N = 7$ received ≥225 × 10^6 CAR-T	At the higher dose levels, ORR 43%, PR 28%, VGPR 14% CRS 45% (all grade 1), no neurotoxicity
NCT02203825 Phase 1	NKG2D	Human NKG2D Gamma retroviral vector	No lymphodepletion 1 × 10^6- 3 × 10^7 CAR-T	$N = 5$ MM ($n = 7$ AML) 100% ≥5 prior lines of therapy	ORR 0% No CRS/ICANS/neurotoxicity
NCT03464916 Phase 1	CD38	CAR2 Anti-CD38 A2 CAR-T	Dose escalation of CAR2	RRMM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab	Not reported
NCT03672318 Phase 1	CD138	ATLCAR Anti-CD138 CAR-T	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 1 × 10^6- 2 × 10^8 CAR-T	≥ 3 Prior lines of therapy including PI/IMiD, or 2 prior lines if refractory to both	Not reported
NCT03958656 Phase 1 CARAMBA	SLAMF7	Sleeping Beauty gene transfer	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 Escalating doses	≥ 3 Prior lines of therapy, Prior PI/IMiD	Not reported

such as MCL-1 [79]. IMiDs stimulate upregulation of NFKB expression [80] and increase CD8 positive T-cells and memory T-cell subsets [81]. The addition of a cereblon E3 ligase modulator (CelMod), mezigdomide, to a BCMA-bispecific antibody led to improved T-cell activation and cell killing in a preclinical model [82], and IMiDs have been shown to enhance BCMA CAR-T function in vitro [83]. Lenalidomide or mezigdomide maintenance strategies post CAR-T cell therapy are being tested in ongoing clinical studies (NCT05032820, NCT06048250), as is the combination of lenalidomide with a BCMA CAR-T at the time of infusion (NCT03070327).

The checkpoint inhibitor programmed death axis (PD-1/PD-L1) is a well-studied mechanism of immune evasion in myeloma [84, 85]. High levels of PD-1 expressing T-cells have been shown to be associated with inferior in vitro MM cell lysis following treatment with Cilta-cel [86]. Combining checkpoint inhibitors (CPI) with IMiDs in MM was associated with increased mortality in KEYNOTE-185 [87], however studies are ongoing to investigate the role of CPI after CAR-T failure in MM (NCT04205409, NCT05204160, NCT06523621).

Analysis of samples from Cilta-cel treated patients identified increased expression of genes involved in T-cell activation and pro-inflammatory cytokines, such as interleukin-15 (IL-15), in patients with superior outcomes [88]. A fourth generation armoured BCMA CAR-T, engineered to release soluble IL-15, has demonstrated improved MM cell killing in vitro, with further investigation underway [89]. Another pre-clinical study identified increased levels of terminally exhausted T-cells with low levels of BCL2L1 (the gene encoding the anti-apoptotic protein BCL-XL). The authors generated a BCMA-BCL2L1 armoured CAR-T, with promising results shown in a murine MM model [90]. Cancer associated fibroblasts (CAFs) are a part of the immunosuppressive stromal compartment, which impair CAR-T activity and promote MM cell survival. Dual-targeting CAR-Ts, directed against both BCMA and CAFs were shown to improve CAR-T functionality compared with BCMA-CAR-Ts alone in a preclinical model [91].

The CAR-T construct itself can be modified to improve persistence within the immune microenvironment. One factor that may limit efficacy is tonic T-cell signalling in the absence of the target tumour epitope, leading to T-cell exhaustion and anergy. One means of reducing this is to use d-domain proteins instead of scFVs, which are small synthetic proteins that do not induce tonic signalling [92]. A novel BCMA-CAR-T with a completely synthetic d-domain-based antigen binding site (CART-ddBCMA; now called anitocabtagene autoleucel; Anito-cel) has been trialled in 13 patients in a phase 1 study to date, with an ORR of 100% and 89% MRD negativity in evaluable patients [93]. A phase 3 study, iMMagine-3, is enroling patients with RRMM who have received a prior 1-3 lines of therapy, with the view to comparing Anito-cel with pomalidomide, daratumumab or carfilzomib-based regimens. Results are highly anticipated using this novel CAR-T construct.

IMPROVING MANUFACTURE OF CAR-TS

Production of CAR-T cells is a costly and often lengthy process. The patient undergoes leucopheresis to obtain peripheral blood mononuclear cells which are then enriched for T-cells. The CAR is introduced, usually via a viral vector, to generate CAR-T cells which are expanded ex vivo before being re-infused into the patient after lymphodepletion. This process may take weeks, during which time patients may become ineligible for treatment. Within KarMMA, 9% of enroled subjects did not receive their planned infusion of Ide-cel [14], nor did 14% of patients on CARTITUDE-1 [25]. The French Descar-T registry of commercial Ide-cel, reported that 9% of participants were not infused due to either disease progression or manufacturing failure [94]. Earlier use of CAR-Ts within the treatment paradigm may alleviate this issue as patients will have treatment options available whilst awaiting product manufacture. Additionally, given the progressive immune dysfunction that occurs in MM, CAR-Ts from less heavily pre-treated individuals are likely to be more efficacious than those obtained from RRMM patients.

High speed CAR-T generation is starting to enter clinical practice. The FasTCAR platform boasts next day CAR-T manufacture, by concurrently transducing and activating resting T-cells. This technology demonstrated feasibility in acute lymphoblastic leukaemia, and now in the GC012F BCMA/CD19 CAR-T product [70]. T-charge is another process in which CAR-Ts may be produced within 2 days of leucopheresis by removing the requirement for ex vivo expansion. A phase 1 study of PHE885, a BCMA-directed CAR-T product produced using the T-charge platform reported an average 16 day timeline from apheresis to lymphodepletion in 46 RRMM patients, with an ORR of 100% at the highest dose, and MRD negativity in 60% [95]. Furthermore, analysis of the CAR-T product showed preservation of early memory T-cells in the final product [95]. Analysis of Cilta-cel delivered to patients in CARTITUDE-1 demonstrated that a high CD8 positive stem-like phenotype correlated with improved duration of response [96]. Such rapid manufacturing techniques may therefore provide benefits in addition to faster CAR-T generation.

Allogeneic CAR-T cells offer another potential solution to the manufacturing problem. The use of allogeneic T-cells promises an 'off-the shelf' product, and potentially also a more active product. T-cells from patients with monoclonal gammopathy of uncertain significance mount a more robust immune response against MM cells than those from patients with symptomatic MM [97]. CAR-Ts manufactured from healthy donor T-cells, lacking the humoral and cellular immunoparesis typical of MM, may therefore be expected to produce more efficacious cellular therapy products. On the other hand, these products provide their own unique challenges [98].

Graft versus host disease (GvHD) may be prevented by disrupting expression of T cell receptor (TCR) alpha to prevent the patient's immune system from recognizing the CAR-T cell product as foreign. Higher intensity lymphodepletion is also required to improve CAR-T persistence, which confers a higher risk of serious infection. ALLO-715 is a first-in-class allogeneic BCMA-directed CAR-T, with disrupted CD52 expression. In the phase 1 UNIVERSAL trial, 43 patients were treated with escalating doses of ALLO-715 alongside fludarabine at 90 mg/m^2, cyclophosphamide at 900 mg/m^2 and an anti-CD52 antibody, to prevent rejection of the infused product. ORR was 71%, 25% achieved ≥CR and there were no reported cases of GvHD. Overall infection rate was 54%, which is in keeping with Cilta-cel and Ide-cel, however there were 3 deaths out of 43 infused patients due to grade 5 infections. Furthermore, despite the intensive lymphodepletion, only 67% of patients had evidence of CAR-T persistence at 28 days, which correlated with efficacy [99]. This product is not being taken forward in clinical development.

P-BCMA-ALLO1 is an allogeneic BCMA CAR-T manufactured using a non-viral transposon-based integration system (piggyBac). Such systems are less complex and may be cheaper than traditional viral vector-based approaches [100]. Thirty-four patients have been treated to date, with no dose-limiting toxicities or GvHD observed. Grade ≥3 febrile neutropenia occurred in 24%, with a low rate of CRS reported (29%, all Grade 1-2) [101, 102].

Interest in CAR-NK (natural killer) cells is growing as an alternative 'off-the-shelf' product, with preclinical studies of constructs targeting BCMA, CD38 and CD138 reported [103–105]. NK cells act independently of MHC expression, reducing the risk of GvHD compared with allogeneic T-cell products. They also have a different cytokine profile, leading to a reduced likelihood of CRS [106]. Challenges associated with CAR-NK therapies include their inferior persistence [107], and the

Table 4. Universal/Off-the shelf CAR-T and CAR-NK studies.

Study	CAR-T	Study design	Patients	Outcomes
NCT04093596 Phase 1 UNIVERSAL	ALLO-715 TCR alpha and CD52 genes disrupted with TALEN	Various lymphodepletion regimens including use of ALLO-647 (anti-CD52 monoclonal antibody) ALLO-715 40, 160, 320, 480×10^6 CAR-T	$N = 43$ ≥ 3 Prior lines of therapy including PI/IMiD/anti-CD38	Among patients treated with 320×10^6 CAR-T ($n = 24$), ORR 71%, ≥CR 25% CRS 56% (≥ Grade 3 2%), neurotoxicity 14% (all Grade 1/2)
NCT04613557 Phase 1 IMMUNICY-1	CYAD-211 CAR-T co-expresses shRNA targeting CD32 to reduce surface TCR expression	Fludarabine 30 mg/m^2, cyclophosphamide 300 mg/m^2 days -5 to -3 30, 100, 300×10^6 CAR-T	$N = 9$ ≥ 2 Prior lines of therapy, median 4 prior lines	8 patients evaluable for responses, 2 PRs (25%) 1 patient had Grade 1 CRS (11%)
NCT04960579 Phase 1 P-BCMA-ALLO1	P-BCMA-ALLO1 piggyBac system used to knock out TCR beta chain 1 and beta-2-microglobulin	Various lymphodepletion regimens P-BCMA-ALLO1 0.0625-15×10^6 cells/kg	$N = 24$ Triple class-exposed RRMM Median 7 prior lines, 30% previous BCMA-directed therapy	CRS 14% (grade 1), ICANS 4% (1 patient, grade 1), no GvHD
NCT05182073 Phase 1	FT576 BCMA CAR-NK	FT576 1 or 3×10^6 cells±Daratumumab Fludarabine and cyclophosphamide lymphoma depletion	$N = 9$ ≥ 3 Prior lines of therapy including PI/IMiD/anti-CD38	No DLTs CRS 0%, neurotoxicity 0%, GvHD 0%

complex series of activating and inhibitory signalling that controls activity. Strategies to improve persistence include the addition of an IL-15 payload to promote cellular expansion [108, 109]. Technology, such as CRISPR/Cas9-based genome editing offers a means of manipulating effector function, by knocking out multiple inhibitory genes including CD16a and TIGIT, to augment NK-mediated antibody-dependent cellular cytotoxicity [110]. There are various approaches being tested in pre-clinical models, which have yet to fully translate to clinical outcomes. For example, FT576 is a BCMA CAR-NK with a CD38 knock-out to prevent NK fratricide by CD38-directed monoclonal antibodies, such as Daratumumab. Interim results from a phase 1 dose-escalation study have reported no GvHD and no CRS or ICANS of any grade in 9 RRMM patients, however responses have been modest, with VGPR reported in one third of evaluable patients and no further studies in RRMM planned [111]. Other studies are ongoing (eg. NCT05652530, NCT06045091) with results eagerly awaited.

Universal CAR-T or CAR-NK studies are summarised in Table 4. Allogeneic T-cell and NK-based approaches are an ongoing area of interest and development, but require significant improvement before they reach the clinic.

IMPROVING SAFETY OF CAR-T CELL THERAPY IN MM: CRS, NEUROTOXICITY, IEC-HS AND CYTOPENIAS

Cytokine release syndrome (CRS) is common side-effect of CAR-T cell therapy. Rates reported following BCMA CAR-T in MM are high, but generally grade 1-2, with high tumour burden and rapidly progressive disease identified as major risk factors [14, 19, 25, 31, 112]. Increasing clinician familiarity alongside consensus guidelines, may lead to earlier recognition and prompt treatment with the interleukin-6 (IL-6) receptor antagonist, tocilizumab [113]. Other approaches include use of the IL-1 inhibitor anakinra, the JAK1/2 inhibitor ruxolitinib and cyclophosphamide [114, 115]. Safety switches may be incorporated into CAR-T designs to mitigate refractory cases, by choosing to selectively destroy circulating CAR-T cells. For example, expression of the endothelial growth factor receptor (EGFR) enables used of EGFR inhibitors, and herpesvirus thymidine kinase confers sensitivity to ganciclovir [116, 117]. Another approach being tested in several ongoing clinical trials is the provision of a fractionated CAR-T product. Administering the CAR-T over 2-3 days could stagger the rise in cytokines, tempering the peak levels reached, which may translate to less severe CRS. No grade ≥3 CRS was experienced by the first 30 patients who received the ARI0002 product, however updated results reported an overall CRS rate of 90% with 5% developing grade 3 [118, 119]. A recent meta-analysis has failed to identify significant evidence of improved safety with this approach, however a number of studies are ongoing [120].

Immune effector cell-associated HLH-like syndrome (IEC-HS), a poorly understood hyperinflammatory syndrome stimulated by CAR-T therapy, may be seen in up to one fifth of patients receiving BCMA-directed CAR-T cells [121]. Risks are enriched in patients with high tumour burden, especially with concomitant or preceding severe CRS or ICANS, and fatalities have been reported in the literature [122]. Treatments include high-dose steroids and anakinra, alongside supportive care [112].

Neurotoxicity, in the form of ICANS was another anticipated consequence of these therapies. Rates of overall neurotoxicity were similar in the early phase KarMMa and CARTITUDE-1 studies (18% and 21% respectively), however 5 patients in CARTITUDE-1 developed unexplained parkinsonian-like symptoms, termed MNTs. Development of MNTs was shown to be associated with high baseline tumour burden, high baseline IL-6 levels, grade 2 or higher CRS, ICANS, high absolutely lymphocyte count post-Ciltacel infusion and strong CAR-T expansion and persistence. Use of bridging chemotherapy and prompt treatment of CRS and ICANS

successfully reduced the incidence of MNTs from 5% to <1% in subsequent CARTITUDE patients [123]. Movement disorders have also been reported post Ide-cel, suggesting this may be a class effect rather than specific to Cilta-cel [124–126]. A potential hypothesis involves damage to the striatum, which receives dopaminergic innervation from the substantia nigra. Reduced uptake was demonstrated by PET-CT in some affected patients [124, 127]. Conflicting results have been obtained regarding CNS BCMA expression. Analysis of RNA sequencing has demonstrated low levels of BCMA expression within the striatum of children and young adults only, with no convincing evidence demonstrated by immunohistochemistry [128], whereas another group identified localised RNA expression in the caudate nucleus within the basal ganglia in adults [127].

In addition to ICANS and MNTs, cranial nerve (CN) palsies were observed in 6% of Cilta-cel-treated patients within CARTITUDE-1, -2 and -4, with no clear predictive factors identified. In all cases, CN VII was involved, and the majority responded to corticosteroid treatment [129]. Further research is required to understand the aetiology of MNTs following BCMA CAR-T cell therapy, and how to optimize risk in patients pre-treatment.

Although certain features are known to increase the risk of CRS and ICANS, there are currently no widely recognized prediction models for these side effects. The Glasgow prognostic score (GPS), is a simple metric comprised of serum albumin and C-Reactive Protein (CRP) on day of pre-CAR-T lymphodepletion. In a cohort of 139 RRMM patients, of which 83% received Ide-cel and 13% Cilta-cel, high-risk patients by the GPS were significantly more likely to develop severe CRS, any grade ICANS, and have inferior 6-month PFS and OS [130]. Identifying patients more likely to develop sustained cytopenias should also be considered. The CAR-HEMATOTOX score was developed in the setting of anti-CD19 CAR-T cell therapy for B-cell malignancies, and has recently been validated in MM. In a cohort of 113 patients, high-risk individuals, with evidence of pre-lymphodepletion cytopenias and inflammation (raised CRP or ferritin), had significantly longer durations of severe neutropenia (9 vs. 3 days) and higher rates of severe infection (40% vs. 5%). Moreover, one-year non-relapse mortality was 13% compared with 2% in the low-risk group [131].

PATIENT SELECTION FOR CAR-T THERAPY

Alongside identifying and proactively managing patients at increased risk of toxicity, it is important to consider which subgroups are likely to glean the greatest efficacy benefit. The recently published MyCARe (Myeloma CAR-T Relapse) model can be used to identify RRMM patients at risk of early progression, based on the presence of extramedullary disease, plasma cell leukaemia, lenalidomide-refractory disease and elevated serum ferritin at the time of lymphodepletion. Patients with none of these risk factors had a 5-month incidence of relapse/progression of 7%, compared with 53% for those meeting all 4 criteria. This score was derived and validated in a heavily pre-treated, high-risk population, with a median 6 prior lines of therapy. Around 75% of the cohort had adverse cytogenetics, 45% had received previous BCMA-directed therapy and 86% were triple-class refractory. Whether this score can predict outcomes in NDMM is therefore not known [132].

A recent meta-analysis also reviewed 17 trials of 723 RRMM patients receiving a variety of commercial and academic CAR-Ts. The target was BCMA in the majority of cases, with dual BCMA-CD19 and BCMA-CD38 also included. This study again confirmed the poor prognostic impact of the presence of extramedullary disease, which conferred a 44% increase in the risk of relapse/progression or death after treatment. High-risk cytogenetics were also associated with reduced ORR (risk ratio 0.86; 95% CI 0.76-0.97) and a 70% increased risk of progression/relapse or death [133].

The impact of high tumour burden on outcomes is less certain. In CARTITUDE-1, bone marrow plasma cell (BMPC) percentage of 60 or higher was associated with reduced PFS and OS compared with BMPC < 30% [28, 134]. These results have not been recreated within subsequent CARTITUDE trials or the KarMMa studies. Increasing disease burden is known to impair T cell function in vitro and has been demonstrated to adversely impact responses to BCMA-directed bispecific antibodies in preclinical studies [135]. Its relevance to CAR-T outcomes may become clearer with future research.

Determining whether upfront CAR-T therapy can counteract the adverse effects of high-risk features is a crucial question. Optimising bridging therapies may also be a means of improving outcomes. Use of high-doses of alkylators has been shown to produce inferior results [136], whereas there is recent evidence to suggest that pre-CAR-T bispecific antibody treatment may alter subsequent CAR-T expansion dynamics and improve early responses [137]. Radiotherapy, which has immunomodulatory effects alongside cytotoxicity, may also have a beneficial role within bridging therapy, as shown in a number of cases [138, 139].

Currently, patient selection necessitates careful consideration of both patient and disease-related factors. Ultimately, a patient-centred approach should be prioritised.

CONCLUSIONS

CAR-T therapy in MM offers the promise of inducing meaningful remissions in patients with relapsed, high-risk disease, for whom effective treatments are lacking. Cilta-cel and Ide-cel are approved in Europe, the USA and elsewhere in RRMM, with Cilta-cel now an option in lenalidomide-refractory patients after one prior line of therapy in a number of countries. Results are eagerly awaited from upfront studies in NDMM, where these therapies could potentially lead to long-term deep remissions, and possibly even the hope for cure.

However, MM is a complex disease, characterised by numerous subclones with different levels of target antigen expression and different potential mechanisms of treatment resistance. Patients not infrequently succumb to their disease while awaiting CAR-T manufacture, and after successful infusion, these treatments can also confer the risk of significant morbidity, the aetiology of which is not fully understood. In order to bring CAR-T cell therapy into routine clinical practice, these challenges need to be optimized.

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AUTHOR CONTRIBUTIONS

DS wrote the manuscript, DM provided expert review, JH supervised the project and provided critical appraisal.

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DS: none; DM: Employment: Johnson and Johnson; JH: none.

ADDITIONAL INFORMATION

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