**Abstract**

Despite major advances in the treatment of multiple myeloma (MM), it remains a largely incurable disease with long-term control often dependent on continuous therapy. More effective, better tolerated treatments are therefore required to achieve durable remissions and to improve the quality of life of MM patients. Adoptive immunotherapy employing T cells expressing chimeric antigen receptors (CAR) is currently among the most promising treatment approaches in cancer. Within the target portfolio for MM immunotherapy, B-cell maturation antigen (BCMA) is among the most widely studied target antigens. BCMA is consistently expressed on MM cells and, importantly, is not expressed in critical healthy tissue. For this reason, it is an ideal target for MM immunotherapy. Several clinical trials evaluating different BCMA-targeting CAR constructs have been initiated and early results are very promising. However, in this rapidly developing clinical landscape, the ultimate role of BCMA-specific CAR-T cell therapy remains unclear. In this review, we will summarize currently available clinical data on BCMA-directed CAR-T cells and discuss potential future perspective for this promising treatment approach in MM.

**Key words**

adoptive immunotherapy, B-cell maturation antigen, BCMA, chimeric antigen receptor, multiple myeloma

**Abbreviations:**

ALL, acute lymphoblastic leukemia; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CAR-Ts, chimeric antigen receptor T cells; CLL, chronic lymphocytic leukemia; CR, complete response; CRES, CAR-T-related encephalopathy syndrome; CRS, cytokine release syndrome; Cy, cyclophosphamide; DL, dose level; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; Flu, fludarabine; Fred Hutch, Fred Hutchinson Cancer Research Center; HR, high-risk; IMiD, immunomodulatory drug; MAPK, mitogen-activated protein kinases; MM, multiple myeloma; MRD, minimal residual disease; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; ORR, overall response rate; PC, plasma cell; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sBCMA, soluble form of B-cell maturation antigen; scFv, single-chain variable fragment; sCR, stringent complete response; TNFRSF17, tumor necrosis factor receptor superfamily member 17; VGPR, very good partial response.

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1 | INTRODUCTION

The outcomes of patients with multiple myeloma (MM) have significantly improved over recent decades following the widespread introduction of novel agents such as proteasome inhibitors, immuno-modulatory drugs (IMiDs) and monoclonal antibodies into routine clinical care. Despite this progress, the duration of remissions achieved in certain patient populations, in particular, those classified as genetically “high-risk” (HR), can still be relatively short and almost all patients eventually experience relapse and finally succumb to the disease. Chimeric antigen receptor (CAR) T cells (CAR-Ts) are new tools in the growing armamentarium against MM. In other hematological malignancies, namely, acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL), CD19-specific CAR-Ts achieved promising response rates in heavily pretreated patients.1-3 This led to FDA and EMA approval of Kymriah and Yescarta as the first two commercially available CAR-T products. CAR-T therapy target antigens that have been clinically evaluated in MM include CD19,4,5 CD138,6 the kappa light chain7 and SLAMF7/CS1 (NCT03710421). Of the CAR-T targets assessed to date, B-cell maturation antigen (BCMA) is one of the most intensively studied and is probably the most promising with the potential to significantly influence the therapeutic landscape in MM.

2 | BCMA: EXPRESSION AND FUNCTION

Expression of the surface protein BCMA, also known as CD269 or tumor necrosis factor receptor superfamily member 17 (TNFRSF17), first occurs in late memory B cells and is ubiquitously expressed on plasma cells (PCs).8,9 The B-cell activation and proliferation-inducing ligands, BAFF and APRIL, bind to BCMA and consequently promote NFκB and mitogen-activated protein kinases (MAPK) pathway activation.10 BCMA seems to be important for long-lived PC maturation and survival but may be less critical to the overall humoral B-cell response.11,12 BCMA is regularly expressed on MM cells13 at a broad range of epitope densities and can promote MM growth and immunosuppression in the bone marrow (BM) microenvironment.14 Membrane-bound BCMA can be cleaved by γ-secretase, a process which may lead to reduced overall BCMA cell surface expression as well as to the formation of a soluble form (sBCMA) that interferes with BCMA-binding therapeutic molecules.15 Importantly, no significant BCMA expression has been observed on nonhematological tissues.16

3 | BCMA-TARGETED CAR-T CONSTRUCTS IN CLINICAL EVALUATION

Several BCMA-specific CAR-T constructs are currently under clinical evaluation for the treatment of MM. The design of the most clinically advanced CAR constructs is summarized in Table 1. The CAR constructs developed at the National Cancer Institute (NCI)17 and by Bluebird Bio (BB2121)18 both utilize a murine single-chain variable fragment (scFv). For the earlier CD19-directed CAR-Ts, anti-murine CAR host immune responses were reported that may have limited efficacy by prevention of in vivo expansion.19 As a result, there has been increasing use of human-derived scFvs in newer BCMA-

### TABLE 1
Selection of BCMA-targeting CAR constructs in clinical development

| Developer/References | Construct | scFv | Vector | Costimulatory domain | Comment |
|----------------------|-----------|------|--------|----------------------|---------|
| NCI Ali et al.17      | CAR-BCMA  | 11D5-3 (murine) | γ-Retrovirus | CD28 | First clinically evaluated BCMA CAR-construct. Further clinical development is probably not planned. |
| Bluebird Bio/Celgene Friedman et al.18 | BB2121 | 11D5-3 (murine) | Lentivirus | 4-1BB | Most advanced in clinical development. Expected to become the first approved BCMA CAR-T cell product. |
| MSKCC Smith et al.20 | MCARH171 | Human | γ-Retrovirus | 4-1BB | Construct will probably stay in academic evaluation. Approval is not expected. |
| Novartis/UPenn Bu et al.21 | CART-BCMA | Human | Lentivirus | 4-1BB | Further clinical development probably not planned due to lower efficacy compared to other constructs. |
| Juno/Celgene Mallankody et al.22 | JCARH125 | Human | Lentivirus | 4-1BB | The developer will probably focus on bb2121 and no further develop this construct. |
| Fred Hutch Green et al.23 | FCARH143 | Human | Lentivirus | 4-1BB | Construct will probably stay in academic evaluation. Approval is not expected. |
| Legend Biotech/J&J Zhao et al.24 | LCAR-B38M/ JNJ-4528 | “Dual-epitope” (human) | Lentivirus | 4-1BB | Second most clinically advanced BCMA CAR-T cell product. Published data is primarily from Chinese patients. |
| Poseida Therapeutics Gregory et al.25 | P-BCMA-101 | Centyrin | Nonviral (piggyBac) | 4-1BB | Promising BCMA CAR-T cell product with the advantage of nonviral gene transfer and unique binding molecule. |

Abbreviations: Fred Hutch, Fred Hutchinson Cancer Research Center; J&J, Johnson & Johnson; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; UPenn, University of Pennsylvania; scFv, single-chain variable fragment.
| Trial/phase construct References | Center/sponsors | Patients BCMA expression | Pretreatment/HR cytogenetics | Cell dose | Conditioning | Response |
|----------------------------------|----------------|--------------------------|-----------------------------|-----------|-------------|----------|
| NCT02215967 | NCI | All: 26 DL1: 3: 10 DL4: 16 | BCMA expression >50% | DL4: Median 9.5 lines (range 3-19) PI + IMiD: 100%, HD/auto: 83% | Flu 30 mg/m² for 3 days | ORR: 79% |
| Phase I | CAR-BCMA | Ali et al.17 and Brutno et al.26 | DL4: Median 9.5 lines (range 3-19) PI + IMiD: 100%, HD/auto: 83% | DL1: 0.3 x 10⁶ DL2: 1 x 10⁶ DL3: 3 x 10⁶ DL4: 9 x 10⁶/kg CAR-Ts | 31 weeks |
| NCT02546167 | UPenn | All: 25 DL1: 9 DL2: 5 DL3: 11 | BCMA expression not required | Median 7 lines PI + IMiD: 100% HR cytogenetics: 96% | DL1: None | ORR: 33% |
| Phase I | CART-BCMA | Cohen et al.27 | Median 7 lines PI + IMiD: 100% HR cytogenetics: 96% | DL1: 1.5 x 10⁷ DL2: 1.5 x 10⁷ DL3: 1.5 x 10⁷ CAR-Ts | Median PFS: 125 days |
| NCT03070327 | MSKCC | All: 11 Positive BCMA expression | Median 6 lines (range 4-14) | DL1: 72 x 10⁶ DL2: 137 x 10⁶ DL3: 475 x 10⁶ CAR-Ts (mean) | Flu 30 mg/m² for 3 days | ORR: 64% |
| Phase I | MCARH171 | Mailankody et al.28 | Median 6 lines (range 4-14) | All pretreated with PI + IMiD. CD38 mAb and HD/auto HR cytogenetics: 82% | Flu 30 mg/m² for 3 days | ORR: 64% |
| NCT03338972 | Fred Hutch | All: 7 BCMA expression ≥5% by flow cytometry | Median 7 lines (range 6-11) HD/auto: 71%, Allo: 43% HR cytogenetics: 100% | 5-15 x 10⁷ Defined composition of CD4+CD8+ T cells | Flu/Cy for 3 days | ORR: 100% |
| Phase I | FCARH143 | Green et al.23 | Median 7 lines (range 6-11) HD/auto: 71%, Allo: 43% HR cytogenetics: 100% | Flu/Cy for 3 days | ORR: 100% |
| NCT02658929 (CRB-401) | Multicenter | All: 33 DE cohort: 21 Ex cohort: 12 BCMA expression in DE cohort: >50%, in Ex cohort not required | Median 7 lines (range 3-23) PI + IMiD: 100% CD38 mAb: 82% HD/auto: 97% HR cytogenetics: 45% | Flu 30 mg/m² | ORR: 90% |
| Phase I | BB2121 (bb2121) | Raje et al.29 | Median 7 lines (range 3-23) PI + IMiD: 100% CD38 mAb: 82% HD/auto: 97% HR cytogenetics: 45% | Flu 30 mg/m² | CR: 50% |
| NCT03274219 (CRB-402) | Multicenter | All: 12 DL1: 12 BCMA expression >50% by IHC | Median 7 lines (range 4-17) PI + IMiD: 92%, mAb: 75% HD/auto: 83% HR cytogenetics: 58% | Flu 30 mg/m² | ORR: 83% |
| Phase I | BB2121 (bb2121) | Shah et al.30 | Median 7 lines (range 4-17) PI + IMiD: 92%, mAb: 75% HD/auto: 83% HR cytogenetics: 58% | Flu 30 mg/m² | CR/sCR: 25% |
| NCT03430011 (EVOLVE) | Multicenter | All: 44 DL1: 14 DL2: 28 DL3: 2 BCMA expression not required | Median 7 lines (range 3-23) PI + IMiD: 100% CD38 mAb: 100% HD/auto: 95% HR cytogenetics: 77% | Flu 30 mg/m² | ORR: 82% sVGPR: 48% |
| Phase I/II | JCARH125 | Mailankody et al.22 | Median 7 lines (range 3-23) PI + IMiD: 100% CD38 mAb: 100% HD/auto: 95% HR cytogenetics: 77% | Flu 30 mg/m² | ORR: 79% |
| | | | | Flu 30 mg/m² for 3 days | CR/sCR: 25% | MRD: 100% |

(Continues)
TABLE 2 (Continued)

| Trial/phase construct | Center/sponsors | Patients | BCMA expression | Pretreatment/HR cytogenetics | Cell dose | Conditioning | Response |
|-----------------------|----------------|----------|-----------------|-----------------------------|-----------|--------------|----------|
| NCT03548207 (CARTITUDE-1) | Multicenter Janssen | All; 29 | Median 5 lines (range 3-18) | 0.75 × 10^9/kg CAR-Ts (target 0.5-1.0 × 10^9) | Flu 30 mg/m² | O/R: 100% CR/sCR: 69% VGPR: 17% PR: 14% MRD: 100% MRD- |
| NCT0328493 | Multicenter Poseida Therapeutics | All; 23 | Majority ≥6 lines | DL1: 51 × 10^6 | Flu 30 mg/m² | ORR: 68% |

Abbreviations: CAR-Ts, chimeric antigen receptor T cells; CR, complete response; Cy, cyclophosphamide; DE, dose escalation; DL1, dose level 1; DL2, dose level 2; DL3, dose level 3; EC, expansion cohort; Ex, expansion; Flu, fludarabine; Fred Hutch, Fred Hutchinson Cancer Research Center; HD/auto, high-dose chemotherapy and autologous stem cell transplantation; HR, high-risk; HR cytogenetics, high-risk cytogenetics including del(17p), t(4;14), t(14;16) or t(14;20); IHC, immunohistochemistry; IMiD, immunomodulatory drug; LV, lentivirus; mAb, monoclonal antibody; MSKCC, Memorial Sloan-Kettering Cancer Center; n/a, data not available; NCI, National Cancer Institute; PI, proteasome inhibitor; PR, partial response; ref, refractory; RV, γ-retrovirus; sCR, stringent complete response; VGPR, very good partial response.
1.5 × 10^7 CAR-T with Cy conditioning (n = 5) and DL3—1.5 × 10^8 CAR-Ts with prior Cy (n = 11). The ORR in DL1 was 44% with one sCR and two VGPR, in DL2 20% with one PR, and in DL3 64% with one CR and three VGPR. Three of 25 patients (12%) remained progression-free at 11, 14 and 32 months postinfusion. The median PFS was 125 days for cohort 3. In most of the newer CAR-T studies, Flu was added to Cy for conditioning therapy. The community believes that the addition of Flu to Cy is beneficial for efficient adoptive immunotherapy. However, no clinical data is available supporting that the addition of Flu to this CAR-T product would have improved efficacy.

A study at the MSKCC which started recruitment in 2017 reported on BCMA-CAR-T treatment of 11 RRMM patients with a median of six treatment lines prior to CAR-T infusion (range 4-14; NCT03070327). Treatment was conducted in four escalating dose cohorts (72 × 10^6, 137 × 10^6, 475 × 10^6 and 818 × 10^6 mean transduced CAR+ cells). The ORR was 64% with a median duration of response of 106 days. Importantly, patients treated at the higher dose levels (DL3 and DL4) all showed an objective response. Three of these five patients sustained response for more than 6 months.

The Fred Hutch presented clinical trial data on seven RRMM patients who had received BCMA-directed CAR-Ts (NCT03338972). Patients had a median of eight treatment lines prior to CAR-T administration (range 6-11). They were divided into two cohorts based on the BM PC burden (A 10%-30%, B >30% BM PCs). Patients received between 5-15 × 10^7 CAR+ T cells in a fixed ratio of CD4+ and CD8+ cells. All evaluable patients responded to the treatment and all achieved MRD-negativity.

In parallel with these primarily academia-driven investigator-initiated trials, there have been a number of biopharmaceutical industry-driven multicenter clinical trials with BCMA-specific T cells. Bluebird Bio and Celgene reported on 33 RRMM patients enrolled in a 2016 multicenter phase I study (NCT02658929). Patients were treated in both dose-escalation (n = 21) and expansion cohorts (n = 12). The optimal CAR-T dose for the expansion cohort was defined as greater than 150 × 10^6 cells. Patients in the dose-escalation and expansion cohorts had a median of 7 and 8 prior treatment lines (range 3-14 and 3-23, respectively). The ORR was 90% with a CR rate of 50% in patients who received more than 150 × 10^6 CAR-Ts. All responding patients evaluated for MRD were MRD-negative (n = 16). The median progression-free survival (PFS) was 11.8 months for the 18 patients receiving 150 × 10^6 or more CAR-Ts in the dose-escalation cohort. Furthermore, the median PFS of the 16 MRD-negative patients was 17.7 months. However, in contrast to CAR-T studies with CD19-targeted cell production in ALL and DLBCL, no plateau was seen in our study suggesting limited long-term disease control in heavily pretreated MM patients. The phase II KarMMa study was initiated to further investigate safety and efficacy of bb2121 in RRMM (NCT03361748). The study completed enrolment at the end of 2018. In addition, the phase II KarMMa-2 study for HR RRMM (NCT03601078) and a randomized phase III trial comparing bb2121 with a choice of state-of-the-art triplet regimen in RRMM have been initiated (KarMMa-3, NCT03651128). Furthermore, BB2121 is under investigation in a 2017 multicenter phase I trial based on an optimized production protocol involving the phosphoinositide 3 kinase (PI3K) inhibitor bb007 during ex vivo T cell cultivation (bb21217; NCT03274219). Twelve RRMM patients were treated with bb21217 in the lowest DL1 cohort with 150 × 10^6 BCMA-CAR-Ts. They had a median of seven lines of treatment (range 4-17) prior to CAR-T application. The ORR was 83% with 25% CR/sCRs.

BCMA-CAR-T cells from Bluebird Bio are currently most advanced in clinical development. However, with JCARH125 in the EVOLVE study, Celgene is investigating another CAR-T cell construct in a multicenter phase I/II study in RRMM (NCT03430011). The study opened for recruitment in 2018. In the latest report, 44 patients with a median of seven prior treatment lines (range 3-23) were treated with BCMA-specific CAR-Ts. The ORR of all evaluable patients was 82% with an ORR of 79% and a sCR/sCRs rate of 43% in the lowest DL. In a phase I study started by Poseida Therapeutics in 2017, 23 RRMM patients received P-BCMA-101, a CAR-T with two novel features: BCMA targeting is not based upon a conventional scFv for BCMA recognition it utilizes a nonviral gene transfer technology (NCT03288493). The majority of patients had six or more prior treatment lines. The ORR in the 19 evaluable patients was 68% with 100% ORR in the recommended phase 2 dose.

Most CAR development that is currently under clinical evaluation has been performed in the US and most of the clinical CAR trials, including BCMA-targeted CARs, are conducted there. However, China has an emerging biotechnology industry with several novel CAR-T products that are already in clinical trials. In February 2020, a search at clinicaltrials.gov for the key words “multiple myeloma,” “chimeric antigen receptor” and “BCMA” identified 19 clinical trials in the US and 22 trials in China. Europe is clearly under-represented with only four trials. Therefore, academia as well as industry must be encouraged to conduct more adoptive immunotherapy trials in Europe. A summary of the most advanced Chinese BCMA-CAR-T trials is provided in Table 3. The clinically most advanced Chinese CAR construct targeting BCMA is LCAR-B38M/JNJ-4528 from Legend Biotech. It was first evaluated in a multicenter phase I study in China (NCT03090659) and is now being developed in cooperation with J&J. A single-center experience (The Second Affiliated Hospital of Xi’an Jiaotong University) involving 57 RRMM patients who were treated with LCAR-B38M was recently published. With a median of three (range 1-9) prior treatment lines, these patients were less heavily pretreated when compared to the subjects in comparative trials. They received a median of 0.5 × 10^6 cells/kg CAR-Ts after preconditioning with Cy. An ORR of 88% was reported with 68% CRs and MRD-negativity in 63% of evaluated patients. The median PFS after CAR-T application was 15 months. Promising results from this Chinese clinical trial led to the evaluation of this CAR-T product in the international multicenter phase I/II CARTITUDE-1 trial (NCT03548207) achieving an ORR of 100% in 29 RRMM patients with a median of five prior treatment lines. Furthermore, a multicenter phase I study sponsored by CARsgen Therapeutics with a fully human BCMA-targeting CAR-T construct (CT053) reported an ORR of 100% with
| Trial/phase References | Center/sponsor | PatientsBCMA expression | Construct | Pretreatment | Cell dose | Conditioning | Response |
|------------------------|----------------|-------------------------|-----------|-------------|-----------|-------------|----------|
| NCT03090659 (LEGEND-2) | Multicenter (single-center results published) Legend Biotech | All: 57 Clear expression | LCAR-B38M/JNJ-4528 | Median 3 (1-9) | Median $0.5 \times 10^6$ cells/kg Cy 300 mg/m² for 3 days | ORR: 88% CR: 68% 63% MRD- Median PFS: 15 months |
| NCT03302403 NCT03716856 NCT03800039 | Multicenter CARsgen Therapeutics | All: 17 ≥50% | CT053 human scFv 4-1BB | Median 4 (2-11) PI: 100% IMiD: 94% mAb: 18% HD/auto: 53% | $1.5 \times 10^9$ cells, $1 \times 0.5 \times 10^6$, $1 \times 1.8 \times 10^9$ CAR-Ts Flu 20-25 mg/m² Cy 300-500 mg/m² for 3 days | ORR: 100% CR: 36% VGPR: 43% |
| NCT03093168 | The Second Affiliated Hospital of Henan University | All: 17 >5% | Vector: RV scFv: n/a CoS: 4-1BB | ≥3 prior treatment regimens, including PI and IMiD | $9 \times 10^6$ CAR-Ts/kg Flu 25 mg/m² Cy 300 mg/m² for 3 days | ORR: 79% CR/sCR: 41% |
| ChiCTR-OPC-16009113 | Tongji Hospital | All: 30 not required | Vector: LV scFv: murine CoS: n/a |Median 4.5 (3-12) PI: 97% IMiD: 83% mAb: 17% HD/auto: 37% | $5.4-25.0 \times 10^6$ CAR-Ts/kg Flu 25 mg/m² Cy 25 mg/kg for 3 days | ORR: 93% CR/sCR: 50% VGPR: 13% |
| NCT03455972 (SZ-MM-CART02) | The First Affiliated Hospital of Soochow University Shanghai Unicar | All: 10 BCMA or CD19-positive by flow cytometry | Vector: LV scFv: humanized CoS: OX40/CD28 | First line. Consolidation after HD/auto for HR MM patientsa | CART-19: $1 \times 10^7$/kg (day 1/2) CART-BCMA: 2-6 $10^7$/kg (day 14-20) Busulfan/Cy | ORR: 100% CR/sCR: 40% VGPR: 60% 60% MRD- |

Abbreviations: CAR-Ts, chimeric antigen receptor T cells; CoS, costimulatory domain; CR, complete response; Cy, cyclophosphamide; Flu, fludarabine; Fred Hutch, Fred Hutchinson Cancer Research Center; HD/auto, high-dose chemotherapy and autologous stem cell transplantation; HR, high-risk; IHC, immunohistochemistry; IMiD, immunomodulatory drug; LV, lentivirus; mAb, monoclonal antibody; n/a, data not available; PI, proteasome inhibitor; PR, partial response; RV, γ-retrovirus; sCR, stringent complete response; VGPR, very good partial response.

aHR defined as PR or less after 4 cycles of PAD triplet induction, IgD or IgE MM, extramedullary disease or HR cytogenetics (del(17p), t(4;14), t(14;16), t(14;20)).
36% CRs in 17 RRMM patients.32 CARsgen Therapeutics received Investigational New Drug (IND) clearance for BCMA-CAR-T Cells from the FDA in June 2019. This decision also indicates that CAR-T constructs developed and evaluated in China have the potential to progress rapidly through the regulatory evaluation required for the US and European markets.

Several other smaller phase I studies with BCMA-specific CAR-Ts have been conducted in China and initial results are available. For example, a single-center study at the Second Affiliated Hospital of Henan University achieved ORRs of 79% with 18% CRs in 17 RRMM patients33 and at the Tongji Hospital treated 30 RRMM patients with an ORR of 93% and 50% CRs.34

All of these trials have been evaluating BCMA-CAR-Ts in RRMM. In contrast, the First Affiliated Hospital of Soochow University is currently conducting a clinical BCMA-CAR-T trial as consolidation in first-line treatment for HR patients. A total of 10 MM patients received CD19-specific and BCMA-specific CAR-Ts developed by Shanghai Unicar after autologous stem cell transplantation (autoSCT). An ORR of 100% with an improvement of remission after CAR-T administration from 40% CR to 70% CR/sCR was reported. In addition, MRD negativity increased from 44% to 60%.35 Due to the limited patient numbers and short follow-up, formal evaluation of the efficacy of a CAR-T-based consolidation approach, especially when compared to standard maintenance strategies, is required.

In summary, these preliminary clinical results of BCMA-directed CAR-Ts are promising. However, cross-comparison of the studies to identify the most potent CAR-T product is difficult due to major differences in CAR design, cell production protocols and patient characteristics. In addition, despite the high rates of MRD-negativity, the duration of responses is relatively short. Therefore, treatment of larger patient populations and longer follow-up will be necessary to better understand the relative strengths and weaknesses of the different CAR-T constructs. Among all evaluated BCMA-CAR-Ts, bb2121 is the clinically most advanced cell product. It is expected that bb2121 will be the first CAR-T therapy to be approved for the treatment of MM and approval is expected in 2020. This first indication will probably be for RRMM patients with at least three previous treatment lines including IMiDs, PIs and CD38 antibodies. Furthermore, triplet as well as quadruplet regimens in earlier lines of treatment will challenged and even study concepts for first-line high-risk MM patients (eg, with R-ISS III) are initiated.

### 4.1 Side effects of BCMA-targeting CAR-Ts

Typical side effects reported for CD19-targeting CAR-Ts, the most intensively evaluated CAR-T therapy, are cytokine release syndrome (CRS) and neurotoxicity (“CAR-T related encephalopathy syndrome”; CRES).34 A recent consensus paper by the American Society for Transplantation and Cellular Therapy (ASTCT) provides recommendations for the grading of CRS and CRES.37 The interleukin (IL)-6 inhibitor tocilizumab and corticosteroids are now standard of care for the treatment of higher grade CRS and CRES.35

| Trial References | Center Construct | CRS | CRES |
|------------------|------------------|-----|------|
| NCT02215967 Ali et al.17 and Brudno et al.26 | NCI CAR-BCMA | DL1-3: Grade ≥3: 0% DL4: All grades: 93% Grade ≥3: 43% | Grade 3/4: 4% |
| NCT02546167 Cohen et al.27 | UPenn CART-BCMA | All grades: 88% Grade 3/4: 32% | All grades: 32% Grade 3/4: 12% |
| NCT03070327 Mailankody et al.28 | MSKCC M CARH171 | Grade 1/2: 40% Grade 3: 20% | Grade 2: 10% |
| NCT03338972 Green et al.23 | Fred Hutch FCARH143 | Grade 1/2: 86% | None |
| NCT02658929 Raje et al.29 | Multicenter BB2121 (bb2121) | All grades: 76% Grade ≥3: 6% | All grades: 42% Grade 3 ≥ 3%
| NCT03274219 Shah et al.30 | Multicenter BB2121 (bb2121) | All grades: 67% Grade 3: 8% | Grade 4: 8% |
| NCT03430011 Mailankody et al.28 | Multicenter JCARH125 | Grade 1/2: 71% Grade 3/4: 9% | Grade 1/2: 18% Grade 3/4: 7% |
| NCT03548207 Madduri et al.31 | Multicenter JNJ-4528 | All grades: 93% Grade ≥3: 7% | All grades: 10% |
| NCT03288493 Gregory et al.32 | Multicenter P-BCMA-101 | Grade 1/2: 10% | All grades: 5% |

Abbreviations: CAR-Ts, chimeric antigen receptor T cells; CRES, CAR-T related encephalopathy syndrome; CRS, cytokine release syndrome; DL1, dose level 1; DL2, dose level 2; DL3, dose level 3; Fred Hutch, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute.

The frequency and severity of CRS and CRES observed in different BCMA-CAR-T trials are summarized in Table 4. CRS with BCMA-CAR-Ts is common but is mainly grade 1-2. CRS associated with BCMA-specific CAR-Ts so far appears to be manageable and the rates of CRES seem to be relatively modest compared to those seen with CD19-specific CAR-Ts.

In addition to these specific CAR-T related toxicities, prolonged cytopenia is frequently observed. This is thought to be principally due to the use of myelosuppressive conditioning therapy (Cy ± Flu) in this heavily pretreated patient population.

A major potential concern with gene therapy is insertional mutagenesis. In contrast to studies conducted with hematopoietic stem cells, T cells seem to be less susceptible to secondary malignancies arising from insertional mutagenesis. In contrast to studies conducted with hematopoietic stem cells, T cells seem to be less susceptible to secondary malignancies arising from insertional mutagenesis. However, lentiviral integration of a CD19-directed CAR into the tumor suppressor gene, TET2, has been reported.38 Unexpectedly, this led to clonal...
expansion of a single CAR-T clone that promoted enhanced anti-tumor activity.

Safety switches can be used to eradicate CAR-Ts in case of severe side effects. They include suicide gene-based approaches such as the herpes simplex thymidine kinase (HSV-TK)\textsuperscript{39} or inducible caspase 9,\textsuperscript{40,41} tetracycline-based on/off switches\textsuperscript{42} as well as antibody-based T cell depletion strategies such as truncated epidermal growth factor receptors (tEGFR).\textsuperscript{43} However, the side effects of CAR-Ts are, for the most part, sufficiently treatable with tocilizumab and corticosteroids. For this reason, to the best of our knowledge, the use of such safety switches to eradicate CAR-Ts has not yet been reported. Nonetheless, safety switches may have a role in next-generation CAR-T constructs with enhanced T-cell activity (fourth-generation CAR-Ts).\textsuperscript{44}

### 4.2 Predictors of response

When making the case for cost and labor-intensive novel treatment approaches such as CAR-Ts, reliable predictive markers would be very useful for identifying the patients who are likely to benefit the most. However, due to the small numbers of patients treated with BCMA-specific CAR-Ts and the limited follow-up so far, it is difficult to define reliable predictors of response.

In several phase I studies, a dose-dependent increase in response rates was seen at higher DLs (Table 2).\textsuperscript{26,27,29} In addition, it appears that peak peripheral blood CAR-T expansion levels may correlate with response.\textsuperscript{26,28,32} However, the underlying mechanisms promoting these peak expansion levels is not yet clearly understood. Conditioning may not be mandatory for response to BCMA-CAR-Ts in MM patients but may be associated with more durable expansion and is therefore generally recommended.\textsuperscript{27} Furthermore, T-cell phenotype as well as T-cell fitness may have an impact on the success of BCMA-directed CAR-Ts. It was reported that higher CD4:CD8 T-cell ratios in the leukapheresis product and at the start of CAR-T culture but not in the final cell product were associated with enhanced CAR-T expansion and a better clinical response.\textsuperscript{27} Furthermore, a higher number of CD8+ T cells with a less-differentiated memory phenotype (CD45RO –, CD27+) in the leukapheresis product may affect in vivo T-cell expansion and treatment response.\textsuperscript{27} Similar observations were reported for patients with chronic lymphocytic leukemia (CLL).\textsuperscript{45}

Baseline patient characteristics, in contrast, do not seem to influence CAR-T expansion and the response to BCMA-CAR-Ts in MM patients. This includes age, isotype, time from diagnosis, number of prior therapies, HR cytogenetics, BM MM tumor burden, soluble BCMA concentration or the treatment regimen given before leukapheresis or CAR-T-BCMA infusions.\textsuperscript{27} Importantly, early evidence suggests that the level of BCMA expression on MM cells does not affect treatment response.\textsuperscript{24,29} In addition, although a high tumor burden in the BM can be associated with an increased risk of severe CRS, this does not seem to influence response.\textsuperscript{26,27} Reports on more patients and likely meta-analyses may be helpful to identify and validate predictive biomarkers of CAR-T treatment outcome. In a meta-analysis, clinical results from 285 patients treated in 15 clinical trials were pooled: higher dose levels and absence of high-risk cytogenetics were associated with higher response rates.\textsuperscript{46} Further analysis is necessary to prove these hypotheses.

Albeit prior treatment and BCMA expression may not be direct biomarkers of response, refractoriness and very late CAR-T therapy application rather than earlier has been discussed as less advantageous for prolonged efficacy. In our experience with 40 CD19+ lymphoma patients, multiple treatment with cytostatic drugs, particularly bendamustine, exerted a negative effect on quantity and quality of CD3+ T cells for further production into CARTs. Currently, the BELINDA as well as the ZUMA-7 trials are ongoing to clarify for CD19+ lymphoma patients whether the use of CAR-T cell therapy in second line is better than in third line. The same applies to myeloma patients and makes early use of this treatment modality to achieve a very deep remission upfront very tempting.

To achieve optimal safety for CAR T cell treatment of myeloma patients, the expertise of both, auto- and allo-teams, should be combined.\textsuperscript{47}

### 4.3 Mechanisms of resistance to BCMA-targeting CAR-Ts

The limited number of patients treated so far precludes meaningful analysis of the mechanisms underlying primary and secondary resistance to BCMA-specific CAR-Ts. One mechanism could be the down-regulation of BCMA on MM cells. Decreased or absent BCMA expression was reported in patients who relapsed after BCMA-CAR-T therapy.\textsuperscript{23,26} The mechanisms underlying this reduction in surface BCMA expression have yet to be elucidated.

Importantly, the immunosuppressive MM microenvironment, especially in the setting of highly refractory disease, may be responsible for treatment failure with BCMA-CAR-Ts. T cells in MM patients develop features of exhaustion and senescence at the tumor site.\textsuperscript{48} Strategies to modulate the immunosuppressive nature of the MM microenvironment may therefore be warranted. Furthermore, the quality and fitness of T cells used for CAR-T production seem to be an important factor in adoptive immunotherapy. Moreover, a higher proportion of less differentiated T cells in the leukapheresis product appears to correlate with the clinical response.\textsuperscript{27} However, it is currently unclear if an optimization of production protocols to enrich for less-differentiated CAR-Ts affect product efficacy.

In summary, further investigation of resistance mechanisms is required to develop strategies to overcome treatment failure.

### 4.4 Optimization of production protocols

For CAR-T therapy, both the CAR constructs and the CAR-T production process affect treatment efficacy. However, cell production protocols are often treated as commercially sensitive information and are not made publically available. This limits our collective ability to meaningfully compare the different CAR-T studies.
Less-differentiated T cells in the final cell product, especially those with a naïve-like (T_N) or stem cell memory-like (T_SCM) phenotype, are thought to affect long-term engraftment and sustained antitumor activity. Cytokines such as IL-2, IL-7 and IL-15 can influence the composition of different T-cell subsets during CAR-T generation. In addition, pharmacological pathway inhibition during ex vivo T-cell expansion as well as different T-cell activation strategies such as the use of retronectin can influence the differentiation state of T cells. The PI3K/AKT/mTOR pathway is involved in T-cell activation, survival, expansion and differentiation. AKT or PI3K inhibition during T-cell expansion was shown to enrich less-differentiated T cells in the final cell therapy product, thereby enhancing antitumor activity. For BCMA-directed CAR-Ts, Bluebird Bio initiated a clinical trial with bb21217 (NCT03274219), a CAR-T product based on the BB2121 CAR construct but generated in the presence of the PI3K inhibitor, bb007, during ex vivo T-cell expansion. Early clinical results appear promising with ORRs of 83% including 25% CR/sCRs in heavily pretreated patients (median 7 lines of previous treatments).

CAR-T generation in the majority of cases relies on viral gene transfer. However, virus-based gene manipulation techniques require robust safety precautions and are expensive. Nonviral vector systems for the generation of CAR-Ts are therefore under evaluation. Early reports from trials using CD19-specific CAR-Ts based on the sleeping beauty/transposon system for gene manipulation have demonstrated the feasibility as well as safety and efficacy of this CAR-T generation approach. The clinical trial with P-BCMA-101 from Poseida Therapeutics uses the piggyBac transposon system for transfer of their anti-BMCA CAR construct into T cells. Besides feasibility, safety and efficacy, it was reported that the final cell product was enriched with early memory T cells.

The application of CAR-Ts in a defined CD4:CD8 ratio has been proposed to be superior to the application of bulk generated CAR-Ts. The first results with BCMA-directed CAR-Ts in a defined CD4:CD8 ratio were reported by the FHCC and are encouraging with six of six patients achieving MRD-negative responses. However, this information is too preliminary to allow for any more general recommendations regarding the value of defined CD4:CD8 ratios.

It is highly desirable to launch more CAR-T cell studies combined with in-house production of CAR-Ts developed by academic institutions. This will make all data available to the scientific community straight from the leukapheresis and the CAR T-cell product till the clinical response data, the frequency and immunophenotype of the circulating CAR-Ts. We think that only an algorithm comprising all these data layer will allow us to define the type of patients who will eventually profit from CAR-T cell therapy. Moreover, early phase I investigator-initiated trials allow to test innovative targets and CAR constructs which will be overtaken by the pharmaceutical industry for further evaluation in phase II or III trials. National and international third-party funding for early phase trials is highly desirable, particularly in Europe where gene immuno-cell therapy is so much behind the US and China.

FIGURE 1 Concepts to improve BCMA-specific CAR-T therapy with combinatorial approaches [Color figure can be viewed at wileyonlinelibrary.com]

4.5 Combination therapy

Targeted cancer treatment against a single therapeutic target may lead to the development of resistance. Dual-targeting is therefore an attractive option to overcome resistance and improve outcomes after BCMA-directed CAR-T treatment. Combination strategies may include the addition of small molecules or antibodies with immunomodulatory functions as well as the simultaneous targeting of two or more antigens, either using a single CAR-T clone or two different cell products (Figure 1).

Increased expression of immune checkpoints leading to T-cell exhaustion is proposed as one of the possible mechanisms of CAR-T resistance. Inhibition of PD1/PD-L1 alone seems to be insufficient to achieve relevant clinical responses in MM. However, in a single-arm phase II trial, the combination of pembrolizumab with pomalidomide and low-dose dexamethasone led to durable responses in RRMM patients. Unfortunately, several phase III trials investigating combinations of PD-1/PD-L1 inhibitors with immunomodulators, such as lenalidomide or pomalidomide, were terminated due to safety issues. Nevertheless, the combination of BCMA-CAR-Ts with a PD-1/PD-L1 inhibitor may be an option to improve treatment response and achieve long-term remissions. Treatment of patients with pembrolizumab after BCMA-CAR-T failure was recently reported. Five patients received pembrolizumab in combination with either lenalidomide or pomalidomide and dexamethasone. Minimal response was achieved in four patients and stable disease in one patient. It is of note that this was a heavily pretreated patient cohort, all harboring HR cytogenetics, with a median of nine prior treatment lines and all of...
them were refractory towards a prior treatment with pomalidomide.67 Further investigations are necessary to see whether inhibition of the PD-1/PD-L1 axis may be a safe and effective option after CAR-T failure. Preclinical studies suggested that IMiDs such as lenalidomide can improve the antitumor activity of CAR-Ts. The addition of lenalidomide to CD19 or CD20-specific CAR-Ts for the treatment of B-cell lymphoma and to SLAMF7-specific CAR-Ts for MM indicates synergistic effects with enhanced antitumor activity in mouse models.68,69 Furthermore, lenalidomide can also improve efficacy of BCMA-targeted CAR-Ts in preclinical studies.70 Therefore, a clinical phase I trial at MSKCC is currently evaluating the combination of lenalidomide with BCMA-targeted CAR-Ts in MM (NCT03070327). In addition, the phase I KarMMa-4 study (NCT04196491) is evaluating bb2121 followed by lenalidomide maintenance in newly diagnosed high-risk MM patients.

Besides the addition of drugs stimulating the immune system, targeting more than one antigen may reduce the risk of target antigen escape. These additional CARs can either be included in the same construct as BCMA to obtain bi-specific CAR-Ts or can be on two different CAR-T products. Possible further targets in MM may be CD19, CD138 or SLAMF7/CS1. CD19 was identified on a minor subset of MM cells with less differentiated or B cell-like phenotypes and these were felt to possibly represent MM progenitor or stem cells. Targeting CD19 may therefore be a strategy to eradicate MM cells and was therefore evaluated as a consolidation strategy after salvage autoSCT at UPenn (NCT02135406). The application of CD19-CAR-Ts in 10 patients was reported and prolongation of PFS compared to that expected according to their previous transplantation was achieved in two patients.5 In addition, clinical trials evaluating CAR-Ts against SLAMF7/CS1 (NCT03710421) or CD138 (NCT03473496, NCT03672318) are underway and additional trials are in preparation.

A Chinese clinical phase I/II trial evaluating a combination of CD19 and BCMA-specific CAR-Ts as consolidation for HR MM in the first-line setting was discussed above.35 Furthermore, the Medical University Zhuijiang Hospital Guangdong in China initiated a clinical trial for RRMM with a single or two CAR-T products targeting BCMA, CD138, CD56 or CD38 (NCT03473496).

Another dual-targeting approach in the context of BCMA is based on APRIL, a natural ligand of BCMA. APRIL is also a ligand of TACI that is also commonly expressed on MM cells.71 The targeting of BCMA and TACI by APRIL-specific CAR-Ts is currently in phase I clinical evaluation as it demonstrated promising results in preclinical models and may reduce the risk of target escape by down-regulation or structural modulation of surface BCMA.72 Bivalent chimeric antigen receptors targeting both CD19 and CD22 have been generated for the treatment of B-cell malignancies73 and bivalent BCMA-CARs are under development.

In summary, combination therapy is probably an important strategy for successful BCMA-directed CAR-T therapy and several new combination strategies are or soon will be clinically evaluated. The advantage of adding small molecules (eg, IMiDs and proteasome inhibitors) or monoclonal antibodies (eg, against CD38 and SLAMF7) to CAR-Ts is that translation of this approach to the clinic will be relatively simple. On the other hand, antigen escape can be prevented by dual targeting. The combination of several approaches including targeting of the tumor microenvironment, inhibition of immune evasion and achievement of sustained antitumor activity by CAR-Ts may therefore be necessary for long-term remissions.

4.6 | Perspective

BCMA-directed CAR-Ts have so far mainly been evaluated as salvage treatment in the highly refractory “last line” setting (Figure 2A). However, impaired T-cell fitness in this heavily pretreated patient population may be in part responsible for limited long-term disease control. Therefore, BCMA-targeted CAR-Ts may be more effective in earlier lines of treatment, for example, in first relapse after high-dose chemotherapy (Figure 2B). Furthermore, their administration as consolidation treatment after high-dose chemotherapy, even in the first-line setting, especially for patients with insufficient response, such as persistent minimal residual disease, or the presence of HR cytogenetics, may be a promising strategy to achieve deep and durable responses (Figure 2C). MRD testing could be used as a trigger for CAR-T-based
consolidation. Long-term remissions of more than 24 months and even cure of MM by MRD eradication should be the goal of this complex, labor-intensive and expensive technology.

In DLBCL, salvage autologous transplantation is already being directly compared to CD19-CAR-Ts in the ZUMA-7 clinical trial (NCT03391466). In MM, BCMA-directed CAR-Ts will definitely be evaluated in the first-line setting and may even challenge front-line high-dose chemotherapy as a possibly less toxic treatment approach that can better preserve the quality of life of MM patients (Figure 2D). CAR-Ts may even be an effective consolidation treatment for elderly and frail patients who would not be eligible for autologous transplantation in the first-line setting.

Maintenance therapy after high-dose chemotherapy is currently accepted as the standard-of-care in MM. However, a “one-shot” treatment approach with CAR-T cells may achieve sufficiently deep remissions that maintenance therapy could be omitted (Figure 2E). This would remove the requirement of continuous treatment and thereby improve the quality of life as well as treatment costs.

However, whether CAR-T cell treatment will be able to overcome the adverse prognosis of biologically high-risk MM, whether epitope exposure in an MRD-positive disease status will be sufficient for T-cell expansion, and whether only costly, relative toxic combination regimens can deliver meaningful long-term remissions in a complex disease like MM are challenging questions that need to be assessed and evaluated in many future clinical trials.

5 | CONCLUSIONS

In conclusion, the field of adoptive immunotherapy is developing rapidly. For the treatment of MM, there are currently several targets under investigation. BCMA is among the most studied as well as being one of the most promising targets for CAR-T therapy. It is expected that one of the BCMA-directed CAR-T constructs will be the first genetically modified cellular product approved for the treatment of MM. This may significantly change the treatment landscape of MM, leading to more durable disease control and represents an important addition to the growing armamentarium of therapies in our quest to ultimately cure patients with MM.

CONFLICT OF INTEREST

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