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CAR-T cells in multiple myeloma: current status

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Summary Starting with the approval of bortezomib, a proteasome-inhibiting drug, tremendous progress has been achieved in the treatment of multiple myeloma (MM) patients during the last 15 years. Due to a plethora of novel drugs such as second generation proteasome inhibitors, immunomodulating agents and monoclonal antibodies the 5-year survival of MM patients has been extended from 33% at the turn of the millennium to approximately 60% in younger patients (<65–70 years) who were eligible for consolidation with high-dose chemotherapy and autologous stem cell transplantation. Unfortunately, virtually all patients suffer from relapse and ultimately succumb to the disease, indicating the need for additional treatment strategies. Currently there are two promising immunologic approaches. First, bispecific antibodies called BITE (*bi*specific *T*-cell *e*nhancer), which act as fusion proteins with two single-chain variable fragments, target antigens on malignant cells and bind the CD3 receptor and thereby recruit T-cells to the target cells. The second strategy is chimeric antigen receptor (CAR) engineered T-cell therapy that attacks myeloma cells by recognizing specific targets such as CD138, BCMA (B-cell maturation antigen), light-chains, SLAM-F7 (signaling lymphocytic activation molecule family member 7) or the pan B-cell antigen CD19.
Several early phase clinical trials show encouraging results in patients who have relapsed after modern treatment including proteasome inhibitors, immunomodulating drugs and monoclonal antibodies. Here, we briefly summarize current clinical knowledge about CAR-T cell treatment in multiple myeloma, including clinical data presented at the 61st American Society of Hematology annual meeting held in December 2019 in Orlando.

Keywords Multiple Myeloma · CAR-T cells · Immunotherapy

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CAR-T targeting BCMA

B-cell maturation antigen (BCMA) is a transmembrane receptor which belongs to the tumor necrosis factor (TNF) family [1]. In multiple myeloma (MM) BCMA shows an increased expression on malignant plasma cells (PC) with a variable expression rate of 25–100% [2]. In normal tissue BCMA is almost exclusively expressed on mature B-cells and plasma cells (PC), especially long-lived PC. Therefore, it constitutes an attractive target for CAR-T cell therapy [3–6]. The ligands of BCMA include B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL), which promote B-cell maturation and protect malignant plasma cells from apoptosis [7, 8].

The first in-human clinical trial of CAR-T targeting BCMA was conducted by Brudno et al. from the National Cancer Institute (NCI), USA. The 16 relapsed/refractory MM (RRMM) patients had received a median of 9.5 prior therapy lines. They were treated with 9×10^6 CAR-T cells/kg, which was the highest dosage administered in this study, and showed an overall response rate (ORR) of 81% with 63% very good partial response (VGPR) or better and approximately 68% bone marrow residual disease negative status. Cytokine release syndrome (CRS) grade ≥3 occurred in 6 of those 16 patients, but was reversible under vasopressor support, tocilizumab and corticosteroids. The

median progression-free survival (PFS) was 31 weeks [9].

Since then, a variety of BCMA-CAR-T therapies have been designed and preclinically/clinically tested, of which some are summarized in Table 1 and described briefly below.

BB2121 (Bluebird Bio, Celgene) contains a murine-derived anti-BCMA single-chain variable fragment (scFv) and a CD3ζ/4-1BB signaling domain. A phase 1 study consisting of two phases (a dose-escalation phase and a dose-expansion phase) was conducted on 33 RRMM patients who had received a median of 7.5 previous therapy lines in the dose-escalation group and 8 previous therapy lines in the dose-expansion group. The study reported an 85% ORR including 45% complete responses (CR). In all, 76% of patients developed CRS, of which most cases were limited to grade 1 or 2. Other adverse events occurred in all patients (97% adverse events ≥ grade 3), primarily neutropenia, leukopenia, anemia and thrombocytopenia. The median PFS was 11.8 months with 40% of the patients being progression-free at the 12-month mark. The study comprised two phases: a dose-escalation phase and a dose-expansion phase [10].

KarMMa is a phase 2 study of BB2121, which completed enrollment (of approximately 150 patients) in 2019. KarMMa-2 is also a phase 2 study of BB2121, which is still in the enrollment process and will compare the efficacy of BB2121 as a ≥ third line treatment versus as a second line treatment in patients who show an insufficient response to or an early relapse after first line therapy. KarMMa-3 will be the first phase 3 randomized clinical trial comparing BB2121 to standard therapy in patients with 2–4 prior therapy lines (planned enrollment of 381 patients) [11–14].

BB21217 is the successor of BB2121. The structure of B21217 is very similar to B2121 except for the addition of a phosphoinositide 3-kinase inhibitor bb007, which is meant to enhance the persistence and potency of the CAR-T cells. A phase 1 trial revealed an ORR and tolerability similar to BB2121 in patients who had received a median of 7 previous therapy lines. However, updated data will be necessary to sufficiently evaluate if progression-free survival (PFS)/overall survival (OS) rates suggest an improved efficacy compared to BB2121 [15].

L-CAR B38M is a dual epitope-binding CAR-T directed targeting BCMA. Zhao et al. reported a study with 57 RRMM patients (median of 3 previous therapy lines), who received L-CAR B38M in three separate infusions instead of the usual single-administration. There was an ORR of 88% with 68% CR and 63% minimal residual disease negative status and a median PFS of 15 months. The authors reported a manageable safety profile with CRS in 90% of patients, but only 7% ≥ grade 3. They did not find a correlation between clinical response and BCMA expression levels [16].

Xu et al. compared clinical response in 17 RRMM patients (median of 4 previous therapy lines) who were either treated with three or one LCAR B38M infusions. There was an ORR of 88.2% with 13 patients achieving stringent CR and 2 patients reaching VGPR. No difference in clinical response or CRS rate was detected in the two subgroups [17].

Cohen et al. tested the clinical activity of a fully human BCMA-specific CAR in 25 patients (≥3 previous therapy lines or ≥2 previous therapy lines and dual refractory to proteasome inhibitors [PI] and immunomodulatory imide drugs [IMiD]). Patients were divided into three cohorts: cohort 1 received 1×10^8 to 5×10^8 BCMA-CAR-T cells only (ORR 44%), cohort 2 received cyclophosphamide with 1×10^7 to 5×10^7 BCMA-CAR-T cells (ORR 20%) and cohort 3 received cyclophosphamide with 1×10^8 to 5×10^8 BCMA-CAR-T cells (ORR 64%) [18]. They found a decreased BCMA expression on residual MM cells in responders and an increased expression at progression in most patients.

C-CAR088 is a novel BCMA-CAR-T containing a scFv from a high-affinity human monoclonal antibody. C-CAR088 is currently in an ongoing phase 1 clinical trial. Three patients with 7 prior lines of therapy have been treated so far, whereof two achieved VGPR and one a PR [19].

CT103A is another CAR-T containing a fully human scFv and additionally a CD8a hinge domain, which is supposed to improve the post-infusion expansion and persistence of CAR-T cells. Between September 2018 and August 2019, 16 patients (≥3 previous therapy lines) were treated with CT103A, of which 4 had previously relapsed after murine BCMA CAR-T cell therapy. ORR was 100% with 37% CR and 13% VGPR. All 4 patients who had participated in prior CAR-T trials achieved VGPR or better [20].

CT053 is a second-generation CAR with a fully human scFv and was studied in a phase 1 trial on a total of 24 RRMM patients who had received at least two prior myeloma regimens. An ORR of 87.5% included 79.2% of CR; 9 patients progressed after a median PFS of 9 months, while 13 subjects had ongoing CR (median follow-up 383 days). No dose-limiting toxicities were observed, CRS occurred in 62.5% of all patients and did not exceed grade 2 [21].

P-BCMA-101 is a BCMA-CAR-T cell produced with the piggyBac® DNA Modification system (transposon-based) instead of a viral vector. Hence, it is less costly and achieves a higher percentage of T-memory stem cells. Moreover, it allows for the integration of multiple additional genes including a safety switch and a selection gene. Instead of the traditional antibody-based scFv, P-BCMA-101 contains Centyrin™, a fully human protein, which is smaller, more stable and potentially less immunogenic. After a phase 1 trial obtained promising results, phase 2 studies are currently being initiated for patients who have received three or more lines of previous treatment [22].

Table 1 Clinical trials using CAR-T cells in multiple myeloma patients

Study	CAR	Target	No. of patients	ORR	CR	VGPR	Median PFS, mo. (median FU, mo.)	Therapy lines prior to CAR-T
Brudno[a], 2018 [9]	CAR-T-BCMA (murine scFv)	BCMA	16	81%	13%	50%	31 (n. a.)	Median: 9.5 Range: 3–19
Raje, 2019 [10]	B2121	BCMA	33	85%	45%	*n. a.*	11.8 (11.3)	*Escalation:* Median: 7.5 Range: 3–14 *Expansion:* Median: 8 Range: 3–23
Berdeja, 2019 [15]	B21217	BCMA	22	83%	*n. a.*	*n. a.*	To be evaluated	Median: 7 Range: 4–17
Zhao, 2018 [16]	L-CAR B38M	BCMA (dual epitope)	57	88%	68%	5%	15 (8)	Median: 3 Range: 1–9
Xu, 2019 [17]	L-CAR B38M	BCMA (dual epitope)	17	88.2%	76%	12%	82% at 6 mo., 53% at 12 mo. (14)	Median: 4 Range: 3–11
Cohen, 2019 [18]	CAR-T-BCMA (human scFv)	BCMA	25	Variable in the three different cohorts, ORR range 20–64%				≥3 or ≥2 and dual refractory to PI and IMiD
Yao, 2019 [19]	C-CAR088	BCMA	3 (as of July 2015)	n. a.	n. a.			≥3
Li, 2019 [20]	CT103A	BCMA	16	100%	38%	13%	n. a.	≥3
Jie, 2019 [21]	CT053	BCMA	24	87.5%	79.2%	n. a.	9 patients progressed after a median of 9 mo. PFS, 13 patients with ongoing CR	≥2
Fu, 2019 [23]	CAR-T-BCMA + safety switch (tEGFR)	BCMA	44	79.6%	40%	18%	15 (n. a.)	≥2
Raje, 2019 [24]	PF-3135	BCMA, CD3	17	6%	0%	0%	Ongoing clinical trial	Median: 11
Li, 2019 [25]	BM38	BCMA, CD38	16	87.5	50	12.5	PFS at 9 mo. 75%	≥2
Popat[b], 2019 [26]	AUTO2	BCMA, TACI	7	43%	0	14	n. a.	≥2 or dual refractory to PI and IMiD
Garfall, 2018 [32]	CTL019 + ASCT	CD19	10	80%	n. a.	n. a.	PFS 1 = after prior ASCT, PFS 2 = after ASCT + CTL019; PFS 2 > PFS 1 in 2 patients	Median: 6 Range: 2–10
Yan, 2019 [34]	CAR-T-BCMA, CAR-T-CD19	CD19, BCMA	27	92.6%	40.7%	29.6%	n. a.	Median: 3 Range: 2–8
Zhang, 2019 [36]	Bispecific BCMA-CD19-CAR-T	CD19, BCMA	5	100%	20%	60%	n. a.	Median: 3 Range: 1–5
Guo, 2015 [45]	CAR-T138	CD138	5	0%	0%	n. a.	n. a.	Median: 8 Range: 5–18

Mo. Months, *ORR* overall response rate, *CR* complete remission, *VGPR* very good partial remission, *n. a.* not available, *FU* follow-up, *scFv* single-chain variable fragment, *PI* proteasome inhibitor, *IMiD* immunomodulatory imide drugs
[a]These 16 patients were the patients treated with 9×10^6 CAR-T cells/kg
[b]The results listed here refer to the 7 out of the 12 patients who were in the $\geq 225 \times 10^6$ dose cohorts

Fu Sr. et al. developed a BCMA-CAR-T cell product with an integrated safety switch in the form of a truncated epidermal growth factor receptor (tEGFR). A phase 1 trial conducted on 46 RRMM patients (≥2 previous therapy lines) reached an ORR of 79.6% in the 44 evaluable patients, with 40% CR or better. Only a strikingly small number of patients developed CRS (23% grade 1–2, 7% grade 3) [23].

All of these clinical trials mainly included RRMM patients, who did not show an adequate response to conventional therapy regimens (≥3 therapy lines preceded CAR-T cell therapy in most studies listed here). Overall response rates up to 100% suggest that BCMA is a promising target for CAR-T cell therapy in RRMM patients.

Bispecific BCMA-CAR-T cell therapy

PF-3135: BCMA + CD3

PF-3135 is a bispecific, humanized monoclonal antibody consisting of BCMA- and CD3-targeting arms and thus binding myeloma cells and T-cells. There is an ongoing dose-escalation multicenter phase 1 study evaluating the efficacy of PF-3135 in RRMM patients who had received a median of 11 previous therapy

lines. Interim results showed a clinical benefit rate of 41% (defined as best response ≥ stable disease) and moderate CRS events. Results of additional dose cohorts will be reported in the future [24].

BM38: BCMA + CD38

Li et al. conducted the first in-human phase 1 clinical trial of a dual-target BM38 CAR containing an anti-BCMA and an anti-CD38 scFv. As of July 2019, 16 RRMM patients (≥2 previous therapy lines) received treatment with BM38. The ORR was 87.5 with 50% CR. The elimination of 5 extramedullary lesions (100% in this study) was reported as well as manageable toxicity and prolonged CR [25].

AUTO2: BCMA + TACI

Popat et al. designed a novel CAR, using a truncated form of APRIL (a proliferation-inducing ligand) as the tumor-targeting domain which recognizes both BCMA and TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) on MM cells. Similar to BCMA, TACI also belongs to the TNF family and promotes B-cell maturation. Interim phase 1 results ($n = 12$ patients, ≥2 previous therapy lines or dual refractory to PI and IMiD) show that the therapy was well-tolerated at doses up to 900×10^6 CAR-T cells and achieved an ORR of 43% in the $\geq 225 \times 10^6$ dose cohorts [26].

CAR-T targeting CD19

While CD19 is present on normal PC, myeloma cells typically do not express CD19 [27, 28]. However, patients with monoclonal gammopathy of undetermined significance (MGUS) have a high expression of CD19 on their bone-marrow plasma cells, which indicates that CD19-expressing PC might act as myeloma stem cells [29, 30]. **CTL019** (tisagenlecleucel) is a CAR-T cell therapy approved for the treatment of advanced acute lymphoid leukemia and diffuse large B cell lymphoma [31]. An early phase clinical trial by Garfall et al. assessed the efficacy of CTL019 combined with ASCT in MM. All 10 patients who were treated with ASCT and CTL019 had previously undergone ASCT as a component of first-line therapy and had received a median of 6 therapy lines in total. In all, 8 of the 10 patients showed partial response (PR) or better 100 days after ASCT. To determine how greatly CTL019 contributed to this ORR, the authors compared the PFS following ASCT + CTL019 to the PFS following prior ASCT. They found a significantly longer PFS after ASCT + CTL019 in only 2 out of 10 subjects. Possible explanations for this low clinical benefit might be inadequate in vivo engraftment and the low dosage of CTL019 used [32].

In multiple studies, CAR-T cells with different targets have been combined, aiming to reduce resistance due to antigen loss [33]. Recently, there have been trials investigating the efficacy of the combination BCMA-CD19 CAR-T.

Yan et al. performed a phase 1 clinical trial on 28 RRMM patients (median of 3 previous therapy lines) who received sequential infusion of autologous CD19-CAR-T cells and BCMA-CAR-T cells. Among the 27 patients available to follow-up the ORR was 92.6% with 40.7% complete remissions [34].

Shi et al. compared the efficacy of combined infusion of anti-CD19 and anti-BCMA CAR-T cells following ASCT (infused on day 14 to day 20 after transplantation) in different therapy lines. The ORR was 100% with 72% CR. ASCT and CAR-T therapy were either administered as first-line therapy (group 1), as second line (group 2) or as salvage therapy at third line or more. They found that efficacy was higher in front line. The response (CR or better) was 78% in group 1, 100% in group 2 and 44% in group 3 [35].

In a study by Zhang et al., a bispecific BCMA-CD19-CAR was produced by joining BCMA and CD19 scFv with a CD8 hinge. Preclinical as well as clinical data illustrate that the bispecific CAR-T cells are effective in the treatment of MM. In their clinical study 5 patients (median of 3 previous therapy lines) were treated and evaluated 15–59 days later: 1 patient achieved CR, 3 achieved VGPR and 1 achieved PR. The toxicity was remarkably low with three cases of only grade 1 CRS and no neurotoxicity [36].

CAR-T targeting SLAM-F7

SLAMF7, also known as CS1, belongs to the signaling lymphocyte activating-molecule-related receptor family [37]. It has been found to be expressed at high levels on PC and MM cells and at lower levels on natural killer cells, CD8+ cells, activated monocytes and dendritic cells [38].

SLAMF7 is targeted by the monoclonal antibody elotuzumab, which is approved for the treatment of MM [39].

Gogishvili et al. designed a CAR targeting SLAMF7, which is derived from the huLuc63 antibody (elotuzumab). A single administration of SLAMF7-CAR-T cells was able to eliminate extramedullary and medullary MM manifestations in a murine xenograft model. They confirmed that the fratricide caused by SLAMF7-CAR-T cells only affects SLAMF7$^{+/high}$ cells. Due to the fact that SLAMF7$^{-/low}$ cells of all cell subsets (natural killer cells, CD4+, CD8+, B-cells) are spared, a number of functional lymphocytes remain [40]. A compound CAR (cCAR) T-cell consisting of two complete and independent anti-BCMA and anti-SLAMF7 CAR receptors has shown promising in vitro and in vivo anti-myeloma activity [41]. Phase 1 clinical trials of SLAMF7 CAR-T cells are currently ongoing.

CAR-T targeting CD138

CD138, also known as syndecan-1, is an integral membrane proteoglycan containing both heparan sulfate and chondroitin sulfate [42]. A preclinical study investigated the capability of CD138 antibody therapy in conjunction with radioimmunotherapy in the therapy of MM in mice [43]. Moreover, CD138 CAR-T cells both from healthy donors and MM patients showed promising anti-myeloma activity without any on-target/off-tumor cytotoxicity against normal epithelial/endothelial cells in vitro and in a mouse model [44]. CD138 CAR-T cells administered to 5 patients (median of 8 previous therapy lines) in a phase 1 clinical trial in China led to stable disease in 4 of 5 patients and showed a manageable toxicity profile [45]. Other phase I trials using anti-CD138 CAR-T are ongoing.

Conclusion

Using CAR-T cell therapy, impressive results have been achieved in mostly heavily pretreated patients with multiple myeloma (MM). However, this treatment harbors potentially life-threatening complications and requires careful patient selection and a treatment team that is experienced in autologous and allogeneic cell therapies. Moreover, the responses using current CAR-T strategies are frequently not durable and most of the patients suffer a relapse. The mechanisms of resistance against CAR-T in MM are not completely understood. Basically, there are two mechanisms hampering the efficacy of CAR-T: antigen loss or antigen modification by the myeloma cells and T-cell failure, respectively. Briefly, T-cell failure, i.e. the nondurable T-cell persistence, and T-cell exhaustion, i.e. the gradual loss of T-cell function, are important obstacles for a long-lasting antimyeloma response. Loss of target antigens on the myeloma cells can occur. A proportion of patients relapsing after CAR-T are antigen negative and others are antigen low-expressors. Myeloma cells can downregulate target antigens and, another mechanism, T-cells can acquire antigens from myeloma cells by trogocytosis (active transfer of antigens from MM cells to T-cells), thereby decreasing the amount of target antigen on MM cells and, moreover, promoting the killing of such antigen-loaded T-cells by other T-cells, leading to T-cell exhaustion. Moreover, it is likely that CAR-T cells manufactured from leukapheresis obtained early during the disease course are more clinically effective than cells harvested from heavily pretreated MM patients. Current research activities regarding CAR-T in MM include the combination with other immunological strategies such as immunomodulating drugs or checkpoint inhibitors, enhancing CAR-T efficacy by creating CAR-T that can recognize more than one antigen and genetic modifications to enhance their efficacy as well as the safety of this treatment. CAR-T cell therapies are at an early stage in MM and preclinical as well as clinical research is moving rapidly forward and the gain of knowledge is growing continuously. Clinical phase 3 trials will provide more robust data on their efficacy and tolerability in myeloma patients and should provide the basis for consensus guidelines that will help to identify the optimal candidates for this promising but also potentially toxic and expensive treatment.

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Conflict of interest N. Steiner and E. Gunsilius declare that they have no competing interests.

References

1. Madry C, Laabi Y, Callebaut I, Roussel J, Hatzoglou A, Le Coniat M, et al. The characterization of murine BCMA gene defines it as a new member of the tumor necrosis factor receptor superfamily. Int Immunol. 1998;10(11):1693–702.
2. Bu DX, Singh R, Choi EE, Ruella M, Nunez-Cruz S, Mansfield KG, et al. Pre-clinical validation of B cell maturation antigen (BCMA) as a target for T cell immunotherapy of multiple myeloma. Oncotarget. 2018;9(40):25764–80.
3. Laabi Y, Gras MP, Brouet JC, Berger R, Larsen CJ, Tsapis A. The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed. Nucleic Acids Res. 1994;22(7):1147–54.
4. Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res. 2013;19(8):2048–60.
5. O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med. 2004;199(1):91–8.
6. Friedman KM, Garrett TE, Evans JW, Horton HM, Latimer HJ, Seidel SL, et al. Effective targeting of multiple B-cell maturation antigen-expressing hematological malignances by anti-B-cell maturation antigen chimeric antigen receptor T cells. Hum Gene Ther. 2018;29(5):585–601.
7. Moreaux J, Legouffe E, Jourdan E, Quittet P, Rème T, Lugagne C, et al. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. Blood. 2004;103(8):3148–57.
8. Tai YT, Acharya C, An G, Moschetta M, Zhong MY, Feng X, et al. APRIL and BCMA promote human multiple myeloma growth and immunosuppression in the bone marrow microenvironment. Blood. 2016;127(25):3225–36.

9. Brudno JN, Maric I, Hartman SD, Rose JJ, Wang M, Lam N, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. J Clin Oncol. 2018;36(22):2267–80.
10. Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380(18):1726–37.
11. D'Agostino M, Raje N. Anti-BCMA CAR T-cell therapy in multiple myeloma: can we do better? Leukemia. 2019; https://doi.org/10.1038/s41375-019-0669-4.
12. U.S. National Library of Medicine. Efficacy and safety study of bb2121 versus standard triplet regimens in subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMma-3). 2019. https://clinicaltrials.gov/ct2/show/NCT03651128. Accessed 26 Nov 2019.
13. U.S. National Library of Medicine. An efficacy and safety study of bb2121 in subjects with relapsed and refractory multiple myeloma and in subjects with high-risk multiple myeloma (KarMma-2). 2019. https://clinicaltrials.gov/ct2/show/NCT03601078. Accessed 22 Nov 2019.
14. U.S. National Library of Medicine. Efficacy and safety study of bb2121 in subjects with relapsed and refractory multiple myeloma (KarMma). 2019. https://clinicaltrials.gov/ct2/show/NCT03361748. Accessed 11 Sept 2019.
15. Berdeja JG, Alsina M, Shah ND, Siegel DS, Jagannath S, Madduri D, et al. Updated results from an ongoing phase 1 clinical study of bb21217 Anti-Bcma CAR T cell therapy. 2019. https://ash.confex.com/ash/2019/webprogram/Paper126660.html. Accessed: 1 Dec 2019.
16. Zhao WH, Liu J, Wang BY, Chen YX, Cao XM, Yang Y, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. J Hematol Oncol. 2018;11(1):141.
17. Xu J, Chen LJ, Yang SS, Sun Y, Wu W, Liu YF, et al. Exploratory trial of a biepitopic CAR T-targeting B cell maturation antigen in relapsed/refractory multiple myeloma. Proc Natl Acad Sci U S A. 2019;116(19):9543–51.
18. Cohen AD, Garfall AL, Stadtmauer EA, Melenhorst JJ, Lacey SF, Lancaster E, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J Clin Invest. 2019;129(6):2210–21.
19. Yao X, Zhu S, Huang J, Qu X, Zhu J, Wei Y, et al. Developing a novel anti-Bcma CAR-T for relapsed or refractory multiple myeloma. Blood. 2019;134(Supplement_1):50.
20. Li C, Wang J, Wang D, Hu G, Yang Y, Zhou X, et al. Efficacy and safety of fully human Bcma targeting CAR T cell therapy in relapsed/refractory multiple myeloma. Blood. 2019;134(Supplement_1):929.
21. Jie J, Hao S, Jiang S, Li Z, Yang M, Zhang W, et al. Phase 1 trial of the safety and efficacy of fully human anti-Bcma CAR T cells in relapsed/refractory multiple myeloma. Blood. 2019;134(Supplement_1):4435.
22. Costello CL, Gregory TK, Ali SA, Berdeja JG, Patel KK, Shah ND, et al. Phase 2 study of the response and safety of P-Bcma-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM) (PRIME). Blood. 2019;134(Supplement_1):3184.
23. Fu W, Du J, Jiang H, Cheng Z, Wei R, Yu K, et al. Efficacy and safety of CAR-T therapy with safety switch targeting Bcma for patients with relapsed/refractory multiple myeloma in a phase 1 clinical study. Blood. 2019;134:3154.
24. Raje N, Jakubowiak A, Gasparetto C, Cornell R, Krupka H, Navarro D, et al. Safety, clinical activity, pharmacokinetics, and pharmacodynamics from a phase I study of PF-06863135, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). Blood. 2019;134:1869.
25. Li C, Mei H, Hu Y, Guo T, Liu L, Jiang H, et al. A bispecific CAR-T cell therapy targeting Bcma and CD38 for relapsed/refractory multiple myeloma: updated results from a phase 1 dose-climbing trial. 2019. https://ash.confex.com/ash/2019/webprogram/Paper130340.html. Accessed: 1 Dec 2019.
26. Popat R, Zweegman S, Cavet J, Yong K, Lee L, Faulkner J, et al. Phase 1 first-in-human study of AUTO2, the first chimeric antigen receptor (CAR) T cell targeting APRIL for patients with relapsed/refractory multiple myeloma (RRMM). Blood. 2019;134(Supplement_1):3112.
27. Cannizzo E, Carulli G, Del Vecchio L, Ottaviano V, Bellio E, Zenari E, et al. The role of CD19 and CD27 in the diagnosis of multiple myeloma by flow cytometry: A new statistical model. Am J Clin Pathol. 2012;137(3):377–86.
28. Mateo G, Montalbán MA, Vidriales MB, Lahuerta JJ, Mateos MV, Gutiérrez N, et al. Prognostic value of immunophenotyping in multiple myeloma: a study by the PETHEMA/GEM cooperative study groups on patients uniformly treated with high-dose therapy. J Clin Oncol. 2008;26(16):2737–44.
29. Zandecki M, Facon T, Bernardi F, Izydorczyk V, Dupond L, François M, et al. CD19 and immunophenotype of bone marrow plasma cells in monoclonal gammopathy of undetermined significance. J Clin Pathol. 1995;48(6):548–52.
30. Feinberg D, Paul B, Kang Y. The promise of chimeric antigen receptor (CAR) T cell therapy in multiple myeloma. Cell Immunol. 2019;345:103964.
31. Mohty M, Gautier J, Malard F, Aljurf M, Bazarbachi A, Chabannon C, et al. CD19 chimeric antigen receptor-T cells in B-cell leukemia and lymphoma: current status and perspectives. Leukemia. 2019;33(12):2767–78.
32. Garfall AL, Stadtmauer EA, Hwang WT, Lacey SF, Melenhorst JJ, Krevvata M, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. JCI Insight. 2018; https://doi.org/10.1172/jci.insight.120505.
33. Lin Q, Zhao J, Song Y, Liu D. Recent updates on CAR T clinical trials for multiple myeloma. Mol Cancer. 2019;18(1):154.
34. Yan L, Yan Z, Shang J, Shi X, Jin S, Kang L, et al. Sequential CD19- and Bcma-specific chimeric antigen receptor T cell treatment for RRMM: Report from a single center study. Blood. 2019;134(Supplement_1):578.
35. Shi X, Yan L, Shang J, Kang L, Jin S, Kang H, et al. Combined infusion of anti-CD19 and anti-Bcma CAR-T cells after early or later transplantation in the front line was superior to salvage therapy for high risk MM. Blood. 2019;134(Supplement_1):1949.
36. Zhang H, Gao L, Liu L, Wang J, Wang S, Gao L, et al. A Bcma and CD19 Bispecific CAR-T for relapsed and refractory multiple myeloma. Blood. 2019;134:3147.
37. Kumaresan PR, Lai WC, Chuang SS, Bennett M, Mathew PA. CS1, a novel member of the CD2 family, is homophilic and regulates NK cell function. Mol Immunol. 2002;39(1–2):1–8.
38. Hsi ED, Steinle R, Balasa B, Szmania S, Draksharapu A, Shum BP, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. Clin Cancer Res. 2008;14(9):2775–84.
39. Radhakrishnan SV, Bhardwaj N, Steinbach M, Weidner J, Luetkens T, Atanackovic D. Elotuzumab as a novel anti-myeloma immunotherapy. Hum Vaccin Immunother. 2017;13(8):1751–7.
40. Gogishvili T, Danhof S, Prommersberger S, Rydzek J, Schreder M, Brede C, et al. SLAMF7-CAR T cells elimi-

nate myeloma and confer selective fratricide of SLAMF7. Blood. 2017;130(26):2838–47.
41. Chen KH, Wada M, Pinz KG, Liu H, Shuai X, Chen X, et al. A compound chimeric antigen receptor strategy for targeting multiple myeloma. Leukemia. 2018;32(2):402–12.
42. Saunders S, Jalkanen M, O'Farrell S, Bernfield M. Molecular cloning of syndecan, an integral membrane proteoglycan. J Cell Biol. 1989;108(4):1547–56.
43. Gouard S, Pallardy A, Gaschet J, Faivre-Chauvet A, Bruchertseifer F, Morgenstern A, et al. Comparative analysis of multiple myeloma treatment by CD138 antigen targeting with bismuth-213 and melphalan chemotherapy. Nucl Med Biol. 2014;41(Suppl):e30–e5.
44. Sun C, Mahendravada A, Ballard B, Kale B, Ramos C, West J, et al. Safety and efficacy of targeting CD138 with a chimeric antigen receptor for the treatment of multiple myeloma. Oncotarget. 2019;10(24):2369–83.
45. Guo B, Chen M, Han Q, Hui F, Dai H, Zhang W, et al. CD138-directed adoptive immunotherapy of chimeric antigen receptor (CAR)-modified T cells for multiple myeloma. J Cell Immunother. 2015; https://doi.org/10.1016/j.jocit.2014.11.001.