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Successful treatment of systemic light chain amyloidosis with a novel high-avidity BCMA CAR

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Abstract

B-cell maturation antigen (BCMA) is a promising target for immunotherapy in plasma cell dyscrasias, but no commercial BCMA-directed CAR T-cell product is approved in Europe for patients with systemic light chain (AL) amyloidosis. We used the in-house manufactured 2nd-generation BCMA-directed MDC-CAR-BCMA001 for the treatment of patients with relapsed/refractory (R/R) AL amyloidosis. This is the first experience with this new high-avidity, academic CAR T-cell product in this population. Seven patients received 800×10^6 CAR T-cells after lymphodepletion. Leukapheresis, manufacturing and administration of CAR T-cells were performed in-house. Six patients had triple-class refractory disease (5/7 (71%) with prior high-dose chemotherapy). Active disease was present in 6/7 (86%) patients prior to CAR T-cell infusion. Overall response was observed in 6/7 patients (ORR 86%, 3 MRD-negative complete remissions). All patients with durable hematologic responses showed organ responses (cardiac, renal, improvement in polyneuropathy and myopathy) with rapid suppression of amyloidogenic free light chains. Six patients (86%) are alive, and 3/6 responders remain in remission after a median follow-up of 10.9 months. All patients experienced cytokine release syndrome, 5/7 grade ≤ 2, two grade 3, resolving after tocilizumab and/or dexamethasone. One patient experienced low-grade late immune effector cell-associated hematotoxicity. No neurotoxicity was observed. MDC-CAR-BCMA001 demonstrates high efficacy with manageable toxicity, making it a promising treatment for AL amyloidosis patients with preexisting organ insufficiencies. Deep responses and MRD negativity enable meaningful organ responses. Further evaluation as second-line therapy is planned in the ongoing clinical trial designated *CLEAR AL* (EU CT No. 2025-520790-39-00).

Keywords Systemic light chain amyloidosis (AL amyloidosis), CAR (chimeric antigen receptor) T-cell therapy, B-cell maturation antigen (BCMA)

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To the Editor,

Systemic light chain (AL) amyloidosis is a life-threatening protein deposition disorder caused by toxic monoclonal light chains produced by an abnormal plasma cell clone [1]. Patients with relapsed/refractory (R/R) disease have poor outcomes after failure of daratumumab-based therapy due to progressive organ dysfunction. B-cell maturation antigen (BCMA) is an already established target in other plasma cell disorders. Although the bispecific T-cell engager teclistamab has shown feasibility and efficacy in AL amyloidosis [2], no approved BCMA-directed treatments are available in Europe, and patients are largely excluded from CAR T-cell trials. We therefore chose to treat for this unmet need with the in-house manufactured, BCMA-directed CAR T-cell product *MDC-CAR-BCMA001* [3] in R/R AL amyloidosis and report on its first use in this setting.

Seven consecutive patients with R/R immunohistochemistry-typed AL amyloidosis (either high-dose chemotherapy-pretreated or -ineligible) were treated at Heidelberg University Hospital between July 2023 and October 2025 in the compassionate use setting with a fixed dose of 800×10^6 MDC-CAR-BCMA001 cells. Leukapheresis, manufacturing, and administration were performed in-house; construct and production details are provided in the supplementary data. Lymphodepletion consisted of fludarabine/cyclophosphamide or bendamustine in cases of severe nephropathy or neuropathy. Hematologic and organ responses were assessed according to International Society of Amyloidosis criteria as applicable [4, 5], measurable residual disease (MRD) by next-generation flow cytometry (10^{-5}), and adverse events according to CTCAE v5.0, ASTCT-CRS/ICANS [6], and EHA/EBMT-ICAHT criteria [7, 8]. Data cutoff was December 8th, 2025. Analyses were descriptive; survival was estimated using Kaplan-Meier methodology. Written informed consent was obtained, and the study adhered to the Declaration of Helsinki.

Median age was 62 years (range 57–70), and 6/7 patients were male. Involved light chain was lambda in 6/7; 4/7 showed adverse cytogenetics including del17p, with gain(1q) being the most frequent aberration. Two patients had cardiac (European modification of Mayo stage) stage IIIa disease, two patients had stage II renal involvement (one of them with concomitant stage II cardiac disease), one patient had stage I, and two patients had predominantly neuropathic disease (one of them with concomitant myopathy). Median prior therapies were 5 (range 2–5); 6/7 had triple-class refractory disease and 5/7 had prior autologous stem cell transplantation. Before infusion, 6/7 had progressive disease or no response to the last line of therapy. Manufacturing succeeded in all cases, and all patients received a single infusion.

Overall response rate was 86% (6/7), including 3 complete responses (CR), 2 very good partial remissions and one low-*difference of involved and uninvolved serum free light chains* (dFLC) partial response (Fig. 1a). All three patients with CR showed no evidence of MRD shortly after achieving CR. Mean reduction in the dFLC was − 89.6% among responders, reflecting potent suppression of amyloidogenic light chains (Fig. 2a). The sole non-responder achieved partial remission after elotuzumab/pomalidomide/dexamethasone. All patients achieving a durable hematologic response developed organ responses, including cardiac, renal, neuropathy, and myopathy improvement, which deepened over time. After median follow-up of 10.9 months, 6/7 patients were alive, and 3/6 responders remained in remission (Fig. 1b, c); resulting in a respective median PFS of 9.83 months (95% confidence interval 1.9 months – *not reached*).

CAR T-cell expansion peaked at median day + 12, with persistence beyond one year in two responders (Fig. 2b).

All patients developed CRS; 5/7 were grade ≤ 2 and 2/7 grade 3, resolving with tocilizumab and/or dexamethasone. No ICANS occurred. Early ICAHT occurred in 4/7 patients, and one patient developed late grade 2 thrombocyte-ICAHT with spontaneous improvement to mild residual thrombocytopenia. Hypogammaglobulinemia as an expected event of B-cell depletion was observed in all patients. Early infections were frequent but manageable and late infections occurred in 2/7 patients. No treatment-related mortality was observed. Further details on patient characteristics and treatment are provided in the Supplementary Material.

MDC-CAR-BCMA001 achieved high response rates with manageable toxicity in heavily pretreated R/R AL amyloidosis, extending the limited clinical experience with BCMA-directed CAR T-cell therapy in this setting [9, 10]. This study is subject to all the limitations inherent to a single-center retrospective study. Meaningful responses have been demonstrated, while predictors of response and durability remain to be defined. While not a mandatory prerequisite, the CD28-costimulatory domain likely enables a rapid effector phase, distinguishing this construct from 4-1BB–based CAR T-cells such as cilta-cel or NXC-201 [10, 11]. Deep hematologic responses, including MRD-negative CR, and rapid suppression of amyloidogenic free light chains resulted in clinically meaningful organ responses, underscoring the requirement for profound hematologic response in AL amyloidosis. Delayed deepening of hematologic response can occur even months after CAR T-cell infusion and beyond the initial CAR T-cell expansion as observed in other CAR T-cell–treated malignancies [12]. CAR T-cell persistence beyond one year in selected patients could be observed, although persistence was not required for response. CRS was frequent but clinically manageable

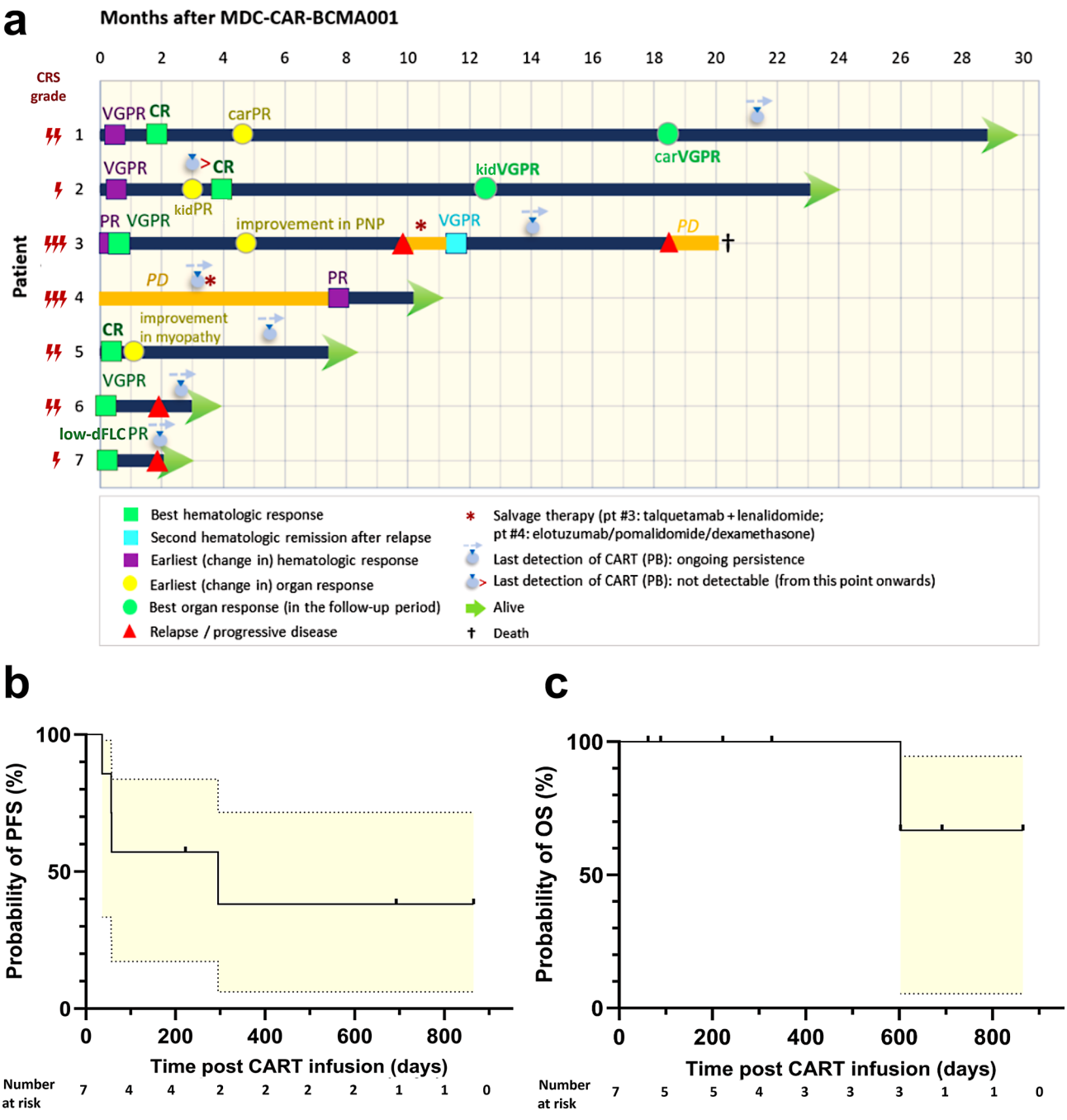

Fig. 1 Outcomes of patients after treatment with MDC-CAR-BCMA001. **a**: swimmer plots of all treated patients. Patients #2, #5 and #7 received bendamustine as lymphodepleting chemotherapy. Patient #7 achieved low-dFLC-PR with positive immunofixation, considered equivalent to VGPR. **b**: PFS of patients after CART administration with shaded 95%-confidence region (calculated using an asymmetrical method involving Greenwood's standard error with a log–log transformation). **c**: Overall survival of patients after CART administration with shaded 95%-confidence region (calculated using an asymmetrical method involving Greenwood's standard error with a log–log transformation). Abbreviations: car-: cardiac, CART: chimeric antigen receptor T-cells, CR: complete response, dFLC: difference of involved and uninvolved serum free light chains, kid-: renal, OS: overall survival, PB: peripheral blood, PFS: progression-free survival, PNP: polyneuropathy, PR: partial response, pt: patient, VGPR: very good partial response

with early cytokine-directed therapy, and no ICANS or treatment-related mortality occurred. These results support further evaluation in the ongoing *CLEAR AL* trial (EU CT-no. 2025-520790-39-00).

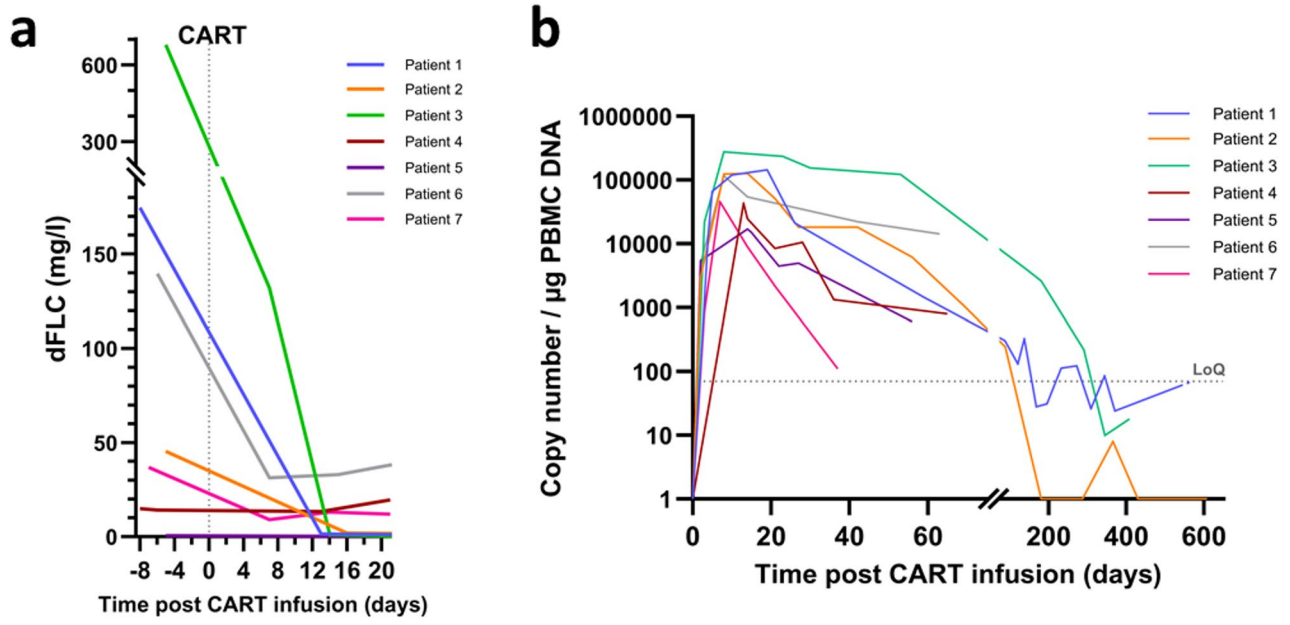

Fig. 2 Rapid and profound dFLC decrease in treated patients and expansion of MDC-CAR-BCMA001 in the peripheral blood. **a**: Early responses within the first weeks to near-total unmeasurable dFLC levels. **b**: Uniform peak expansion of CAR T-cells between day + 7 and + 19 (median day + 12); undetectable CAR T-cell frequency by qPCR in one patient, plateau of persistent CAR T-cells in the further follow-up period in two patients. Abbreviations: AL: systemic light chain amyloidosis, CART: chimeric antigen receptor T-cell treatment, dFLC: difference between involved and uninvolved free light chains, DNA: deoxyribonucleic acid, LoQ: limit of quantification, PBMC: peripheral blood mononuclear cells, qPCR: quantitative polymerase chain reaction

Abbreviations

AL	Systemic (amyloid) light chain
ASTCT	American Society for Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
cilta-cel	Ciltacabtagene autoleucel
CR	Complete response
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
dFLC	Difference of involved and uninvolved serum free light chains
EBMT	European Society for Blood and Marrow Transplantation
EHA	European Hematology Association
ICAHT	Immune effector cell–associated hematotoxicity
ICANS	Immune effector cell-associated neurotoxicity syndrome
MRD	Measurable residual disease
PFS	Progression-free survival
R/R	Relapsed/refractory

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-026-01865-9.

Supplementary Material 1

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Author contributions
KMNF, UHe, SS, AS, MSR, PD, CMT and MS treated patients. AR and UEH provided essential reagents (BCMA-CAR GMP-grade retroviral supernatant; CAR T-cell manufacturing technology). KMNF, UHe, SS and MS collected and organized data. KMNF, UHe, SS, UEH, MSR, AR, AS, PD and MS discussed and interpreted data. KMNF and MS wrote the primary manuscript. KMNF, AH, BN and MS designed and generated figures. KMNF, UHe, SS and MS designed and generated tables. All authors revised the work within this manuscript. All authors edited the manuscript and approved the final version for publication. All authors agreed to be accountable for all aspects included in this work.

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Data availability
The datasets supporting the conclusions of this article is included within its additional file (supplementary material).

Declarations

Ethics approval and consent to participate
All patients gave written informed consent to the treatment including its compassionate use nature. The present study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
All patients gave written informed consent to the scientific use of their data and its publication.

Competing interests
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