Efficacy and Safety of Anti–B-Cell Maturation Antigen Chimeric Antigen Receptor T-Cell for the Treatment of Relapsed and Refractory AL Amyloidosis

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ABSTRACT

PURPOSE The use of anti–B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CART) therapy for AL amyloidosis (AL) is limited owing to patient frailty. HBI0101 anti-BCMA CART was the first proof of concept for its applicability to AL. This report addresses the AL patient cohort treated to date within the phase Ia/Ib clinical trial (ClinicalTrials.gov identifier: NCT04720313).

METHODS After lymphodepletion, most AL patients were infused with 800 × 10^6 CARTs.

RESULTS Sixteen patients were treated, with a median of four previous lines of therapy (range, 3-10), 14/16 were triple class refractory, and 6/16 were refractory to belantamab. Most patients (13/16) had cardiac involvement, including five with MAYO stage IIIa/IIIb at study entry. Cytokine release syndrome was frequent (14/16) but mostly low grade (grade 3: 3/16, no grade 4/5). No neurologic toxicity or treatment-related deaths were observed. There were five grade 3 AL-related organ deteriorations resolved quickly with supportive care. The overall hematologic response rate was 15/16 (94%) and complete response (CR) was 12/16 (75%). Minimal residual disease negativity was achieved in 9/14 evaluable patients. Most patients (8/13 evaluable) achieved an objective organ response. Seven patients died during long-term follow-up, three while in CR/very good partial response, and the median overall survival was 10.1 months (95% CI, 5.8 to not reached).

CONCLUSION This largest clinical trial of AL patients treated with anti-BCMA CART demonstrates acceptable and manageable toxicity in a highly frail and resistant population with remarkable efficacy, leading to fast organ responses. Among patients with baseline advanced cardiac disease, deaths in the first year were frequent, suggesting that this effective therapy should be considered earlier in the course of therapy. Anti-BCMA CART may become a powerful tool for improving organ function and survival in patients with AL.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

AL amyloidosis (AL) is a rare plasma cell (PC) dyscrasia characterized by multiorgan damage because of misfolded light chains (LCs) secreted by clonal abnormal PCs.[1,2] Despite significant progress in the care of AL patients, the prognosis for many remains poor, particularly for those with severe cardiac disease and/or multiorgan involvement, or patients with advanced disease.[3,4] Moreover, because organ function improvement usually lags many months after the cessation of further secretion of toxic amyloidogenic LC, advanced patients will die of previous, mostly cardiac, organ damage, never profiting from the beneficial effects of achieving a hematologic response.[5] Consequently, achieving a rapid and deep response has been shown to translate into significant organ responses and survival benefit.[6] Because of its rarity, prospective clinical trials in AL are difficult to conduct, and AL treatment strategies have followed those of multiple myeloma (MM).[1,6]

Chimeric antigen receptor T-cell (CART) anti–B-cell maturation antigen (BCMA) therapy is emerging as an extremely efficient immune therapy for MM.[7,8] Two anti-BCMA CART

CONTEXT

Key Objective

Is anti–B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CART) safe and efficacious in AL amyloidosis (AL)?

Knowledge Generated

A phase I study with academic anti-BCMA CART HBI0101 AL patients was included. Fourteen patients were treated in the study, and two additional patients who received compassionate treatment were included in the analysis. The cohort consisted of heavily pretreated AL patients, including those with severe cardiac involvement. CART was safe with no treatment-related deaths, manageable cytokine release syndrome, or neurotoxicities. Responses were almost universal (15/16), with frequent complete responses (12/16), translating into organ responses.

Relevance *(S. Lentzsch)*

The trial reports the first data of anti-BCMA CART treatment in AL amyloidosis. The high response rates and manageable toxicity profile are promising and provide the basis for future CART trials in AL amyloidosis.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

products have been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of relapsed/refractory MM, with unprecedented level of deep and prolonged responses that make this technology highly efficacious.[9,10]

Our locally produced academic CART, HBI0101, is a second-generation anti-BCMA CART. In a phase Ia/Ib study, HBI0101 demonstrated manageable safety and high therapeutic efficacy in MM.[11,12]

Although promising, CART is associated with serious toxicities. These include serious life-threatening adverse events, such as cytopenia, infections, cytokine release syndrome (CRS), and neurologic toxicity. Another major caveat is its limited availability and the extremely high costs of this advanced technology.[8,11,13]

Given the deep responses achieved in patients with MM treated with CART and the crucial unmet need in AL amyloidosis for such deep hematologic responses to achieve organ responses,[6] this therapy appears promising. However, safety has become a significant concern, considering the frailty of AL patients, further questioning the ability of this patient population to endure severe CART-mediated toxicities.[2,14,15] The previously reported lower expression of BCMA in the PC of AL patients compared with MM PCs is another potential concern[16,17]; however, this was found by us to be insignificant in vitro.[18]

Thus far, experience with CART in AL amyloidosis is limited to retrospective case reports of patients with AL and concurrent lymphoma (one case), treated with anti-CD19 CART[19] or (mostly) concurrent MM.[20-22]

To our knowledge, we were the first to report on a prospective experience with CART in AL and showed the feasibility of production and treatment by CART with the first four AL patients included in our study with the academic CART HBI0101 (ClinicalTrials.gov identifier: NCT04720313).[18] These four patients reported, albeit with multiorgan and severe cardiac involvement, endured the treatment safely, with manageable toxicities and remarkable efficacy. This proof of concept has promoted the further use of HBI0101 for AL amyloidosis. Herein, we report the safety and efficacy of the AL cohort of patients treated and analyzed as a subgroup within the phase Ia/Ib study.

METHODS

Patients and Study Design

This trial is a single-arm, open-label, phase Ia/b study evaluating the locally produced anti-BCMA CART HBI0101, conducted at the Department of Hematology and the Department of Bone Marrow Transplantation and Cancer Immunotherapy, Hadassah Medical Center, Jerusalem, Israel. The majority of enrolled participants have MM; however, AL patients were not excluded. As such, AL patients were eligible to this clinical trial. The AL subgroup was analyzed as a separate cohort. The AL cohort of the phase Ia/Ib study has completed recruitment. The 16 patients reported were the only AL patients who were referred for HBI0101 therapy. A complete detailed description of the study design with the study protocol has been previously reported.[11] Briefly, key eligibility criteria were ≥three previous lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 antibody; however, the criteria were relatively permissive, with a minimum

threshold platelet count of 30×10^9/mL, creatinine clearance of 20 mL/min, left ventricular ejection fraction of 40%, and performance status (PS) of 2 on the Eastern Cooperative Oncology Group (ECOG) scale. All cardiac stages by Mayo Clinic cardiac staging and New York Heart Association (NYHA) scale for heart failure were allowed. Two patients were treated on a compassionate basis with a cell dose that was tested in parallel at the time of enrollment in the study (one patient with severe pancytopenia because of myelodysplastic syndrome [MDS]), and a second patient with an ECOG-PS of 4 because of advanced cardiac amyloidosis (patients 4 and 7, respectively, in Appendix Table A1, online only). Both patients' treatments were authorized by the local institutional review board (IRB) and Israeli Ministry of Health, and both patients were consented.

HBI0101 CART Manufacture and Administration

HBI0101 CART products were manufactured within 8-10 days at the Facility for Advanced Cellular Therapy at the Hadassah Medical Center, Israel. Details of the process and sample handling, CART detection and determination of BCMA expression, as well as the lymphodepletion process are presented in the Appendix 1, and were previously reported.[11]

Patients with significant AL-related heart disease were electively admitted to the intensive cardiac care unit (ICCU) for monitoring on day −1 and until recovery from acute toxicity after infusion.

Ethics

This study was authorized by the Health Medical Organization IRB and by the Israeli Ministry of Health. This study was registered at ClinicalTrials.gov (identifier: NCT04720313).

Assessments

Adverse effects were assessed according to the Common Terminology Criteria for version 5.0. CRS and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded according to the 2019 American Society for Transplantation and Cellular Therapy criteria on the basis of the highest individual symptom grade.[23] Hematologic and organ responses were defined according to published criteria.[24-26] Minimal residual disease (MRD) was evaluated by flow cytometry in accordance with Euroflow standards, with a minimum cutoff of 10^{-5} cells.

Statistical Analysis

Descriptive statistics were used to describe patient and treatment characteristics. Event-free survival (EFS) was defined as the time from CART infusion to hematologic progression or therapy change because of inadequate response or death. The duration of response (DOR) was defined as the time from the first response to hematologic progression or therapy change because of inadequate response or death. Overall survival (OS) was defined as the time from CART infusion to death from any cause. The Kaplan-Meier method was used to assess the EFS and OS, while the reverse Kaplan-Meier method was applied to estimate the median follow-up. Statistical significance was set at $P < .05$. Statistical analyses were performed using GraphPad Prism Version 9.5.0 and JMP Pro 17.

RESULTS

Patients and Treatment

Between September 12, 2021, and May 2024, 14 patients with AL were enrolled and infused with HBI0101, and two patients who were treated on a compassionate basis. There were neither apheresis failures nor production failures, and all recruited patients received lymphodepletion and CART infusion.

The patient characteristics are shown in Table 1 and Appendix Table A1. The median age was 64 years (range, 55-82), with a median of 4.2 years (range, 0.4-19) since diagnosis. Two patients had concurrent MM-related organ involvement (lytic lesions). Thirteen patients (81%) had cardiac involvement, with a median B-type natriuretic peptide (pro-BNP) of 964 pg/mL (range, 220-28,000), including five patients with MAYO cardiac stage IIIa/IIIb and six with NYHA scale stage III/IV at study entry and screening. Patients were heavily pretreated, with a median of four (range, 3-10) previous lines of therapy. The majority of patients (14/16, 88%) were triple refractory (refractory to an IMiD, PI, and an anti-CD38 antibody), and six (38%) were refractory to the anti-BCMA antibody drug conjugate belantamab mafodotin (Table 1).

Most of the patients (13/16) were included in cohort 3 of the phase Ia study or in phase Ib study and received a target dose of 800×10^6 CARTs (range of 570×10^6-$1{,}050 \times 10^6$).

Only one patient received bridging therapy between apheresis and CART with venetoclax for 82 days (Appendix Table A1).

Most patients (13/16, 81%) received fludarabine and cyclophosphamide lymphodepletion. Five patients with significant cardiac involvement at study entry were electively admitted to the ICCU for 48 hours of monitoring during CART infusion.

Safety

Adverse events are outlined in Table 2 and Appendix Table A2.

Hematologic Toxicities

Early (before day +28 postinfusion) hematologic toxicities were common, including grade 4 lymphopenia in all patients,

TABLE 1. Patient Characteristics at Study Entry

Variable	Cohort (N = 16)
Age, years, median (range)	64 (55-82)
Males, No.	11
Females, No.	5
Time since diagnosis, years, median (range)	4.2 (0.4-19)
Involved light chain, No.	
Kappa	7
Lambda	9
Concurrent clinical MM, n/N (%)	2/16 (13)
Bone marrow plasma cells percentage (range)	1 (0.3-15)
dFLC, mg/L, median (IQR)	105 (50-550)
Karyotype, n/N (%)	
t(11:14)	7/16 (44)
17p−	2/16 (13)
1q+	3/16 (19)
Other	t(4:14)−n = 1; t(14:16)−n = 1
Involved organs, n/N (%)	
Heart	13/16 (81)
Kidneys	11/16 (69)
Soft tissue	6/16 (38)
PNS	6/16 (38)
Liver	6/16 (38)
GI	5/16 (31)
Lung	1/16 (6)
Pro-BNP,[a] pg/mL, median (range)	964 (220-28,000)
Cardiac Mayo stage, n/N (%)	
I-II	11/16 (69)
IIIa	4/16 (25)
IIIb	1/16 (6)
NYHA scale for heart failure stage,[a] n/N (%)	
I-II	10/16 (62)
III	3/16 (19)
IV	3/16 (19)
ECOG-PS scale, n/N (%)	
0-1	12/16 (75)
2	3/16 (19)
3-4	1/16 (6)
Previous lines of therapy, No., median (range)	4 (3-10)
Triple drug refractory, n/N (%)	14/16 (88)
Belantamab mafodotin refractory, n/N (%)	6/16 (38)
Last line refractory, n/N (%)	15/16 (94)

Abbreviations: dFLC, difference between involved and noninvolved free light chains; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; MM, multiple myeloma; NYHA, New York Heart Association; PNS, peripheral nervous system; Pro-BNP, B-type natriuretic peptide.
[a]In 13/16 patients with cardiac involvement.

grade 3-4 anemia in 5/16 (31%), and grade 3-4 neutropenia in 10/16 (63%). No grade 3-4 thrombocytopenia was observed (excluding the patient with preexisting MDS with pretreatment grade 4 thrombocytopenia). However, hematologic toxicities were short-lived, with resolution of anemia by day +28 in 14/16 patients (one patient had persistent grade 2 anemia and in a second patient, the anemia resolved on day +31), and recovery of neutrophil counts to at least 1×10^9/L by day +28 in 14/15 (one patient recovered neutrophil counts at day +54, excluding the patient with preexisting MDS with pretreatment grade 3 neutropenia). No late hematologic toxicities were observed, except for patient 1 (Appendix Table A2), who developed late occult MDS, as previously reported.[27]

CRS and ICANS

CRS was observed frequently (14/16, 88%). Most patients had CRS grades 1 or 2 (grade 1: three patients; grade 2: eight patients), and three had grade 3 CRS (19%). None of the patients had a grade 4 or 5 CRS. All CRS events occurred early (median of 1 day after CART infusion to onset, range 1-3) and were brief (median duration of 2 days, range 1-5). Tocilizumab was used in 12/14 (86%) patients with CRS (median of one dose, range 1-3) and corticosteroids (dexamethasone 20-40 mg once daily for 2-3 days) in 3/14 (21%), and there were no cases of ICANS, Parkinsonian-like symptoms, cranial nerve palsy, or other forms of neurotoxicity. One patient with depression experienced exacerbation of his disease unrelated to CART infusion.

AL Target Organ and Other Organ Decompensations

There were nine occurrences of AL-related organ deterioration in a total of 7/16 patients: three events of grade 3 acute cardiac failure exacerbations, four events of acute kidney injury (AKI; three of grade 1 and one of grade 2), and two events of acute liver injury (both grade 3). None of the cardiac events required treatment within the ICCU. One cardiac exacerbation and AKI occurred in the same patient during lymphodepletion, whereas all other organ decompensations occurred concurrently with CRS. Four patients (without AL-related liver involvement) had elevated liver function test (grade 1: two patients; grade 3: two patients). All organ toxicity events (whether in organs with or without preexisting AL-related dysfunction) resolved to baseline function or better with supportive care.

Infections

Early (≤day +28) infections occurred in 9/16 (56%) patients: six had grade 3 infections (five events of febrile neutropenia and one pneumonia), two had grade 1-2 respiratory infections, and one had early cytomegalovirus (CMV) reactivation without CMV disease, yet required antiviral preemptive therapy. None had grade 4/5 infections. All patients developed hypogammaglobulinemia below 600 mg/dL, with a median trough level of 291 mg/dL. During the first year after infusion, three patients received immunoglobulin replacement therapy. Eleven late infections occurred in seven

TABLE 2. Adverse Events

Variable	Toxicity Result	
Hematologic toxicity, n/N	Total	Grade 3-4
Anemia	12/16	5/16
Thrombocytopenia	9/16	0/16
Neutropenia	12/16	10/16
Lymphopenia	16/16	16/16
CRS, n/N (%)		
No CRS	2/16 (12)	
Grade 1	3/16 (19)	
Grade 2	8/16 (50)	
Grade 3	3/16 (19)	
Grade 4/5	0/16 (0)	
Time to onset of CRS, days, median (range)	1 (1-3)	
Duration of CRS, days, median (range)	2 (1-5)	
Tocilizumab use, n/N with CRS (%)	12/14 (86), median of one dose (range, 1-3)	
Corticosteroid use, n/N with CRS (%)	3/14 (21)	
Vasopressor use, n/N with CRS (%)	2/14 (14)	
High-flow oxygen use, n/N with CRS (%)	2/14 (14)	
ICANS and other neurotoxicity, n/N (%)	0/16 (0)	
Organ function toxicity, n/N	Total	Grade 3-4
Congestive heart failure exacerbation	3/16	3/16
Acute kidney injury	4/16	0/16
Hepatic injury	6/16	4/16
Infections, n/N		
Febrile neutropenia	5/16	5/16
Early infections (until day +28)	9/16	6/16
Late infections (after day +28)	7/16	5/16
Treatment-related mortality, n/N (%)	0/16 (0)	

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

TABLE 3. Efficacy

Variable	Efficacy Result
Best hematologic response, n/N (%)	
CR	12/16 (75)
VGPR	2/16 (13)
Partial response	1/16 (6)
No response	1/16 (6)
Overall response	15/16 (94)
iFLC at best response, mg/L, median (range)	1 (0-67)
dFLC at best response, mg/L, median (range)	0 (0-62)
Time to best hematologic response, days, median (range)	17 (5-74)
MRD negativity, 10^{-5}, n/N evaluable (%)	
At any point	9/14 (64)
Day +30	7/13 (54)
Day +180/later	4/5 (80)
Organ response, n/N evaluable (%)	
Any organ	8/13 (62)
Cardiac	7/9 (78)
Renal	2/6 (33)
Hepatic	1/5 (20)
Improvement in NYHA scale for heart failure cardiac stage, n/N evaluable (%)	5/10 (50)
Follow-up, median, months (95% CI)	8.4 (4 to 31.5)
EFS, median, months (95% CI)	9.6 (3.3 to NR)
DOR, median, months (95% CI)	8 (2 to NR)
OS, median, months (95% CI)	10.1 (5.8 to NR)
Alive at last follow-up, n/N	9/16
Cause of death, No.	
Cardiac, while in relapse	4
Cardiac, while in VGPR	1
COVID-19, while in CR	1
Other, while in CR	1

Abbreviations: CART, chimeric antigen receptor T-cell; CR, complete response; dFLC, difference between involved and noninvolved free light chains; DOR, duration of response; EFS, event-free survival (the time from CART infusion to hematologic progression or therapy change for inadequate response or death); iFLC, involved free light chain; MRD, minimal residual disease; NR, not reached; NYHA, New York Heart Association; OS, overall survival; VGPR, very good partial response.

patients, including one grade 5 COVID-19 infection, one grade 3 COVID-19 infection, and three cases of grade 3 pneumonia.

Cardiac Intensive Care Course

All five patients admitted to the ICCU had uneventful monitoring and required no further cardiac supportive care.

Deaths

There were no treatment related deaths.

Compassionate-Basis Treated Patients

Albeit not fitting the inclusion criteria, there were no excess safety issues observed in these patients.

Efficacy

Efficacy results are outlined in Table 3 and Appendix Table A3.

Hematologic Responses

The overall hematologic response rate (ORR) was 15/16 (94%), including 12 patients (75%) with a complete response (CR), two with a very good partial response (VGPR), and one

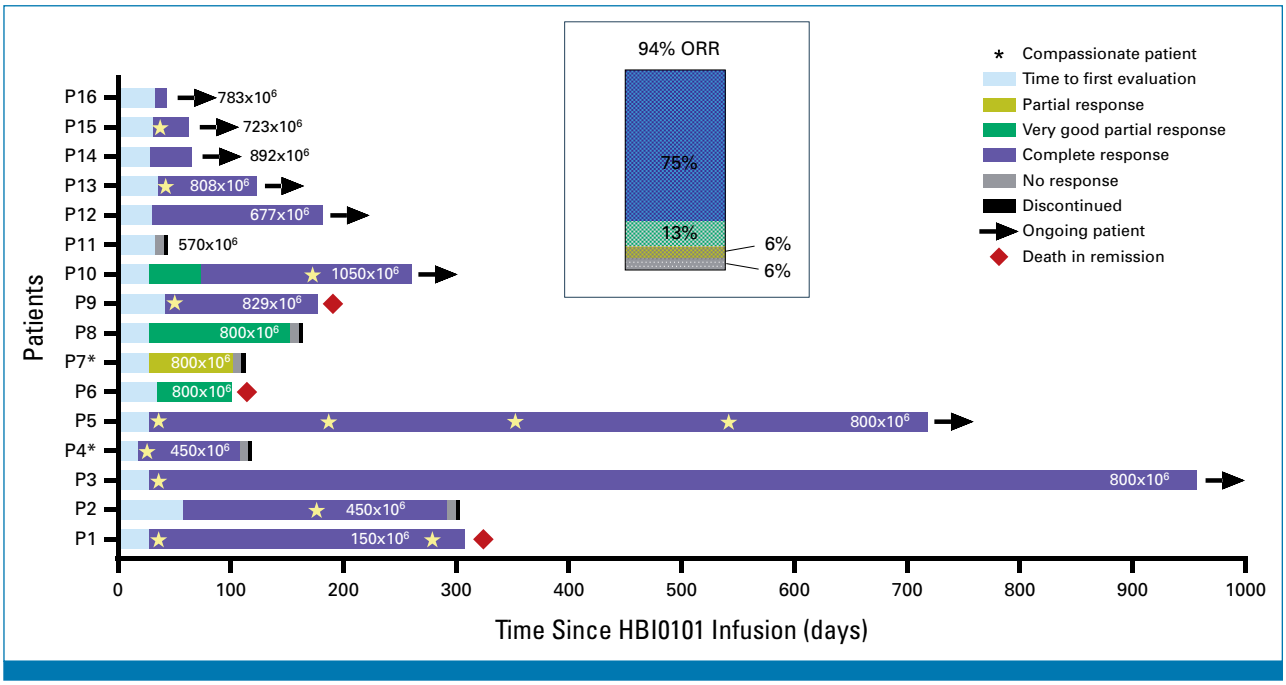

FIG 1. Response of AL patients to HBI0101 therapy. Swimmer plot of responses of AL to HBI0101 therapy over time. HBI0101 cell dose is indicated within each patient's bar. Inset: Best ORR achieved in 16 AL patients infused with HBI0101 CARTs. Hematologic response to HBI0101 therapy was assessed according to accepted criteria.[22] MRD was assessed by flow cytometry (10^{-5} cells), and MRD negativity is designated with a yellow star at the indicated time points. AL, AL amyloidosis; CART, chimeric antigen receptor T-cell; MRD, minimal residual disease; ORR, overall hematologic response rate.

with a partial response (PR; Table 3; Fig 1). The median time to first response (at least PR) was 10 days (range, 4-35) and the median time to best response was 17 days (range, 5-74; Table 3; Fig 2A). Nine of the 14 evaluable patients (64%) achieved MRD negativity at least at one time point after infusion (Table 3; Fig 1). Excluding the two ineligible patients, the ORR was 13/14 (11 CR and two VGPR), and 8/13 evaluable patients achieved MRD negativity.

Organ Responses

The majority of patients achieved organ responses (8/13 evaluable, 62%). Nine of 13 patients with cardiac involvement were evaluated for cardiac response (the other four had a low pro-BNP at study entry), of whom seven (78%) had a response. This included one CR, three VGPR, and three PR according to the proposed new organ response criteria of Muchtar et al.[26] In addition, 5/10 evaluable patients showed functional improvement at the NYHA scale stage (Table 3; Appendix Table A3).

An example of a complete renal response was seen in patient 3, who achieved CR and MRD negativity after CART (Appendix Table A3), resulting in a complete resolution of proteinuria within 6 months, in a patient who never achieved a complete organ response during the course of 15 disease years. One patient with severe orthostatic hypotension had resolution of autonomic neuropathy within 2 months after therapy.

Survival

At the data cutoff, with a median follow-up was 8.4 months (range, 4-31.5), the median EFS was 9.6 months (95% CI, 3.3 to not reached [NR]) and the median DOR was 8 months (95% CI, 2 to NR; Appendix Fig A1). Of the 12 patients who achieved a CR, the median EFS was 10.1 months (95% CI, 2.4 to NR). Excluding the two ineligible patients, the median EFS was 9.6 months (95% CI, 3.3 to NR) and the median DOR was 9 months (95% CI, 2 to NR). Seven patients died, three of whom were in CR/VGPR: one from COVID-19 disease, one from complications of depression and malnutrition, and one from AL amyloidosis–related cardiac disease. Four of the patients died of advanced cardiac AL amyloidosis following disease progression after the initial response. All four were heavily pretreated patients (one exhausting four previous lines of therapy within 8 months after diagnosis and three with 6-10 previous lines of therapy). All had severe cardiac involvement at study entry (Mayo stage IIIa/IIIb and/or NYHA scale stage IV). All four patients initially responded to HBI0101, and 3 of 4 patients also achieved a cardiac response, but eventually experienced hematologic progression and consecutive deterioration of cardiac function, and finally died of cardiac disease.

The median OS (mOS) was 10.1 months (95% CI, 5.8 to NR). Excluding the two ineligible patients, the mOS was 12.2 months (95% CI, 5.8 to NR).

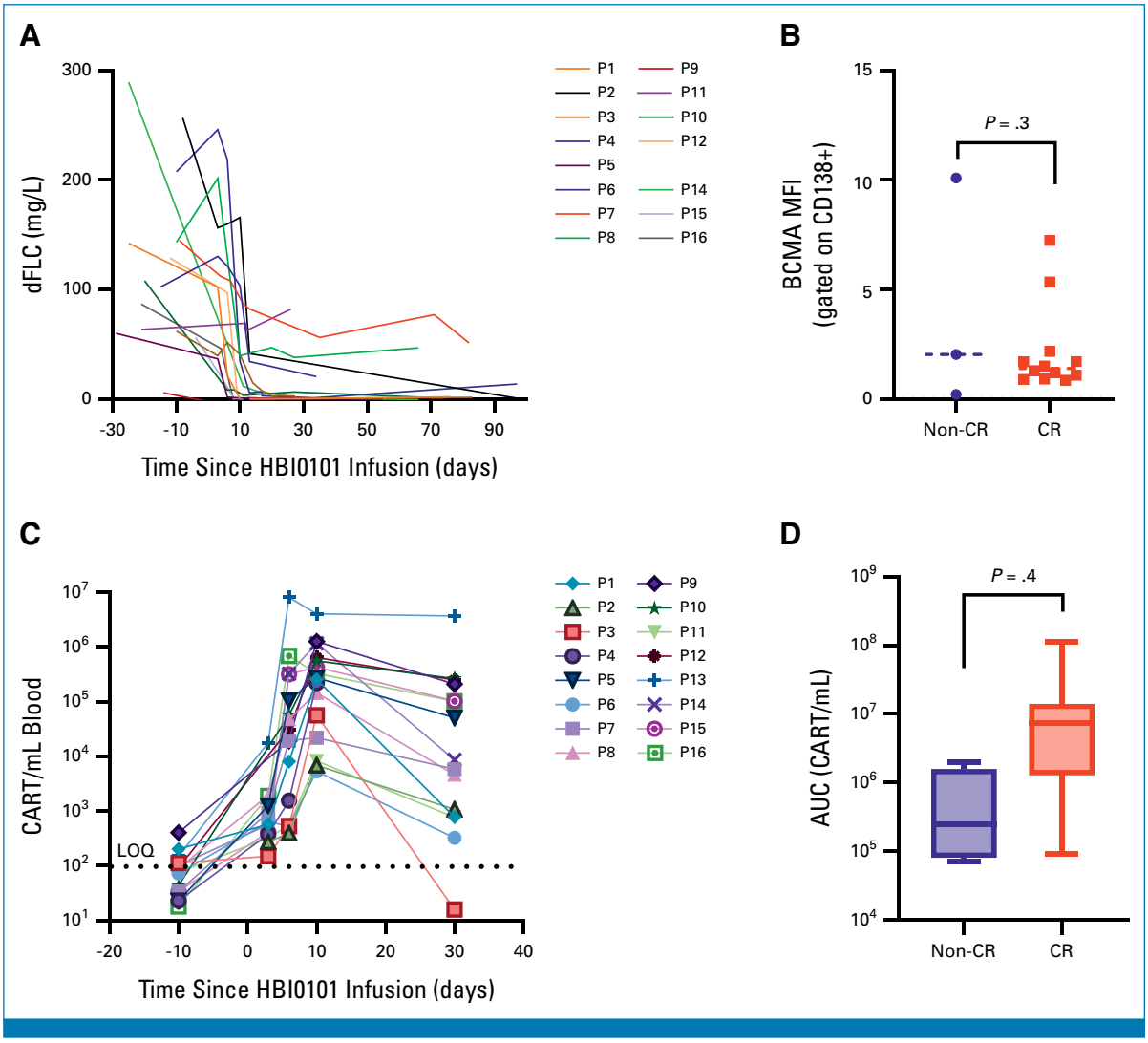

FIG 2. HBI0101 CART kinetics and persistence in the peripheral blood of infused AL patients. (A) dFLC was calculated for each patient before CART infusion and at the indicated time points. (B) Median of BCMA expression by MFI was determined on plasma cells of AL bone marrow samples (gated on CD138+). (C) HBI0101 CAR+ cell kinetics in the peripheral blood of AL patients infused with HBI0101 CAR+ cells. HBI0101 vector transgene/mL of whole blood was quantified by real-time PCR, and translated into number of CARTs /mL by adjusting for the percent of transduction. (D) AUC of CART expansion in the blood in the first month following CART infusion in (C) was calculated for each patient and grouped according to response (CR, red box, n = 12) versus non-CR (blue box, n = 4) groups. AL, AL amyloidosis; BCMA, B-cell maturation antigen; CART, chimeric antigen receptor T-cell; CR, complete response; dFLC, difference between involved and noninvolved free light chains; LOQ, limit of quantification; MFI, mean fluorescence intensity; PCR, polymerase chain reaction.

BCMA Expression and HBI0101 Kinetics

These are detailed in the Appendix 1 and illustrated in Figures 2B-2D.

DISCUSSION

To our knowledge, we present the largest cohort of AL patients treated with anti-BCMA CART within the first registered and performed clinical CART trial, which included AL amyloidosis (and has completed accrual). Herein, we demonstrate that CART for AL amyloidosis is safe, with acceptable and manageable toxicity, even in advanced cardiac patients, and shows remarkable hematologic efficacy, translating into prominent organ responses.

There were no treatment-related deaths or irreversible toxicities, even in patients with very frail cardiac AL. Several actions were taken to achieve this goal: (1) The treatment was performed in a tertiary care AL amyloidosis center, and a thorough cardiac evaluation was performed before treatment by a cardiologist who was an expert in amyloidosis care. (2) Optimization of the patients' circulatory and respiratory status before cell infusion, including intensive

diuresis, drainage of pleural effusions, and cardiac rate control. (3) Elective admission to the ICCU for the critical days after infusion (although uneventful in our cohort) for close monitoring by expert cardiologists and joint treatment by hematologists and CART team members. (4) Liberal use of tocilizumab in low-grade CRS as per protocol to prevent further deterioration of the syndrome and dangerous hemodynamic and/or respiratory effects. (5) Limited use of high-dose corticosteroid, to only as required by the protocol.

Cytopenias were less challenging than was observed in our MM cohort, and what was reported with other CART for MM.[12,28,29] These were less severe, with a short duration and quick recovery. This observation is probably explained by the smaller PC clone and better marrow reserve in AL patients than in patients with MM. In addition, anemia may potentially exacerbate cardiac dysfunction, and neutropenia poses a risk of severe infections in this frail population. Thus, the limited hematologic toxicity observed in this cohort is very encouraging regarding the future use of CART in patients with AL.

Although hypogammaglobulinemia is universal after CART targeting PC,[30] infections were overall manageable, with the same supportive care taken in patients undergoing CART for MM.[31,32]

A critical safety point unique to AL, in contrast to MM and lymphoma, is the potential worsening of AL-related organ function during and after the procedure. These may be severely affected by tachycardia, blood pressure changes, and respiratory insufficiency induced by CRS, as well as during the lymphodepletion stages. With meticulous supportive care, as described above, these patients were managed successfully. All organ toxicities were reversible, allowing for organ restoration and subsequent organ responses observed, including the two patients treated on a compassionate basis.

As expected, the responses after CART infusion were remarkably rapid, deep, and meaningful. In this very heavily pretreated cohort, only one patient did not respond to therapy (ORR 15/16, 94%). Similar ORRs (90%) were seen in our parallel MM patient cohort.[12] Our experience of both safety and efficacy is in line with previous case reports of CART in AL.[19-22]

We show that after HBI0101 CART therapy, the serum involved free light chains and difference between involved and noninvolved free light chains decrease to almost zero, reflecting very deep responses. Moreover, because of the profound and quick reduction of the toxic LC, organ responses were observed early. Although in patients with advanced cardiac amyloidosis, there was no early treatment-related mortality, deaths due to cardiac disease in the first year were frequent. Advanced cardiac involvement is a major cause of mortality, even in patients achieving a rapid response.[33] These heavily pretreated patients, with no other available effective therapies, and with advanced irreversible cardiac involvement at study entry, unfortunately could not benefit from the efficiency of therapy, albeit the high levels of responses. This is further highlighted by the extension of the DOR and OS once the two patients treated on a compassionate basis were excluded from the analysis.

One limitation of our study is the relatively short follow-up period, which limits the ability to draw firm conclusions on durability. However, HBI0101 demonstrated durability in MM.[12] We believe that the AL cohort will behave similarly with a longer follow-up and more patients included.

We believe that the durability of hematologic responses may be longer when administered at earlier lines. Using CART earlier in the disease course, before permanent organ damage ensues and highly resistant PCs evolve, may lead to better AL amyloidosis organ responses and patient survival.

Another obvious limitation of this report is the relatively small number of patients treated, although, to our knowledge, this is the largest series reported to date.

In summary, to our knowledge, our report of the first clinical trial with anti-BCMA CART for AL amyloidosis patients provides evidence that this therapy is safe and highly efficacious for the treatment of AL, even in the frailest and heavily pretreated patients. Safety concerns should not prevent wider implementation of this effective therapy in this population.

Clearly, a larger, multicenter study for AL should be performed (already launched [ClinicalTrials.gov identifier: NCT06097832]). Anti-BCMA CART may become a powerful tool to improve organ function and survival in patients with AL amyloidosis.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Anti–B-Cell Maturation Antigen Chimeric Antigen Receptor T-Cell for the Treatment of Relapsed and Refractory AL Amyloidosis

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APPENDIX 1

Additional Data—Methods

HBI0101 Chimeric Antigen Receptor T-Cell Manufacture and Administration

HBI0101 chimeric antigen receptor T-cell (CART) products were manufactured within 8-10 days at the Facility for Advanced Cellular Therapy at the Hadassah Medical Center, Israel. For the first eight patients, the CARTs were formulated in saline solution with 2.5% human albumin and freshly infused to patients within 8 hours after formulation, while for the successive eight patients, the CARTs were formulated in CryoStor CS5, cryopreserved, and infused to patients after lymphodepletion according to the protocol. Although the target dose was 800×10^6, the actual cryopreserved dose fluctuated from 570×10^6 to $1{,}050 \times 10^6$, because of differences in cell recovery after thawing. The details of the HBI0101 manufacturing process have been reported elsewhere.[11]

Lymphodepletion included fludarabine 25 mg/m^2 once daily and cyclophosphamide 250 mg/m^2 once daily on days −5 to −3 before infusion. Bendamustine 90 mg/m^2 once daily on days −4 and −3 was administered to patients with a creatinine clearance of <30 mL/min.

Sample Collection and Mononuclear Cell Isolation and Storage

Whole-blood samples were collected from AL patients in heparin and serum collection tubes before (at screening) and after HBI0101 infusion (at the indicated time points). Bone marrow (BM) samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes. Patient sera were collected by centrifugation and frozen at −20°C.

CART Detection in Patients' Peripheral Blood

Genomic DNA was isolated from 250 μL whole-blood samples collected at the indicated time points using the Maxwell RSC Buffy Coat DNA Kit on a Maxwell instrument (Promega, Madison, WI), according to the manufacturer's instructions. Real-time polymerase chain reaction for the quantification of HBI0101 CARTs in 1 mL of blood was performed as detailed previously.[11]

Determination of B-Cell Maturation Antigen Expression

BM samples were collected in EDTA tubes and stained for CD138 (Beckman Coulter, Brea, CA) and B-cell maturation antigen (BCMA; BioLegend, San Diego, CA) for 20 minutes at room temperature, as previously described.[18] RBCs were then lysed using IOTEST-3 (Beckman Coulter), and samples were acquired using a Navios flow cytometer (Beckman Coulter). Isotype-matched controls were used to rule out nonspecific binding. Data analysis was performed using the Kaluza 2.1 software.

Additional Data—Results

BCMA Expression and HBI0101 Kinetics

The correlation between basal BCMA expression on CD138+ plasma cell and the depth of response showed no significant difference in the mean fluorescence intensity of BCMA between patients who achieved and those who did not achieve complete response (CR; Fig 2B; $P = .29$).

HBI0101 Kinetics

HBI0101 CART expansion in the blood was robust in all 16 patients (Fig 2C). Although the AUC of CART expansion was higher in patients who achieved CR, the difference was not statistically significant ($P = .36$; Fig 2D). The median day of CART persistence in the peripheral blood of patients who responded to HBI0101 therapy (n = 15) was 55 days (range, 14-196).

TABLE A1. Patient Characteristics—Individual Data

	Patient No.															
Characteristic	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age, years	64	58	82	63	64	72	55	68	78	59	64	64	63	67	70	58
Years since diagnosis	10.5	4	15	4.5	2	3.5	0.8	11	6	0.8	19	1.4	6.3	0.7	11	0.4
Sex	Male	Female	Male	Male	Male	Female	Female	Male	Male	Male	Female	Male	Female	Male	Male	Male
Involved LC	K	L	L	L	L	L	K	L	K	L	K	L	L	K	K	K
dFLC, mg/L	143	177	50	550	51	103	196	408	41	108	64	129	83	275	49	86
BMPC%	3	15	1	15	0.1	1	1	10	15	1	1	1	0.5	1.5	0.5	0.3
Karyotype	t(11:14)	t(14:16) 1q+	14q−	t(11:14)	t(11:14)	t(11:14) 1q+	14q−	17p−	Normal	17p−	t(4:14) 1q+	t(11:14)	t(11:14)	Normal	t(11:14)	Normal
Concurrent MM	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Organ involved	Cardiac, renal, PNS	Cardiac, renal, hepatic	Renal, GI	Cardiac, hepatic, lung, soft tissue, PNS	Cardiac, soft tissue, PNS	Cardiac, renal, hepatic	Cardiac, soft tissue	Cardiac, renal, soft tissue	Renal	Cardiac, renal, PNS	Cardiac, renal, GI, hepatic, soft tissue, PNS	Cardiac, renal	Cardiac, renal, soft tissue, GI	Hepatic	Cardiac, PNS, GI	Cardiac, renal, GI, hepatic
NYHA scale for heart failure stage	III	IV	I	III	II	IV	IV	II	I	II	II	I	II	III	II	II
Pro-BNP, pg/mL	7,500	2,008	119	2,773	731	28,000	6,600	220	930	669	211	3,158	281	191	107	964
Mayo stage	IIIa	IIIa	I	IIIa	II	IIIb	II	I	I	II	II	IIIa	I	I	I	II
ECOG-PS scale	0	2	0	0	1	2	4	0	1	1	1	1	1	2	0	1
Previous lines	8	6	6	10	3	4	4	7	4	3	8	4	4	3	6	3
Best previous response/which line	VGPR/third	VGPR/second	CR/ first	CR/first, fourth	VGPR/second	VGPR/second	VGPR/third	VGPR/first, second	CR/ fourth	VGPR/third	CR/second, fifth, sixth, eighth	PR/second, fourth	CR/second	PR, third	VGPR/sixth	NR
Previous ASCT	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No
Triple refractory	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Belantamab refractory	No	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No
Last line refractory	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

Abbreviations: ASCT, autologous stem-cell transplant; BMPC, bone marrow plasma cell percentage; CR, complete response; dFLC, difference between involved and noninvolved free light chains; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; K, kappa; L, lambda; MM, multiple, myeloma; NR, no response; NYHA, New York Heart Association; PNS, peripheral nervous system; PR, partial response; Pro-BNP, B-type natriuretic peptide; VGPR, very good partial response.

TABLE A2. Safety—Individual Data

	Patient No.															
Characteristic	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ICCU monitoring	No	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Hematologic toxicity																
Anemia, grade	1-baseline	1-baseline	1	3	1	2	2	1-baseline	3	2-baseline	2	1	3	3	1	3
Anemia full recovery, days	NA	NA	13	8	8	2	Remained G2	NA	2	NA	12	18	14	13	31	3
Thrombocytopenia, grade	0	2	2	4-baseline	1	0	0	2	0	0	2	1	1	2	2	0
Thrombocytopenia full recovery, days	NA	225	45	NA	8	NA	NA	8	NA	NA	6	1	11	6	3	NA
Neutropenia, grade	3	3	3	4	4	0	2	4	0	0	3	2	4	0	3	3
Neutropenia full recovery, days	5	6 to G2	170	92 to G2	54	NA	12	66	NA	NA	26	18	9	NA	51 to G1	63
Neutropenia recovery to G2, days	2	6	28	92	54	NA	NA	20	NA	NA	2	NA	8	NA	2	2
Lymphopenia, grade	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
CRS and ICANS																
CRS	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CRS grade	NA	2	3	3	1	NA	1	2	2	2	1	2	2	2	2	3
Time to onset, days	NA	2	3	1	2	NA	2	2	1	1	1	1	1	1	1	1
CRS duration, days	NA	2	4	1	1	NA	1	1	3	1	3	3	5	3	4	1
Tocilizumab use, No. of doses	NA	1	3	1	1	NA	0	1	3	1	0	3	2	1	2	1
Steroid use	NA	No	No	No	No	NA	No	No	Yes	For other reason	No	Yes	No	No	No	Yes
Vasopressor use	NA	No	Yes	No	No	NA	No	No	No	No	No	No	No	No	No	Yes
High-flow oxygen	NA	No	Yes	Yes	No	NA	No	No	No	No	No	No	For other reason	No	No	No
ICANS	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Organ toxicity and other																
CHF exacerbation, no/yes (grade)	No	G3	No	G3	No	G3	No	No	No	No	No	No	No	No	No	No
Acute kidney injury, no/yes (grade)	No	No	No	No	No	G2	No	No	G1	G1	No	G1	No	No	No	No
Hepatic dysfunction, no/yes (grade)	No	G3	No	No	No	No	No	No	G1	No	No	G1	G3	No	G3	G3
Other	PE d270, MDS d288	No	No	No	No	Pruritus G2	DVT d14	No	Drug toxicity d7	Depression exacerbation d40	No	No	No	No	No	No

(continued on following page)

TABLE A2. Safety—Individual Data (continued)

Characteristic	Patient No. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Infections																
Febrile neutropenia, grade	0	0	3	3	0	0	0	3	3	0	0	0	3	0	0	0
Early infections (≤d28), grade	0	3	3	3	1	0	2	3	3	0	0	0	3	2	0	0
Hypogammaglobulinemia (<600 mg/dL)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IVIG replacement	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No
Late infections (>d28)	PNA d248, COVID d290	OM d33	PNA 620d, 690d	FN + PNA d64, CDAD + Salmonela d100	FN + PNA d62, PNA d270	No	PNA d120	No	No	No	No	No	No	NA	NA	COVID-19 d30

Abbreviations: CDAD, Clostridium difficile–associated diarrhea; CHF, congestive heart failure; CRS, cytokine release syndrome; d, day; DVT, deep vein thrombosis; FN, febrile neutropenia; G, grade; ICANS, immune effector cell–associated neurotoxicity syndrome; ICCU, intensive cardiac care unit; IVIG, intravenous immunoglobulin; MDS, myelodysplastic syndrome; NA, not applicable; OM, osteomyelitis; PE, pulmonary embolism; PNA, pneumonia.

TABLE A3. Treatment and Efficacy—Individual Data

	Patient No.															
Characteristic	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
CART infused ($\times 10^6$)	150	450	800	450	800	800	800	800	829	1,050	570	677	808	892	723	783
Bridging	No	No	No	No	No	No	No	No	No	No	No	Ven. with PR	No	No	No	No
Lymphodepletion	Flu-Cy	Flu-Cy	Flu-Cy	Flu-Cy	Flu-Cy	Benda	Flu-Cy	Flu-Cy	Benda	Benda	Flu-Cy	Flu-Cy	Flu-Cy	Flu-Cy	Flu-Cy	Flu-Cy
Hematologic response																
Best hematologic response	CR	CR	CR	CR	CR	VGPR	PR	VGPR	CR	CR	NR	CR	CR	CR	CR	CR
Lowest iFLC, mg/L	0.6	0.9	1	7	0.4	26	56	38	0.4	0.9	67	0.5	1.6	0.6	0.6	1.8
Lowest dFLC, mg/L	0	0	0	1.4	0.1	20	55	37	0	0.6	62	0	0.6	0	0	0
MRD d30	Yes	NA	Yes	Yes	Yes	No	NA	No	Yes	No	No	No	Yes	No	Yes	NA
MRD d180	NA	Yes	NA	NA	Yes	NA	NA	NA	NA	Yes	NA	No	NA	NA	NA	NA
Other MRD time points, days	Yes 270	NA	NA	NA	Yes 360,540	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Time to first hematologic response, days	6	12	14	10	6	13	35	10	5	6	NA	9	28	11	4	4
Time to best hematologic response, days	27	57	17	17	6	13	35	10	5	74	NA	13	28	28	8	9
Organ response																
Cardiac response (grade[26])	VGPR	PR	NA	VGPR	PR	No	PR	Inevaluable	NA	CR	No	VGPR	Inevaluable	NA	Inevaluable	Inevaluable
NYHA scale for heart failure stage change	III to II	IV to II	NA	III to II	No	IV to III	IV to III	No	NA	No	No	NA	No	NA	Inevaluable	Inevaluable
Renal response (grade[26])	Inevaluable	Inevaluable	CR	NA	NA	No	NA	Inevaluable	No	CR	No	No	Inevaluable	NA	NA	Inevaluable
Other organ response	NA	Liver	NA	No	NA	No	NA	NA	NA	Orthostatism resolved	No	NA	NA	No	NA	Inevaulable
Survival																
EFS—event (which)/censored	Death	Progression	Censored	Progression	Censored	Death	Progression	Progression	Death	Censored	No response	Censored	Censored	Censored	Censored	Censored
EFS, days	308	292	958	73	718	101	102	153	177	257	33	182	123	66	63	33
OS	Died	Died	Alive	Died	Alive	Died	Died	Died	Died	Alive	Alive	Alive	Alive	Alive	Alive	Alive
OS, days	308	372	1,018	223	752	101	197	210	177	319	256	223	144	70	63	60
Cause of death	COVID-19 disease	Cardiac	NA	Cardiac	NA	Cardiac	Cardiac	Cardiac	Depression	NA	NA	NA	NA	NA	NA	NA
Disease status at death	CR	PD	NA	PD	NA	VGPR	PD	PD	CR	NA	NA	NA	NA	NA	NA	NA

Abbreviations: benda, bendamustine; CART, chimeric antigen receptor T-cell; CR, complete response; d, day; dFLC, difference between involved and noninvolved free light chains; EFS, event-free survival; Flu-Cy, fludarabine and cyclophosphamide; iFLC, involved free light chain; MRD, minimal residual disease (10^{-5} by flow cytometry); NA, not applicable; NR, no response; NYHA, New York Heart Association; OS, overall survival; PD, progressive disease; PR, partial response; Ven., venetoclax; VGPR, very good partial response.

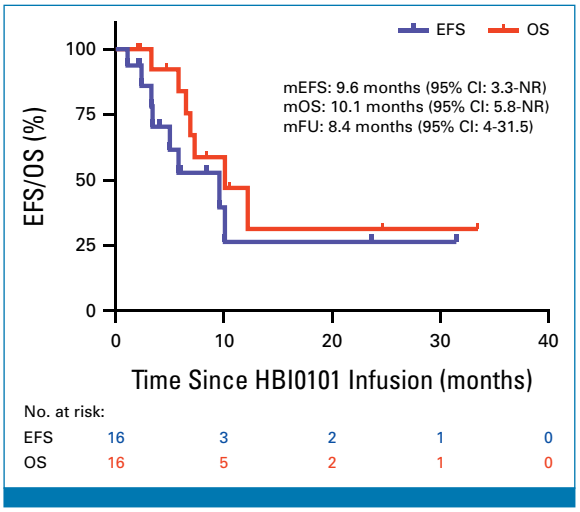

FIG A1. Kaplan-Meier survival curves. EFS and OS were calculated for the AL patient cohort (N = 16). AL, AL amyloidosis; EFS, event-free survival; mEFS, median EFS; mFU, median follow up; mOS, median overall survival; NR, not reached; OS, overall survival.