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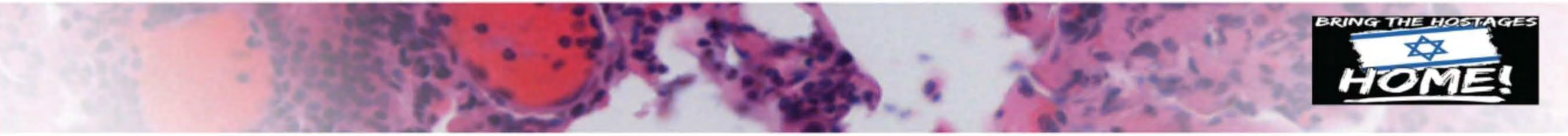

Efficacy and Safety of Anti-BCMA Chimeric Antigen Receptor T-Cell (CART) for the Treatment of Relapsed and Refractory AL amyloidosis

Eyal Lebel[1,2], Nathalie Asherie[1,2*], Shlomit Kfir-Erenfeld[1,2*], Shlomo Elias, MD, PhD[1,2], Sigal Grisariu, MD[1,2*], Batia Avni, MD[1,2], Miri Assayag[1,2], Tali Dubnikov-Sharon[2], Rivka Alexander-Shani[2], Nomi Bessig[2], Alaa Shehadeh[2], Aseel Ishtay[2], Shelly Pimienta[2], Vladimir Vaistein[1,3], Eran Zimran[1,2], Marjorie Pick[1,3], Yael C. Cohen[4,5], Irit Avivi[4,5], Cyrille Cohen[6], Polina Stepensky[1,2 †], **Moshe E Gatt**[1,3 †]*

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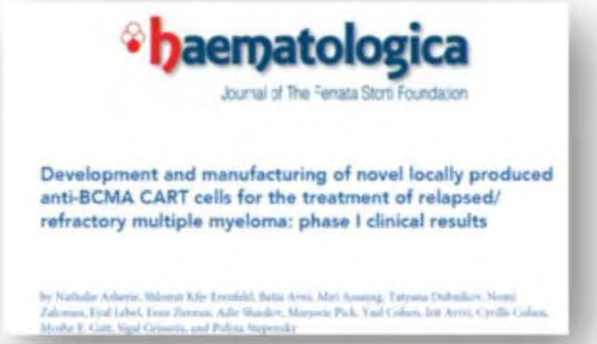
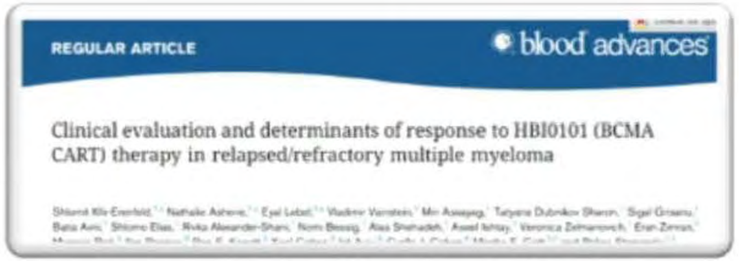
Introduction

- Treatment for R/R AL amyloidosis is an unmet need
- Anti-BCMA CART have proven safe and efficient in MM
- HBI0101 therapy is a novel anti-BCMA CART, developed at Hadassah Medical Center for MM and amyloidosis treatment


haematologica
Journal of The Ferrata Storti Foundation
Development and manufacturing of novel locally produced anti-BCMA CART cells for the treatment of relapsed/ refractory multiple myeloma: phase I clinical results

(Asherie et al. *Haematologica*. 2022 Nov).


REGULAR ARTICLE
blood advances
Clinical evaluation and determinants of response to HBI0101 (BCMA CART) therapy in relapsed/refractory multiple myeloma

(Kfir Erenfeld et al. *Blood Adv* 2024 Aug).

- In a phase Ia/Ib study (NCT04720313), HBI0101 has demonstrated manageable safety with therapeutic efficacy. [over 100 MM patients]

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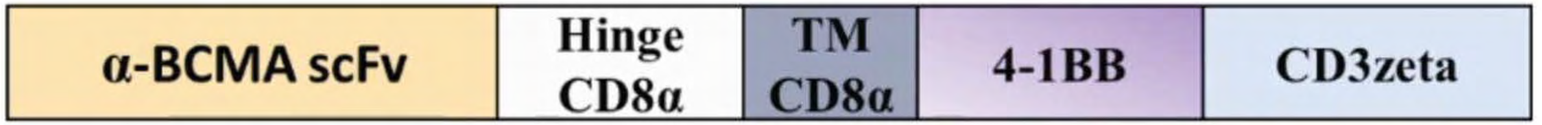
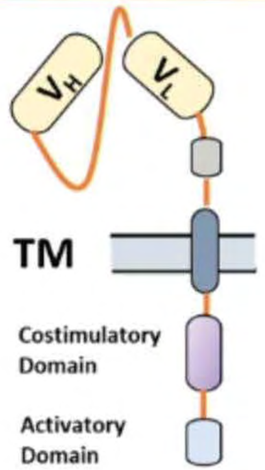
HBI0101 anti-BCMA CART





haematologica

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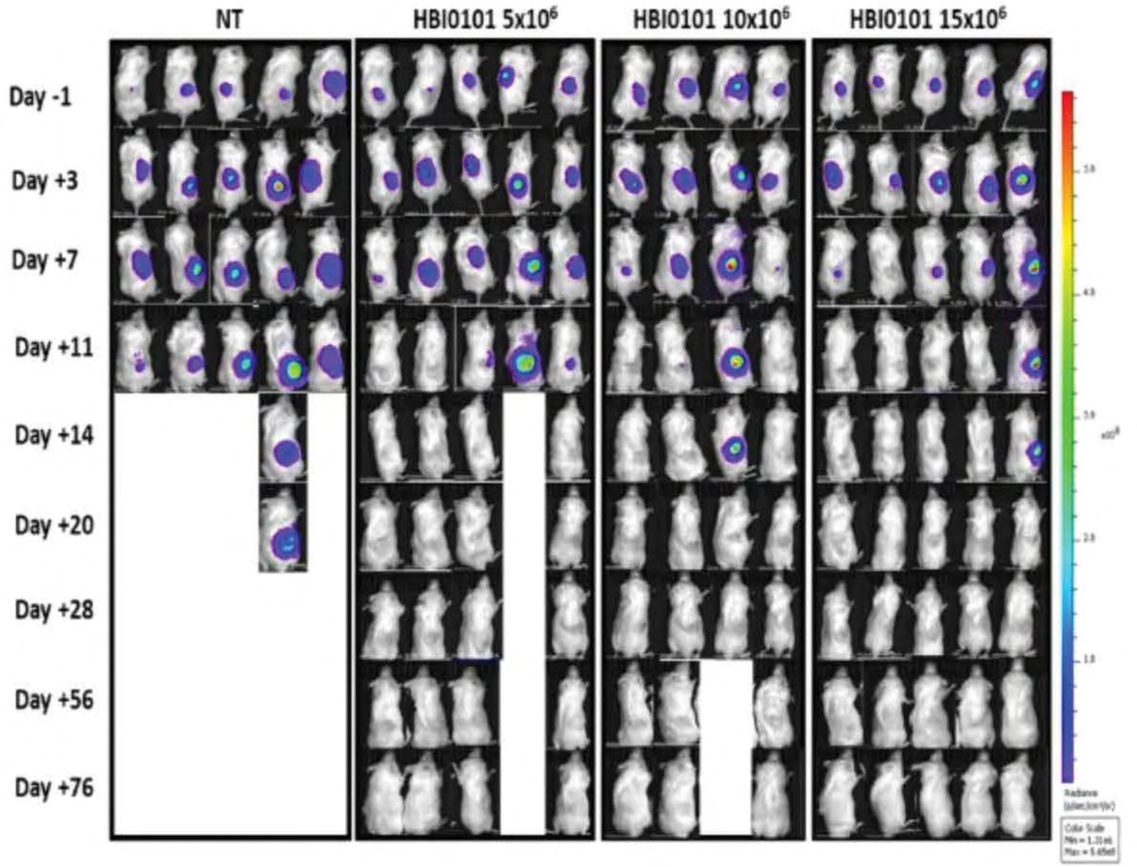
Preclinical evaluation and structural optimization of anti-BCMA CAR to target multiple myeloma

(Harush et al. *Haematologica*. 2022 Mar).



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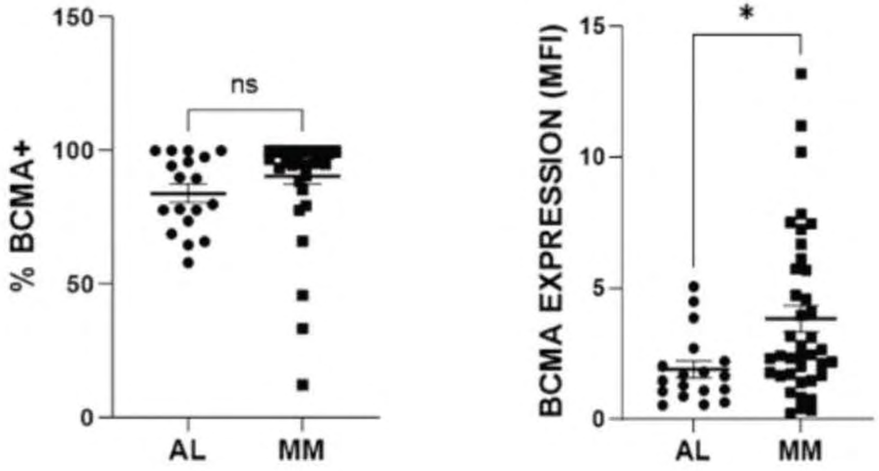
CART in AL amyloidosis

Goals:

- Deep responses are crucial in AL
- Such desired responses are observed with CART and bispecific Ab's in MM

Challenges:

- Lower BCMA expression levels are seen in AL plasma cells compared to MM plasma cells
- Frail patients-
  - Cardiac disease
  - Kidney disease
  - Multi-organ involvement



Kfir- Erenfeld et al Clin Cancer Res 2022;28:5156–66)

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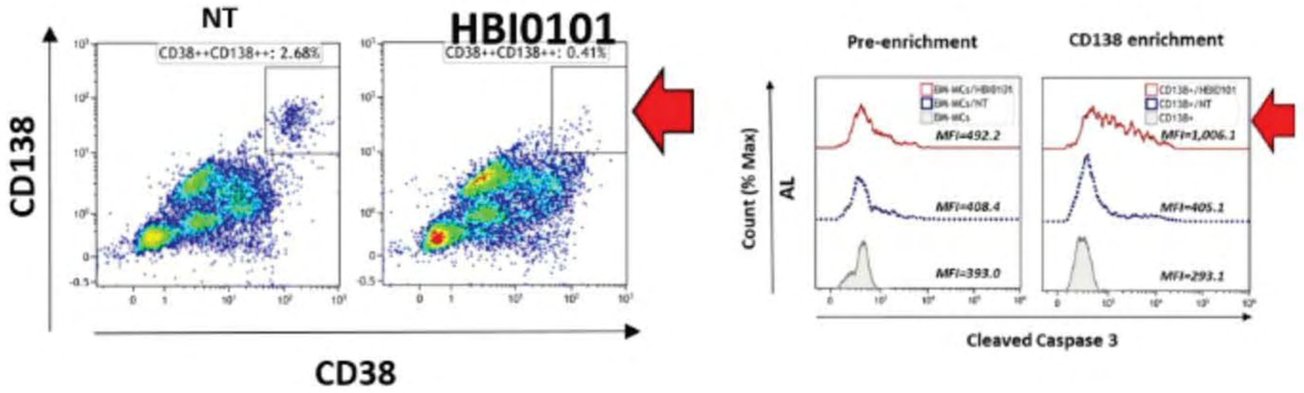
CART in AL amyloidosis



Kfir- Erenfeld et al Clin Cancer Res 2022;28:5156–66

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Feasibility of a Novel Academic BCMA-CART (HBI0101) for the Treatment of Relapsed and Refractory AL Amyloidosis

Shlomit Kfir-Erenfeld[1], Nathalie Asherie[1], Sigal Grisariu[1], Batia Avni[1], Eran Zimran[1,2], Miri Assayag[1], Tatyana Dubnikov Sharon[1], Marjorie Pick[2], Eyal Lebel[2], Adir Shaulov[2], Yael C. Cohen[3], Irit Avivi[3], Cyrille J. Cohen[4], Polina Stepensky[1], and Moshe E. Gatt[2]

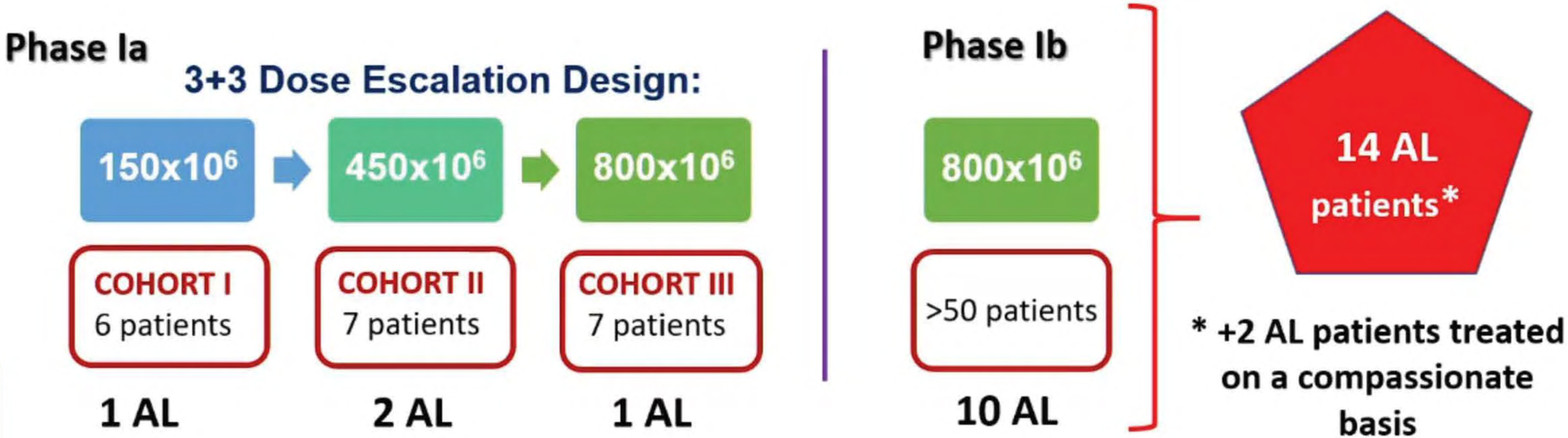
- We reported on the first 4 AL patients treated with our local BCMA.CART

The results of the phase-1 study on 16 patients with AL amyloidosis are reported here

Hadassah University Hospital

Clinical trial of HBI0101- NCT04720313

- A Phase Ia\Ib Study of HBI0101 anti-BCMA CART in R/R MM and AL amyloidosis
- Phase Ia was designed as a dose-escalation 3X3 protocol. (20 pts.)
- Phase Ib tested 800 $X10^6$ cart cells (phase 2 is ongoing)



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Clinical trial of HBI0101- NCT04720313

Inclusion criteria:

3 prior lines including PI, IMiD, anti-CD38

Compared to other studies-

very permissive organ function criteria:

- ✓ PLT ≥ 30 $x10^9/L$ **
- ✓ CRCL ≥ 20 ml/min
- ✓ EF ≥ 40%. **NO upper proBNP limit**
- ✓ ECOG-PS ≤ 2**

✓ 10 days manufacturing time*

*** Phase 1b allowed cryopreservation of CART cells and bridging therapy (Mostly for MM patients and utilized in only one AL patient)**

✓ Lymphodepletion:

- fludarabine 25mg/m^2 and cyclophosphamide 250mg/m^2 on days -5 to -3
- For patients with creatinine clearance <30ml/min: bendamustine 90mg/m^2 on days -4 and -3

Hadassah University Hospital

**** 2 compassionate treated patients:1 with MDS and 1 with ECOG PS 4**

Patients' baseline characteristics

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 (315)
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 stage,[a] n/N (%)	
I-II	10/16 (62)
III	3/16 (19)
IV	3/16 (19)
ECOG-PS, 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)

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Results: Safety

TABLE 2. Adverse Events

	Toxicity Results
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)

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

TABLE 2. Adverse Events

	Toxicity Results	
Variable	Total	Grade 3-4
Hematological toxicity, n/N		
Anemia	12/16	5/16
Thrombocytopenia	9/16	0/16
Neutropenia	12/16	10/16
Lymphopenia	16/16	16/16
Organ function toxicity, n/N		
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)	

Efficacy

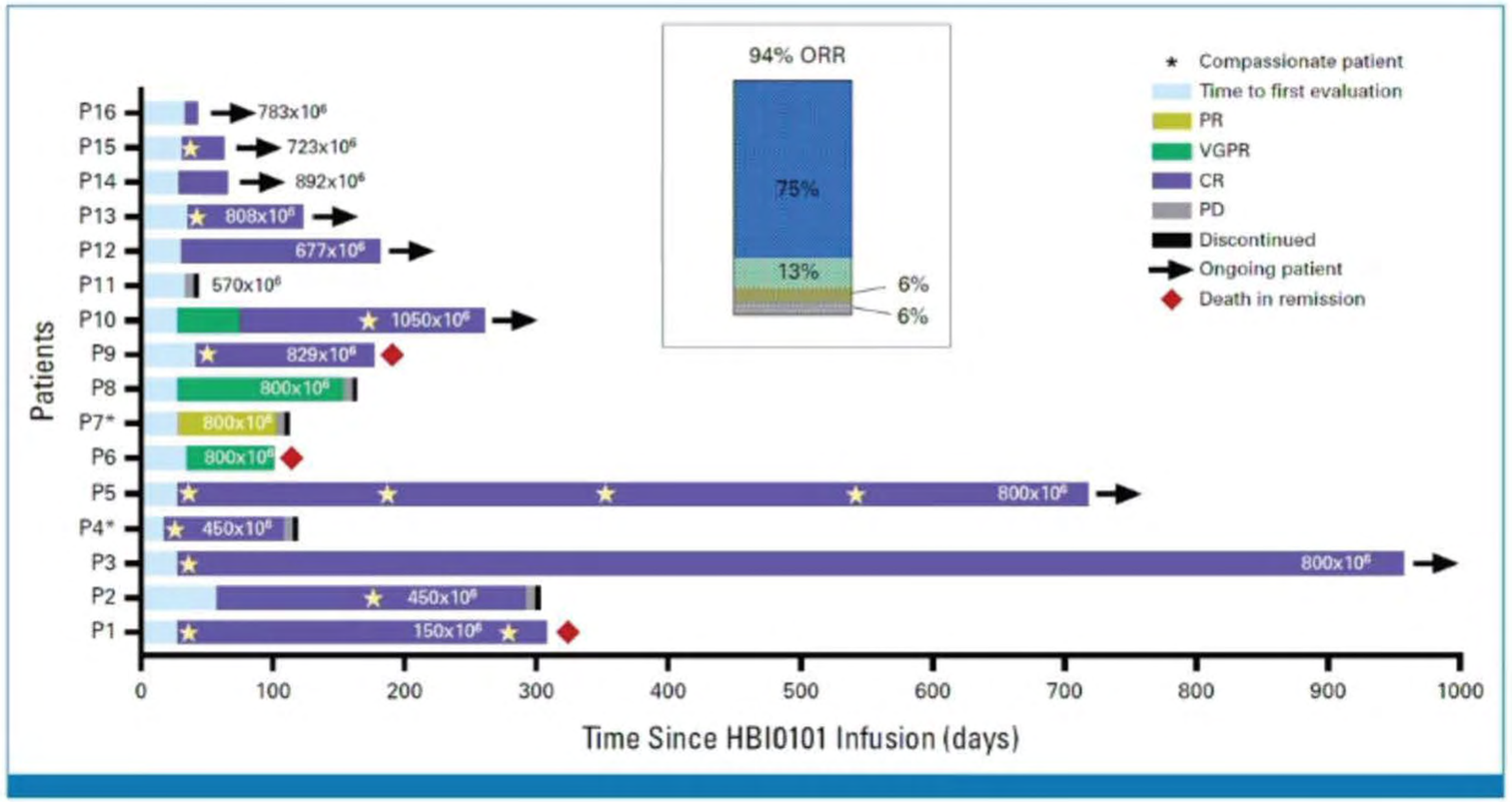
TABLE 3. Efficacy

Variable	Efficacy Results
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)

TABLE 3. Efficacy

Variable	Efficacy Results
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 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

Efficacy



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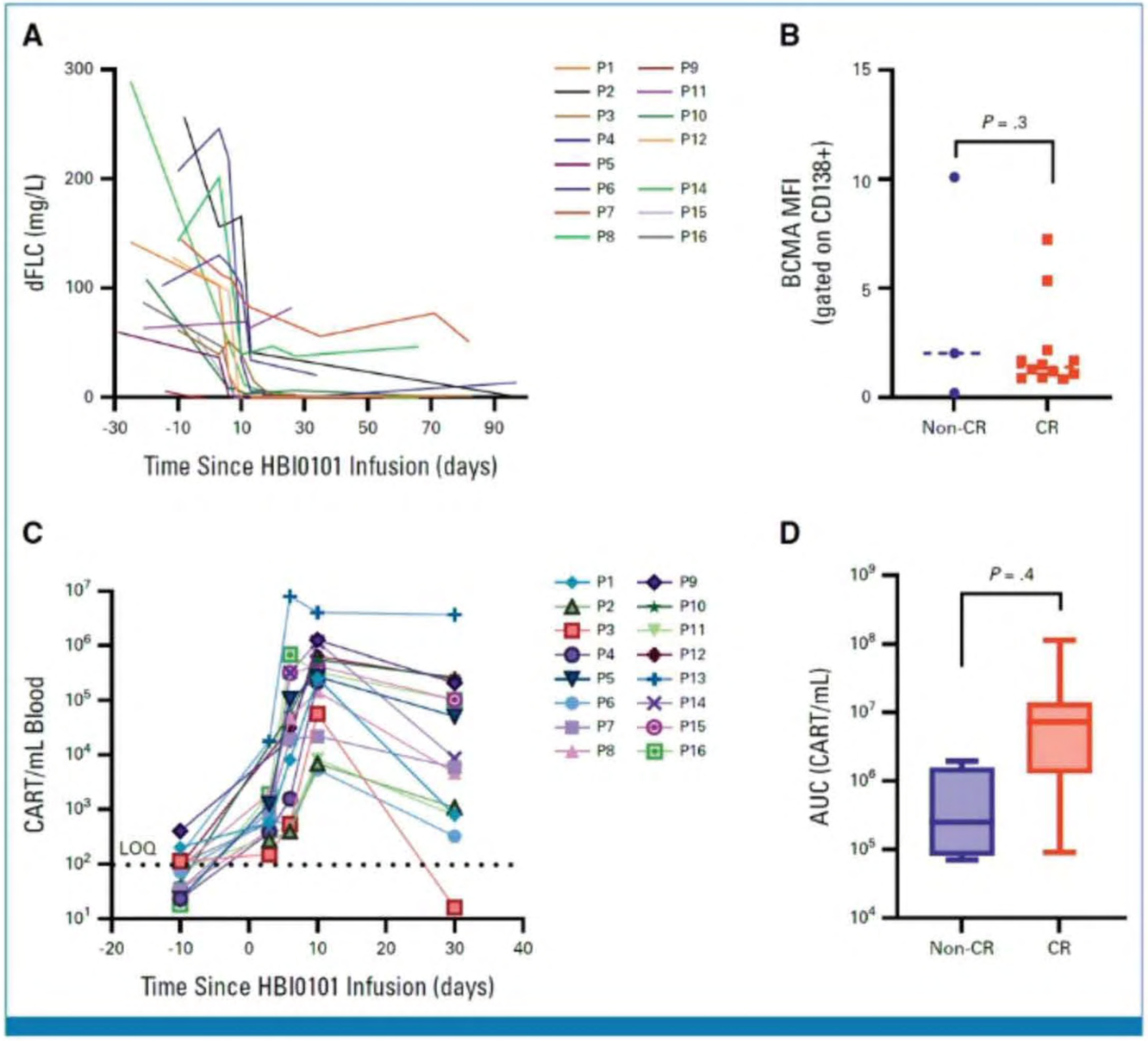
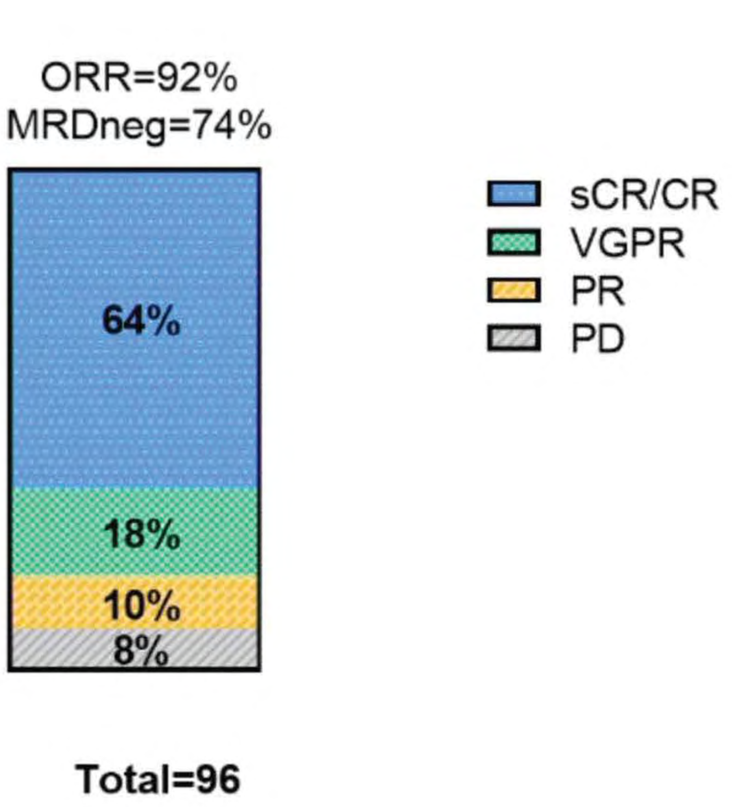
Efficacy

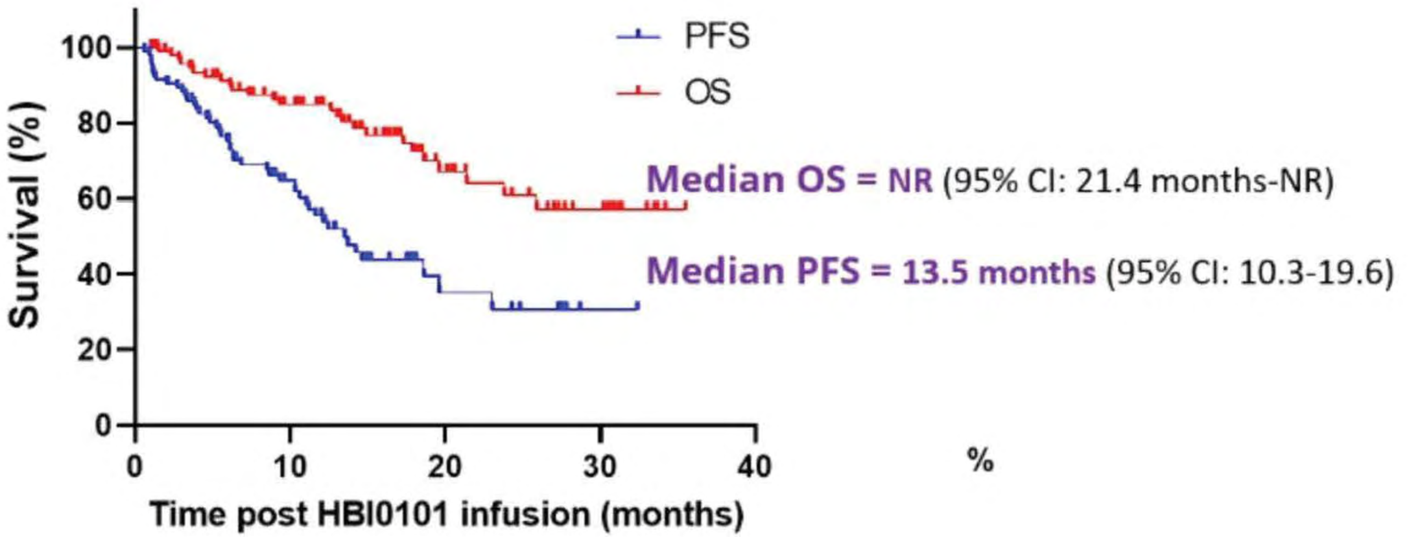

A
dFLC (mg/L)
300
200
100
0
-30
-10
10
30
50
70
90
Time Since HBI0101 Infusion (days)
P1
P2
P3
P4
P5
P6
P7
P8
P9
P11
P10
P12
P14
P15
P16
B
BCMA MFI (gated on CD138+)
15
10
5
0
P = .3
Non-CR
CR
C
CART/mL Blood
10^7
10^6
10^5
10^4
10^3
10^2
10^1
LOQ
-20
-10
0
10
20
30
40
Time Since HBI0101 Infusion (days)
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
P11
P12
P13
P14
P15
P16
D
AUC (CART/mL)
10^9
10^8
10^7
10^6
10^5
10^4
P = .4
Non-CR
CR

HBI0101 in MM- 96 pts receiving 800x10^6 CART cells

Patients:

- Median of 4 (3-13) prior lines, 85% triple-refractory, 34% penta-refractory
- 25% EMD, 38% prior anti-BCMA, 49% Not eligible for KARMMA & CARTITUDE 1





Abstract #1030 presented by Dr. Lebel
In parallel: Monday, December 9; 17:15. Marriot Marquis Pacific Ballroom Salons 24-26

Conclusions

- ✓ This trial reports the first data of anti-BCMA CART treatment in AL amyloidosis, including frail cardiac patients.
- ✓ Due to the deep and quick reduction of light chain toxicity, *organ response is observed quickly*
- ✓ Organ Deconditioning was manageable. However cardiac related death in the first year were frequent, arguing for earlier usage in the course of disease.
- ✓ The high response rates and manageable toxicity profile are promising and provide the basis for future CART trials in AL amyloidosis.

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Original Reports | Hematologic Malignancy

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

Eyal Lebel, MD*; Nathalie Askenasi, PhD; Shlomit Kfir-Erenfeld, PhD; Sigal Sviatoi, MD; Sahia Avni, MD; Shlomo Elias, MD, PhD; Miri Assayag, PhD; Tali Dubnikov Sharon, PhD; Marjorie Pick, PhD; Rivka Alexander Shani, MSc; Noam Bessaig, PhD; Shlomit Hen, MSc; Alaa Shehadeh, MSc; Aseel Ishtay, BSc; Shelly Perreta, BSc; Vladlena Vainstein, MD; Eran Zimran, MD; Yael Cohen, MD; Irit Avivi, MD; Cyrille Cohen, PhD; Polina Stepensky, MD; and Moshe E. Gatt, MD*

DOI: https://doi.org/10.1200/JCO.24.02252

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. Hillcrest 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

Accepted November 11, 2024
Published XX XX, 2024

J Clin Oncol 00:1-10

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INTRODUCTION

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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

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עמילואידוזיס ישראל (ע"ר)
Amyloidosis Israel org.

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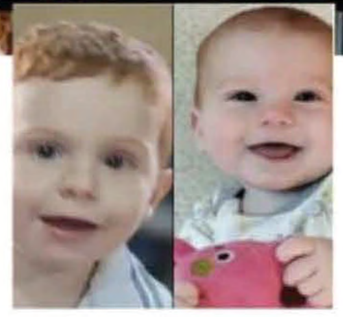
Hadassah Hebrew University Medical Center



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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).[3,4]

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

Efficacy and Safety of Anti-BCMA Chimeric Antigen Receptor T-cell (CART) for the Treatment of Relapsed and Refractory AL amyloidosis

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