Sheba's point of care CAR-T cell therapy for relapsed-refractory multiple myeloma (RRMM) - preliminary results

Hila Magen, Shalev Fried, Orit Itzhaki, Noga Shem-Tov, Ivetta Danylesko, Ronit Yerushalmi, Roni Shouval, Lee Nevo, Ronnie Shapira-Frommer, Arnon Nagler, Avichai Shimoni, Eden Shkury, and Abraham Avigdor

Sheba Medical Center

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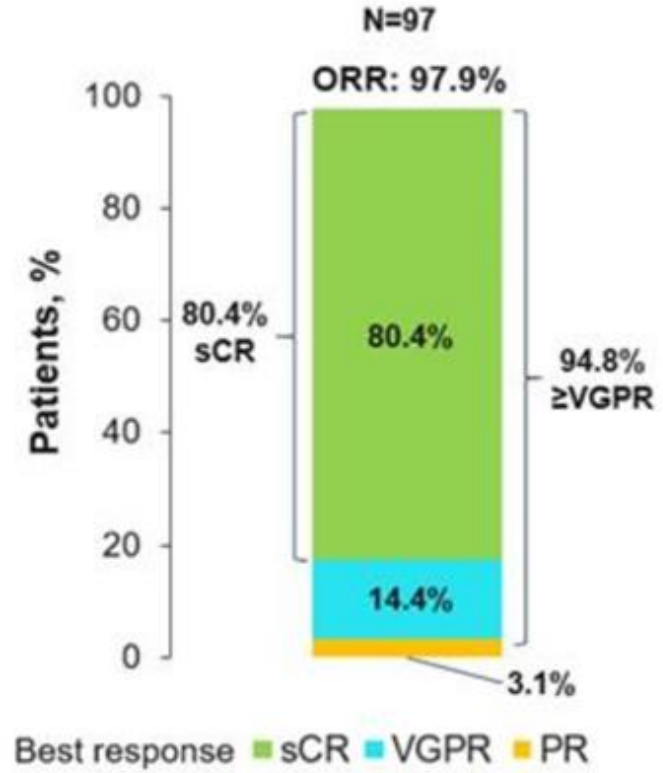
Cilta-cel achieves deep responses in RRMM

CARTITUDE 1 – phase Ib/II study

- N-97 RRMM patients (standard and high-risk) after ≥ 3 prior therapy
- After apheresis, patient received a single cilta-cel infusion (target dose 0.75×10^{6} CAR+ viable T cells/kg)
- At 27-months PFS and OS rates were 54.9% (95% CI, 44.0 to 64.6) and 70.4% (95% CI, 60.1 to 78.6), respectively



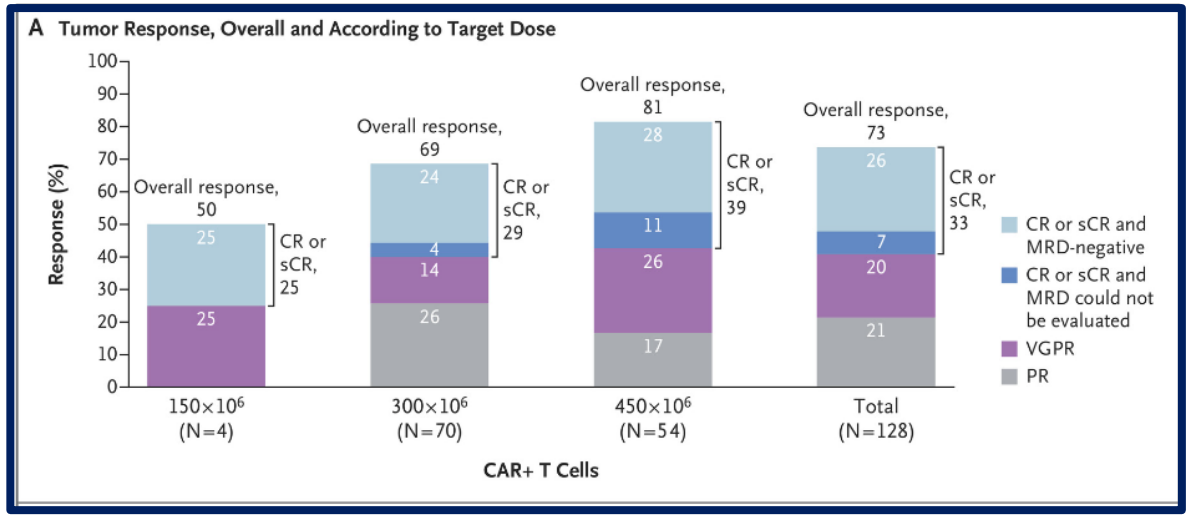
ORR - overall response rate; PR – partial response;
Scr – stringent complete response;
VGPR – very good PR

Berdeja JG et al., The Lancet, 2021

Ide-cel delivers high Response rate and PFS in RRMM

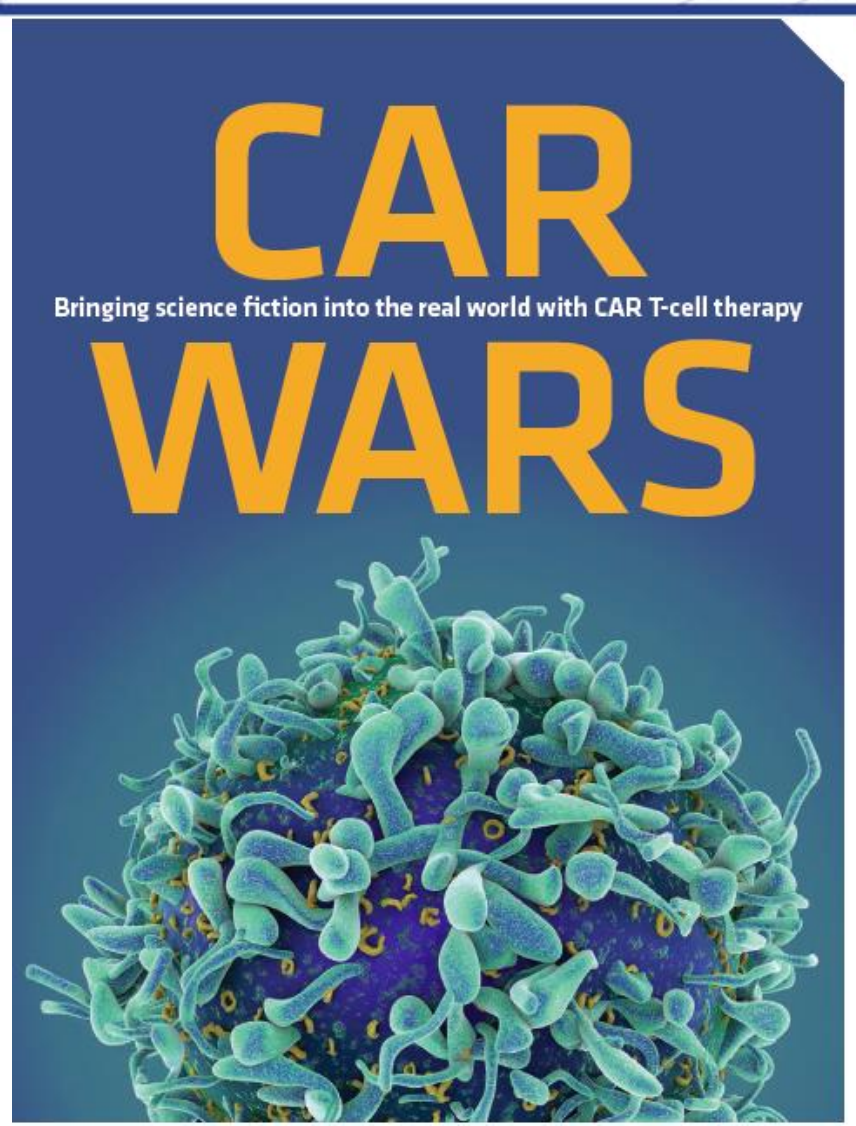
KarMMa phase 2 study

- N-128 RRMM patients after ≥ 3 prior therapy lines
- Received ide-cel target doses of 150×10^6 to 450×10^6 CAR- T cells
- At a median follow-up of 13.3 months: The median PFS was 8.8 months



Munshi NC *et al., NEJM, 2021*

Point of care autologous CAR T-cells in Sheba Medical Center



The program at Sheba:

- Single center, phase 1b/2 study of anti CD19 (since 06/2016) AND anti BCMA CAR T-cell therapy (since 11/2021)
- Utilizes in – house production of CAR T- cells (Laboratories at Ella Lemelbaum Institute for Immuno Oncology)
- Enables treatment locally

Advantages:

- Uses fresh cells
- Abrogates the need for cryopreservation and shipment of cells
- Reduces costs involved
- Any R/R lymphoid malignancies/triple refractory MM
- Very short production time (vein to vein: 10-11d)

Sheba Point-of-care[1-6] anti-CD19 CAR T-cell have comparable outcome to approved CAR T in aggressive B cell lymphomas

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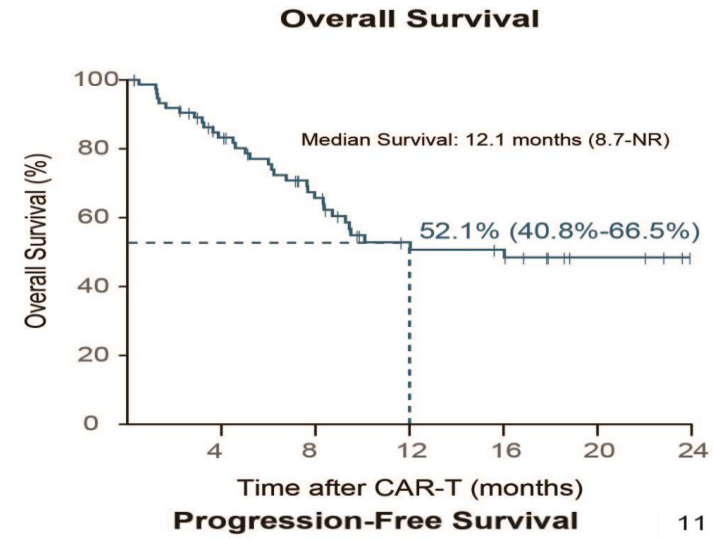
Enrollment from June 2016 until September 2022:
Total: 257 patients
Adults: 181 (started in February 2017)
Children: 76

Adult cohort	
Disease entity, n	**181**
DLBCL/HGBCL/DHL	98
PMBCL	13
Grey zone lymphoma	1
MCL	8
Burkitt	2
FL	26
CLL/PLL/other low grade other	6
B-ALL	24
AML expressing CD19	3



[1] Phase 1b/2 trial (NCT02772198). [2] Itzhaki, Orit et al. J Immunother Cancer. 2020. [3] Jacoby, Elad et al. Am J Hematol. 2018.
[4] Fried, Shalev et al. Bone Marrow Transplant. 2019. [5] Kedmi, Meirv et al. JTCT. 2022. [6] Fried, Shalev et al. L&L. 2022.

Point of care autologous anti BCMA CAR T-cells for RRMM in Sheba Medical Center

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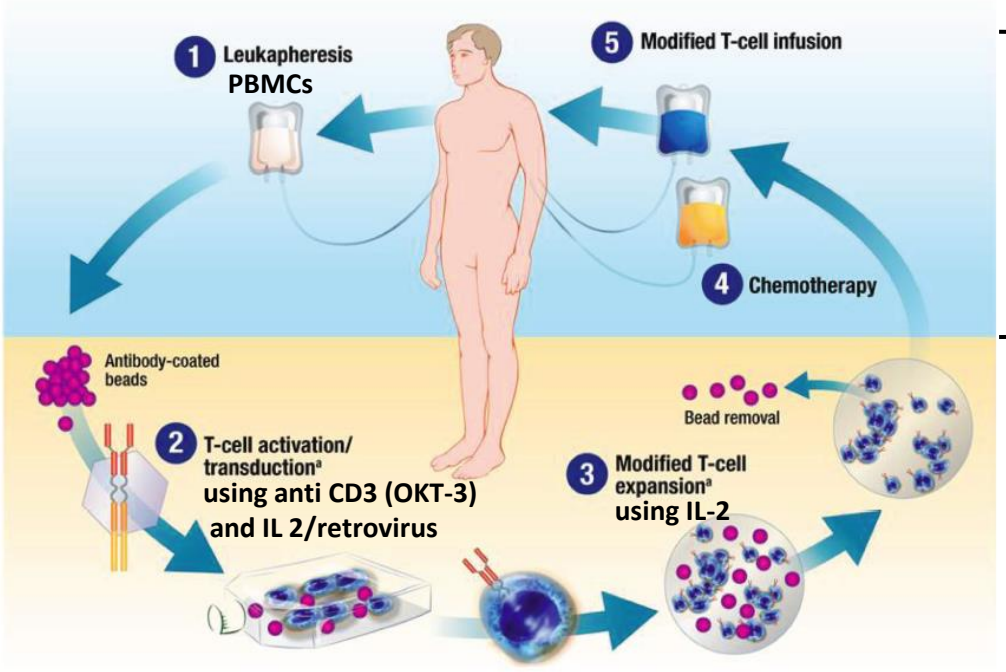
The retroviral vector construct encoding the CAR-BCMA contains the 11D5-3 anti-BCMA single chain variable fragment, CD8α hinge and transmembrane regions, the cytoplasmic portion of the CD28 costimulatory moiety, and the CD3z T-cell activation domain.



Lymphodepletion (days -4 to -2):
Flu 30 mg/m^2 X 3d
CTX 300 mg/m^2 x 3d

Target cell Dosing:
6×10^6/kg dose level I [n=3]
9×10^6/kg dose level II [n=29]
fresh transduced T-cells

Duration:
9-10 days

Eligibility and end points

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Key inclusion criteria:

- Documented diagnosis of MM according to IMWG
- Subjects must have measurable MM
- At least 3 prior treatment regimens
- Seronegative for HIV- 1, 2
- No active HBV and HCV
- ANC ≥ 500, PLT ≥ 30,000
- Systemic anti-myeloma therapy are not allowed within 2 weeks prior to the leukapheresis
- Cardiac ejection fraction ≥ 45%

Key exclusion criteria:

- Subjects with second malignancies
- Active systemic infections
- Active HBV and HCV infection which is identified by positive PCR to viral nucleotides in blood.
- Inadequate renal and hepatic function
- Subjects with CNS involvement

Primary end-points: safety and ORRs 28 days after CAR - T cells infusion

Secondary end-points: OS and PFS

Patient and myeloma characteristics

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Enrollment from November 2021
Data cut-off February 2023

	n=32
Median age (IQR) – years	60 (54, 67)
Gender, male	13 (41%)
KPS < 90%	21 (66%)
High-risk cytogenetics at enrollment	10 (34%)
Double hit myeloma at enrollment	7 (22%)
Extramedullary involvement at enrollment	17 (57%)
> 3 prior treatment lines	20 (62%)

	n=32
IMiD-agent refractory	32 (100%)
Proteasome inhibitor refractory	32 (100%)
Daratumumab refractory	31 (97%)
Exposure to belantamab-mafodotin	5 (16%)
Exposure to talqeutamab	2 (6.2%)
Previous therapy refractoriness	
Double-refractory	1 (3%)
Triple-refractory	1 (3%)
Quad-refractory	11 (34%)
Penta-refractory	19 (59%)

Only 17 (53%) and 2 (16%) patients were eligible to enroll in the KarMMa and CARTITUDE-1 studies, respectively

Safety

Characteristic	N = 32
Maximal CRS grade:	
0	6 (19%)
1	21 (66%)
2	4 (12%)
3	1 (3.1%)
Tocilizumab administration	4 (12%)
CRS duration (IQR)	4.5 (1.5, 6.0)
ICANS	0

Characteristic	N = 32
Grade 3-4 neutropenia	31 (97%)
Neutropenia beyond day 60	3 (9%)
Grade 3-4 thrombocytopenia	16 (50%)
Thrombocytopenia beyond day 60	11 (34%)
Anemia requiring PRBC	14 (44%)
Anemia beyond day 60	12 (38%)

No grade 4 adverse events nor cellular therapy-related deaths were observed

Production results and response

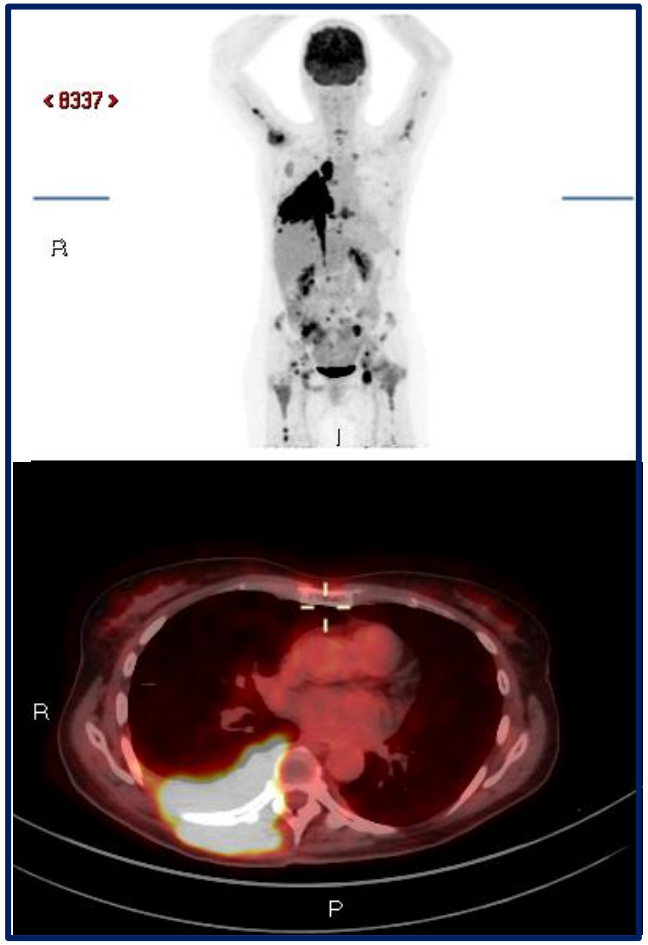
- Production feasibility- 100%
- Median (IQR) vein-to-vein production time: 11 days (10-11)
- Only 2 patients received bridging chemotherapy
- Best Overall response (PR at least) - 59%
- Best Overall response (VGPR at least) - 40%
- Median time to first response - 31 days (95% CI: 26-33)

Best response	N = 32
sCR	5 (16%)
CR	4 (12%)
nCR	2 (6.2%)
VGPR	2 (6.2%)
PR	6 (19%)
MR	1 (3.1%)
SD	11 (34%)
PD	1 (3.1%)

M.S.– 54 year old woman, double gain 1q, and hyperdiploidity, post 3 lines of therapy: PET-CT and BM

BMB
Normocellular bone marrow showing a monoclonal plasma cell infiltrate kappa light chain predominant, comprising approximately 40-50% of the bone marrow cell population.
The features are compatible with a residual/relapsing BCL-1 positive plasma cell myeloma

Before CAR T



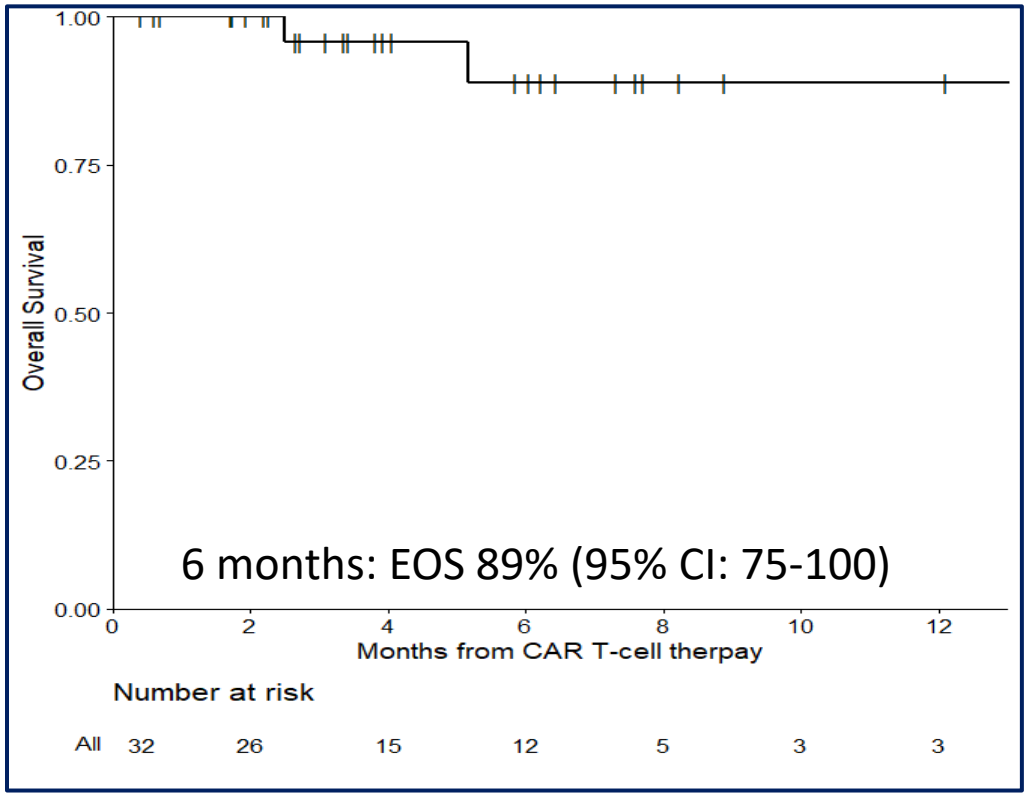
After CAR T (day +150)

BMB (day +126)
Normocellular bone marrow, showing a polyclonal plasma cell infiltrate comprising approximately 1-3% of the bone marrow cell population.
The morphologic findings are consistent with remission

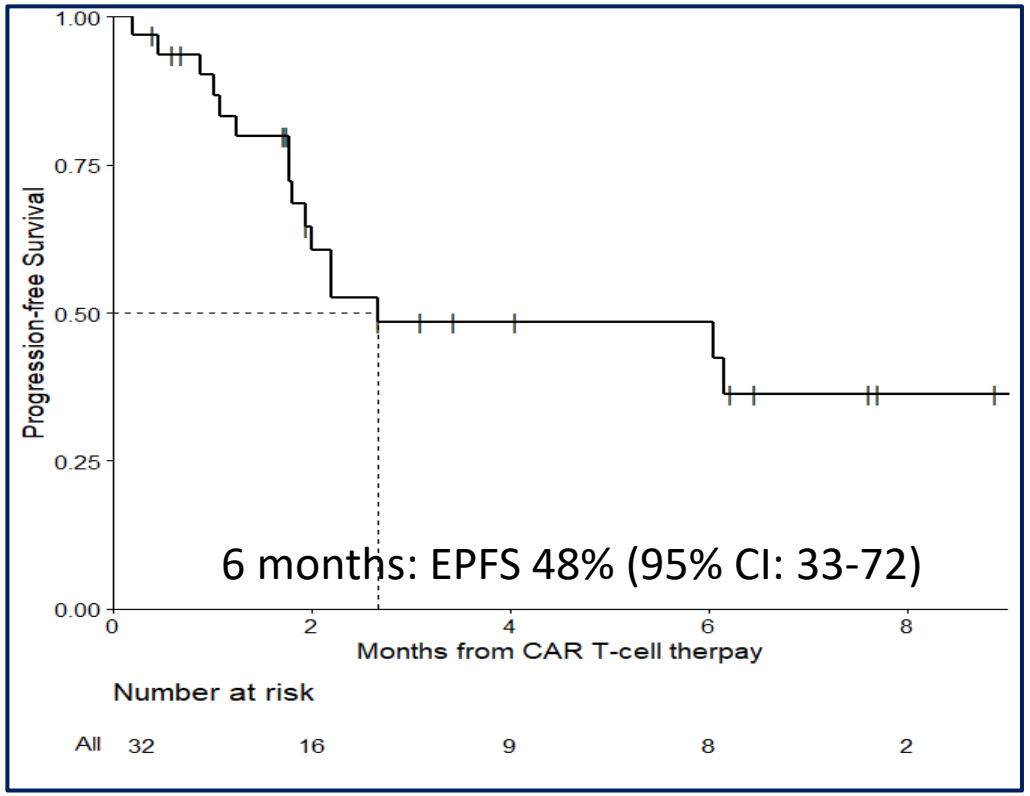
Survival outcomes

- The median follow-up was 3.9 months (IQR 2.6-7.3)

Overall survival



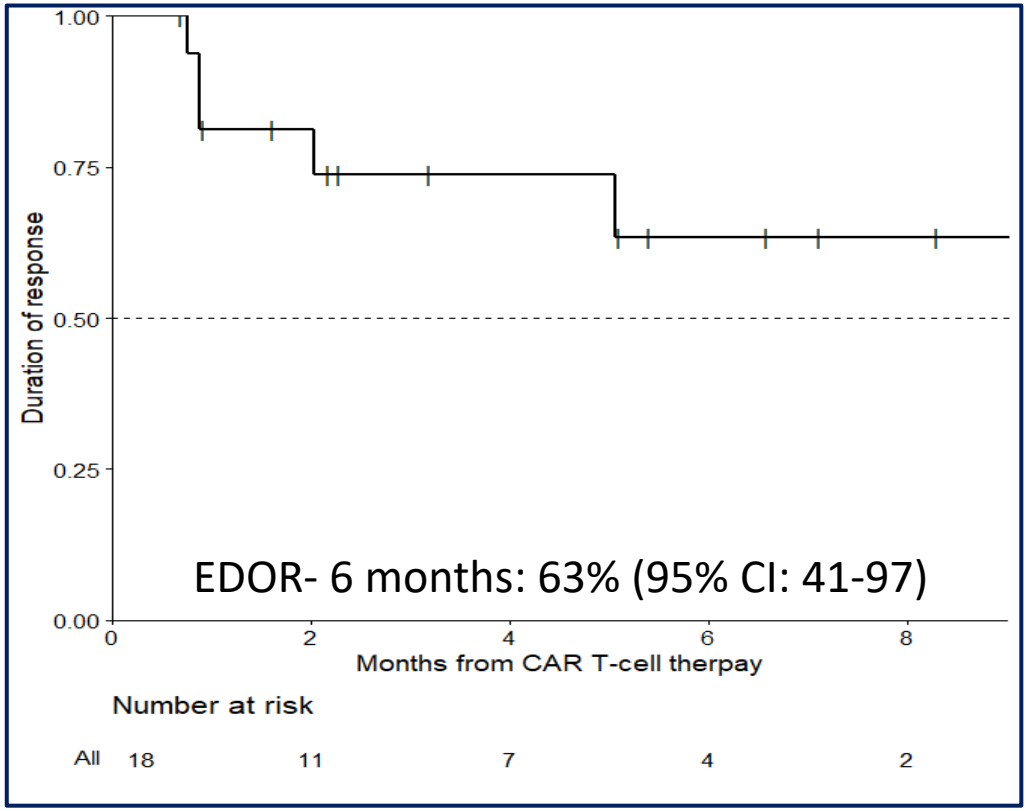
Progression-free survival



Survival outcomes (cont.)

- The median follow-up was 3.9 months (IQR 2.6-7.3)

Duration of response



Patients with prior exposure to BCMA-targeted therapies had an inferior 6 months PFS

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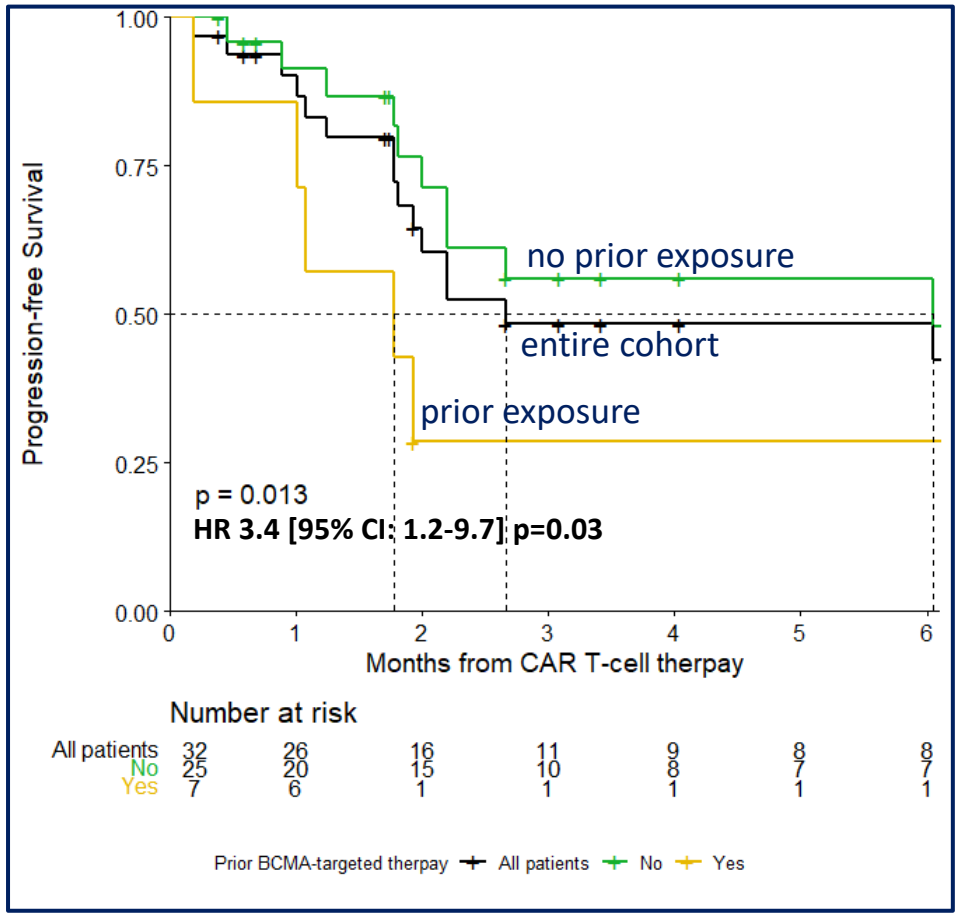
PFS according to prior exposure to BCMA-targeted therapies



Patients exposed to prior BCMA-targeted therapies:

Total - 7

ADC - 5

BsAb - 2

Conclusions

- Point of care anti-BCMA CAR T-cells induced high response rates with a good safety profile in RRMM
- Most patients in the current cohort were not eligible for enrollment in the pivotal trials of the approved anti BCMA CAR-Ts (ide-cel and cilta-cel)
- The rapid CAR-T production time obviated the need for bridging therapy in most patients
- Prior exposure to BCMA-targeted therapies is associated with dismal PFS, hence those therapies should be carefully considered when CAR T-cell therapy might be intended
- Enrollment is ongoing

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