OUTCOMES OF MULTIPLE MYELOMA PATIENTS PROGRESSING AFTER BCMA-TARGETED CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

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INTRODUCTION

BCMA-directed CAR T has demonstrated remarkable efficacy in patients with relapsed/refractory multiple myeloma (RRMM). There are now 2 FDA-approved CAR T products in triple-class-exposed RRMM. Despite high response rates, relapses are common.

The **outcomes of patients with disease recurrence after BCMA-directed CAR T** has not been comprehensively studied. Understanding the natural course of patients with post-CAR T progression will enable a better navigation of treatment options for these patients.

METHODS

We analyzed **salvage treatments and outcome of 79 patients with RRMM from 2 academic institutions who had progression of disease after treatment with BCMA-directed CAR T** on a phase 1/2 clinical trial (**Figure 1**). Timepoint at which patients had PD to BCMA-directed CAR T was defined as T0. If reinfusion was attempted as part of study protocol (N=13), T0 was defined as time of PD after attempted reinfusion.

We retrospectively collected **demographics, baseline disease characteristics, pre- and post-CAR T treatment regimens, responses to post-CAR T salvage therapy, and clinical outcomes**.

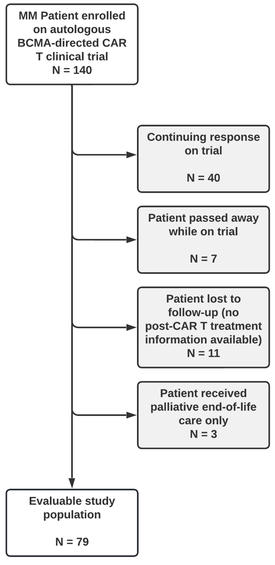
RESULTS

- Demographics, disease characteristics, cytogenetics and prior treatments are highlighted in **Table 1**.
- At a median follow-up time of 22.8 months, the **median OS from T0 for the cohort was 17.9 months** (95% C.I. 14.0-NE) (**Figure 2**).
- Median OS according to treatment refractoriness and characteristics is shown in **Figure 3**.
- The 79 patients received a median of 2 salvage treatment lines (range 1-10). **Median PFS for the first attempted salvage therapy was 3.5 months**.
- Characteristics of the first-line salvage are summarized in **Table 2**. **ORR for first regimen was 43.4%.**
- **Salvage with T cell-engaging therapies or transplant** is feasible and can lead to durable responses (**Figure 4**).

RESULTS

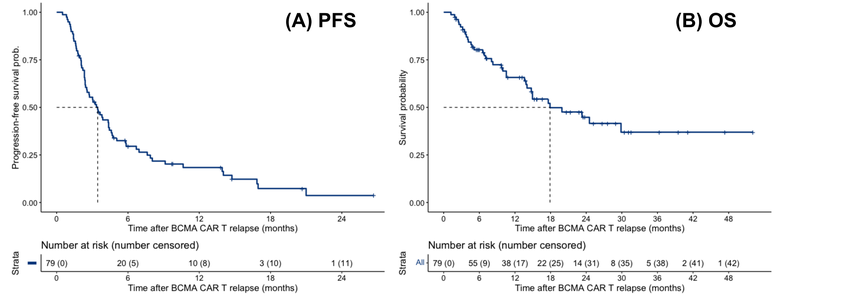
	Salvage therapy N = 79	
Demographics:		
Age (y)	60	(35-78)
Male gender	47	59.5%
Disease characteristics:		
IgG	41	51.9%
IgA	16	20.3%
Light chain disease only	22	27.8%
Cytogenetics:		
Hyperdiploidy	43	54.4%
t(11;14)	14	17.7%
t(4;14)	4	5.1%
t(14;16)	5	6.3%
del17p	12	15.2%
1q gain	55	69.6%
All high risk	64	81.0%
Time since diagnosis (mo)	74	(22-282)
Number of treatment lines prior to CAR T	5	(1-18)
Prior treatment exposure:		
Auto-SCT	75	94.9%
Lenalidomide	79	100.0%
Pomalidomide	67	84.8%
Bortezomib	75	94.9%
Carfilzomib	70	88.6%
CD38 mAb	76	96.2%
Elotuzumab	23	29.1%
Alkylating agent*	77	97.5%
Combination chemotherapy**	28	35.4%
Venetoclax	13	16.5%
Selinexor	11	13.9%
Belantamab	0	0.0%
Non-BCMA CAR T	1	1.3%
BCMA-directed bispecific Ab	0	0.0%
Non-BCMA-directed bispecific Ab	5	6.3%
Prior treatment refractoriness:		
Lenalidomide	68	86.1%
Pomalidomide	60	75.9%
Bortezomib	50	63.3%
Carfilzomib	62	78.5%
CD38 mAb	71	89.9%
Triple-class refractory* **	66	83.5%
Penta-drug refractory** **	30	38.0%

* Any treatment with intravenous or oral alkylating agents (incl. melphalan, cyclophosphamide, bendamustine, carmustine, cisplatin).
** Treatment with DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) or PACE (cisplatin, doxorubicin, cyclophosphamide, etoposide).
*** Defined as refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 monoclonal antibody.
**** Defined as refractory to ≥2 immunomodulatory drugs, ≥2 proteasome inhibitors and anti-CD38 monoclonal antibody therapy.
Abbreviations: y, years; Ig, immunoglobulin; mo, months; CAR T, chimeric antigen receptor T cell; Auto-SCT, autologous stem cell transplant; mAb, monoclonal antibody; DCEP, dexamethasone-cyclophosphamide-etoposide-cisplatin; PACE, cisplatin-doxorubicin-cyclophosphamide-etoposide; BCMA, B-cell maturation antigen; Ab, antibody.



↑ ***Figure 1:*** *Consort diagram highlighting the patient cohort included in the analysis.*

← ***Table 1:*** *Clinical and disease characteristics of the study cohort included in the analysis.*

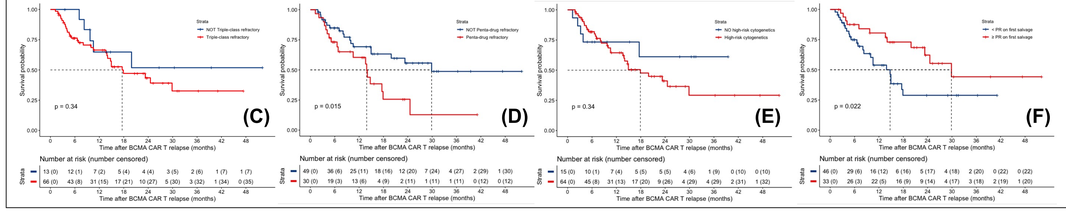


↑ ***Figure 2:*** *Kaplan-Meier curves showing progression-free survival (PFS) of the first salvage therapy (left, A) and overall survival (OS) probability of the cohort after CAR T relapse (right, B).*

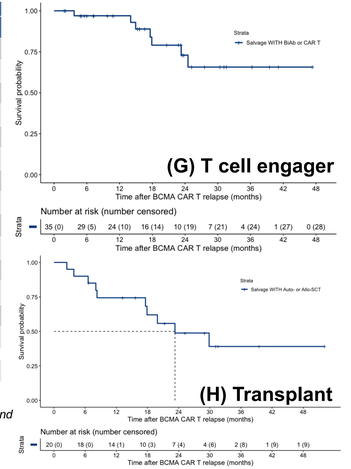
	First line of salvage treatment				All lines of salvage treatment			
Treatment group	**N**	**[%]**	**N ≥ PR**	**ORR**	**N**	**[%]**	**N ≥ PR**	**ORR**
Allogeneic stem cell transplant	0	0.0%	0/0	N/A	7	3.0%	4/4	100.0%
Autologous stem cell transplant	3	3.8%	1/3	33.3%	14	5.9%	10/14	71.4%
BCMA ADC	1	1.3%	0/1	0.0%	9	3.8%	1/8	12.5%
Bispecific trial	11	13.9%	7/10	70.0%	32	13.5%	17/29	58.6%
BCMA-directed bispecific trial	2	2.5%	1/2	50.0%	9	3.8%	4/9	44.4%
Non-BCMA-directed bispecific trial	9	11.4%	6/8	75.0%	23	9.7%	13/20	65.0%
CAR T trial	2	2.5%	2/2	100.0%	6	2.5%	5/6	83.3%
Chemotherapy with or without stem cell support	20	25.3%	11/19	57.9%	53	22.4%	29/51	56.9%
Doublet/triplet/quadruplet combination of approved agents	23	29.1%	7/22	31.8%	56	23.6%	15/53	28.3%
Selinexor-based therapy	5	6.3%	2/5	40.0%	15	6.3%	3/14	21.4%
Venetoclax-based therapy	3	3.8%	2/3	66.7%	14	5.9%	5/14	35.7%
Other combinations (incl. MAPKi, checkpoint inhibitor or other trial)	11	13.9%	1/11	9.1%	31	13.1%	12/31	38.7%
	79	100.0%	33/76	43.4%	237	100.0%	101/224	45.1%
	Total N = 79		Total N = 76		Total N = 237		Total N = 224	

Abbreviations: BCMA, B-cell maturation antigen; ADC, antibody-drug conjugate; MAPKi, mitogen-activated protein kinase inhibitor; PR, partial response; ORR, objective response rate; N/A, not applicable.

↑ ***Table 2:*** *Characteristics and response rate of first and subsequent salvage treatments.*



← ***Figure 3:*** *Overall survival after BCMA-directed CAR T relapse stratified by disease or treatment characteristics: triple-class refractoriness (C), penta-drug refractoriness (D), high-risk cytogenetics (E), and response to first salvage (F).*



↑ ***Figure 4:*** *Overall survival in subgroup of patients who received T cell engager (G) or transplant (H) therapy at any point after relapse.*

CONCLUSIONS

Patients with MM who progress after BCMA-directed CAR T can be salvaged with additional therapies, including on clinical trials.

In the absence of a standard of care approach, a wide range of management strategies were utilized. At median follow-up of almost 2 years, the 79 patients in our cohort received a median of 2 lines of salvage. For the first attempted salvage therapy, the **ORR** was **43.4%** and **PFS** was **3.5 months**.

Multiple lines of salvage contribute to an **OS** of **17.9 months**, comparing favorably with earlier reports in triple-class refractory patients, reflecting the ongoing development of effective treatment options.

Use of **subsequent T cell-engaging therapies** (CAR T or bispecific antibodies), targeting BCMA or alternative antigens, as salvage was associated with a median OS that was not reached after a median follow-up of 23 months, although patient selection plays a role as these patients were all enrolled in clinical trials.

Responses were noted with both autologous and allogeneic stem cell transplants. Patients that were able to receive a transplant had a median OS of about 20 months.

Our data serves as a benchmark for future prospective studies in this challenging patient population. Further biologic insights into the mechanisms of CAR T failure and relapse are required to help guide the optimal sequencing of therapies.

ACKNOWLEDGEMENTS

We thank the clinical staff and research coordinators at the Multiple Myeloma Center of Excellence at Mount Sinai Hospital and at Memorial Sloan Kettering Cancer Center for their support. We thank all patients for their invaluable contribution to this work.

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