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Survival Analysis of Selinexor-Exposed Relapsed/Refractory Multiple Myeloma (RRMM) Treated with Chimeric Antigen Receptor T-Cell (CAR-T) Therapy: A Real-World Exploratory Analysis

Danai Dima[1], Adriana Rossi[2], Bruno Costa[2], Tomer Mark[3], Stephen Ijioma[3], David Ray[3], George Dranitsaris[4], Norah Sadek[2], Jack Khouri[1]

[1]Cleveland Clinic Foundation, Cleveland, OH, USA, [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Karyopharm Therapeutics, Newton, MA, USA, [4]Department of Public Health, Syracuse University, Syracuse, NY, USA

Introduction

- T-cell exhaustion is a physiologic phenomenon where cytotoxic T-cells no longer effectively respond to tumor antigens, and has been associated with lower response to T-cell engaging therapies, such as Chimeric Antigen Receptor T-cell (CAR-T) therapy.[1]
- There are several factors contributing to T-cell exhaustion, such as high tumor burden, comorbidities that cause sustained immune system activation and inflammation, poor nutrition, and prior MM therapies, such as alkylators and proteasome inhibitors.[2,3,4]
- Preclinical evidence suggests selinexor, an XPO1 inhibitor, may increase the CD8 T-cell population and functional secretion of granzyme B without induction of T cell inhibitory markers (e.g., LAG, TIM3, etc.).[5]
- In this exploratory study, we investigate whether treatment with a selinexor regimen prior to CAR-T therapy impacts clinical and safety outcomes in patients with RRMM.

Methods

- The medical records of 45 patients who received a selinexor-containing regimen prior to BCMA-directed CAR-T therapy at two academic cancer centers were reviewed.
- From the CAR-T infusion date until last follow-up, data on hematological parameters, adverse events, response rates, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were collected.
- Selinexor-related data collection included line of therapy, concomitant drug administration, starting dose, duration of therapy, PFS, whether selinexor was part of a bridging regimen and time from the last dose to the administration of CAR-T.
- Given the exploratory nature of the study, there was no formal sample size calculation. The outcomes of the investigation should be viewed as estimation and hypothesis generating.
- Data on patient and disease characteristics were presented descriptively as medians, means, proportions along with measures of variability such as 95%CI and the interquartile range (IQR). Survival curves for PFS and OS were generated by the Kaplan-Meier estimator method, using a censoring date of December 1, 2023.
- Multivariate Cox proportional hazards regression was then used in an exploratory evaluation to identify factors prior to CAR-T cell therapy that were associated with PFS and OS.
- The final variables for model inclusion were identified using a backwards elimination process using the Likelihood ratio test.
- The intent of these exploratory analyses was to identify the best fitting model in terms of factors associated with PFS and OS following CAR-T therapy.

Limitations

- The patient sample was limited to two academic centers in the United States limiting the generalizability of the findings.
- Risk of bias secondary to the impact of unmeasured confounding variables among subgroups.
- Risk of selection bias because patients may have selinexor prior to CAR-T for various reasons not related to drug efficacy or safety.
- There were no adjustments for multiple comparisons. Hence, there is a risk of a Type II error.

Results

- Patients had a median age of 64 years prior to the CAR-T and had been living with MM for approximately 10 years (Table 1).
- The median number of lines of therapy for selinexor use was the seven (range 4-15) (Table 2).
- The median duration of selinexor-based therapy was 2.7 months and the median time from the last dose of selinexor to the CAR-T administration was 3.9 months. Approximately 44.4% of patients received selinexor immediately before CAR-T and 24.4% as part of bridging therapy (Table 2).
- The median number of lines of therapy for CAR-T was nine (range 6-15). A total of 31 of 45 patients (68.9%) received bridging therapy for a median of 21 days (IQR: 4-43).

Outcomes following CAR-T

- The median PFS and OS for patients following CAR T therapy was 8.0 months (IQR: 3.1-39.5) and NR (IQR: 14.2-NR months), respectively (Figure 1 and 2). The median OS for the subgroup analysis of patients treated with selinexor in line immediately prior to CAR-T vs those who were not was 11.2 months (11.2-NR) and NR (13-NR months), respectively (Figure 3).
- The first endpoint evaluated was PFS following CAR-T therapy, the multivariate analysis identified five factors that were associated with PFS. These were use of a selinexor-based regimen in the line prior to CAR-T, patient performance status, presence of extramedullary disease (EMD), gender, and time from the last dose of selinexor to CAR-T infusion (Table 3).
- The second endpoint evaluated was OS following CAR-T therapy. There were four variables retained in the model and these consisted of using a selinexor-based regimen in the line prior to CAR-T, patient age ≥ 60 years, albumin level prior to CAR-T and time from the last dose of selinexor to CAR-T infusion (Table 4).

Table 1. Demographic and clinical characteristics of patients prior to the start of CAR-T therapy

Parameter	Overall (n=45)
Median age at MM diagnosis (range) Median age at the start of CAR-T (range)	54 (37 – 75) 64 (50-78)
Female sex	55.6% (25)
Race	
White	75.6% (34)
Black	17.8% (8)
Other	6.7% (3)
ISS prior to CAR-T	
Stage I	31.1% (14)
Stage II	48.9% (22)
Stage III	11.1% (5)
Not documented	8.9% (4)
ECOG Performance Status	
0 or 1	88.9% (40)
Cytogenetics	
t(4;14)	11.1% (5)
t(14;16)	4.4% (2)
del(17p)	15.6% (7)
gain/amp[1q21]	55.6% (25)
High-risk cytogenetic abnormalities*	40% (18)

Abbreviations: MM, multiple myeloma; ECOG, Eastern Cooperative Oncology Group; ISS, international staging system. *Presence of del(17p), t(4;14) and/or t(14;16).

Table 2. Characteristics of selinexor therapy prior to CAR-T therapy

Parameter	Overall (n=45)
Line of therapy (median, IQR)	7 (4 to 15)
Median duration of therapy in months (IQR) PFS with selinexor in months (IQR)	2.7 (0.7 to 11.3) 2.3 (1 to 13.3)
Median time from last dose of selinexor to CAR-T (mon) Selinexor part of bridging regimen before CAR-T Selinexor part of the LOT given immediately before CAR-T	3.9 (0.7 to 22) 24.4% (11) 44.4% (20)

Abbreviations: IQR, interquartile range; PFS, progression-free survival; LOT, line of therapy. Selinexor as a bridging regimen and part of the LOT given immediately before CAR-T were not mutually exclusive groups.

Table 3. Exploratory multivariate Cox regression analysis on PFS following CAR-T

Variable*	Hazard Ratio†	(95%CI)	Impact on risk of progression
Selinexor used in line prior to CAR-T	0.40	(0.14-1.09)	↓ by 60%
ECOG PS: ≥ 1 vs. 0	2.30	(0.88-6.10)	↑ 2.3 times
EMD present prior to CAR-T therapy	3.54	(1.26-9.92)	↑ 3.5 times
Male gender	0.46	(0.19-1.12)	↓ by 54%
Time from the last dose of selinexor to CAR-T (mon)	0.94	(0.89-1.00)	↓ by 6% for each additional month

Abbreviations: PFS = progression free survival, EMD = extramedullary disease, ECOG PS = Eastern Cooperative Oncology Group performance status.
*The intent of this exploratory analysis was to identify the best fitting model in terms of factors associated with PFS following CAR-T therapy. The intent was not statistically significant, as the sample size was limited.
†An HR of less than one indicates a lower risk and greater than one an increased risk of disease progression.

Table 4. Exploratory multivariate Cox regression analysis on OS following CAR-T

Variable*	Hazard Ratio†	(95%CI)	Impact on risk of death
Selinexor used in line prior to CAR-T	0.08	(0.02-0.46)	↓ by 92%
Age ≥ 60 years	3.83	(0.94-15.5)	↑ 3.8 times
Albumin level (g/dL) prior to CAR-T	0.16	(0.04-0.62)	↓ risk with higher levels
Time from the last dose of selinexor to CAR-T (mon)	0.86	(0.74-0.98)	↓ by 14% for each additional month

*The intent of this exploratory analysis was to identify the best fitting model in terms of factors associated with PFS following CAR-T therapy. The intent was not statistically significant, as the sample size was limited. †An HR of less than one indicates a lower risk and greater than one an increased risk of death.

Figure 1. Progression-Free Survival

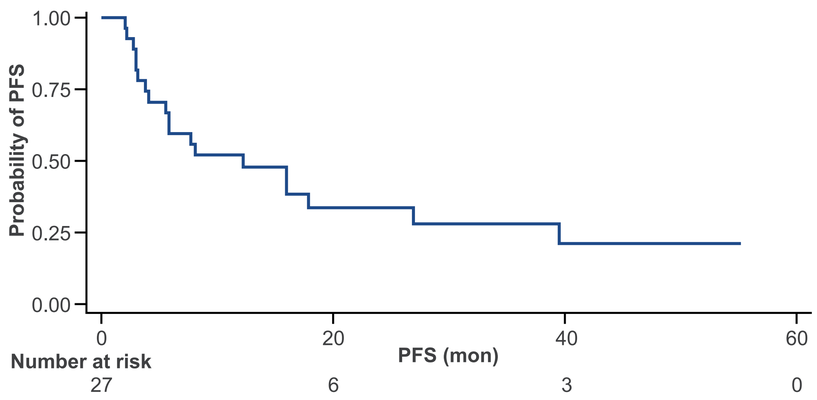


Figure 2. Overall survival

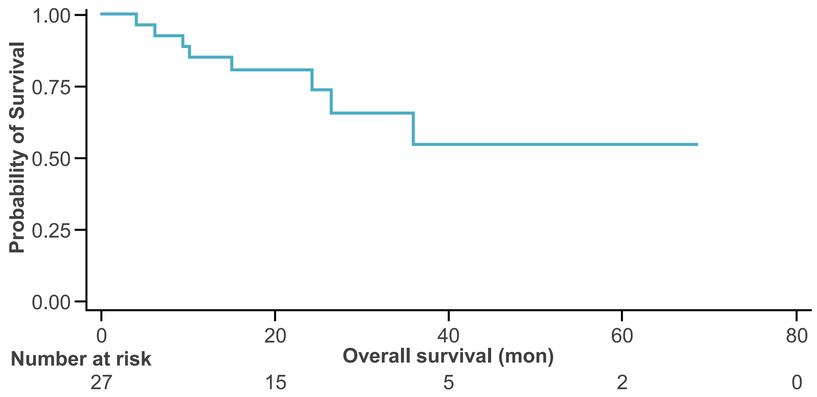
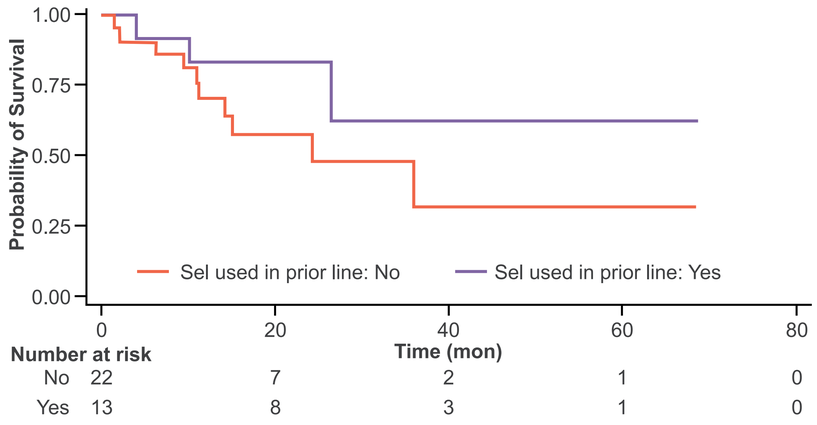


Figure 3. Overall survival if selinexor was used in the prior line of therapy before CAR-T



Conclusions

- The exploratory analysis supports early preclinical findings suggesting selinexor may be a T-cell sparing agent supporting its use prior to CAR-T to optimize outcomes.
- Results of the multivariate analysis suggest patients who received selinexor in the line immediately prior to CAR-T may have a longer PFS and OS survival compared to those who received the drug in earlier lines.
- Prospective trials are needed to verify whether selinexor exposure in the line of therapy prior to CAR-T leads to decreased risk of progression or death compared to other treatments.

References: [1]Friedrich MJ, et al. *Cancer Cell*. 2023;41(4):711-725.e6. [2]Mehta PH, et al. *Front Immunol*. 2021;12:780442. [3]Fang L, et al. *Front Immunol*. 2022;13:979116. [4]Gumber D, et al. *EBioMedicine*. 2022;77:103941. [5]Kang Y, Neff JL, Jeck WR, et al. (2023, September 27-30). *Investigation of T-cell Fitness and Mechanisms of Drug Resistance in Selinexor Treated Patients with Relapsed/Refractory Multiple Myeloma* [Poster Abstract]. 2023 International Myeloma Society Annual Meeting, Athens, Greece.

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Abbreviations: Chimeric Antigen Receptor T-cell, CAR-T; duration of response, DOR; progression-free survival, PFS; overall survival, OS; interquartile range, IQR