Outcomes of Triple Class Refractory Penta-Exposed Multiple Myeloma with Conventional Therapy in Real World vs. Selinexor in STORM Clinical Trial

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Background

- Relapsed and/or refractory MM (RRMM) which becomes triple class refractory (TCR, i.e. refractory to an IMiDs, PIs and CD38 MoABs) has survival measured in months (mos)[1].
- Selinexor is a selective inhibitor of nuclear export compound targeting exportin 1 (XPO1) which is overexpressed in MM cells and essential for MM cell survival.
- In the **STORM** study, selinexor was used in combination with low-dose dexamethasone (Sd) and demonstrated promising efficacy in TCR, penta-exposed (TCR-PE, i.e. exposed to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab) MM[2].
- In the retrospective **MAMMOTH** study, we reported the outcomes of pts with RRMM after they become refractory to CD38 MoABs, including a subset of pts who were TCR[1].

Objective

To conduct a similar cohort analysis from patients in the MAMMOTH and STORM datasets in order to compare conventional care vs. Sd.

Primary Endpoint

- Overall Survival (OS) - calculated from the time of initiation of next line of therapy after TCR-PE status until death or last follow-up.

Methods

- MAMMOTH included patients from 14 US academic institutions

MAMMOTH Inclusion Criteria	Removed	Remaining
Initial population		275
Patients receiving no therapy after becoming refractory to daratumumab.	26	249
Patients not treated with selinexor in subsequent line.	14	235
Patients exposed to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab. Patients refractory to at least 1 PI , 1 IMID and daratumumab. Prior therapy with alkylating agent and corticosteroid. Receiving subsequent therapy	107	**128**

- From STORM we included all patients who received Sd as the first line therapy after they achieved TCR-PE status (n=64).

Results

Table 1 – Baseline Characteristics	STORM N=64	MAMMOTH N=128
Median Age (range) — yr	65 (47–85)	64.5 (28-82)
Male Sex— no. (%)	33 (51.6%)	73 (57.0%)
Time since initial diagnosis (range)— yr	6.4 (1.2-19.9)	5.0 (0.9-14.5)
Prior Treatment Regimens Median (range) — no.	6 (3–18)	6 (3–17)
Chromosomal Abnormality — no. (%)		
High risk overall[a]	32 (50.0%)	65 (53.7%)[b]
del(17p)/p53	13 (20.3%)	34 (28.1%) [b]
t(4;14)	11 (17.2%)	13 (10.7%) [b]
t(14;16)	0 (0.0%)	7 (5.8%) [b]
gain(1q)	23 (35.9%)	39 (32.2%) [b]
Refractoriness to Select Prior Therapies — no. (%)[a]		
At least 1 IMiD, 1 PI, and daratumumab	64 (100%)	128 (100%)
Carfilzomib	62 (96.9%)	105 (82.0%)
Pomalidomide	62 (96.9%)	125 (97.7%)
Carfilzomib, pomalidomide, and daratumumab	60 (93.8%)	104 (81.2%)
Treatment after first becoming TCR		
On clinical trial	64 (100%)	14 (10.9%) [c]
Selinexor, dexamethasone	64 (100%)	-
Carfilzomib-based	-	24 (18.8%) [c]
Pomalidomide-based	-	47 (36.8%) [c]
Daratumumab-based	-	25 (19.5%) [c]
Elotuzumab-based	-	12 (9.4%) [c]
Ixazomib-based	-	13 (10.2%) [c]
Traditional chemotherapy	-	43 (33.6%) [c]
Stem cell transplantation	-	5 (3.9%) [c]

[a]Includes any of del(17p)/p53, t(14; 16), t(4; 14), or 1q21.
[b]Among 121 patients with available FISH information.
[c]Total >100% due to overlapping

Table 2 - Response Rates	STORM N=64		MAMMOTH N=128		
Characteristic	N	Overall Response Rate No. (%)	N	Overall Response Rate No. (%)	P
Overall	64	21 (32.8)	128	32 (25.0)	0.078
High cytogenetic risk	32	7 (21.9)	65	16 (24.6)	
Refractory to carfilzomib, pomalidomide and daratumumab	60	20 (33.3)	104	27 (26.0)	

Figure 1 – OS estimated by Kaplan Meier (unadjusted)

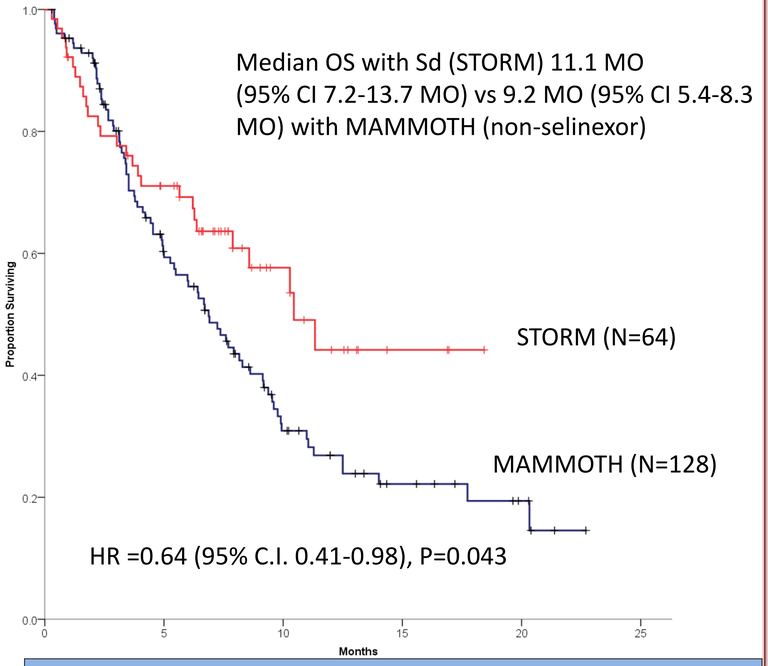

Table 3 – Multivariable Analysis for Risk of Death		
Effect	HR (95% CI)	P-value
Treatment with Selinexor + Dex	0.55 (0.36-0.86)	0.009
Refractory to carfilzomib	2.2 (1.2-4.2)	0.015
High risk cytogenetics	1.7 (1.1-2.4)	0.009

Co-variates: Study group, age, sex, time from diagnosis to study entry, refractoriness to carfilzomib, refractoriness to pomalidomide and cytogenetic risk.

Conclusions

- Use of selinexor-dexamethasone in patients with TCR-PE disease had improved OS with HR of 0.55 compared to other retreatment strategies as evaluated in similar real-world pts from the MAMMOTH study.
- It is important to recognize that clinical trial enrollees generally have superior outcomes compared to real-world patients.
- Carfilzomib refractoriness and high-risk cytogenetics continue to remain independently associated with mortality.

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