Overall Survival of Triple Class Refractory, Penta-Exposed Multiple Myeloma (MM) Patients Treated with Selinexor Plus Dexamethasone or Conventional Care: A Combined Analysis of the STORM and Mammoth Studies

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Background

- Despite dramatic successes in novel drug approvals, almost all MM patients (pts) eventually progress to relapsed refractory MM (RRMM)
- Patients whose disease becomes triple class refractory (TCR, i.e. refractory to an IMiDs, PIs and CD38 mAbs) have survival measured in months (mos)[1]
- Selinexor is a selective inhibitor of nuclear export (SINE™) compound which blocks exportin 1 (XPO1). XPO1 is overexpressed in MM cells and essential for MM cell survival
- In the **STORM** study, selinexor (S) was used in combination with low-dose dexamethasone (Sd) and demonstrated anti-tumor activity 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 a CD38 mAb, including a subset of pts whose disease was documented to be TCR[1]
- Lack of benchmark for outcomes in the TCR-PE population has been a concern

Objective

To compare therapeutic outcomes of similar cohorts of patients treated with Sd in STORM and patients receiving other therapies and included in MAMMOTH.

Methods

- Primary endpoint was overall survival (OS) calculated from the time of initiation of next line of therapy after MM reached TCR-PE status until death or censored at last follow-up
- From STORM, we included all patients who received Sd as the first line therapy after their disease reached TCR-PE status (n=64)
- Dataset from MAMMOTH was interrogated to identify all patients matching STORM patients

MAMMOTH Inclusion Criteria	Removed	Remaining
Initial population		275
Patients receiving therapy after becoming refractory to daratumumab.	26	249
Patients not treated with selinexor in subsequent line.	14	235
Patients treated with bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab *and* with MM refractory to at least 1 PI, 1 IMID and daratumumab. Prior therapy with alkylating agent and corticosteroid required. Receiving subsequent therapy	107	**128**

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]
Refractory 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, daratumumab	60 (93.8%)	104 (81.2%)
First Treatment after T_0		
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 - Responses	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)	

Overall Survival (OS)

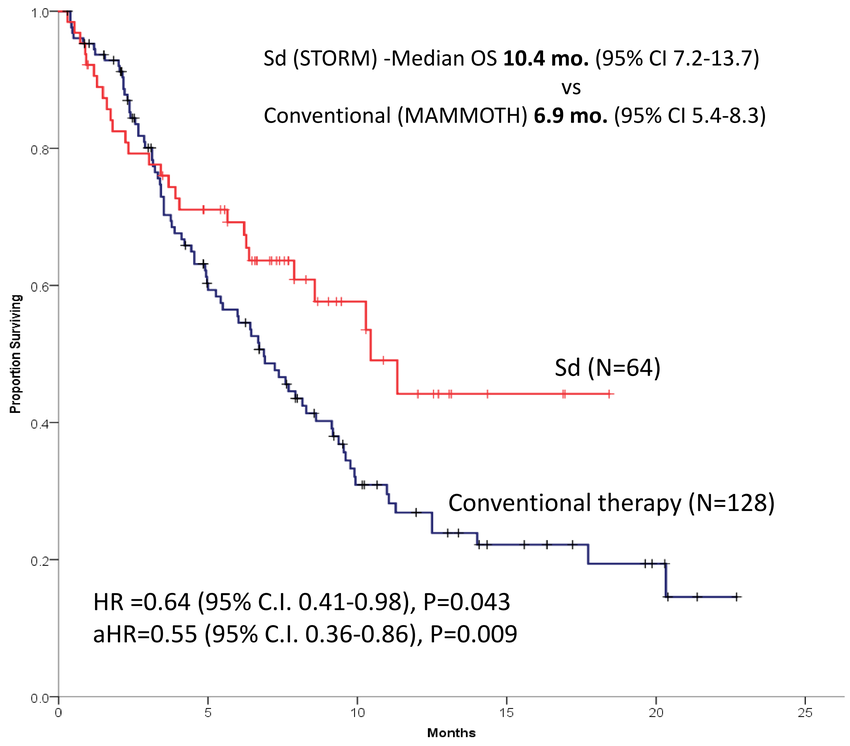

Table 3 – Multivariable Analysis for risk of death		
Effect	HR (95% CI)	P-value
STORM vs MAMMOTH	0.55 (0.36-0.86)	0.009
Refractory to carfilzomib	2.2 (1.2-4.2)	0.015
High risk cytogenetics	1.7 (1.1-2.4)	0.009

Co-variates considered : Study group, age, sex, time from diagnosis to study entry, refractoriness to carfilzomib, refractoriness to pomalidomide and cytogenetic risk.
aHR = adjusted hazard ratio (for carfilzomib refractory and cytogenetics)

Conclusions

- Despite inherent limitations in comparison of trial enrollees vs. real world patients, this analysis suggests improved OS with Sd vs conventional care in patients with TCR-PE RRMM treated in the academic setting
- Prognosis for these patients remains poor and underscores the need for therapeutic advancements

References

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