Clinical Outcomes in Patients with Dose Reduction of Selinexor in Combination with Bortezomib, and Dexamethasone (XVd) in Previously Treated Multiple Myeloma from the BOSTON Study

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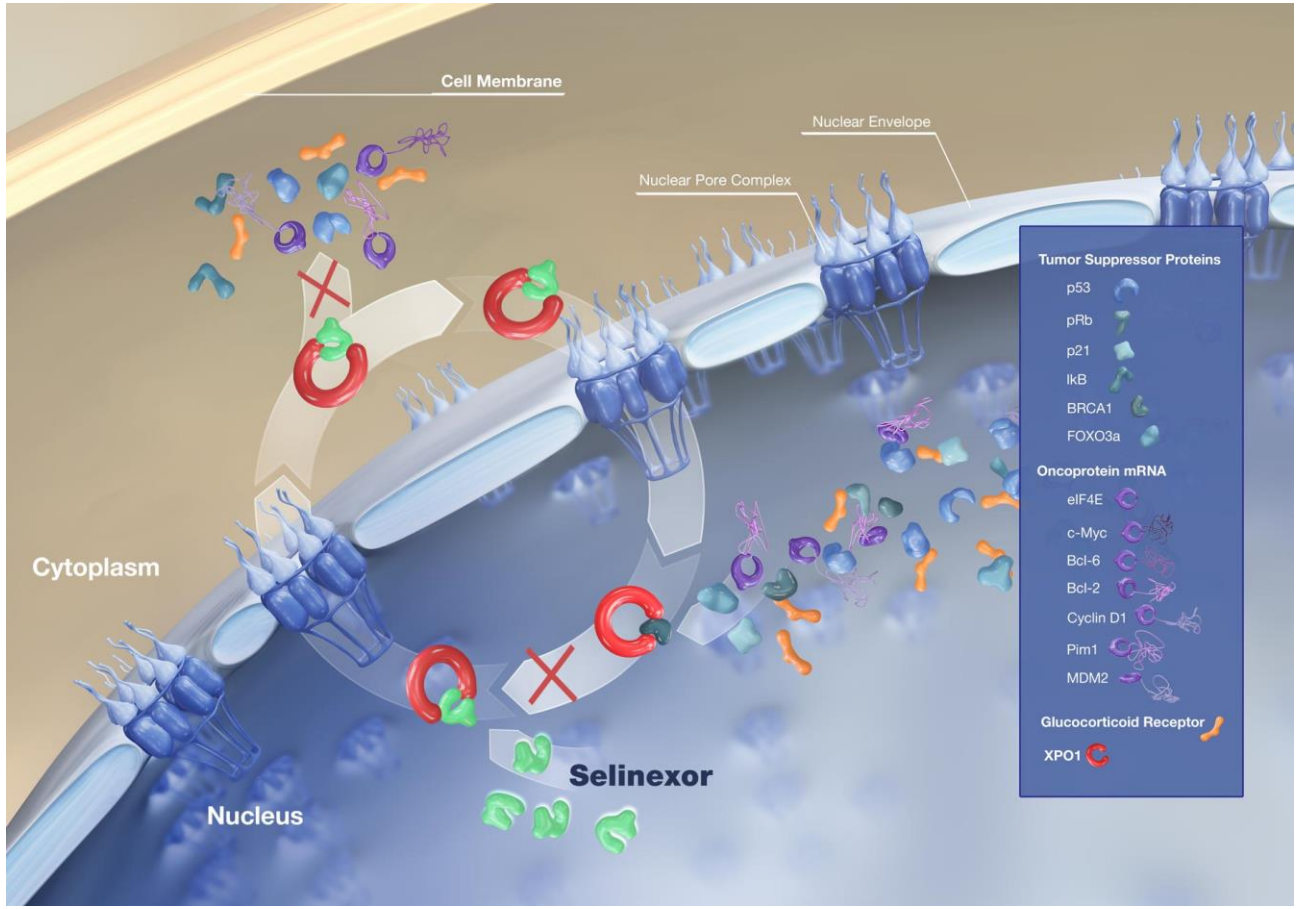
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export[1-11]

Demonstrates synergistic activity in combination with bortezomib *in vitro* and *in vivo*

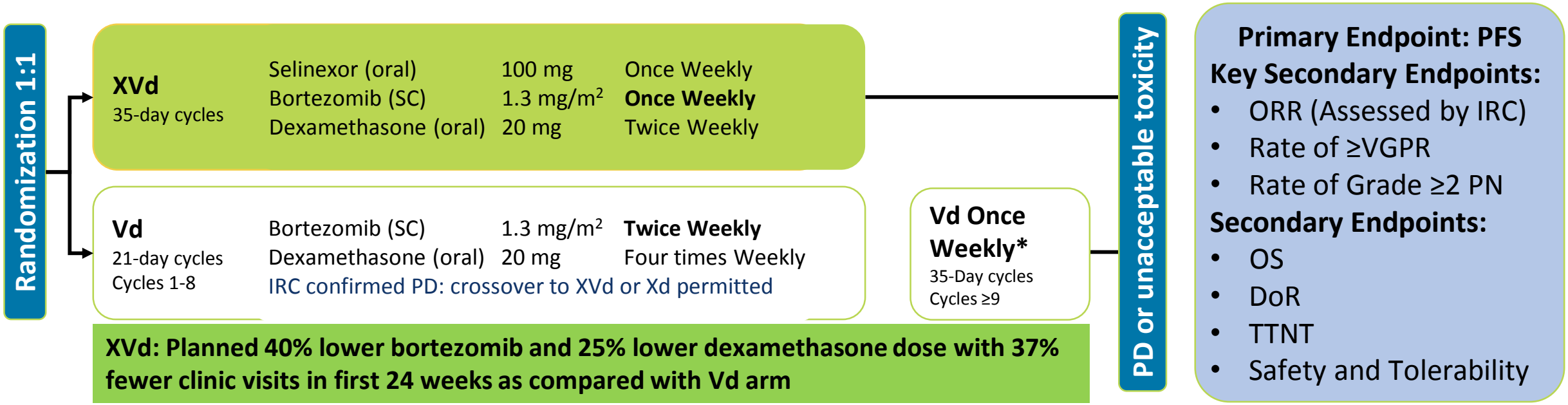


- **Exportin 1 (XPO1)** is overexpressed in MM and its levels correlate with poor prognosis and drug resistance
- **XPO1 Overexpression Causes:**
  - Tumor suppressor proteins (e.g., p53, IκB and FOXO) and glucocorticoid receptor inactivation along with enhanced oncoprotein (e.g., c-Myc, Bcl-xL, cyclins) translation
- **Selinexor (X) is an oral, selective inhibitor of XPO1-mediated nuclear export (SINE) that reactivates multiple TSPs and inhibits oncoprotein translation**
- **Selinexor is now FDA approved:**
  - In combination with bortezomib and dexamethasone (XVd) for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy (BOSTON Trial)
  - In combination with dexamethasone for the treatment of relapsed / refractory MM (Xd) (STORM Trial)
  - Monotherapy (X) for the treatment of patients diffuse large B-cell lymphoma (DLBCL) who have received 2 prior lines of systemic therapy (SADAL Trial)

1. Gupta A, et al. Therapeutic targeting of nuclear export inhibition in lung cancer. J Thorac Oncol. 2017;12(9):1446-1450. 2. Sun Q, et al. Inhibiting cancer cell hallmark features through nuclear export inhibition. Signal Transduct Target Ther. 2016;1:16010. 3. Gandhi UH, et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2018;18(5):335-345. 4. Gravina GL, et al. Nucleo-cytoplasmic transport as a therapeutic target of cancer. J Hematol Oncol. 2014;7:85. 5. Fonseca, 2009; 6. Sonneveld, 2016 7. Avet-Loiseau, 2013; 8. Shah, 2018 9. Grosicki S, et al. Lancet. 2020, 10. Kalakonda N, et al. Lancet Haematol. 2020, 11. Chari A, et al., New England Journal of Medicine. 2019

BOSTON Study Trial Design

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with MM who had Received 1–3 Prior Therapies



Stratification Factors:

Prior PI therapies (Yes vs No); Number of prior anti-MM regimens (1 vs >1); R-ISS stage at study entry (Stage III vs Stage I/II)

- Anti-emetic prophylaxis with 5HT-3 antagonists recommended

CR= complete response, DoR = duration of response, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, MM = Multiple Myeloma, ORR = Overall Response Rate, OS = overall survival, PD = progressive disease, PI = Proteasome Inhibitor, PFS = progression free survival, PR = partial response, PN = peripheral neuropathy, R-ISS = Revised International Staging System, sCR = stringent complete response, TTNT = time to next therapy, VGPR = very good partial response. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. *Vd once weekly dosing and schedule for cycles≥ 9 as per XVd arm description.

Overall Efficacy Results XVd vs. Vd

	XVd	Vd
Primary Endpoint PFS, median Hazard Ratio; (p value)	13.93 months *0.70 (p=0.0075)*	9.46 months
ORR (secondary endpoint)	76.6%	62.3%
≥VGPR	44.6%	32.4%
DOR	20.3 months	12.9 months

Methods

We conducted post-hoc analyses of the BOSTON study to determine the efficacy and safety among patients on the XVd arm who had selinexor dose reductions vs. those without selinexor dose reductions

XVd Patients Enrolled (n=195)	With Selinexor Dose Reduction (n=126)	Without Selinexor Dose Reduction (n=69)

Baseline and Disease Characteristics by Selinexor Dose Reduction Category

Characteristic	With Selinexor Dose Reduction (n=126)	Without Selinexor Dose Reduction (n=69)
Median Age, Years (range)	**66** (44, 87)	**66** (40, 84)
Males, n (%)	**67** (53.2)	**48** (69.6)
Females, n (%)	**59** (46.8)	**21** (30.4)
Number of Prior Lines of therapy, n (%) 1 2 3	 **64** (50.8) **42** (33.3) **20** (15.9)	 **35** (50.7) **23** (33.3) **11** (15.9)
Prior ASCT	**53** (42.1)	**23** (33.3)
Median Years Since Diagnosis to Enrollment, (range)	**4.0** (0.6, 23.0)	**3.3** (0.4, 12.9)
High-Risk Chromosomal Abnormality at Initial Diagnosis, n (%) del(17p) / p53; t (4;14); t (14;16) or gain 1q21 (≥3 copies)	**65** (51.6)	**32** (46.4)
Median Selinexor Dose Received per Week (mg), (range)*	**71 mg** (29.7, 101.4)	**100 mg** (33.3, 136.7)
Average Duration of Selinexor Exposure, Weeks (range)	**44.4** (3, 120)	**30.5** (1, 118)

*** The median selinexor dose in the XVd arm overall (n=195) was 80 mg per week**

Adverse Events, All Grades ≥20% Overall

Adverse Event Term, n (%)	With Selinexor Dose Reduction (n=126)		Without Selinexor Dose Reduction (n=69)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thrombocytopenia	88 (69.8)	63 (50.0)	29 (42.0)	14 (20.3)
Nausea	70 (55.6)	12 (9.5)	28 (40.6)	3 (4.3)
Fatigue	62 (49.2)	20 (15.9)	20 (29.0)	6 (8.7)
Decreased Appetite	52 (41.3)	5 (4.0)	17 (24.6)	2 (2.9)
Anemia	50 (39.7)	23 (18.3)	21 (30.4)	8 (11.6)
Diarrhea	49 (38.9)	7 (5.6)	14 (20.3)	6 (5.2)
Neuropathy Peripheral	45 (35.7)	7 (5.6)	18 (26.1)	2 (2.9)
Weight Decreased	40 (31.7)	3 (2.4)	11 (15.9)	1 (1.4)
Asthenia	39 (31.0)	12 (9.5)	9 (13.0)	4 (5.8)
Cataract	34 (27.0)	17 (3.5)	8 (11.6)	0 (0)
Vomiting	30 (23.8)	8 (6.3)	10 (14.5)	0 (0)

- The most common adverse events (dose reduction; without dose reduction) of any grade were thrombocytopenia (69.8%; 42.0%), nausea (55.6%; 40.6%), and fatigue (49.2%; 29.0%)
- The rate of treatment discontinuation in the dose reduction group was 24.6% vs 14.5% without a dose reduction.
- There were 6 (4.8%) deaths in the dose reduction group vs 6 (8.7%) without a dose reduction.

Duration-Adjusted* Incidence of Adverse Events of Clinical Interest

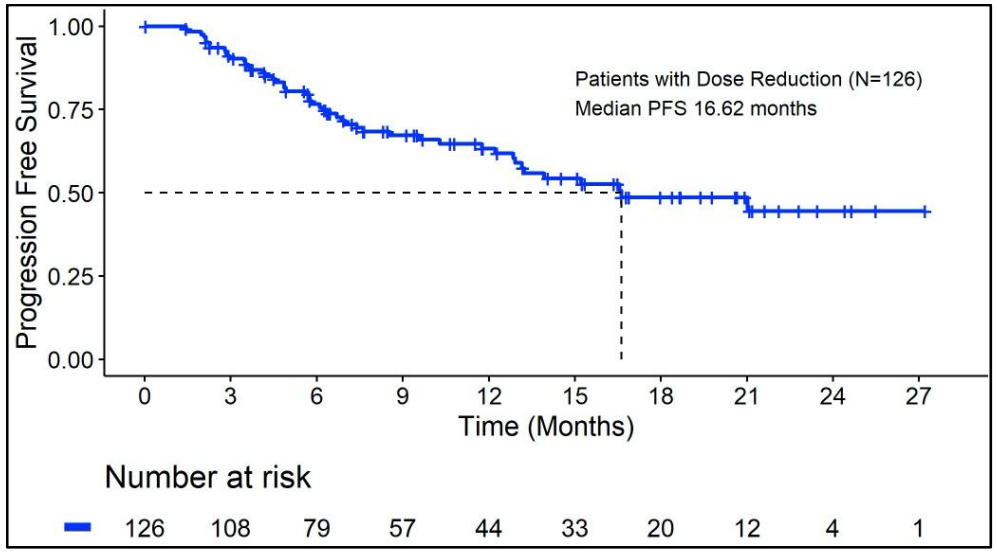
Adverse Event Term, (%)	On or Before First Dose Reduction in Selinexor (n=195)		After First Dose Reduction in Selinexor (n=126)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thrombocytopenia	62.5	29.6	47.6	19.2
Nausea	31.6	3.9	7.3	2.7
Fatigue	28.1	4.1	9.9	2.7
Decreased Appetite	21.5	1.6	6.4	0.4
Anemia	17.9	4.7	10.3	3.2
Diarrhea	12.9	2.0	5.2	0.7
Neutropenia	10.6	4.0	7.7	4.8
Weight Decreased	9.0	0.6	5.9	0.7

*Duration-adjusted incidence of adverse event defined as the average number of events per 100 patients during a 4-week cycle

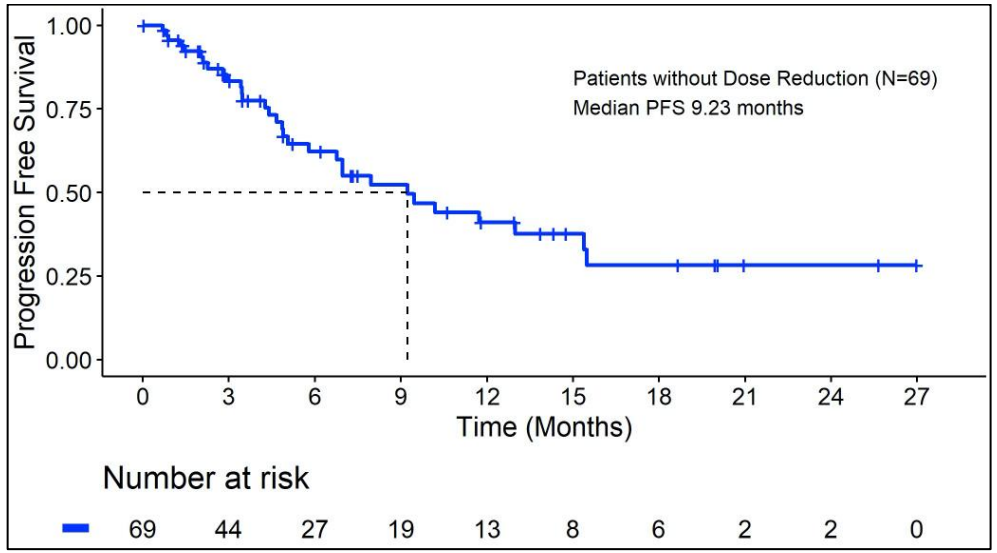
- To better understand the impact of dose reduction on adverse events (AEs), we present the duration-adjusted incidence rates of AEs of clinical interest. The duration-adjusted incidence rates of AEs were lower after a dose reduction of selinexor compared to the rates on or before dose reduction: thrombocytopenia (62.5% vs 47.6%), nausea (31.6% vs 7.3%), fatigue (28.1% vs 9.9%), decreased appetite (21.5% vs 6.4%), anemia (17.9% vs 10.3%), and diarrhea (12.9% vs 5.2%)

XVd is Clinically Meaningful (PFS, ORR, OS) in Patients With *or* Without Selinexor Dose Reduction

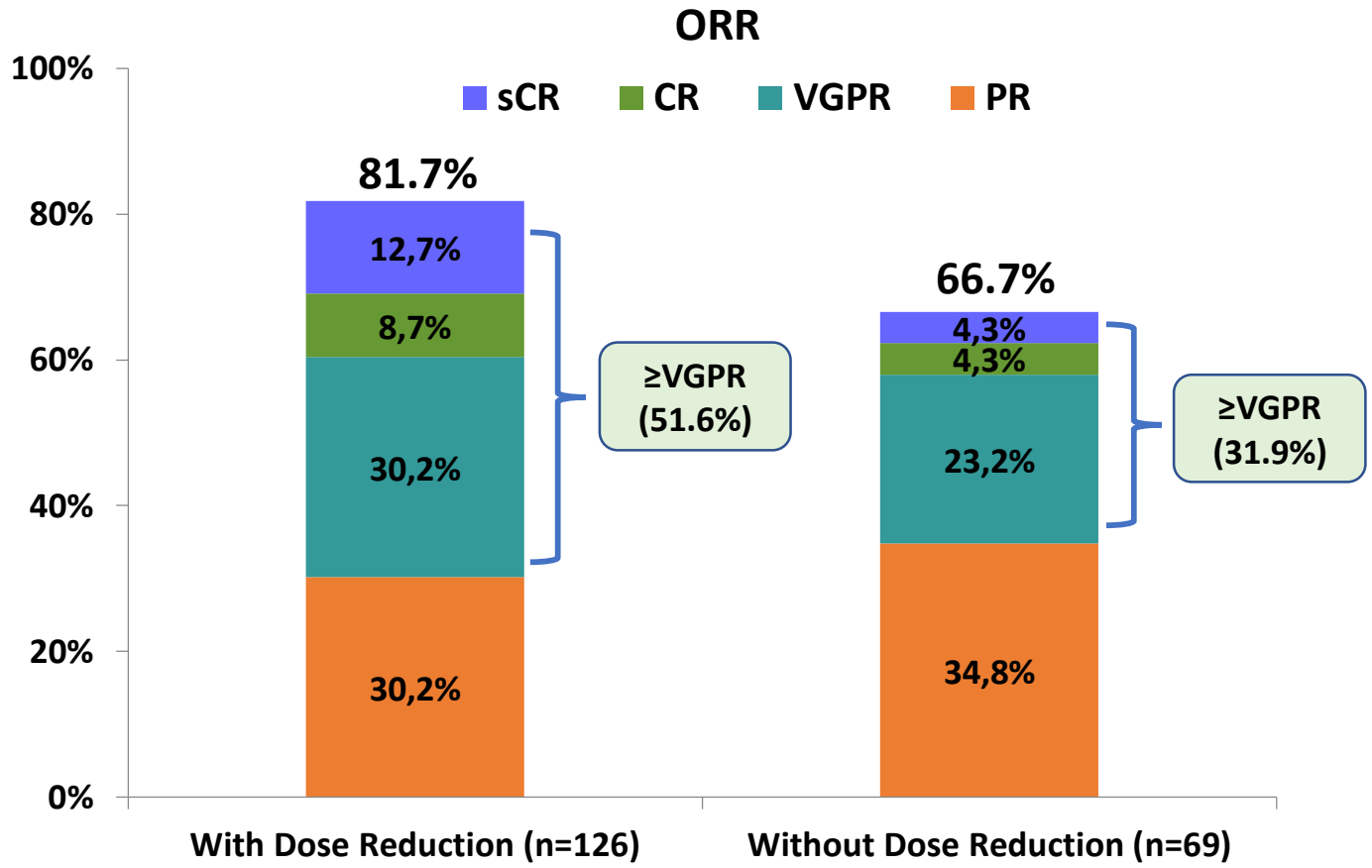
PFS Patients with Dose Reduction



PFS Patients without Dose Reduction



ORR



- **HR for PFS with selinexor dose reduction: 0.5678 [95% CI (0.3614, 0.8919), p= 0.0065]**
- **Median OS not reached for with or without selinexor dose reduction groups**

Conclusions

- **XVd is effective in patients with MM:**
  - **Patients with a dose reduction (to median dose 80mg weekly): PFS (16.62 months); ORR (81.7%) with ≥VGPR (51.6%); median OS was not reached**
  - **Patients without a dose reduction (median dose remained 100mg weekly): PFS (9.23 months); ORR (66.7%) with ≥VGPR (31.9%); median OS was not reached**
- ***Patients with appropriate dose reductions of selinexor had longer PFS and reduced AEs with improved tolerability as compared to those whose dose was not reduced*** ***(p= 0.0065)***
- **<u>The recommended starting dose of selinexor in XVd is 100 mg QW, but the median dose administered for XVd arm patients was 80 mg QW</u>**

As with other drugs, dose reductions are an important tool to individualize and optimize the efficacy of the once weekly XVd regimen in patients with previously treated MM

Conflict of Interest Disclosures

- **TO BE ADDED ACCORDING TO ASH ABSTRACT SUBMISSION**