Selinexor in Combination with Bortezomib and Dexamethasone (SdB) Demonstrates Significant Activity in Patients with Refractory Multiple Myeloma (MM) Including Proteasome-Inhibitor Refractory Patients: Results of the Phase I Stomp Trial

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Abstract

Introduction - Selinexor is a first-in-class Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1). Selinexor with low dose dexamethasone (dex) has demonstrated potent anti-cancer activity in patients with heavily pretreated MM. While the development of proteasome inhibitors (PIs) has transformed the treatment of MM, acquired resistance to PIs limit their efficacy. Preclinical studies have shown that selinexor, when combined with bortezomib, can restore sensitivity of bortezomib-resistant MM to this drug, inducing tumor growth inhibition and increasing survival in MM models in mice. In this clinical trial (NCT02343042), we investigated the safety, tolerability and efficacy of the combination of selinexor, bortezomib and low dose dex (SdB) in patients (pts) with refractory MM.

Methods - This phase 1b/2 dose escalation study using a standard 3+3 design, was designed to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for SdB. The study included pts with refractory MM, after ≥ 1 prior therapy. Pts with prior PI relapsed and/or refractory disease were included, provided the patient's MM was not refractory to bortezomib as last therapy. Selinexor was independently dosed escalated in once-weekly (QW, starting at 80 mg; N=7, 100 mg N=6 pts) or twice-weekly (BIW, starting at 60 mg; N=3, 80 mg N=6 pts) regimens. Bortezomib (1.3 mg/m^2 sc) was administered either once-weekly or twice-weekly and dex was given orally 40 mg QW or 20 mg BIW.

Results - As of July 25th, 2016, enrollment in the dose escalation cohorts has been completed with 22 pts (12 male /10 female). The median age is 65 years (range, 46 - 74), with a median of 4 (range, 1 - 12) prior treatment regimens. One dose limiting toxicity (Grade 4 thrombocytopenia without bleeding) in the 80 mg BIW cohort was observed but the MTD has not been reached. Common related grade 1/2 adverse events (AEs) include: fatigue 41%, nausea 41%, anorexia 36%, and weight loss 18%. Grade 3/4 AEs include: thrombocytopenia 41%, anemia 18%, and neutropenia 18%. One case of grade 1 peripheral neuropathy in the 8 BIW cohort was reported. All pts were evaluable for response. The ORR (≥partial response, PR) was 77% with ≥VGPR 27% (1 and 5 pts in VGPR) and 11 PRs. There were 3 minor responses (14%), 1 stable disease, 1 progressive disease (5% each). Seven of the 12 pts with PI-refractory MM responded (ORR 58%). A summary of response by PI treatment history is shown in Table 1. Ten patients have remained on study >4 months, including 7 patients still on trial (longest >9 months). Based on tolerability and anti-MM activity, RP2D of SdB is selinexor 100 mg, bortezomib 1.3 mg/m^2 and dex 40 mg, all given once weekly. At the RP2D, pts achieved ≥PR (ORR 100%).

Conclusions - Selinexor in combination with bortezomib and dex is well tolerated and highly active in refractory MM. Toxicities are manageable and similar to selinexor or bortezomib monotherapy. Peripheral neuropathy is uncommon, consistent with the use of weekly bortezomib sc and the lack of neuropathy with selinexor. Overall, the SdB regimens induced an ORR of 77% with ≥VGPR of 27%. In patients with PI-refractory MM, the ORR was 58%, indicating that the addition of selinexor restores sensitivity to bortezomib. These results confirm the preclinical data supporting synergistic effects of selinexor when combined with PIs. This promising, once-weekly treatment regimen may provide deeper and more durable responses in pts with relapsed / refractory MM, including those with PI-refractory disease.

Prior PI Status	N	ORR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Refractory (7 Bort, 3 Car, 2 Ixa)	12	7 (58%)	1 (9%)	--	6 (50%)	3 (25%)	1 (8%)	1 (8%)
Bort - Exposed	7	7 (100%)	--	5 (71%)	2 (29%)	--	--	--
Naïve	3	3 (100%)	--	--	3 (100%)	--	--	--
All	22	17 (77%)	1 (5%)	5 (23%)	11 (50%)	3 (14%)	1 (5%)	1 (5%)

CR=Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minor Response, PD=Progressive Disease
SD=Stable Disease, ORR=Overall Response Rate (CR+VGPR+PR)

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Table 1. Best Response by Prior Proteasome Inhibitor (PI) Treatment Status

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- ↵* Asterisk with author names denotes non-ASH members.

Potential Articles of Interest

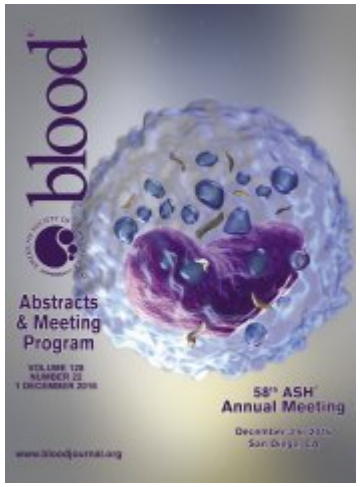
Selinexor in Combination with Weekly Low Dose Bortezomib and Dexamethasone (SVd) Induces a High Response Rate with Durable Responses in Patients with Refractory Multiple Myeloma (MM)
Nizar J. Bahlis et al., Blood

Deep and Durable Responses with Selinexor, Daratumumab, and Dexamethasome (SDd) in Patients with Multiple Myeloma (MM) Previously Exposed to Proteasome Inhibitors and Immunomodulatory Drugs: Results of Phase 1b Study of SDd
Cristina J Gasparetto et al., Blood

Selinexor Plus Low-Dose Bortezomib and Dexamethasone for Patients With Relapsed or Refractory Multiple Myeloma
PracticeUpdate

Exploring novel ways to manage patients with relapsed/refractory multiple myeloma - focus on the clinical development of selinexor
Touch Oncology (Videos)

OC-007 A Multicenter, Double-Blind, Placebo (PBO)-Controlled Ph3 Stu of Ustekinumab (UST), A'Human MAB to IL-12/23P40, IN PTS with Moderately-Severely Active Crohn's Disease (CD) Who are Naïve or not Refractory to anti-TNFA: UNITI-2



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