Phase I/II Trial of the Combination of Selinexor (SEL), Liposomal Doxorubicin (DOX) and Dexamethasone (Dex) for Relapsed and Refractory Multiple Myeloma

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Abstract

Background: SEL, an oral first-in-class inhibitor of XPO1 showed activity in clinical trials for hematologic malignancies. SEL inhibits DNA damage repair and exhibits marked synergy with doxorubicin in preclinical myeloma models. SEL/Dex results in a 20% response rate in penta-refractory myeloma patients. We report here the results of a phase I/II trial of SEL in combination with DOX and Dex in patients with RRMM.

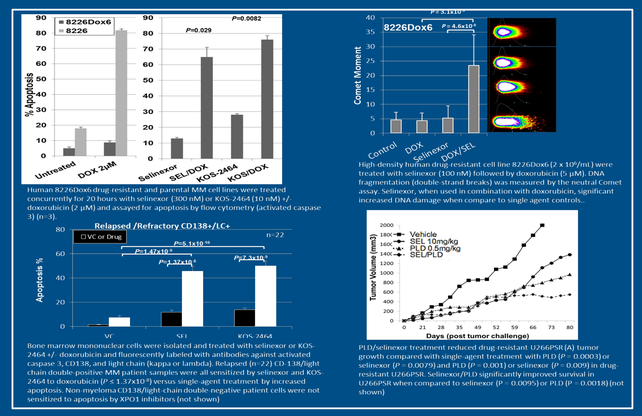
Methods: Eligible patients had RRMM and received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor. Treatment consisted of a loading phase with SEL and Dex for 1-2 weeks; an induction phase with DOX 20 mg/m^2 IV D1, SEL and Dex (once weekly) and a maintenance phase of weekly SEL/Dex (table 1). Two loading phases were evaluated: A. SEL/Dex twice weekly for 2 weeks, B. One dose of SEL/Dex. Primary and secondary end points: maximum tolerated dose (MTD) / recommended phase II dose (RP2D) of the combination, and overall response rate (ORR) per International Myeloma Working Group (IMWG) criteria.

Results: Twenty-seven patients were enrolled (median age of 60 years, median of 6 prior lines (range 2-10)). No dose limiting toxicities (DLT) were noted in dose level (DL) 1. Two patients experienced a DLT in DL2 (Gr4 thrombocytopenia and Gr 3 nausea). The loading phase was shortened to 1 dose of SEL (80 mg) on day -7 (DL2m). 1/6 patients experienced a DLT on DL2m (Gr 3 hyponatremia). Two patients experienced a DLT in dose level 3m (Gr 3 ALT and Gr 3 confusion). The recommended phase II dose was determined to be DL2m (SEL 80 mg D1,8,15, DOX 20 mg/m^2 D1 and Dex 40 mg D1,8,15). Three patients died on study (one from RSV pneumonia, one from Pneumocystis jirovecii and one from advanced myeloma). The most common Gr 3/4 at least possibly related adverse events are as follows: thrombocytopenia 33%, neutropenia 33%, asymptomatic hyponatremia 30%, anemia 26%, nausea / vomiting 11%, hyperglycemia 11%, diarrhea 7%, and fatigue 7% (table 2). Of the 14 patients treated at the RP2D, one was not evaluable (NE), one had a PR and 1 a MR at the time of this analysis. Per protocol, this current level of response does not justify proceeding with the second stage of the phase II study. Of the 27 total patients treated, we noted 2 VGPR, 2 PR, 3MR, 8SD, 4NE with an ORR of 15%, clinical benefit rate (MR and better) of 26% by intent to treat. There was increased nuclear localization of Ikβ post selinexor treatment in responders compared to non-responders (Nuclear / cytoplasmic ratio mean 1.15 ±0.06 versus 0.93 ±0.09; p=0.04).

Conclusions: The addition of DOX to SEL/Dex, while reasonably well tolerated, does not appear to improve the ORR noted with SEL/Dex in this heavily pretreated patient population.

Background

Background: SEL, an oral, first-in-class inhibitor of XPO1 showed activity in clinical trials for hematologic malignancies. Topoisomerase IIα, a substrate for XPO1, is located in the cytoplasm in doxorubicin resistant MM cells versus nuclear localization in sensitive cells). Turner et al have also demonstrated that SEL inhibits DNA damage repair and exhibits marked synergy with doxorubicin in preclinical myeloma models (figure below). In addition, ongoing trial evaluating SEL dexamethasone in quad and penta- refractory MM is underway.



Human 8226Dox6-drug resistant and parental MM cell lines were treated concurrently for 20 hours with selinexor (300 nM) or KOS-2464 (10 nM) +/- doxorubicin (2 μM) and assayed for apoptosis by flow cytometry (activated caspase 3) (n=3).

High-density human drug-resistant cell line 8226Dox6 (2 x 10^6/mL) were treated with selinexor (100 nM) followed by doxorubicin (5 μM). DNA fragmentation (double-strand breaks) was measured by the neutral Comet assay. Selinexor, when used in combination with doxorubicin, significant increased DNA damage when compare to single agent controls..

Bone marrow mononuclear cells were isolated and treated with selinexor or KOS-2464 +/- doxorubicin and fluorescently labeled with antibodies against activated caspase 3, CD138, and light chain (kappa or lambda). Relapsed (n=22) CD-138/light chain double-positive MM patient samples were all sensitized by selinexor and KOS-2464 to doxorubicin ($P < 1.37x10^{-6}$) versus single-agent treatment by increased apoptosis. Non-myeloma CD138/light-chain double-negative patient cells were not sensitized to apoptosis by XPO1 inhibitors (not shown)

PLD/selinexor treatment reduced drug resistant U266PSR (A) tumor growth compared with single-agent treatment with PLD ($P = 0.0003$) or selinexor ($P = 0.0079$) and PLD ($P = 0.001$) or selinexor ($P = 0.009$) in drug-resistant U266PSR. Selinexor/PLD significantly improved survival in U266PSR when compared to selinexor ($P = 0.0095$) or PLD ($P = 0.0018$) (not shown)

Patients and Methods

Eligible patients had relapsed or refractory myeloma and received ≥ 2 prior therapies including lenalidomide and a proteasome inhibitor. The treatment schedule is summarized in the table below. Primary and secondary end points: maximum tolerated dose (MTD) / recommended phase II dose (RP2D) of the combination and overall response rate (ORR) per International Myeloma Working Group (IMWG) criteria. At the recommended phase II dose, we enrolled a total of 14 patients (including 6 in the phase I). If we observed 3 or more PR or better, we would enroll on the second stage an additional 16 patients . The probability of early stopping (in stage I) is 0.058 if the true response rate of the combination is 40%

Results

Twenty-seven patients were enrolled (median age of 62 years, median of 6 prior lines (range 2-10)). Patient characteristics are listed in the table.

Baseline Characteristics

Baseline characteristic	N=27
Median age in years, (range)	60 (49-76)
Gender, N (%) Male	13 (48%)
Median number of prior regimen, (range)	6 (2-10)
Lenalidomide refractory	27 (100%)
Proteasome inhibitory refractory, N (%)	25 (93%)
Prior carfilzomib*, N (%)	23 (85%)
Prior high dose therapy, N (%)	20 (75%)
Quad refractory, N (%)	22 (81%)
Penta refractory, N (%)	15 (55%)
Median hemoglobin (range) g/dL	9.6 (7.1-12.7)
Platelets < 100k	8 (29%)
Median serum creatinine, (range) mg/dL	0.9 (0.5-1.8)
Median serum albumin, (range) g/dL	3.7 (2.6-4.7)
High risk cytogenetics,± N (%)	5 (22%)
Deletion 17p, N (%)	5 (22%)
T(4;14), N (%)	3 (14%)
Trisomy or tetrasomy 1q21, N (%)	13 (56%)

* Includes 1 patient with prior Oprozomib,
± high risk: t(4;14) or del17p

Phase I

No dose limiting toxicities (DLT) were noted in dose level (DL) 1. Two patients experienced a DLT in DL2 (Gr 4 thrombocytopenia and Gr 3 nausea). The loading phase was shortened to 1 dose of SEL (80mg) on day -7 (DL2m). 1/6 patients experienced a DLT on DL2m (Gr 3 hyponatremia). Two patients experienced a DLT in dose level 3m (Gr 3 ALT and Gr 3 confusion). The recommended phase II dose was determined to be DL2m (SEL 80 mg D1,8,15, DOX 20 mg/m^2 D1 and Dex 40 mg D1,8,15).

Dose level	Selinexor doses during loading	DOX IV on D1	Selinexor PO	DLT
1	4 (Days-14, -11,-7, -4)	20 mg/m^2	40 mg/m^2 (~68 mg) D1, 8, 15	0
2	4 (Days-14, -11,-7, -4)	20 mg/m^2	80 mg D1, 8, 15	2 (Gr 3 nausea, Gr 4 platelets)
2m	1 (day -7 only)	20 mg/m^2	80 mg D1, 8, 15	1 (Gr 3 hyponatremia)
3m	1 (day -7 only)	20 mg/m^2	80 mg D1,3,8, 10	2 (Gr 3 confusion and Gr 3 ALT)

IMWG responses

Of the 14 patients treated at the RP2D, one was not evaluable (NE), one had a PR and 1 a MR at the time of this analysis. Per protocol, this current level of response does not justify proceeding with the second stage of the phase II study. Of the 27 total patients treated, we noted 2 VGPR, 2 PR, 3MR, 8SD, 4NE with an ORR of 15%, clinical benefit rate (MR and better) of 26% by intent to treat.

Best Response

	≥ VGPR	≥ PR	≥ MR	SD
All patients, N=27	2 (7%)	4 (15%)	9 (33%)	8 (30%)
At RP2D, N=14	0	1 (7%)	2 (14%)	4 (29%)

Correlatives

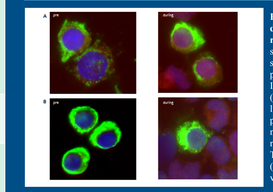


Figure IkBα nuclear localization is increased after selinexor/dexamethasone treatment in responders as compared to non-responders. Bone Marrow aspirates were obtained before and during selinexor/dexamethasone treatment from patients on clinical trial. Cytospin slides of patient mononuclear cells were fixed in paraformaldehyde and permeabilized. The slides were stained to determine intracellular location of IkBα. Figure shows representation plasma cells from **(A)** a responder (VGPR) and **(B)** a non-responder (SD). The plasma cells are identified by light chain antigen staining (green) and nuclei by DAPI (blue) and IkBα protein (red). Images were taken with a Zeiss Z1 Axioimager fluorescence microscope through a oil immersion 40X objective. Nuclear/cytoplasmic ratios were determined using Definiens Tissue Studio Analysis software. The data determined the mean nuc:cyt ratio of responders were higher 1.15 (+/- .06) compared to non-responders 0.93 (+/- .09) during treatment (p-value 0.044).

Adverse Events

Three patients died on study (one from RSV pneumonia, one from Pneumocystis jirovecii and one from progression of myeloma). The most common Gr 3/4 at least possibly related adverse events are as follows: thrombocytopenia 33%, neutropenia 33%, asymptomatic hyponatremia 30%, anemia 26%, nausea / vomiting 11%, hyperglycemia 11%, diarrhea 7%, and fatigue 7%. Number and percentage of patients with worst grade treatment related adverse events are shown below.

AE description	All doses Gr 3/4 N=27	All doses All grades N=27	At RP2D Gr 3/4 N=14	At RP2D All Grades N=14
Neutropenia	33%	41%	21%	21%
Thrombocytopenia	33%	41%	21%	21%
Anemia	26%	26%	14%	14%
Hyponatremia	30%	30%	14%	14%
Nausea / Vomiting	11%	59%		50%
Diarrhea	7%	26%		7%
Hyperglycemia	11%	15%	7%	14%
Fatigue	7%	41%		43%
Anorexia		15%		21%

Conclusion

The addition of DOX to SEL/Dex, while reasonably well tolerated, does not appear to improve the ORR noted with SEL/Dex in this heavily pretreated patient population. PK and additional correlative data are under way and will be reported at the time of publication.