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

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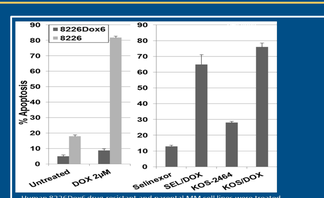
Abstract

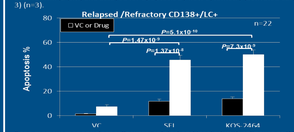
Background: SEL, an oral, first-in-class inhibitor of XPO1 showed activity in clinical trials for hematologic malignancies. SEL inhibits DNA damage repair and exhibits marked synergy with doxorubicin in preclinical myeloma models. We report here the results of a phase I trial of SEL in combination with 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 SELDex. Two loading phases were evaluated: A. SELDex twice weekly for 2 weeks, B. One dose of SELDex. 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:** 13 patients were enrolled (median age of 59 years, median of 6 prior lines (range 2-9)). No dose limiting toxicities (DLT) were noted in dose level (DL) 1. 2 patients experienced a DLT in DL2 (Gr4 thrombocytopenia and Gr 3 nausea). The loading phase was shortened to 1 dose of SEL (80mg) on day -7 (DL2m). 1/3 patients experienced a DLT on DL2m (Gr3 hyponatremia). The most common Grade 3/4 at least possibly related adverse events are as follows: hyponatremia 54%, anemia 45%, thrombocytopenia 54%, neutropenia 54%, diarrhea 18%, vomiting 27%, hyperglycemia 18% and fatigue 18%. 10 patients are evaluable for response: 2 VGPR, 2 PR, 2MR, 3 SD and 1 PD. **Conclusions:** Preliminary responses in heavily pretreated patients support the continued investigation of this combination in patients with RRMM

Background

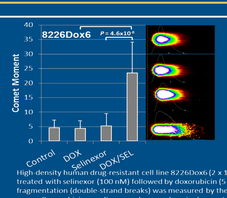
Background: SEL, an oral, first-in-class inhibitor of XPO1 showed activity in clinical trials for hematologic malignancies. Topoisomerase IIα, a substrate for XPO1, is located in the cytoplasm in doxorubicin resistant MM cells versus nuclear localization in sensitive cells). Turner eta l. have also demonstrated that SEL inhibits DNA damage repair and exhibits marked synergy with doxorubicin in preclinical myeloma models (figure 1). In addition, ongoing trial evaluating SEL dexamethasone in quad and penta-refractory MM is underway.



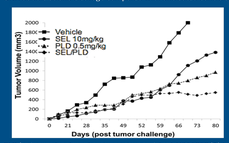
Human 8226Dox6-drug resistant and parental MM cell lines were treated concurrently for 20 hours with selinexor (300 nM) or KOS-2464 (10 nM) +/- doxorubicin (2 μM) and assayed for apoptosis by flow cytometry (activated caspase 3) (n=3).



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^{9}) 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)



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. Doxorubicin or selinexor, when used as single agents, increased DNA double-strand cleavage compared with untreated controls.



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

Dose level	Loading phase	Number of selinexor doses during loading	PLD IV on D1	Selinexor PO
1	A	4 (Days-14, -11,-7, -4)	20 mg/m^2	40 mg/m^2 (~68 mg) D1, 8, 15
2	A	4 (Days-14, -11,-7, -4)	20 mg/m^2	80 mg D1, 8, 15
1m	B	1 (day -7 only)	20 mg/m^2	60 mg D1, 8, 15
2m	B	1 (day -7 only)	20 mg/m^2	80 mg D1, 8, 15
3m	B	1 (day -7 only)	20 mg/m^2	80 mg D1,3,8, 10
4m	B	1 (day -7 only)	30 mg/m^2	80 mg D1,3,8, 10

Results

13 patients were enrolled (median age of 59 years (range 49-76), median of 6 prior lines (range 2-9)).

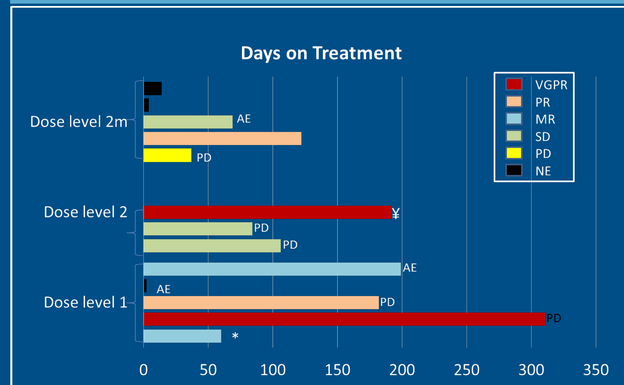
No dose limiting toxicities (DLT) were noted in dose level (DL) 1. 2 patients experienced a DLT in DL2 (Gr4 thrombocytopenia and Gr 3 nausea). The loading phase was shortened to 1 dose of SEL (80mg) on day -7 (DL2m). 1/3 patients experienced a DLT on DL2m (Gr3 hyponatremia).

Baseline Characteristics

Baseline characteristic	N=13
Median age in years, (range)	59 (49-76)
Gender, N (%) Male	7 (54%)
Median number of prior regimen, (range)	6 (2-9)
Lenalidomide refractory, N (%)	13 (100%)
Proteasome inhibitory refractory, N (%)	13 (100%)
Prior carfilzomib*, N (%)	12 (92%)
Prior Pomalidomide / refractory	10 (77%)
Prior high dose therapy, N (%)	10 (77%)
Median β2 microglobulin, (range) mg/L	3.4 (2.1-15.9)
Median serum albumin, (range) g/dL	3.7 (2.6-4.7)
ISS stage II, N (%)	7 (54%)
ISS stage III, N (%)	2 (15%)
Median serum creatinine, (range) mg/dL	0.9 (0.6-1.5)
High risk cytogenetics,± N (%)	1 (9%)
Deletion 17p, N (%)	1 (9%)
T(4;14), N (%)	1 (9%)
Trisomy or tetrasomy 1q21, N (%)	7 (64%)

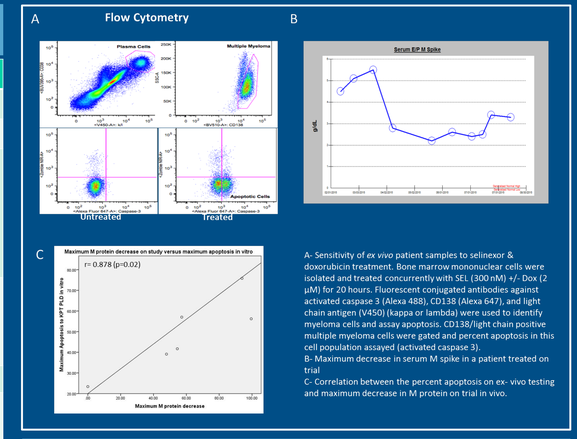
* Includes 1 patient with prior Oprozomib,
± high risk: t(4;14) or del17p

IMWG responses



PD: progressive disease, AE: off study due to adverse event
* Death due to RSV pneumonia while in MR, ¥ Death due to PCP pneumonia while in VGPR
ORR (≥PR) 40%, CBR (≥MR) 60%

Ten patients are evaluable for response: 2 VGPR, 2 PR, 2MR, 3 SD and 1 PD.
There was a correlation between maximum decrease in Monoclonal protein and the percent apoptotic cells treated ex- vivo with the combination of SEL and doxorubicin



A- Sensitivity of *ex vivo* patient samples to selinexor & doxorubicin treatment. Bone marrow mononuclear cells were isolated and treated concurrently with SEL (300 nM) +/- Dox (2 μM) for 20 hours. Fluorescent conjugated antibodies against activated caspase 3 (Alexa 488), CD138 (Alexa 647), and light chain antigen (V450) (kappa or lambda) were used to identify myeloma cells and assay apoptosis. CD138/light chain positive multiple myeloma cells were gated and percent apoptosis in this cell population assayed (activated caspase 3).
B- Maximum decrease in serum M spike in a patient treated on trial
C- Correlation between the percent apoptosis on ex- vivo testing and maximum decrease in M protein on trial in vivo.

Adverse Events

There were two death on study. 1 patient developed RSV pneumonia and ARDS in cycle 3 while in a MR. The patient had undergone her third autologous transplant 3 months prior to enrollment on study Another patient with a baseline lymphocyte count of 600 developed PCP pneumonia (without prophylaxis) in cycle 7. Number and percentage of patients with worst grade treatment related adverse events are shown below.

Adverse Event	Gr 1-2 N (%)	Gr 3 or 4 N (%)
Neutropenia	2 (18%)	6 (54%)
Anemia		5 (45%)
Thrombocytopenia	2 (18%)	6 (54%)
Febrile neutropenia		1 (9%)
Fatigue	4 (36%)	2 (18%)
Hyponatremia		6 (54%)
Nausea / vomiting	4 (36%)	3 (27%)
Diarrhea	3 (27%)	2 (18%)
Hyperglycemia	2 (18%)	2 (18%)

Conclusion

The MTD was not reached and enrollment continues on dose level 2m.

Preliminary responses in heavily pretreated patients support the continued investigation of this combination in patients with RRMM.