A Phase 1 Dose Escalation Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-330 (Selinexor) in Patients (pts) with Relapsed / Refractory Acute Myeloid Leukemia (AML)

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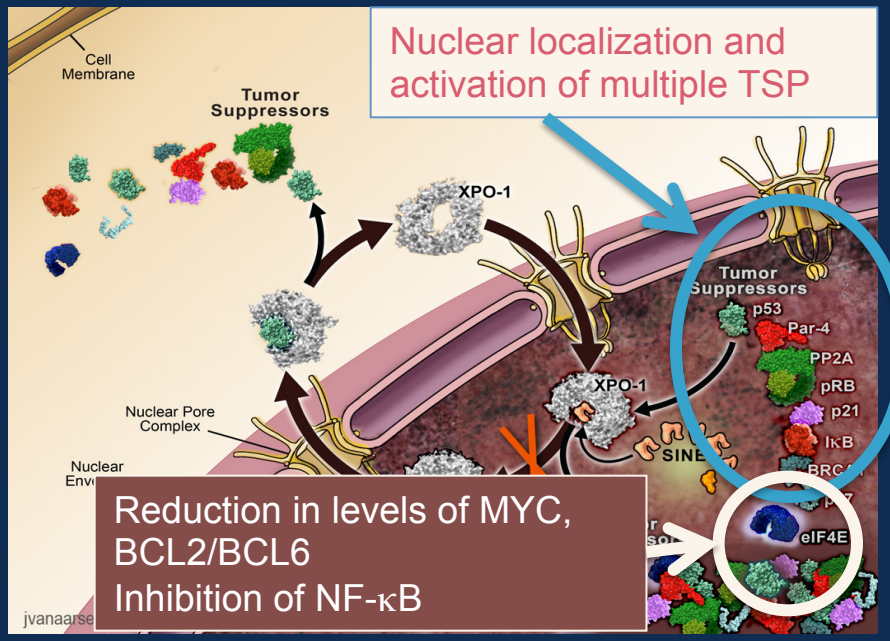
Selective Inhibitors of Nuclear Export (SINE)

- **Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export**
- **XPO1 is elevated in Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), NHL and other malignancies**
- **Exportin 1 (XPO1, CRM1) is the exclusive nuclear exporter of most TSPs**
- **Selinexor (KPT-330) is a covalent, oral Selective Inhibitor of Nuclear Export (SINE) that blocks XPO1**



- Selinexor forces nuclear retention and activation of *multiple* TSPs
- Selinexor reduces proto-oncogene proteins including Flt3, c-Kit,MYC, BCL2/BCL6, MDM2 Cyclin D and elevates IκB, leading to inhibition of NF-κB
- Selinexor shows robust anti-cancer activity in multiple preclinical models of AML and other hematologic malignancies, largely independent of cytogenetics
- We present summary data from ongoing first-in-human Phase 1 study of oral selinexor in hematological malignancies (NCT01607892)

Phase 1, Open Label, Dose Escalation Study in Patients with Advanced, Hematological Malignancies

Study Design:

- Arm 2 included patients with AML.
- Doses 16, 23, 30, 40, 55 and 70 mg/m^2; 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly) or 4 doses/cycle (once weekly)
- Modified “3+3” design

Major Eligibility Criteria:

- Patients with AML with no available standard treatments
- ECOG 0-1
- Documented progression at study entry

DLT Definition

- ≥ 3 missed doses in 28 days at target dose
- Discontinuation of a patient due to a toxicity in Cycle 1

Non Hematologic:

- Grade ≥3 excluding nausea/vomiting or electrolyte imbalances amenable to supportive care and AST/ALT lasting less than 7 days
- Grade ≥3 fatigue lasting ≥5 days while taking supportive care

Selinexor Phase 1 Study in AML: Patient Demographics

Characteristic	N=65
Mean Age (range)	67 (24 – 89)
Male / Female	34 Males : 31 Females
Mean Prior Lines of Treatment (range)	3 (1 – 7)
ECOG performance status, 0/1	18 / 47

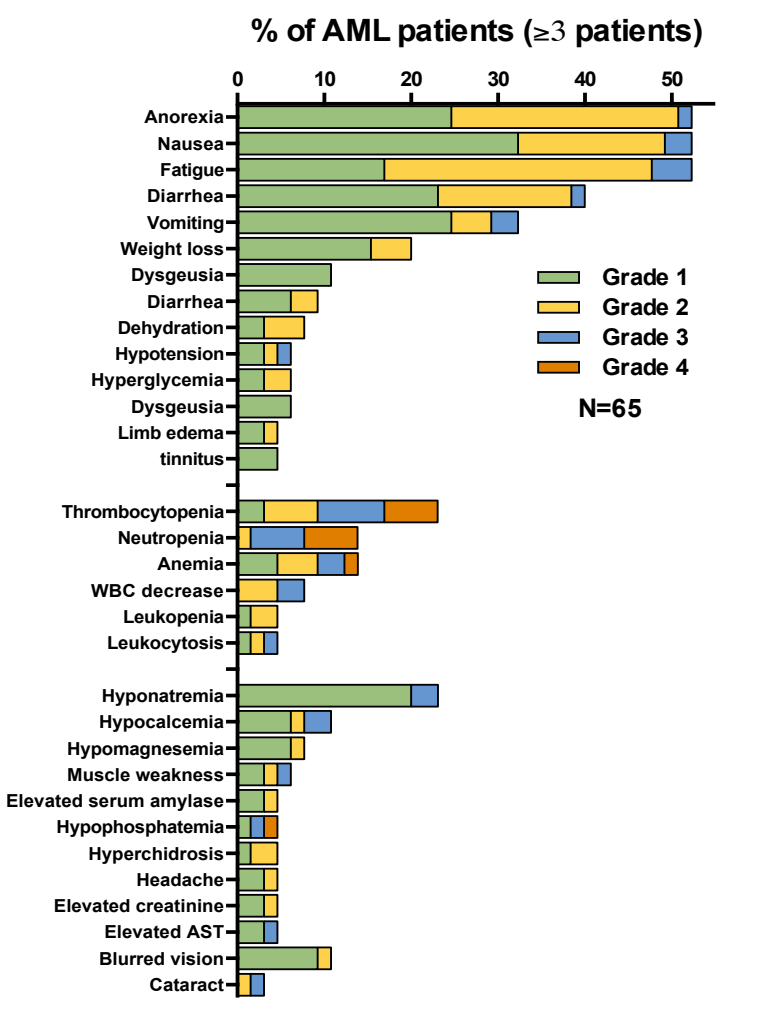
AML Cytogenetic Risk	
Favorable	10 (15%)
Intermediate	28 (43%)
Adverse	23 (35%)
Unknown	4 (6%)

Therapy Line for Disease	
2nd Line AML	15 (23%)
3rd Line AML	13 (20%)
> 3rd Line AML	28 (43%)
Unknown	9 (14%)

Summary: Patients with AML enrolled in KCP-330-001 have heavily pretreated AML with disease that is progressing on study entry. The majority of patients have intermediate or poor cytogenetic risk >50% are over 67 years old.

Selinexor Phase 1 Study: Safety

Selinexor Adverse Events (AEs, Overall)



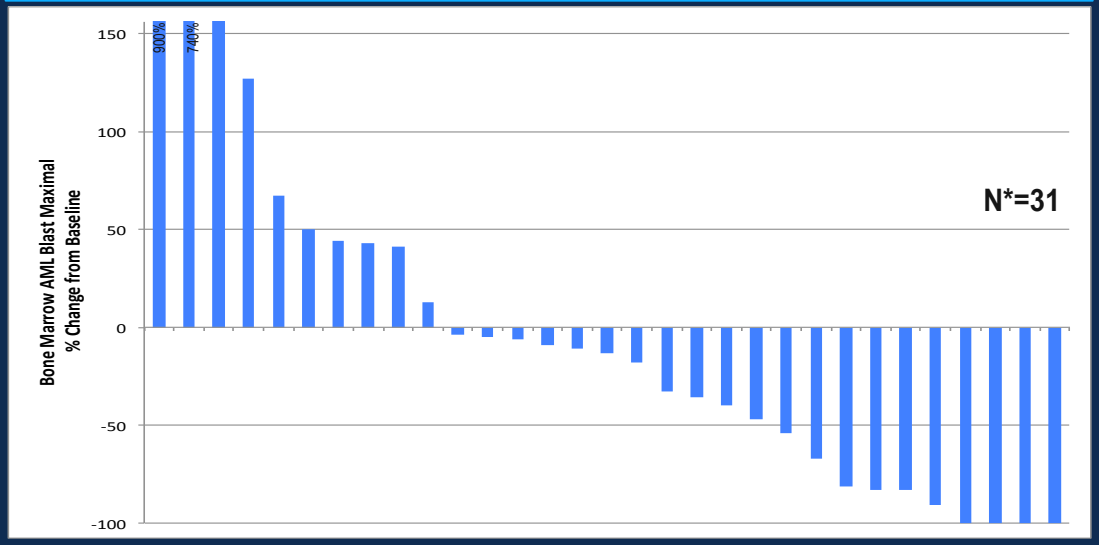
- No DLTs were observed at any dose (16 – 70mg/m^2 administered 2-3 times weekly)
- The majority of adverse events are reversible Grade 1 and 2, primarily anorexia, nausea and fatigue.
- AEs are more common in Cycle 1, and decline in Cycles 2-3 with supportive care and some dose reductions.
- AEs did not show a clear dose response on incidence/severity, likely due to the implementation of required supportive care at higher doses, including appetite stimulants and anti-nausea agents.
- Cumulative toxicities are uncommon, and major organ dysfunction is rare.

Recommended Phase 2/3 Dose of Oral Selinexor for AML is 55 mg/m^2 twice weekly

Selinexor Phase 1 Study: Efficacy and Conclusions

Best Responses in Patients with AML as 13-May-2014									
N	**DCR**	**ORR**	**CR**	**CR(i)**	**PR**	**MLFS**	**SD**	**PD**	**NE**
63	31	10	5	2	1	2	21	16	16
%	49%	16%	8%	3%	2%	3%	33%	25%	25%

Selinexor Induces Blast Count Reductions



- Selinexor (KPT-330) is a covalent, oral SINE XPO1 antagonist that forces nuclear restoration and reactivation of TSP and reduces proto-oncogenes leading to the selective apoptosis of AML cells.
- Common AEs are reversible nausea, anorexia and fatigue; extended dosing feasible with appetite stimulants and anti-nausea agents
- Objective Responses and reduction in BM blasts were observed in heavily pre-treated patients with AML
- Randomized Study of Selinexor 55mg/m^2 PO BIW vs. Physician's Choice 2nd line elderly AML has begun
- Combination studies have begun or are planned.

BM Blast cells were evaluated at screening and at the end of each cycle

* Excludes 14 patients who withdrew consent & 18 patients who clinically progressed before post treatment bone marrow biopsy

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