A First-in-Class, First-in-Human Phase I Trial of KPT-330 (Selinexor), a Selective Inhibitor of Nuclear Export (SINE) in Patients (pts) with Advanced Solid Tumors

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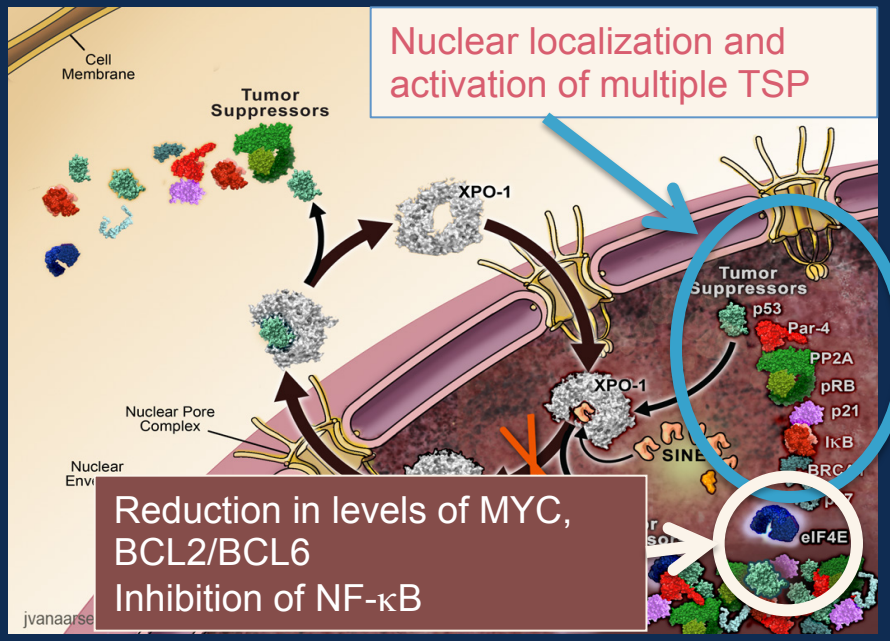
Selective Inhibitors of Nuclear Export (SINE)

- **Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export**
- **XPO1 is elevated in solid tumors (e.g. , melanoma, ovarian, cervical, pancreas, prostate cancers) and hematological malignancies**
- **Exportin 1 (XPO1, CRM1) is the *only* nuclear exporter of most TSPs**
- **Selinexor (KPT-330) is a covalent, oral selective inhibitor of nuclear export (SINE) XPO1**



- Selinexor forces nuclear retention and activation of *multiple* TSPs
- Selinexor treatment reduces proto-oncogene proteins including MYC, BCL2/BCL6, MDM2, Cyclin D and elevates IkB, leading to inhibition of NF-kB
- Selinexor shows robust anti-cancer activity in multiple preclinical models of solid tumors including melanoma, GBM, prostate, ovarian, lung, colon and pancreatic cancers
- Summary data from ongoing first in human phase 1 study of oral Selinexor in solid tumors malignancies (NCT01607905)

Phase 1, Open Label, Dose Escalation Study at 6 Sites in US, Canada and Denmark in Patients with Advanced, Metastatic Solid Tumors

Study Design:

- Doses 3,6,12,17,23,30,35,40,50,65 and 85mg/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:

- Solid tumor patients 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 (nausea/vomiting, electrolyte imbalances must be supported first and AST/ALT lasting more than 7 days)
- Grade ≥3 fatigue lasting ≥5 days while taking supportive care

Hematologic:

- Grade 4 neutropenia ≥7 days
- Febrile neutropenia
- Grade 4 thrombocytopenia that persists for ≥5 days, or Grade ≥3 with bleeding

Selinexor Phase 1 Study: Patient Demographics and Dose Limiting Toxicities

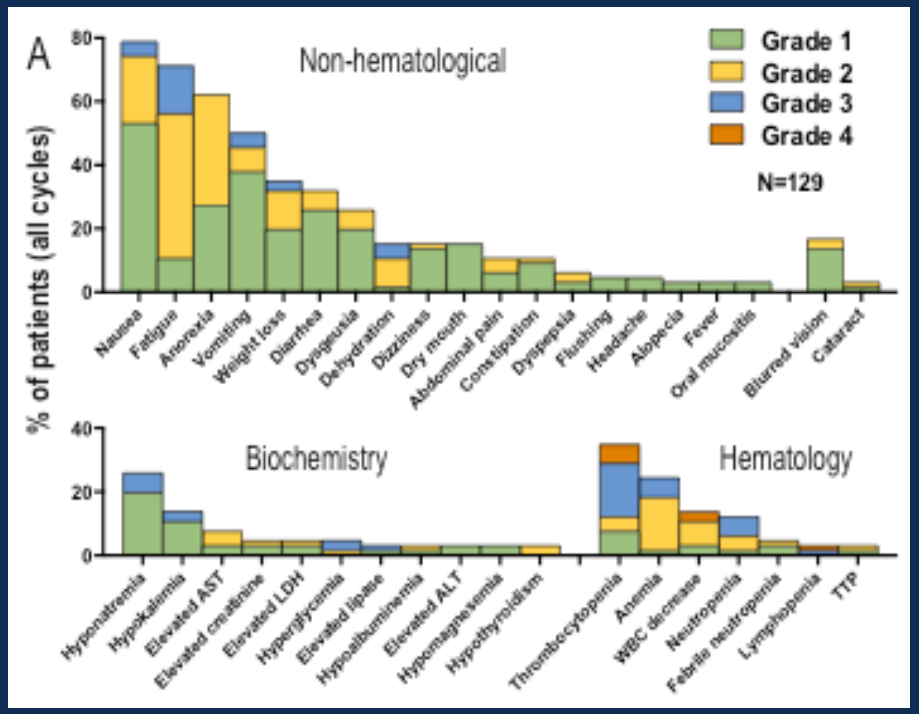
Characteristic N=129	
Mean Age (Range)	59 (29 -79)
Male to Female	75 Males : 54 Females
Mean Prior Treatment Regiments (Range)	3.7 (1-10)
ECOG PS 0:1	31:98

Dose	Doses/Cycle	DLT
40 mg/m^2	10	Grade 3 dehydration
40 mg/m^2	10	Missed 3 doses in cycle 1 due to drug AE (Grade ≤2)
35 mg/m^2	8	Grade 3 Nausea, Vomiting, Fatigue
85 mg/m^2	8	Grade 3 Hyponatremia
85 mg/m^2	8	Acute cerebellar syndrome with markedly improving ataxia and dysarthria. No other CNS toxicities were observed in the other >300 patients treated with selinexor

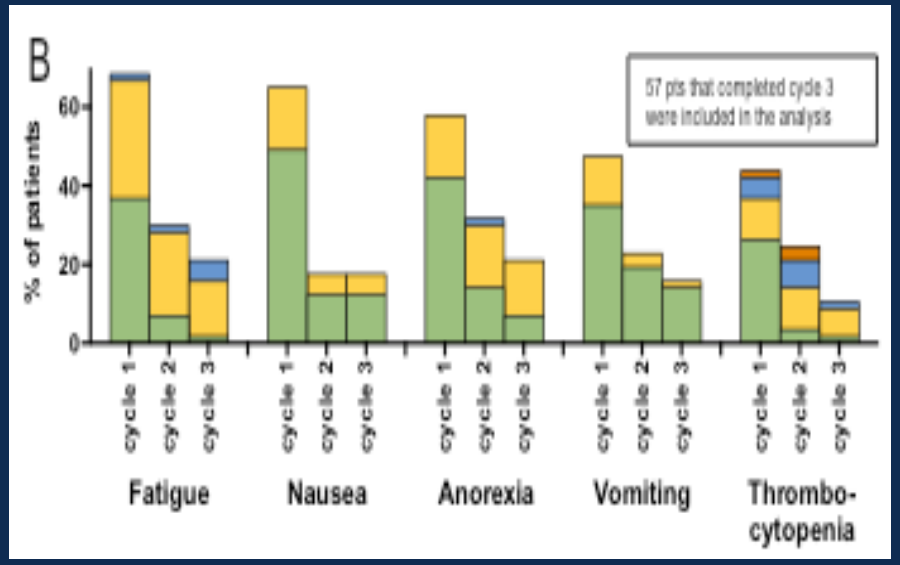
The MTD / RP2D of Oral Selinexor is 65 mg/m^2 twice weekly

Selinexor Phase 1 Study: Safety

Selinexor Adverse Events (Overall)

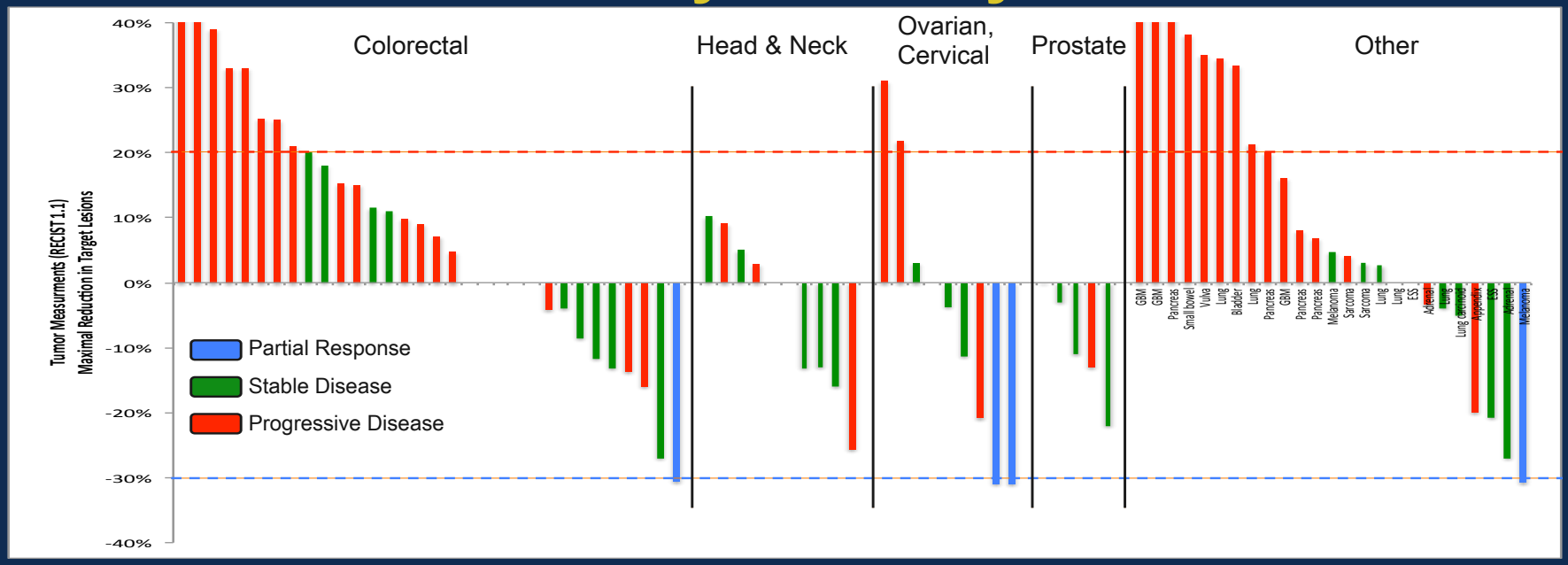


Common Selinexor Adverse Events with Selinexor in N=57 Pts Who Completed ≥3 Cycles



- The majority of adverse events are reversible Grade 1 and 2, primarily nausea, anorexia and fatigue. Thrombocytopenia is the most common hematologic adverse event, rarely with bleeding
- AEs are more common in Cycle 1, and decline in Cycles 2-3 due to supportive care and dose reductions
- The lack of dose-response with many adverse events is likely due to the implementation of required supportive care: appetite stimulants and anti-nausea agents
- Cumulative toxicities are uncommon, and major organ dysfunction is rare

Selinexor Phase 1 Study: Efficacy and Conclusions



Cancer Type	N	PRs and SD (%)	PR (%)	SD (%)	PD (%)
Colorectal	39	14 (36%)	1 (3%)	13 (33%)	25 (64%)
Head & Neck	14	9 (64%)	--	9 (64%)	5 (36%)
Prostate	8	7 (88%)	--	7 (88%)	1 (12%)
Cervical	5	4 (80%)	1 (20%)	3 (60%)	1 (20%)
Ovarian	5	3 (60%)	1 (20%)	2 (40%)	2 (40%)
GBM	5	--	--	--	5 (100%)
Melanoma	3	2 (67%)	1 (33%)	1 (33%)	1 (33%)
Sarcoma	8	7 (88%)	--	7 (88%)	1 (12%)
Other	19	6 (32%)	--	6 (32%)	13 (68%)
Total	**106**	**52 (49%)**	**4 (4%)**	**48 (45%)**	**54 (51%)**

- 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 cancer cells
- Common AEs are reversible nausea, anorexia, fatigue and thrombocytopenia
- Extended dosing feasible with appetite stimulants and anti-nausea agents
- Selinexor can arrest disease progression and induce responses across a variety of heavily pretreated, progressing solid tumors
- Phase 2 single agent (RP2D: 65mg/m^2 PO BIW) and combination studies have begun or are planned

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