A Phase 1/2 Study of the Second Generation Selective Inhibitor of Nuclear Export (SINE) Compound, KPT-8602, in Patients with Relapsed Refractory Multiple Myeloma

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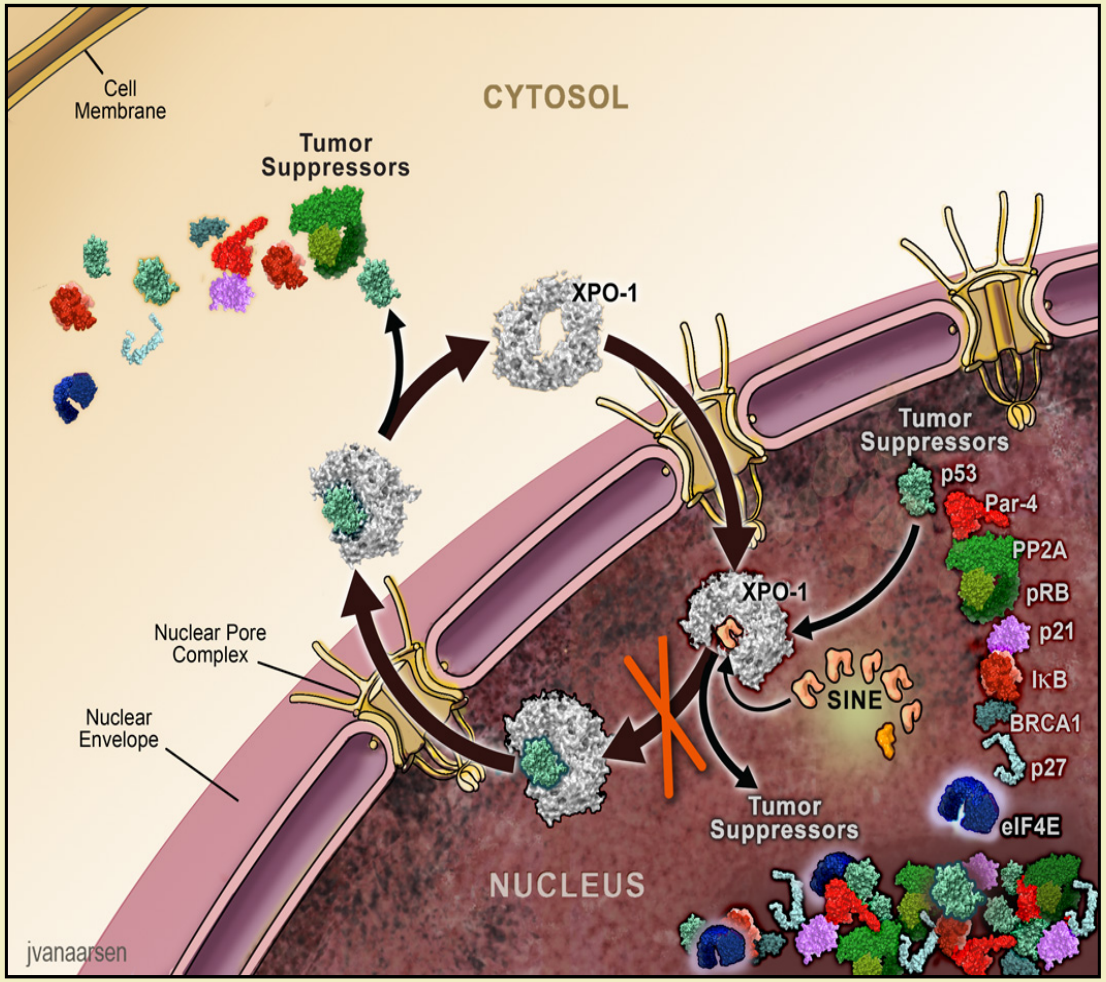
KPT-8602 Mechanism of Action



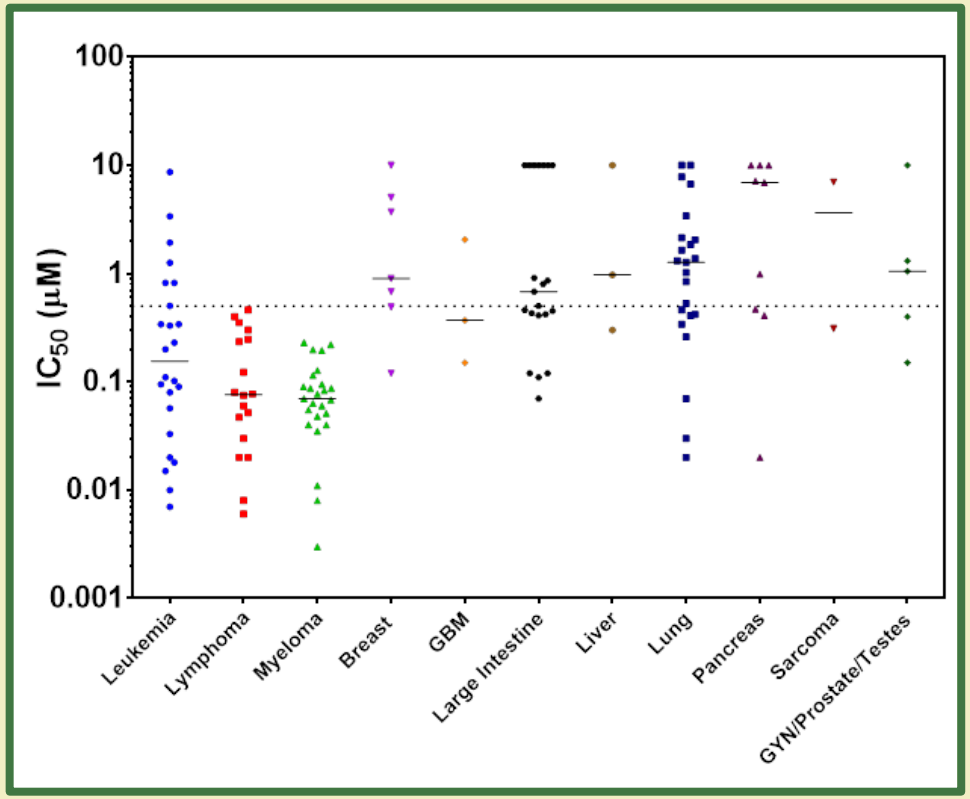
- XPO1 is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs
- Inhibition of XPO1 leads to TSP reactivation, induced GR activity in the presence of steroids, and reduction in c-Myc, Cyclin D1 and other oncoproteins with eIF4E-bound mRNAs
- KPT-8602 is a second generation oral SINE compound with minimal brain penetration that showed improved tolerability in animal models vs selinexor

Rationale for the KPT-8602 Treatment of MM

- By inhibiting XPO1, KPT-8602 reactivates multiple TSPs relevant to MM including p53, IκB and FOXO, and overcomes MDM2-mediated p53 degradation
- KPT-8602 increases IκB levels in the nucleus, which inhibits NF-κB transcriptional activity commonly found in MM

KPT-8602 Preclinical Activity

In vitro potency of KPT-8602 in cancer cell lines

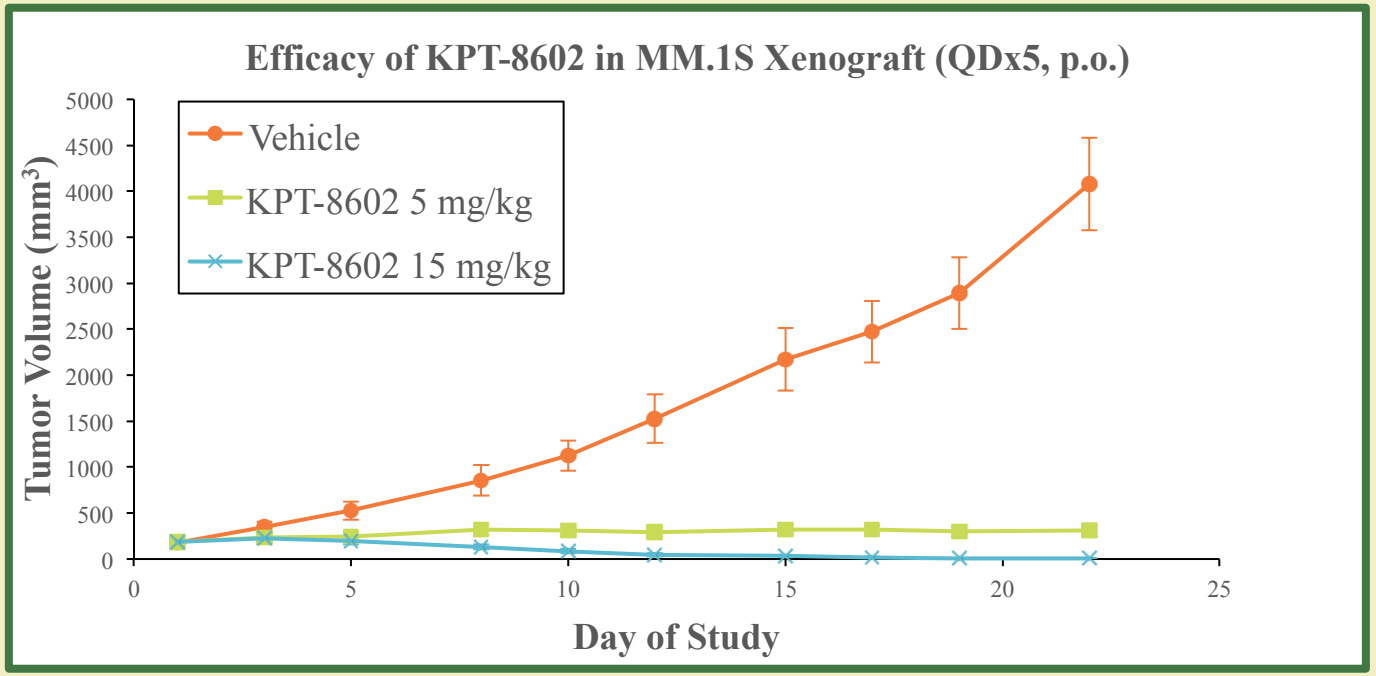


KPT-8602 shows *in vitro* potency across a variety of cancer cell lines and *in vivo* efficacy in mouse xenografts

In vitro potency of KPT-8602 in MM cell lines

Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)	Cell Line	IC_{50} (nM)
KMS11	3	OPM2	77	KHM1B	11	EJM	87	U266B1	230	ANBL-6	220
MM1R	8	AMO1	83	HUNS1	35	MOLP2	87	COLO677	70	KMM1	48
L363	40	KMS28BM	90	JJN3	60	KMS27	195	KMS12BM	127	KMS34	115
LP1	40	KMS21BM	95	KMS26	63	MOLP8	198	KMS20	55	SKMM2	68

Oral KPT-8602 is efficacious in a mouse xenograft of MM



Study Design

KCP-8602-801 is a Phase 1/2 open-label study of the safety, tolerability and efficacy of the Selective Inhibitor of Nuclear Export (SINE) compound KPT-8602 in patients with Relapsed/ Refractory Multiple Myeloma (RRMM)

Dose Escalation (Phase I)

Part A
KPT-8602 Single Agent
To determine the RP2D or MTD of KPT-8602 (possibility to add low dose dex)

Part B
KPT-8602 + dexamethasone
To determine the RP2D or MTD of KPT-8602 + low dose dex

Expansion (Phase II)

KPT-8602 ± dexamethasone
~ 20 patients for safety, tolerability, and preliminary evidence of anti-tumor activity of RP2D or MTD of KPT-8602 ± dex

- **Primary Objectives - Phase I:**
  - Determine the MTD for KPT-8602 administered alone (Part A) or in combination with dexamethasone (Part B)
  - Determine the RP2D, the schedule, and evaluate the safety and tolerability, including dose-limiting toxicity for KPT-8602 +/- dex
- **Primary Objectives - Phase II:**
  - Evaluate the safety / tolerability of the RP2D or MTD for KPT-8602 +/- dex and the dosing schedule(s)
  - Determine the preliminary evidence of anti-tumor activity of KPT-8602 at the RP2D or MTD +/- dex according to International Myeloma Working Group (IMWG) Response Criteria assessed by: Overall Response Rate (**ORR**), Overall Survival (**OS**), Clinical Benefit Rate (**CBR**), Duration of Clinical Benefit, Progression-free Survival (**PFS**)
- **Dose Limiting Toxicity (DLT) Definition**
  - DLT is an AE or abnormal laboratory value (NCI CTCAE v. 4.03) that occurs within the first 28 days of treatment with KPT-8602 or
  - >4 Missed doses of KPT-8602 due to study-drug related toxicity during cycle 1 or
  - Grade ≥3 nausea/vomiting despite optimal supportive medications; any other Grade ≥3 non-hematological toxicity except alopecia or electrolyte abnormalities correctable with supportive therapy or
  - Grade 4 neutropenia lasting > 5 days; febrile neutropenia (ANC<1E9/L, fever>38.5 ^{o}C); Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion is considered a DLT

Patient Population

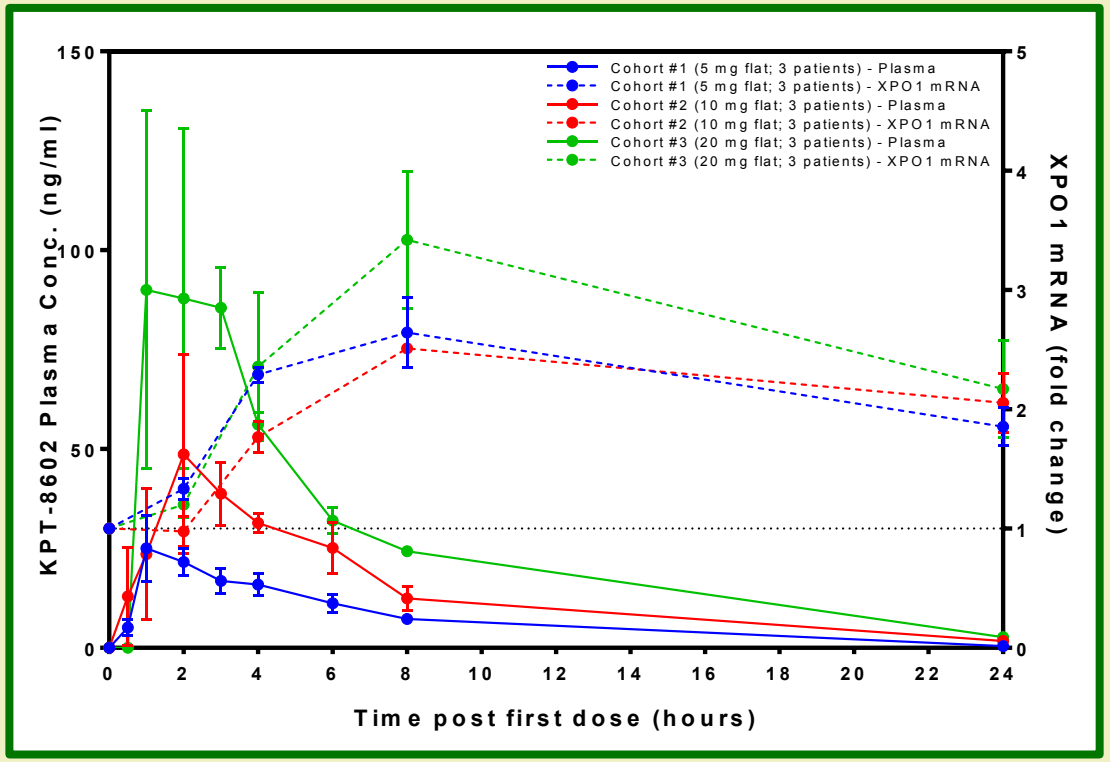
- Patients with confirmed MM, measurable disease per IMWG
- Symptomatic relapsed or refractory MM (based on IMWG guidelines), disease progression, requiring current treatment
- Previously treated with ≥3 prior lines of therapy including: alkylator, immunomodulatory drug, proteasome inhibitor, steroid
- MM refractory to the most recent anti-MM regimen

Patient Characteristics, Cohorts, & Dosing Schedule

Characteristic	Dose Escalation N=12
Median Age (Range)	63.5 (54 – 83)
Male : Female	5 : 7
Median Prior Treatment Regimens (Range)	8 (3 – 15)
Median Prior Anti-MM Agents (Range)	9 (4 – 15)
ISS at Diagnosis (I : II : III : Unk)	3 : 1 : 6 : 2
Median Time Since Diagnosis (Range)	6 years (4.2 – 11.6)
Prior PI and IMID %	100%
Prior Anti-CD38 Ab %	67%
Disease Refractory to Last Therapy %	100%

Cohort	Dose / Schedule	Patients Enrolled
1	5 mg / qdx5	3
2	10 mg / qdx5	3
3	20 mg / qdx5	3
4	30 mg / qdx5	3
5	40 mg / qdx5	enrolling

Pharmacokinetic vs Pharmacodynamic Relationships



Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng*h/mL)	$t_{½}$ (h)	XPO1 mRNA (F_{max})
5	30.6	1.0	164	4.0	2.64
10	60.5	3.0	347	5.1	2.51
20	125	1.0	650	5.0	3.42

- No substantial accumulation evident
- Dose proportional increase in KPT-8602 plasma exposure from 5, 10, and 20 mg dose levels
- KPT-8602 induces XPO1 mRNA expression in PBMCs

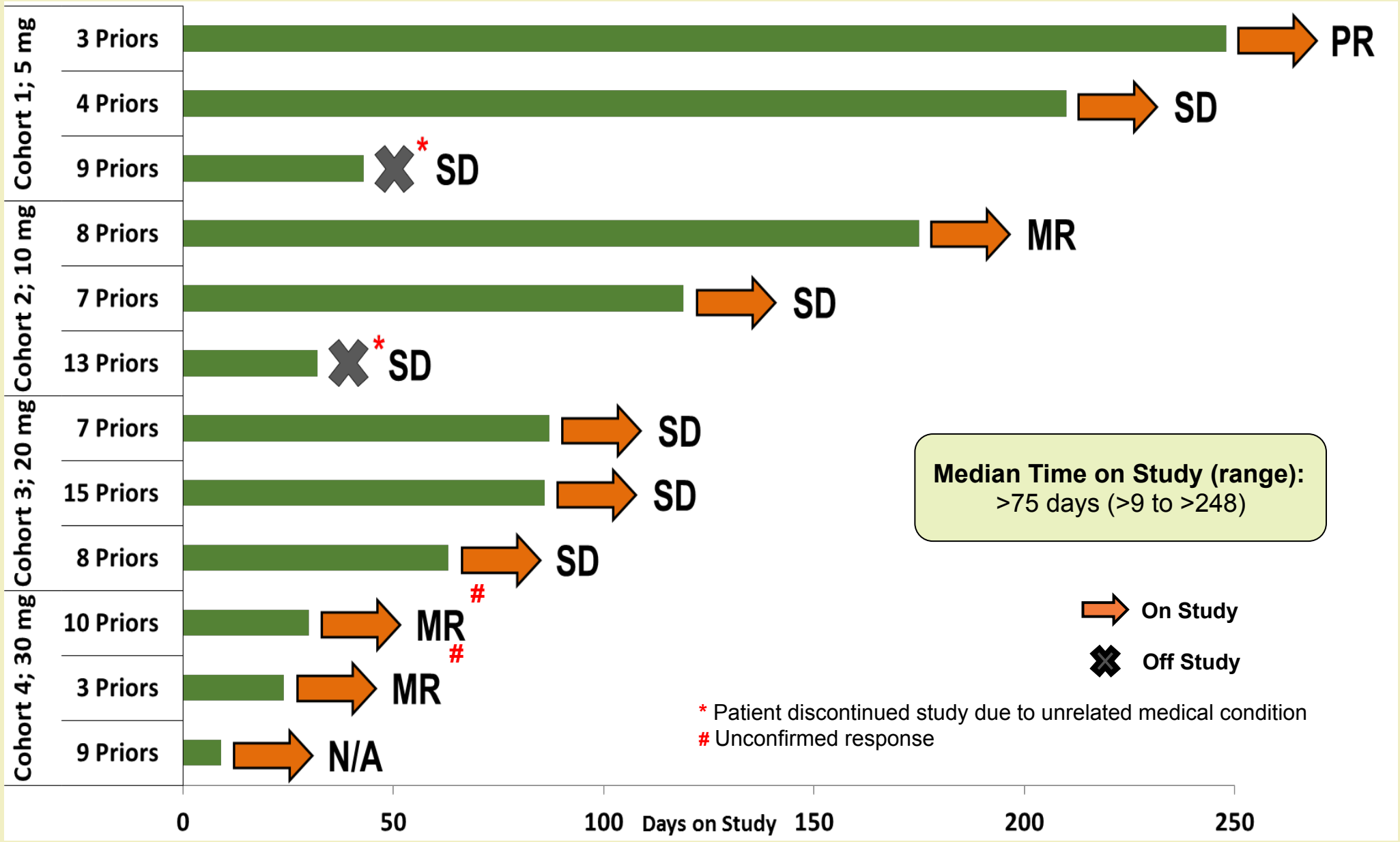
Related Adverse Events

AE Term	Cohort 1 – 5 mg (N=3)				Cohort 2 – 10 mg (N=3)				Cohort 3 – 20 mg (N=3)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	1	1	--	--	--	--	1	1	--	--	1	--
Thrombocytopenia	1	1	--	--	--	1	--	--	2	1	--	--
Leukopenia	1	--	--	--	--	--	2	--	--	1	--	--
Anemia	--	--	--	--	--	1	--	--	--	1	--	--
Nausea	2	--	--	--	--	--	--	--	1	--	--	--
Diarrhea	1	--	--	--	--	1	--	--	--	--	--	--
Fatigue	--	1	--	--	1	--	--	--	--	--	--	--

Adverse Events (AE) Summary

- 9 patients were evaluable for safety (3 patients pending) – no DLTs observed
- Hematologic events were most common as expected for this patient population
- No >Grade 2 AEs at 5 mg dose level, no >Grade 1 nausea across all cohorts
- No anorexia observed
- No apparent dose relationship to reported incidents of nausea, diarrhea, and fatigue
- Cohort 4 (30 mg) cleared DLT; AE data pending for this cohort

Cohort, Prior Therapies, Time on Study, Response



Anti-MM Activity

Best Response as of 18-November-2016						
Investigational Drug	**N**	**ORR (%)**	**PR (%)**	**MR[#] (%)**	**SD (%)**	**CBR (%)**
KPT-8602	11*	1 (9%)	1 (9%)	3 (27%)	7 (64%)	4 (36%)

Responses were adjudicated according to the *International Myeloma Working Group* criteria. **ORR**=Overall Response Rate (VGPR+PR), **PR**=Partial Response, **MR**=Minor Response, **SD**=Stable Disease, **CBR**=Clinical Benefit Rate (VGPR+PR+MR) Responses as of 18-November-2016 based on interim unaudited data. *1 patient pending evaluation; #2 unconfirmed MRs.

Summary and Conclusions

- In patients with refractory MM whose disease has progressed despite most available therapies, KPT-8602 alone or in combination with dexamethasone induces responses or disease stabilization
- To date (N=12), disease progression has not occurred, with the majority of patients having reductions in M-protein
- Dose escalation is still ongoing in Part A (without immediate steroids); tolerability is good; no DLTs have been observed
- As anticipated in this population, the most common adverse effects have been cytopenias (with minimal clinical sequelae)
- Anorexia and weight loss have not been observed to date; fatigue, nausea and diarrhea have been low
- Dexamethasone can safely be given with KPT-8602 and it may improve KPT-8602 anti-MM activity
- The current protocol will be amended to include patients with AML and CLL, along with solid tumors (colorectal cancer and castrate resistant prostate cancer)