Safety, Efficacy, and Determination of the Recommended Phase 2 Dose for the Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330)

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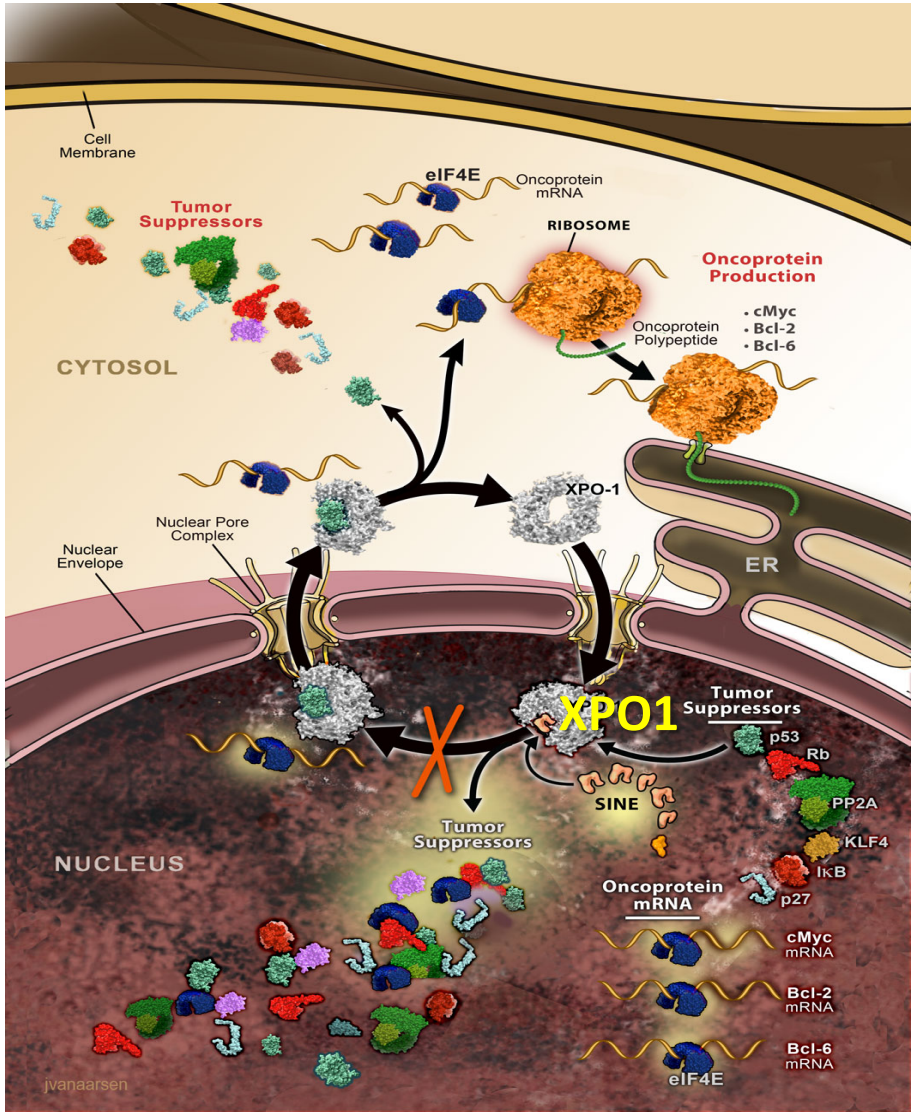
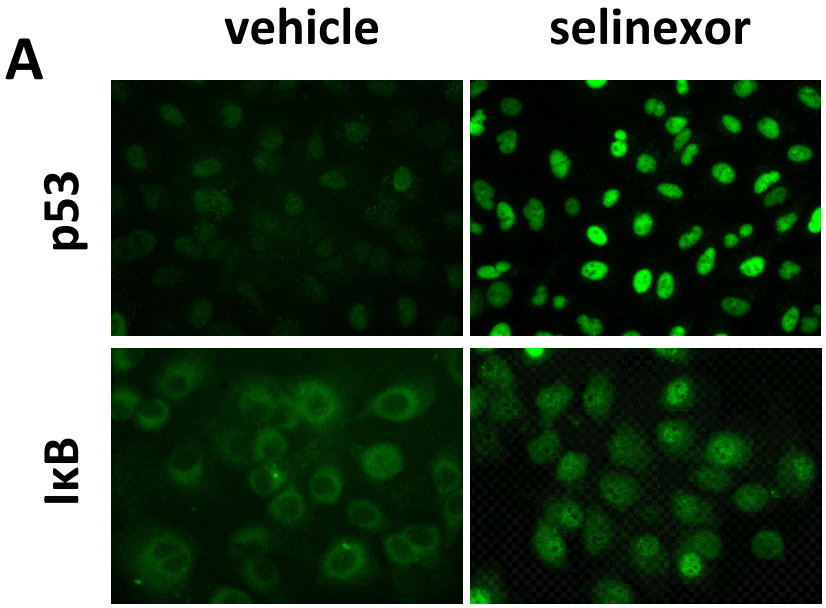
Major Stockholder	NA
Employee, Speakers Bureau	NA

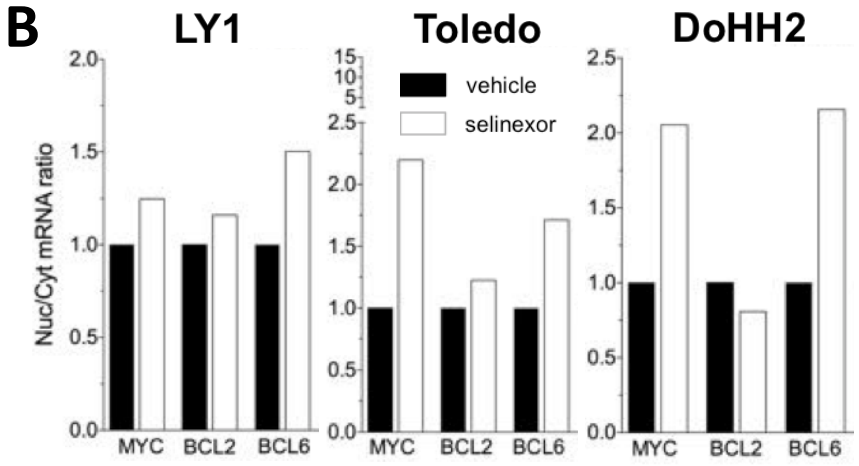
Selinexor Mechanism of Action

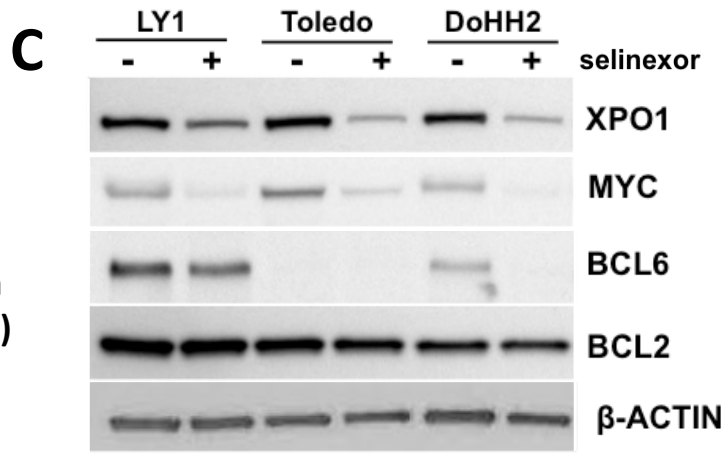
- XPO1 is a nuclear export protein that transports protein cargos from the nucleus to the cytoplasm
- XPO1 is over-expressed in many cancers, including hematologic malignancies
- Selinexor is a Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1, forcing nuclear retention of tumor suppressor proteins (TSPs) and other key regulators of cancer growth and survival
- Key anti-cancer effects:
  - Nuclear retention and reactivation of TSPs (e.g. p53, BRCA1/2, Rb) and IκB
  - Blockade eIF4e-mediated transport of mRNAs leading to decreased oncoprotein expression (e.g. c-Myc, Bcl-2/6)



Induced nuclear retention of TSPs and oncogene mRNAs







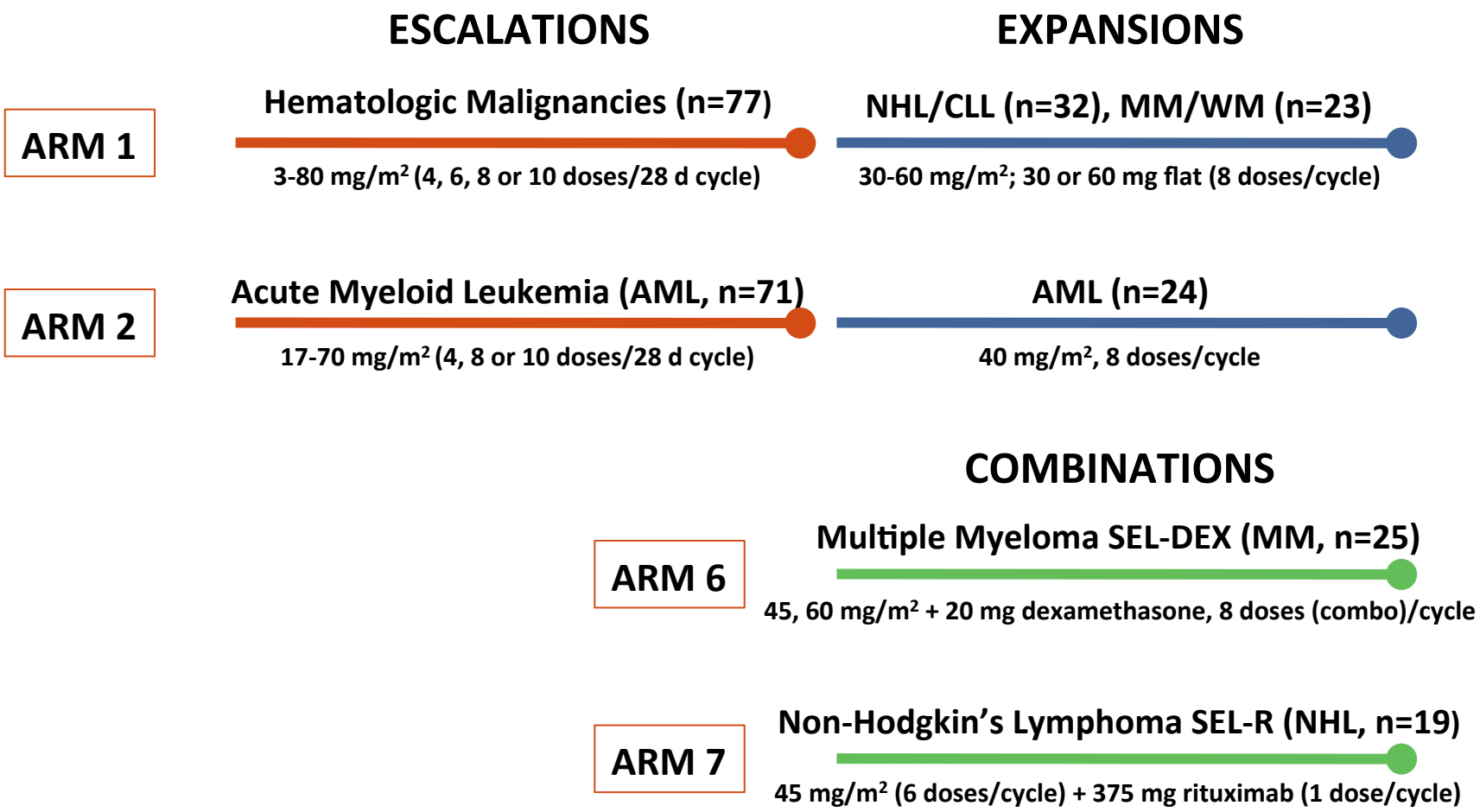
(A) Selinexor (1 µM) induced nuclear retention of tumor suppressor p53 and NF-κB inhibitor IκB in cell culture after 4 h

(B) And (C) Selinexor (0.5 µM) induced nuclear retention of mRNA for MYC and BCL6 and reduced their protein expression after 24 h in DLBCL cell lines (Marullo et al. Cancer Res August 1, 2015 75; LB-062)

Phase 1 study overview

- Phase 1 dose escalation and expansion study of selinexor in patients with advanced hematological malignancies
- Primary objectives to evaluate safety and tolerability of selinexor and determine the recommended Phase 2 dose (RP2D)
- Secondary Objectives to evaluate PK, PD and efficacy
- Main Inclusion Criteria
  - Patients ≥18 years old, ECOG performance status 0-1, no available standard treatments
  - ANC >1000/µL, Platelets >30,000/µL
  - Documented disease progression at study entry

Selinexor Phase 1 study arms

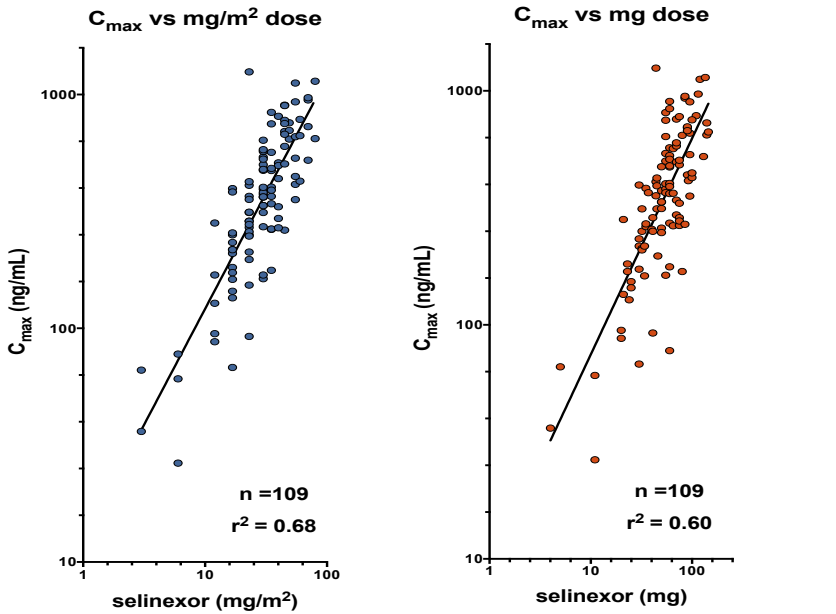


ARMS 3-5 expansions included 14 patients (6 TCL, 1 CML, 7 ALL), 30-40 mg/m², 8 doses/cycle

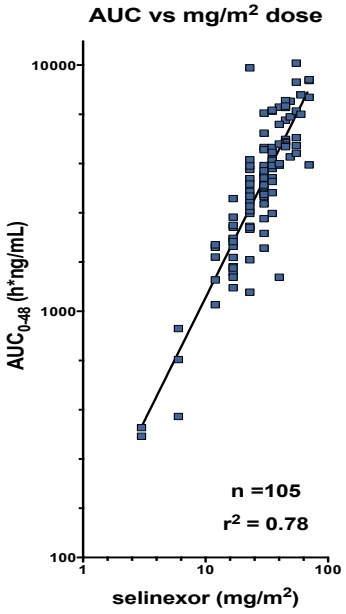
Pharmacokinetic and pharmacodynamic studies

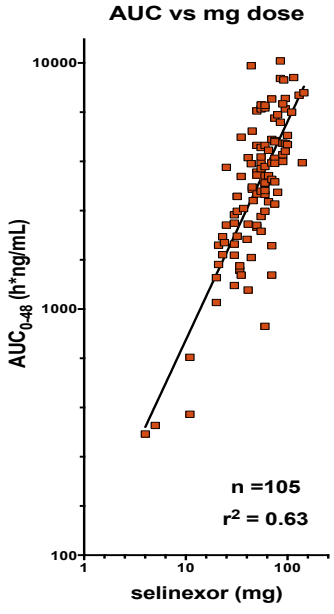
- Pharmacokinetics showed similar C_{max} and AUC with BSA-based (3-80 mg/m^2 range) or flat dosing (4-175 mg range)
- Pharmacodynamic studies showed sustained response >48hrs

Cmax



AUC





- **Supports flat dosing on an intermittent schedule**

Selinexor Phase 1 Demographics

Patient and disease characteristics		N = 266*
Median Age (Range)		64 (23-89)
Acute Myeloid Leukemia (AML)	No. of patients	95
	Median prior regimens (range)	3 (0-8)
	Cytogenetic Risk (Good / Intermediate / Poor)	14 / 25 / 30
	Flt3 mutated	11
Non-Hodgkin's Lymphoma (NHL)	No. of patients	66*
	Median prior regimens (range)	4 (1-12)
	DLBCL (Total / transformed / double hit)	30 / 12 / 6
	Richter's Transformation	8
Multiple Myeloma (MM) / Waldenstrom's macroglobulinemia (WM)	No. of patients	81/3
	Median prior regimens (range)	6 (1-16)
	Proteasome inhibitor and IMiD refractory	62
	Bortezomib, carfilzomib, lenalidomide and pomalidomide exposed	30
ALL / CLL / TCL / CML	No. of patients	7 / 7 / 6 / 1

*does not include NHL rituximab combination pts in Arm 7

Adverse events, DLTs and MTD

Common related AEs - all grades (≥10% of patients, n=266)

ADVERSE EVENTS	Grade 1/2 (%)	Grade 3/4 (%)	Total (%)
GI/CONSTITUTIONAL			
Nausea	60	3	63
Fatigue	49	13	62
Anorexia	52	5	57
Vomiting	35	3	38
Diarrhea	32	3	35
Weight loss	25	2	27
Dysgeusia	18	-	18
Dehydration	11	5	16
HEMATOLOGIC			
Thrombocytopenia	7	34	41
Anemia	9	21	30
Neutropenia	5	20	25
Leukopenia	3	10	13
OTHER			
Hyponatremia	12	13	25
Blurred vision	17	-	17
Muscle weakness	8	3	12
Dizziness	12	-	12

Common grade 3/4 AEs (≥5% of patients, n=266)

ADVERSE EVENTS	Related (%)
HEMATOLOGIC	
Thrombocytopenia	34
Anemia	21
Neutropenia	20
Leukopenia	10
BIOCHEMISTRY	
Hyponatremia	13
Hypokalemia	2
Hyperglycemia	1
CONSTITUTIONAL	
Fatigue	13
INFECTION	
Febrile neutropenia	5
Lung infection	1
GASTROINTESTINAL	
Dehydration	5
Anorexia	5
OTHER	
Muscle weakness	3
Dyspnea	-

- **Most common non-hematologic toxicities were GI and fatigue (Grade 1/2)**
- **Most common Grade 3/4 toxicities were hematologic**
- **4 DLTs were observed**
  - Grade 4 thrombocytopenia (2)
  - Missed doses due to Grade 2 fatigue (1)
  - Withdrawal (1)
- **MTD was not reached**

Serious Adverse Events

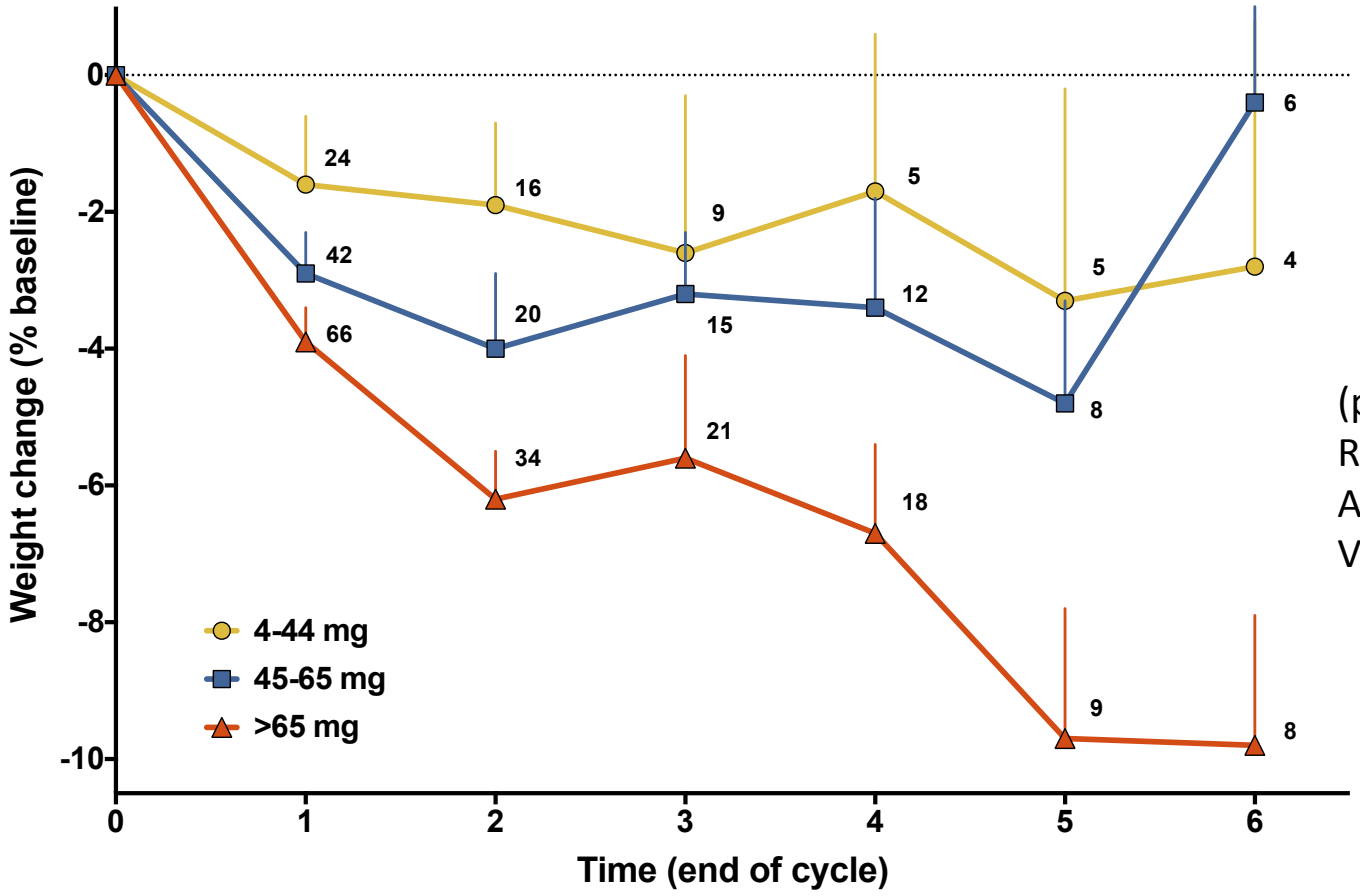
Category	Patients	Patients with SAEs	Total SAEs	Related SAEs	Fatal SAEs
All Patients	266	71 (27%)	119	11	45
Heme Cancer					
AML	95	50 (53%)	85	6	38
MM	81	8 (10%)	16	5	2
NHL/CLL	73	10 (14%)	13	-	3
Other	17	3 (18%)	5	-	2
Sepsis					
AML	95	9 (9%)	9	-	8
NHL/CLL	73	2 (3%)	2	-	1
Pneumonia					
AML	95	7 (7%)	7	-	5
MM	81	1 (1%)	1	-	-
NHL/CLL	73	1 (1%)	1	-	1
Dose Range					
4–44 mg	52	11 (21%)	15	1	9
45–65 mg	75	17 (23%)	35	4	17
>65 mg	139	43 (31%)	69	6	19

- 119 SAEs in 71 of 266 patients (27%)
- All fatal SAEs (45) were unrelated to selinexor
- Most total / fatal SAEs were in AML

- Sepsis and pneumonia most common SAEs – mostly in AML

- SAEs were most frequent with >65 mg dosing of Selinexor

Patients lost significantly less weight on ≤65 mg selinexor



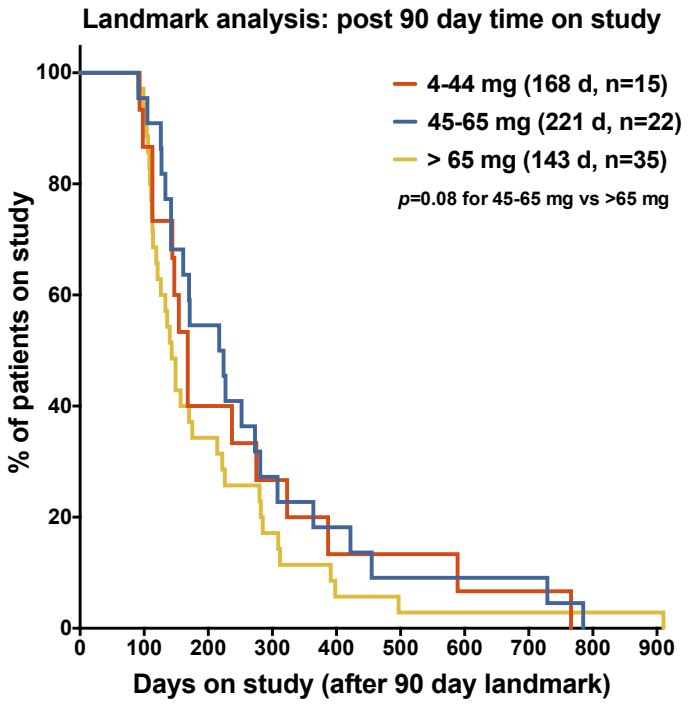
(p<0.001 by Random Model Analysis of Variance)

Number of patients per time point are indicated on the graph

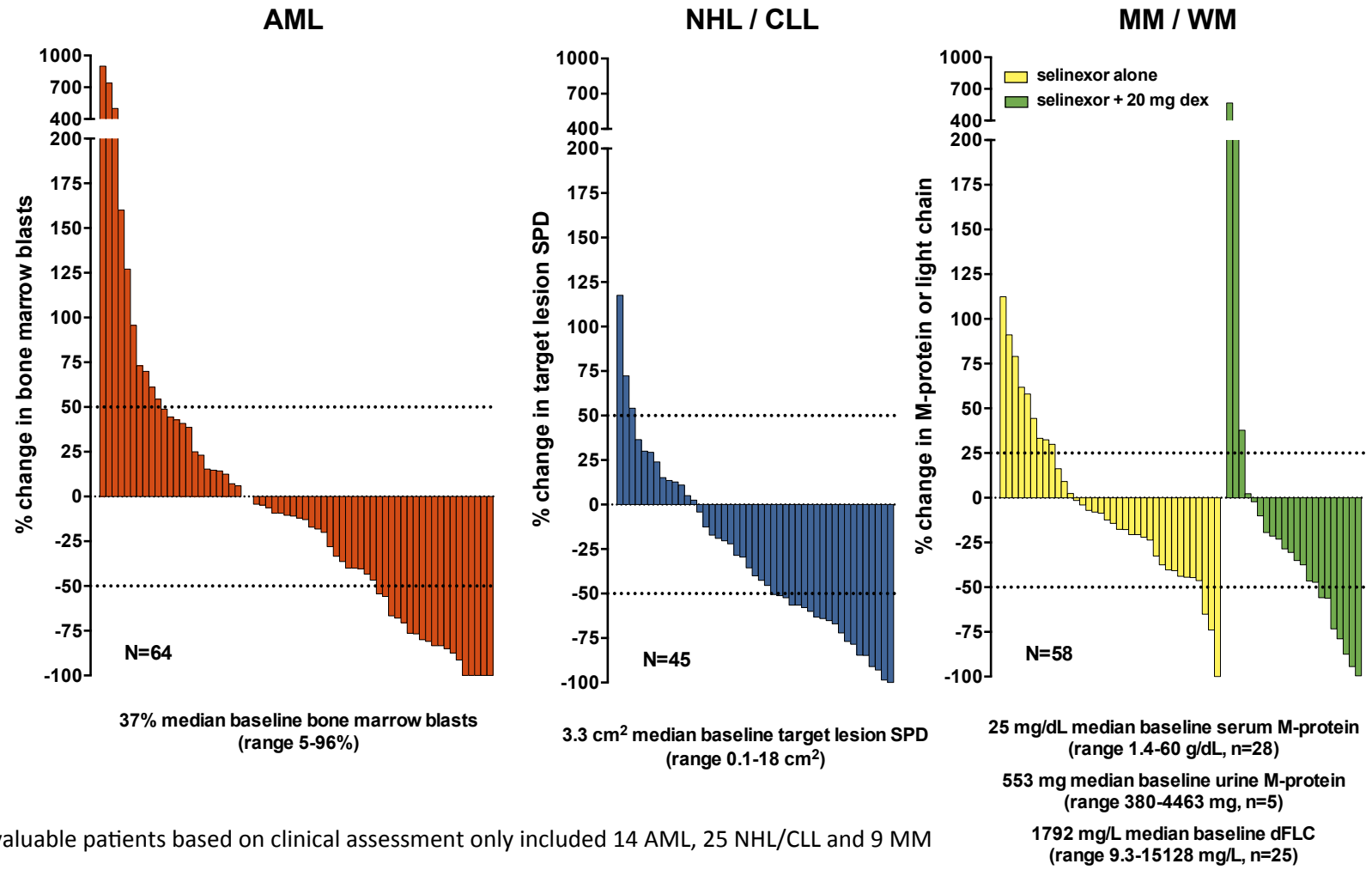
Longer time on study with doses ≤60 mg vs ≥65 mg

Heme Cancer	Evaluable Patients	Selinexor dose range	Median dose	Days on study (avg ± stdev)	% on study ≥4 months
All patients	40	4-44 mg	32 mg	120	31%
	64	45-65 mg	60 mg	120	27%
	117	> 65 mg	90 mg	90	19%
AML	9	21-44 mg	35 mg	59	0%
	17	45-65 mg	55 mg	70	24%
	52	> 65 mg	90 mg	82	19%
NHL/CLL	11	5-44 mg	30 mg	140	36%
	23	45-65 mg	60 mg	151	35%
	31	> 65 mg	105 mg	103	13%
MM/WM	19	4-44 mg	37 mg	141	35%
	13	45-65 mg	60 mg	113	23%
	11	>65 mg	80 mg	62	18%

For patients on >65 mg selinexor, time on study and % on study ≥4 months was decreased compared with lower dose ranges



Selinexor decreased tumor burden



Evaluable patients based on clinical assessment only included 14 AML, 25 NHL/CLL and 9 MM

Selinexor flat dose response rates

- **55-60 mg dosing of selinexor is associated with maximal response**

Heme Cancer	Evaluable Patients	Median dose	CR	PR	MR/SD	PD	ORR	DCR
All major indications	39	32 mg	2 (5%)	4 (10%)	20 (51%)	13 (33%)	6 (15%)	26 (66%)
	53	60 mg	5 (9%)	7 (13%)	25 (47%)	16 (30%)	12 (22%)	37 (69%)
	94	94 mg	5 (5%)	9 (10%)	42 (45%)	38 (40%)	14 (15%)	56 (60%)
AML	9	35 mg	1 (11%)	-	6 (67%)	2 (22%)	1 (11%)	7 (78%)
	17	55 mg	3 (18%)	-	8 (47%)	6 (35%)	3 (18%)	11 (65%)
	52	90 mg	4 (8%)	-	31 (60%)	17 (33%)	4 (8%)	36 (68%)
NHL/CLL	11	30 mg	1 (9%)	2 (18%)	4 (36%)	4 (36%)	3 (27%)	7 (63%)
	23	60 mg	2 (9%)	6 (26%)	10 (43%)	5 (22%)	8 (35%)	18 (78%)
	31	110 mg	1 (3%)	8 (26%)	5 (16%)	17 (55%)	9 (29%)	14 (45%)
MM/WD	19	37 mg	-	-	11 (58%)	8 (42%)	-	11 (58%)
	13	60 mg	-	1 (8%)	7 (54%)	5 (38%)	1 (8%)	8 (62%)
	11	80 mg	-	1 (9%)	6 (54%)	4 (36%)	1 (9%)	7 (63%)
MM (+ 20 mg dex)	11	75 mg	1 (9%)	5 (45%)	4 (36%)	1 (9%)	6 (54%)	10 (91%)
	12	105 mg	-	2 (17%)	6 (50%)	4 (33%)	2 (17%)	8 (67%)

DCR – disease control rate (SD or better)

Summary and Conclusions

- **Selinexor has been evaluated in 266 patients with hematological cancers in a Phase 1 trial at 3-80 mg/m^2 (4-175 mg) dosed 4, 6, 8 or 10 times per 4-week cycle**
- **Selinexor is safe and tolerable with broad anti-tumor activity across hematological cancers**
- **Pharmacokinetics for selinexor based on flat dose was comparable to BSA-based dose and pharmacodynamics support intermittent dosing**
- **The RP2D for selinexor is 60 mg (flat dose) twice weekly, based upon optimal therapeutic window and duration of treatment**

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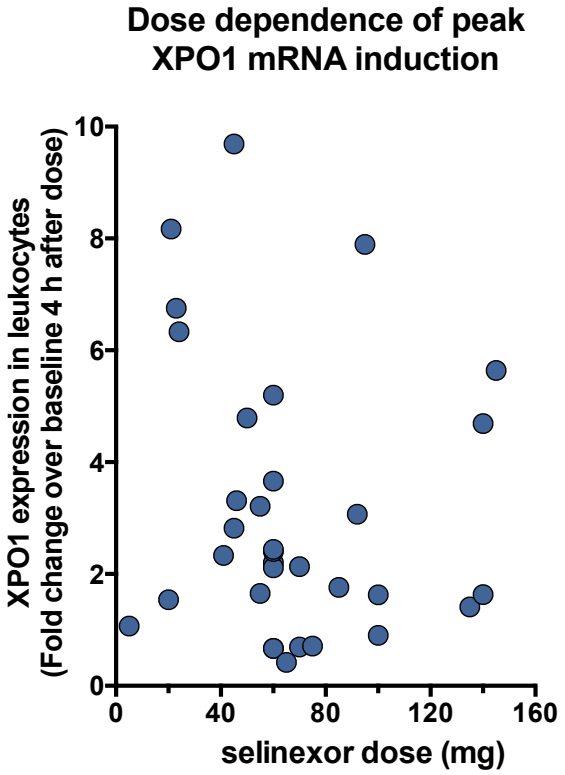
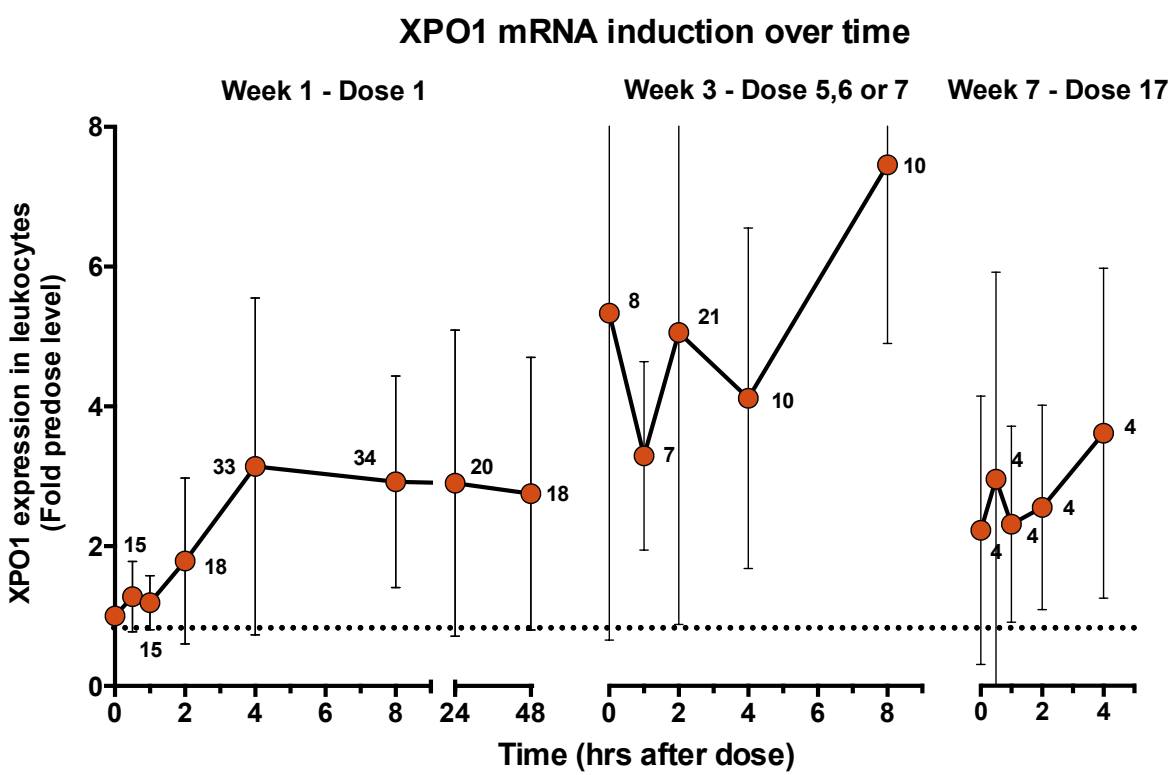
Supplemental slides

Pharmacodynamic induction of XPO1 expression in leukocytes

- XPO1 mRNA levels were induced in leukocytes within 4 hr post dose and the effect was not dependent on selinexor dose
- XPO1 mRNA induction was sustained for at least 48 h after the first dose to a level that persisted over subsequent weeks of dosing





Number of patients per time point are indicated on the graph