A Phase 1 Dose Escalation Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-330 (selinexor) in Patients (pts) with Heavily Pretreated Non-Hodgkin's Lymphoma (NHL)

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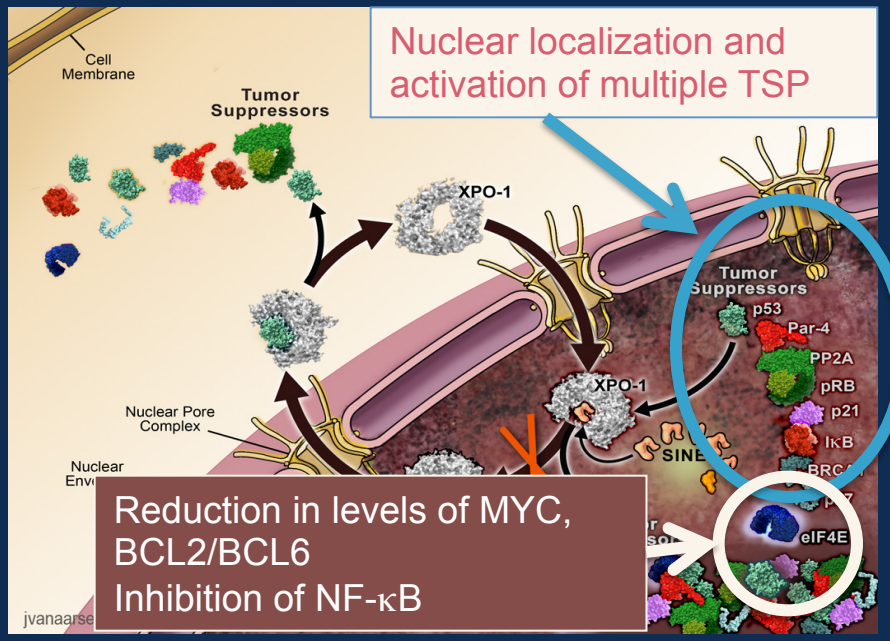
- Consultant/Advisory Role:
- Stock Ownership:
- Honoraria:
- Research Funding:
- Expert Testimony:
- Other Remuneration:

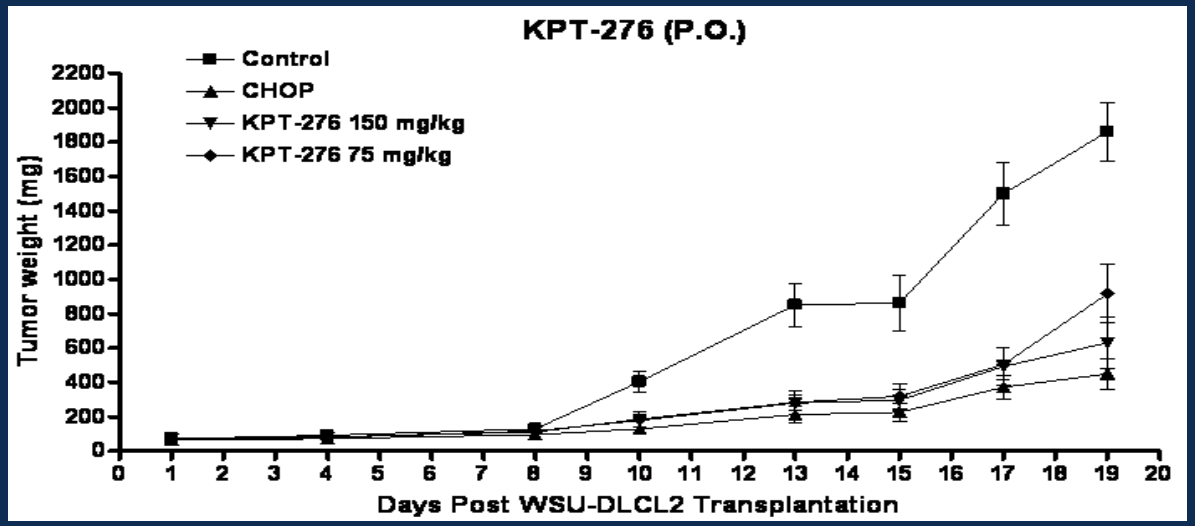
Selective Inhibitors of Nuclear Export (SINE)

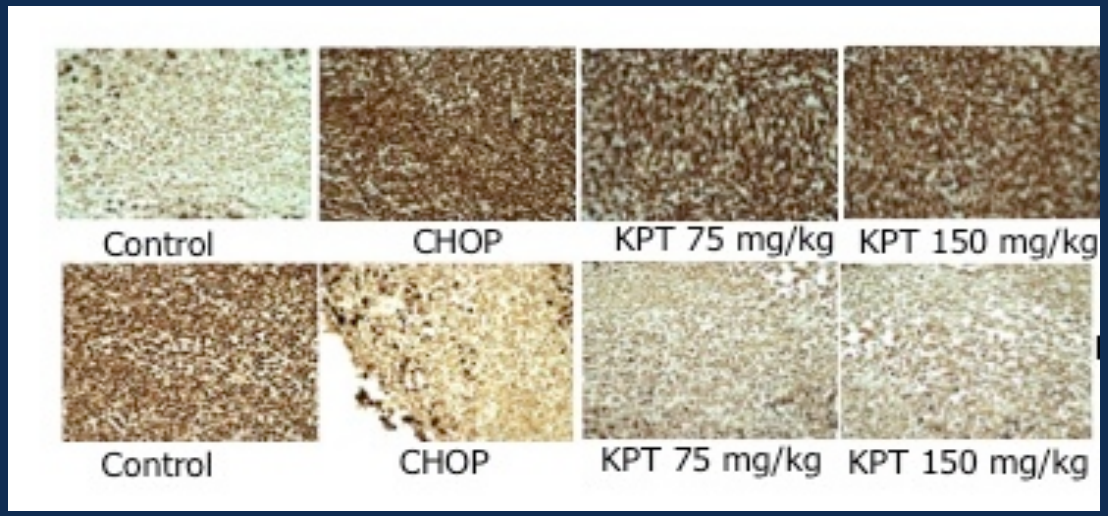
- **Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export**
- **XPO1 is elevated in Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL) and other malignancies**
- **Exportin 1 (XPO1, CRM1) is the *only* nuclear exporter of most TSPs**
- **Selinexor (KPT-330) is a covalent, slowly reversible, oral selective inhibitor of nuclear export (SINE) that inhibits XPO1**



- Selinexor forces nuclear retention and activation of *multiple* TSPs
- Selinexor treatment reduces proto-oncogene proteins including MYC, BCL2/BCL6, BTK, Cyclin D and elevates IkB, leading to inhibition of NF-κB
- Selinexor shows robust anti-cancer activity in multiple preclinical models of NHL, largely independent of genotype
- Summary data from ongoing first in human phase 1 study of oral Selinexor in hematological malignancies (NCT01607892)

SINE Reduce Growth of DLBCL *in Vivo*: Induction of p73 in p53^{mut} DLBCL





Azmi et al, Haematology 2013

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The SINE Verdinexor Demonstrates Anti Cancer Activity in Dogs with Spontaneous NHL

Phase 1	N	PR/CR	Clinical Benefit	Duration of Benefit
Dose Escalation	14	2 (14%)	9 (64%)	66 days (35-256)
Dose Expansion	6	2 (33%)	4 (67%)	83 days (35-354)
Phase 2				
All	58	20 (34%)	32 (55%)	71 days (21-273)
Naive B	28	8 (29%)	16 (57%)	71 days (28-195)
Relapse B	14	4 (29%)	6 (43%)	70 days (23-214)
Naive T	7	4 (57%)	5 (71%)	42 days (21-273)
Relapse T	7	4 (57%)	5 (71 %)	72 days (30-194)

- Verdinexor dosed at 1.25-1.75 mg/kg (25-35 mg/m^2) MWF or MW
- Toxicities were primarily gastrointestinal and were manageable with supportive care, dose modulation and treatment with low dose prednisone
- QOL did not change significantly over the study duration in all dogs enrolled indicating short and long term tolerability

**London et al, PLOS 2014 and London et al, AACR 2014*

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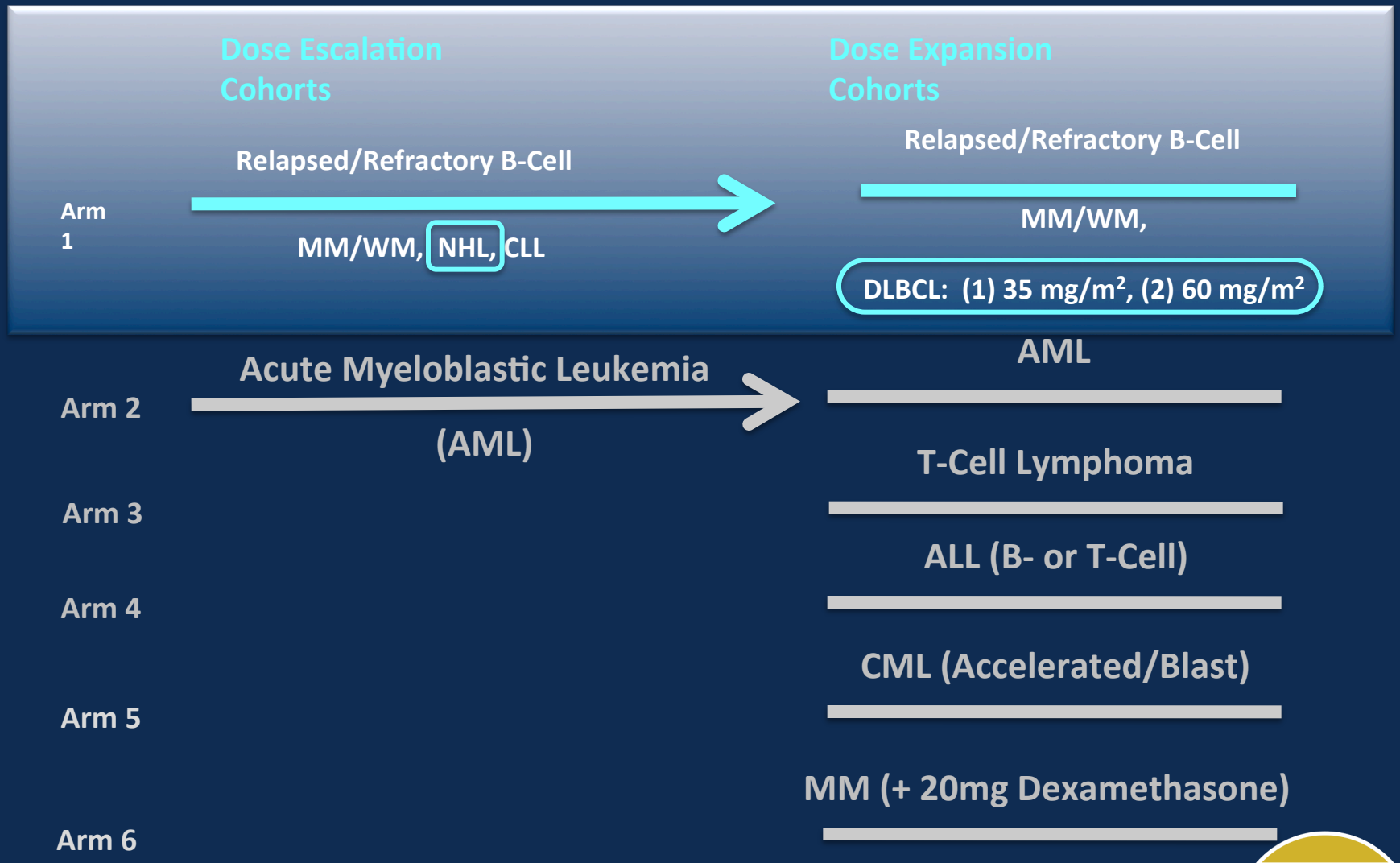
Selinexor Phase 1 Haematological Malignancies Study Design (NCT01607892)



Selinexor Phase 1 Study Design

- Objectives (modified 3+3 design)
  - Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of KPT-330;
  - Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response; confirmation of RP2D of selinexor

- Selinexor dosing
  - 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly) or 4 doses/cycle (once weekly)
  - Doses 3 mg/m^2 – 80 mg/m^2

- Major eligibility criteria:
  - Patients (ECOG ≤1) with relapsed/refractory hematologic tumors with no available standard treatments; No active CNS disease
  - Documented progression at study entry
  - ANC >1000/μL, Platelets >30,000/μL

Selinexor Phase 1: DLT Criteria

- ≥ 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 Characteristics

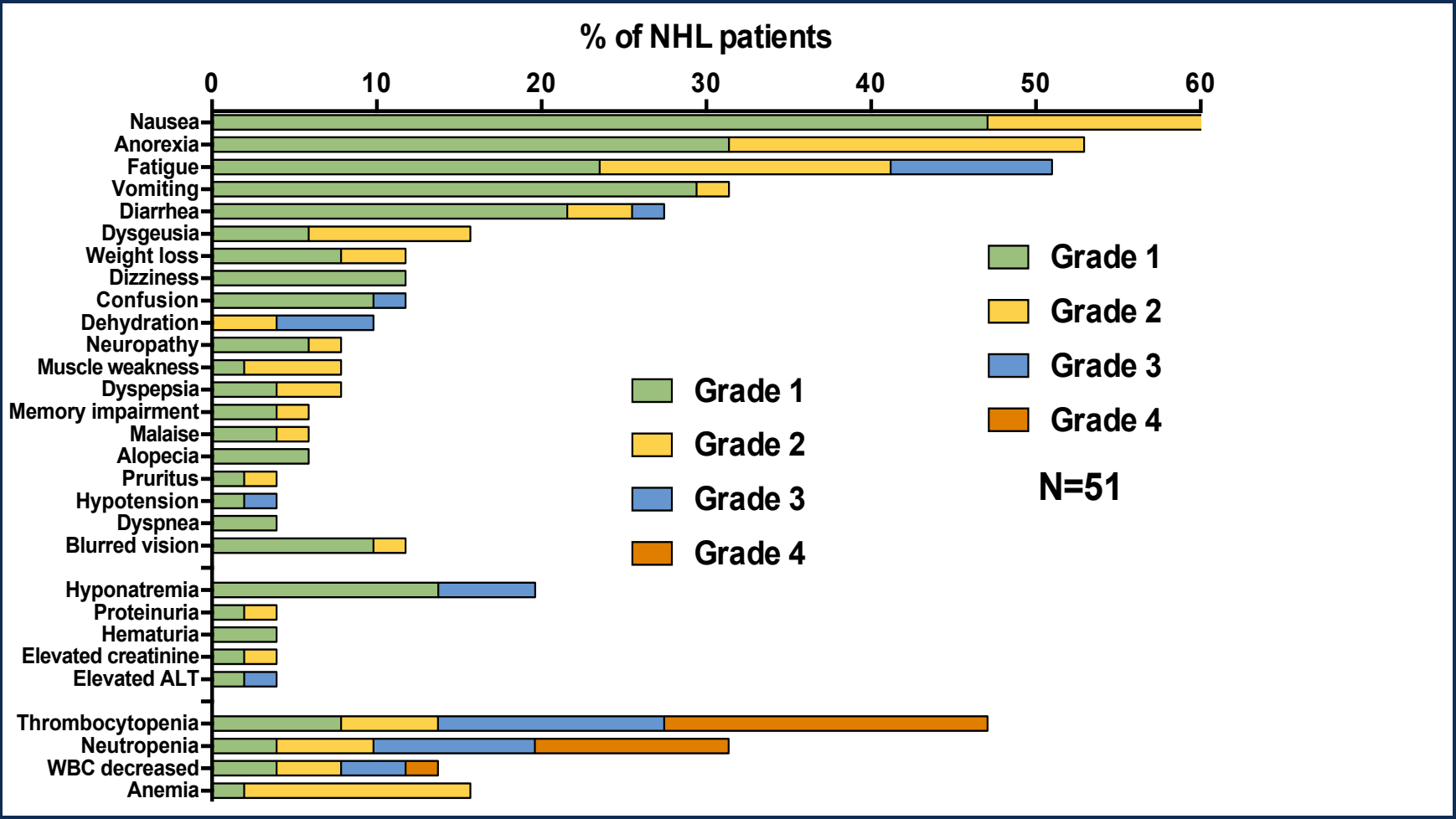
Characteristics	N=51
Mean Age (Range)	60 years (23 – 79)
Male to Female	30 Males : 21 Females
Mean Prior Treatment Regiments (Range)	4.1 (1–11)
ECOG Performance Status (0:1:2)	14 : 29 : 03
Non Hodgkin's Lymphoma (NHL)	
-Diffuse Large B-Cell (DLBCL)	25 Patients
-Follicular	7 Patients
-Mantle Cell	3 Patients
-Transformed	3 Patients
-Marginal Zone	1 Patient
-T Cell	5 Patients
Richter's Transformation	7 Patients

Dose Levels, DLT and MTD

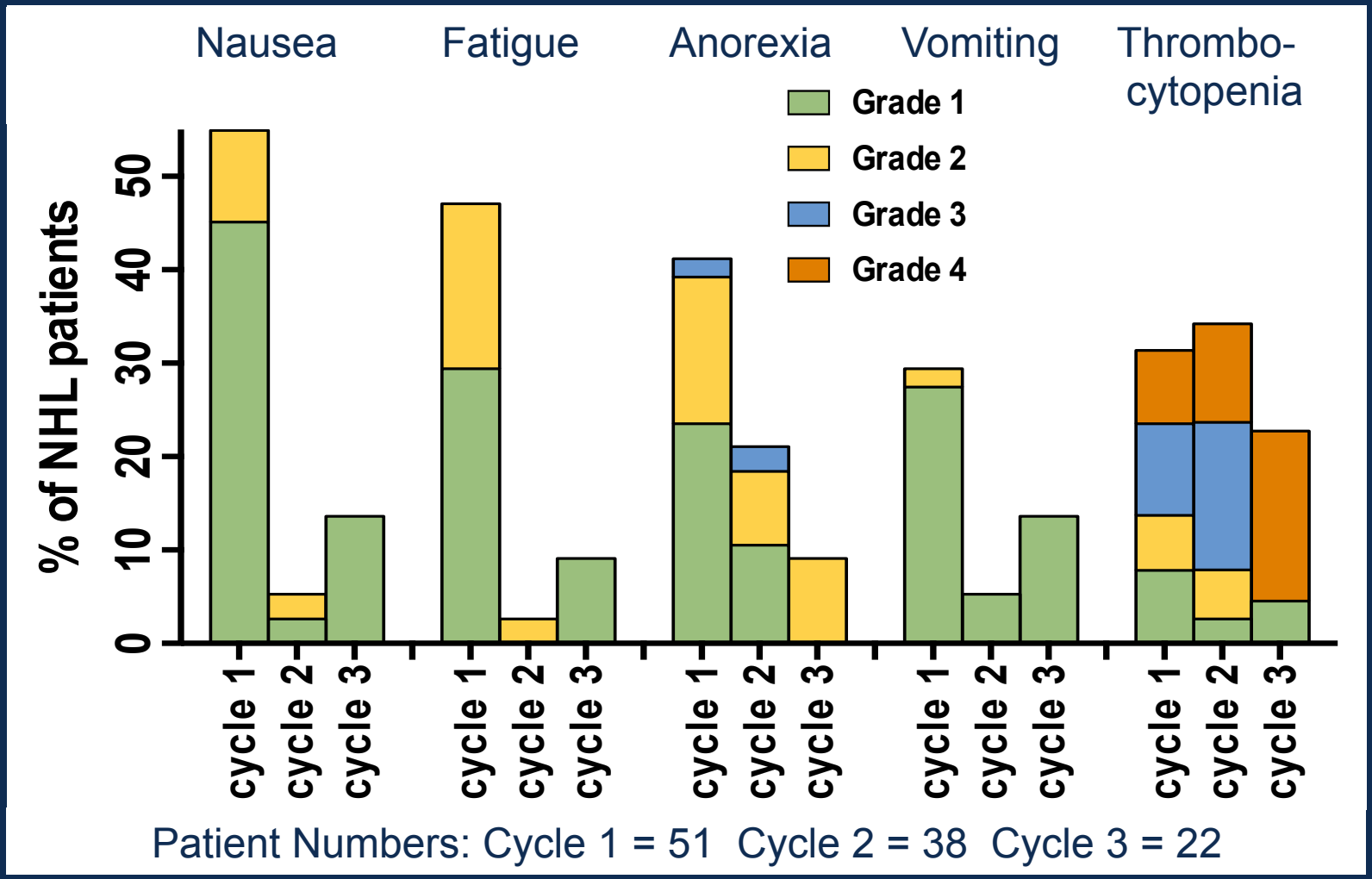
Cohort #	Dose Level (mg/m^2)	Doses /Cycle	DLT Eval. Patients (N=37)	Patients with DLT	DLTs
1	3	10	2	0	
2	6	10	3	0	
3	12	10	5	0	
4	16.8	10	6	1	MM: Grade 4 thrombocytopenia (pt continued on therapy >1 year)
5	23	10	7	1	FL: Grade 4 thrombocytopenia (pt continued on therapy 3 months)
6	30	10	5	1	CLL: Grade 2 fatigue (pt missed three doses continued on therapy 1 month)
7	35	8	3	0	
8	45	8	3	0	
9	60	8	3	0	
10	80	4	1	0	
Exp 1	35	8	N/A		DLBCL, MM, WM Expansion Cohort
Exp 2	60	8	N/A		DLBCL Ongoing Expansion Cohort

All patients in Arm 1 (NHL, CLL, MM and WM) were included for DLT evaluation

Selinexor Phase 1 Study: AE's ≥ 2 pts Drug Related Adverse Events

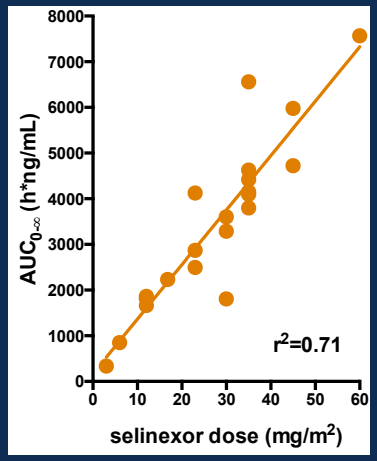


Selinexor Phase 1 Study: Common AE's By Cycle

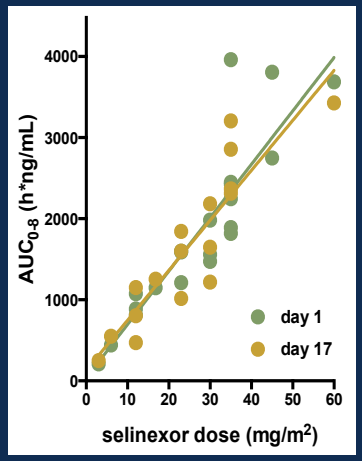


Selinexor Phase 1 Study: Pharmacokinetics

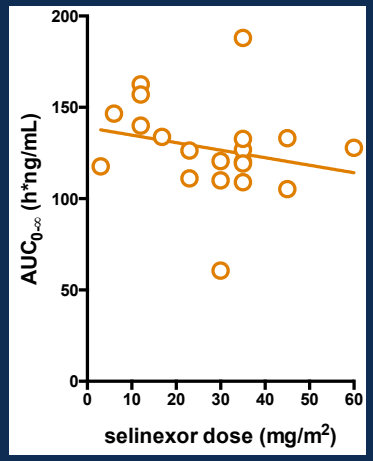
AUC Dose Dependence



AUC Day 1 and Day 17

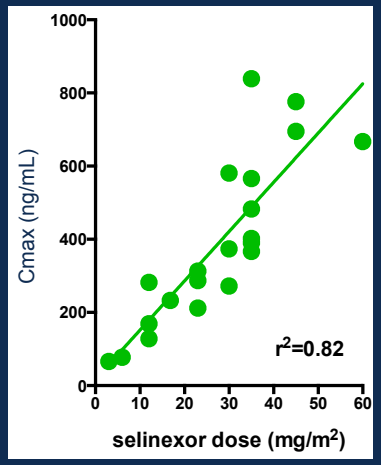


AUC/Dose Analysis

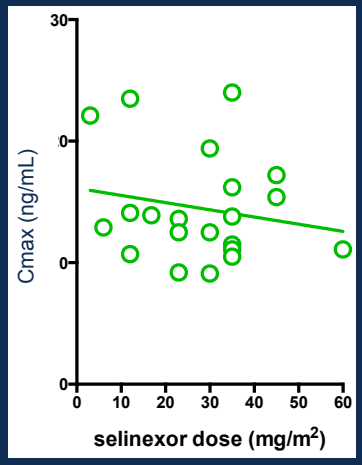


- Plasma selinexor exposure was dose proportional across 3 – 60 mg/m^2 dose range
- The terminal half life was ~ 5 –8 hours and independent of dose
- No evidence of accumulation across all doses

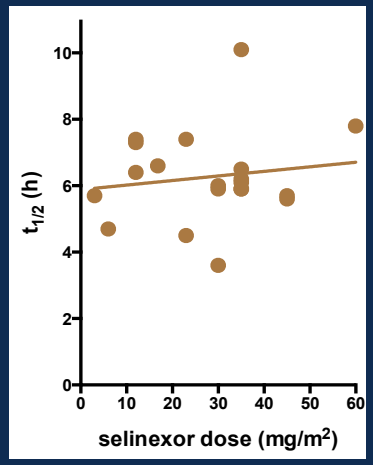
C_{max} Dose Dependence



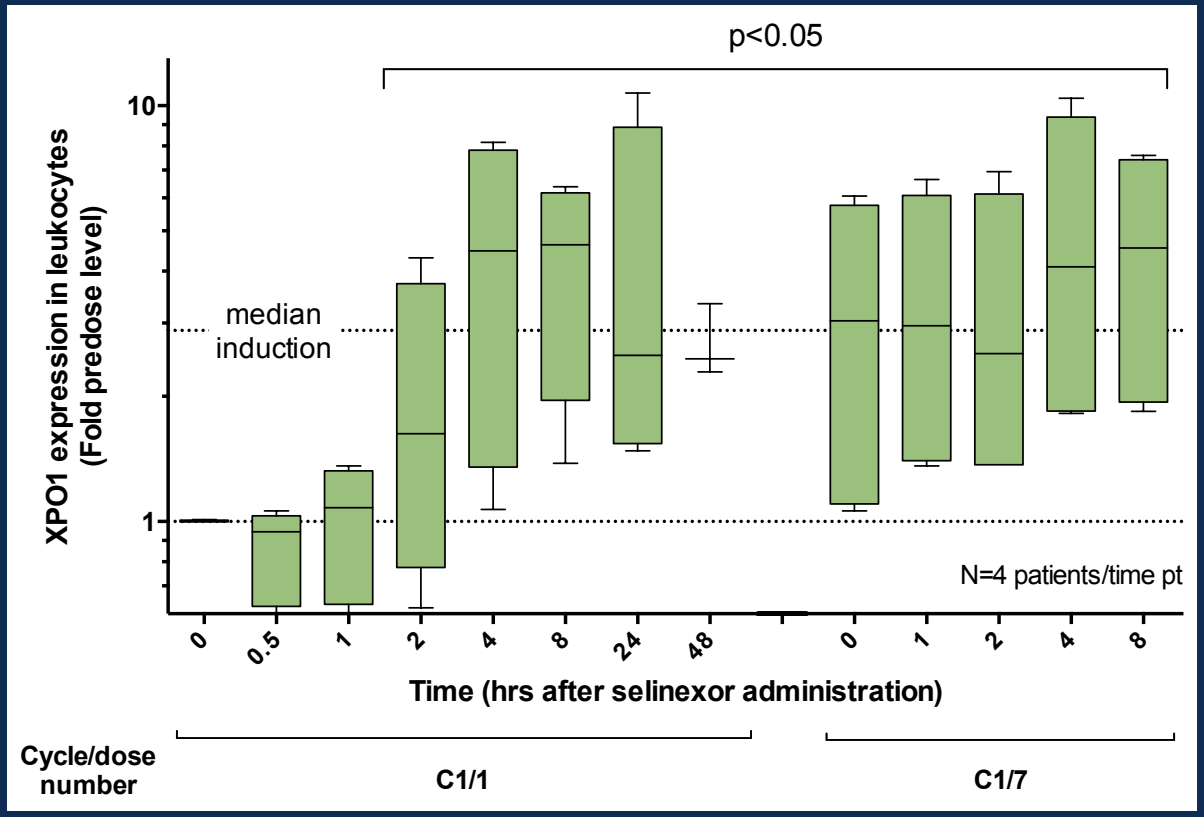
C_{max} / Dose Analysis



$t_{1/2}$ dose dependence



Selinexor PDn Marker: Changes in XPO1 mRNA in Leukocytes



- Selinexor mediated XPO1 inhibition leads to an increase in XPO1 mRNA *in-vitro* and *in-vivo*
- XPO1 mRNA levels were measured in leukocytes from NHL patients following 1st and 7th dose of selinexor
- Increases in mRNA were observed at 4 hrs. post the first dose and subsequent doses maintain elevated expression
- These results support that intermittent dosing schedule optimally induces a steady state with maximal induction of XPO1 mRNA.

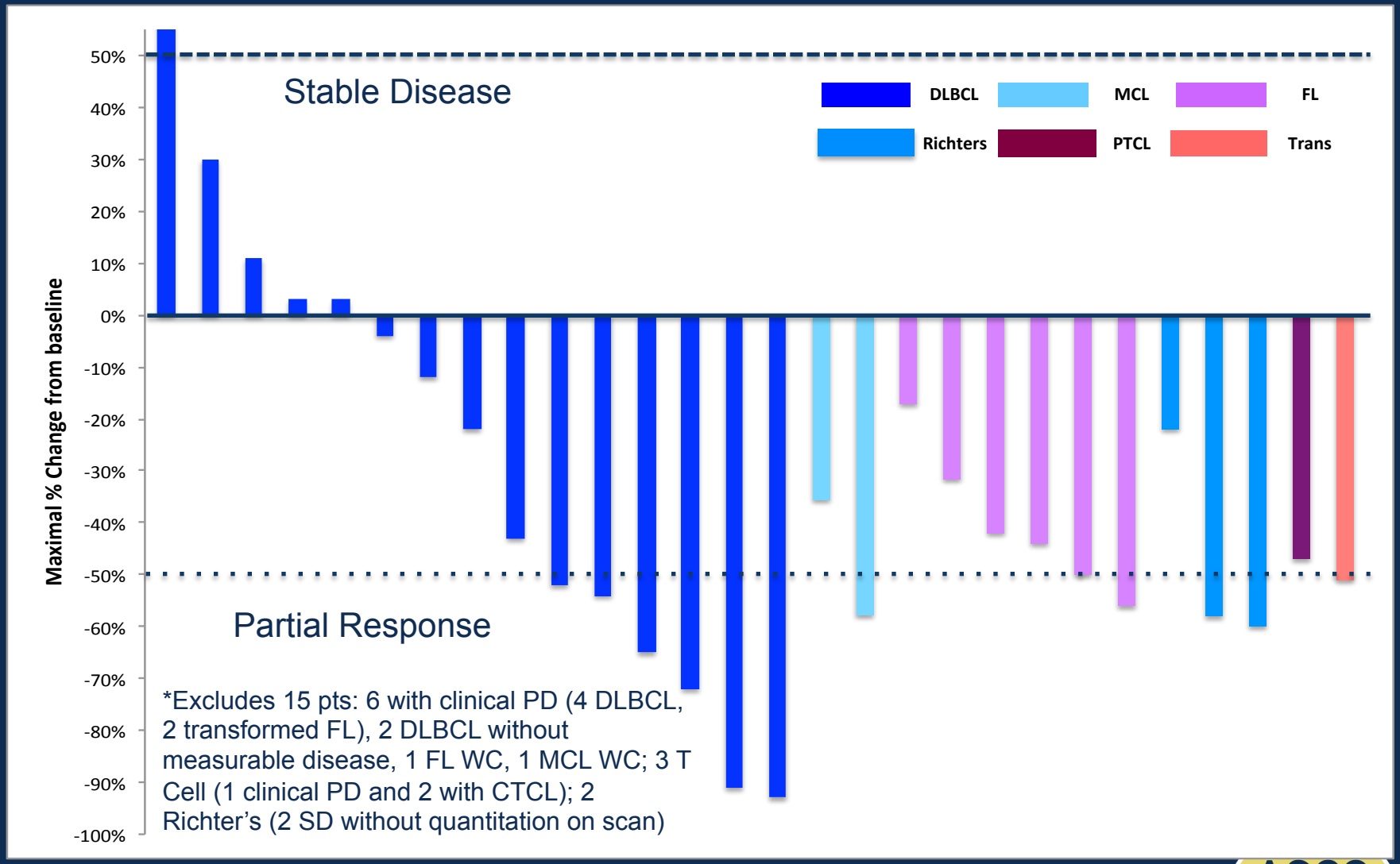
Selinexor Phase 1 Study: Responses in Heavily Pretreated Patients with NHL

Best Responses in NHL/Richter's Syndrome Patients as 13-May-2014								
Cancer	**N***	**DCR (%)**	**ORR(%)**	**CR (%)**	**PR (%)**	**SD (%)**	**PD (%)**	**WC (%)**
DLBCL	21	15 (70%)	6 (29%)	1 (5%)	5 (25%)	9 (40%)	5 (25%)	1 (5%)
Follicular	7	6 (86%)	1 (14%)	--	1 (14%)	5 (71%)	--	1 (14%)
Mantle Cell	3	2 (67%)	1 (33%)	--	1 (33%)	1 (33%)	--	1 (33%)
Transformed	3	1 (33%)	1 (33%)	--	1 (33%)	--	2 (67%)	--
T-Cell	4	3 (75%)	1 (25%)	1 (25%)	--	2 (50%)	--	1 (25%)
Richter's Syndrome	5	5 (100%)	2 (40%)	--	2 (40%)	3 (60%)	--	--
Total	**43**	**32 (74%)**	**12 (28%)**	**2 (5%)**	**10 (23%)**	**20 (47%)**	**7 (16%)**	**4 (9%)**

DCR=Disease Control Rate (CR+PR+SD), ORR=Overall Response Rate, CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, WC=Withdrew Consent

*43 Evaluable Patients were included
(5 pts were not evaluable, 3 pts are pending evaluation)

Selinexor Phase 1 Study: Maximal % Change in Lymph Node from Baseline



Selinexor Phase 1 Study: Responses in Heavily Pretreated Patients with DLBCL By Dose

Responses in Diffuse Large B-Cell Patients as of 13-May-2014								
Initial Dose (mg/m^2)	**Doses/ Cycle**	**N***	**Dose Modification**	**CR (%)**	**PR (%)**	**SD (%)**	**PD**	**WC**
3	10	1	--	--		1 (100%)	--	--
6	10	1	1 pt ↑ $60mg/m^2$	--	1 (100%)	--	--	--
16.8	10	1	--	--	--	--	1 (100%)	--
23	10	1	--	--	--	--	--	1 (100%)
23	8	1	1 pt ↑ $30mg/m^2$	1 (100%)	--	--	--	--
30	10	1	1 pt to 45 mg/m^2 QW	--	--	1 (100%)	--	--
35	8	13	2 pt ↑ $45mg/m^2$	--	3 (23%)	6 (46%)	4 (31%)	--
60	8	3	1 pt: ↓ 45 mg/m^2	--	--	3 (100%)	--	--
80	8	2	1 pt: ↓ 70 mg/m^2	--	1 (50%)	1 (50%)	--	--
Total		**24**		**1 (4%)**	**5 (21%)**	**12 (50%)**	**5 (21%)**	**1 (4%)**

* Excludes 1 pt who is NE
* Includes preliminary results based on PET-CT in Cycle 1 (2 pts at $60mg/m^2$ and 1 pt at $80mg/m^2$)

Selinexor Phase 1 Study: Responses Across Subtypes of Relapsed / Refractory DLBCL

Responses in Diffuse Large B-Cell Patients as of 13-May-2014								
Type	**N**	**DCR (%)**	**ORR (%)**	**CR (%)**	**PR (%)**	**SD (%)**	**PD (%)**	**WC (%)**
GCB	11	8 (72%)	3 (27%)	1 (9%)	2 (18%)	5 (45%)	2 (18%)	1 (9%)
nonGCB	4	3 (75%)	1 (25%)	--	1 (25%)	2 (50%)	1 (25%)	--

Patients with "Double Hit" DLBCL				
Patient ID	**Best Response**	**% Reduction in Lymph Nodes**	**Days on Study**	**Prior Therapies**
046	CR	73% (PET Negative)	239+	**CHOP-R, RICE**
058	PD	--	57	**CHOP-R, RICE**
072	SD	43%	114+	**R-CHOP, Benda, RICE, DHAP-R, BEAM**
086	SD	40% reduction in metabolic activity in C1 PET-CT	49+	**CHOP-R, GDP, Ibrutinib +Lenalidomide**

DCR=Disease Control Rate (CR+PR+SD), ORR=Overall Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, WC=Withdrew Consent
+ pt remains on study

Selinexor Phase 1 Study: Duration of Response and Disease Control

Patient	Disease	Best Response	Maximal Reduction	Days on Study	Off-Study
003	DLBCL	PR	–93%	632+	
046	DLBCL	**CR**	PET negative	239+	
050	DLBCL	PR	–91%	219+	
070	DLBCL	PR	–54%	119+	
067	DLBCL	PR	–65%	78	WC
083	DLBCL	PR	–52%	44	PD
059	Trans-NHL	PR	–51%	45	WC
080	RT	PR	–58%	85+	
027	RT	PR	–60%	35	Transplant
031	FL	PR	–56%	224	Transplant
004	MCL	PR	–58%	168	WC
302	PTCL	**CR**	PET negative	112+	

Patient	Disease	Best Response	Maximal Reduction	Days on Study	Off-Study
028	DLBCL	SD	–12%	366+	
072	DLBCL	SD	–43%	114+	
001	DLBCL	SD	0%	86	WC
054	DLBCL	SD	–4%	84	PD
063	DLBCL	SD	–22%	80	PD
053	DLBCL	SD	+3%	56	PD
044	DLBCL	SD	+30%	55	PD
087	DLBCL	SD	PET –37%	49+	
086	DLBCL	SD	PET –40%	49+	
065	DLBCL	SD	+3%	51	PD
088	DLBCL	SD	PET –0%	49	PD
089	RT	SD	PET –0%	48	PD
039	RT	SD	–22%	37	WC
041	RT	SD		33	WC
022	MCL	SD	–36%	144	WC
029	FL	SD	–32%	171	PD
025	FL	SD	–42%	142	WC
066	FL	SD		135+	
006	FL	SD	-17%	113	Transplant
019	FL	SD	-44%	84	PD
303	CTCL	SD		56	PD
304	CTCL	SD		71+	

Case Study: Patient 040-046: Refractory DLBCL (GCB/Double Hit): Complete Response

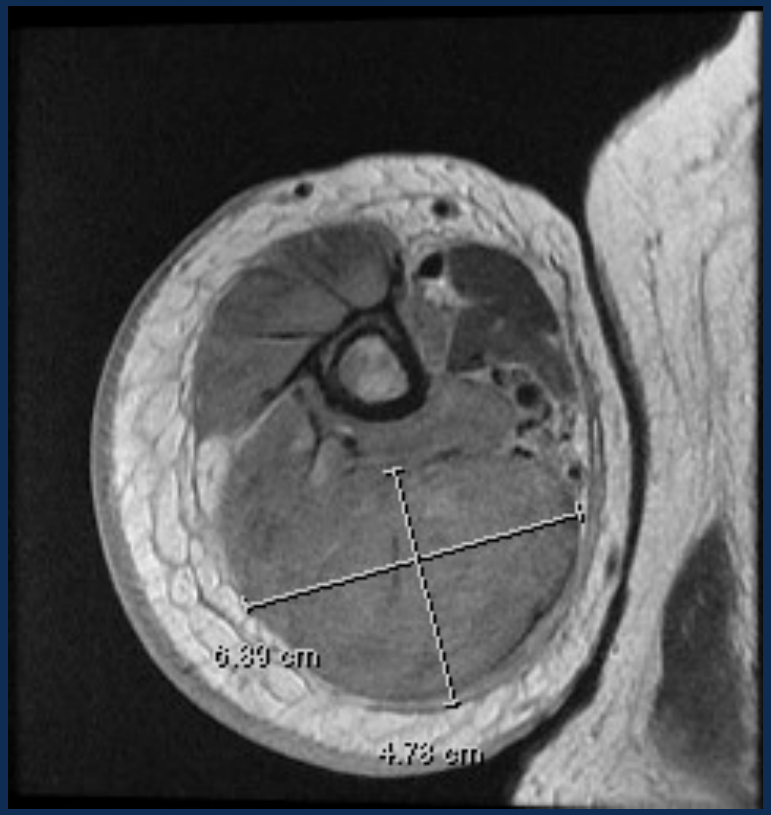
- 73 year old man with Relapsed DLBCL (Feb 2012), GCB & Double-Hit
- Stage 4, bulky disease, possible CNS involvement
- CHOP-R initial therapy + intrathecal (CNS) methotrexate + radiation to R arm with relapse in 10 months
- R-ICE treatment (Jan-Feb 2013) with relapse within 7 months
- R Arm: severe pain, marked edema, non-functioning due to refractory DLBCL

Selinexor Treatment

- Sept 17, 2013, initiates Selinexor 23 mg/m^2 PO QD x 2
- Response within 2 weeks with marked reduction in pain and edema in arm
- MRI: 73% reduction in cycles 1 & 2
- Well tolerated (Remeron + Megace) with minimal side effects, increased dose in Cycle 3 (30mg/m^2)
- PET CT negative Cycle 4, R Arm lesion biopsy negative for tumor: CR

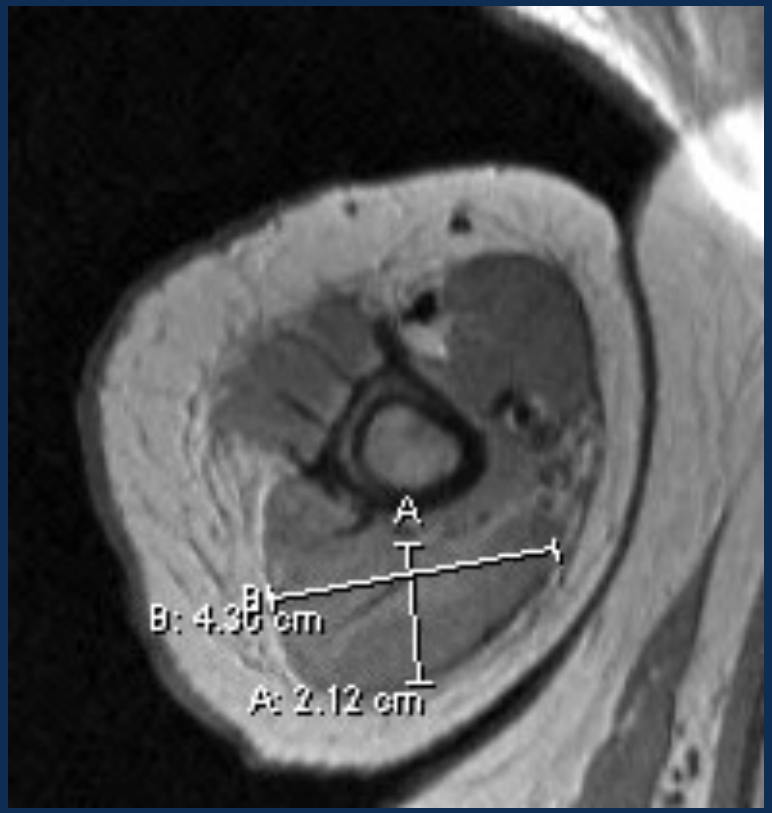
Rel/Ref GCB "Double Hit" DLBCL 040-046: Bulky R Arm Lesion, Complete Response

R Arm Baseline: Sept 16, 2013



6.89 x 4.73 cm (32.59cm^2)

Cycle 1: October 13, 2013



4.30 x 2.12 cm (9.12 cm^2)

Conclusions

- Novel, oral SINE Selinexor (KPT-330) can safely be given as monotherapy to patients with heavily pretreated NHL
  - Main toxicities: anorexia, nausea, fatigue, thrombocytopenia
  - Phase 2/3 Recommended Dose is 60 mg/m^2 BIW
  - Patients remaining on single agent Selinexor >9 months
- Selinexor has favorable PK and PDn characteristics
- Single-agent anti-tumor activity across all NHL types with durable cancer control >9 months
- Marked activity across GCB, nonGCB, and Double-Hit DLBCL
- Future trials in Richter's syndrome and DLBCL are planned

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  - Patients and their families
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    - Gabrail Cancer Center Research
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