Preliminary Evidence Of Anti Tumor Activity Of Selinexor (KPT-330) In a Phase I Trial Of a First-In-Class Oral Selective Inhibitor Of Nuclear Export (SINE) In Patients With Relapsed / Refractory Non Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL)

John Kuruvilla, MD[1], Martin Gutierrez, MD[2], Bijal D. Shah, MD[3], Nashat Y. Gabrail, MD[4], Peter de Nully Brown[5], Richard M. Stone, MD[6], Ramiro Garzon, MD[7], Michael Savona, MD[8], David S. Siegel, MD, PhD[2], Rachid Baz, MD[3], Morten Mau-Sorensen, MD[5], Matthew S. Davids, MD[6], John C. Byrd, MD[7], Sharon Shacham, PhD, MBA[9], Tami Rashal, MD[9], Cindy YF Yau[10], Dilara McCauley, PhD[9], Jean-Richard Saint-Martin[9], John McCartney, PhD[9], Yosef Landesman, PhD[9], Boris Klebanov[9], Trinayan Kashyap[9], Eran Shacham[9], Greg Pond, PhD[10], Amit M. Oza, MBBS, MD[10], Michael Kauffman, MD, PhD[9] and Mansoor R Mirza[5]

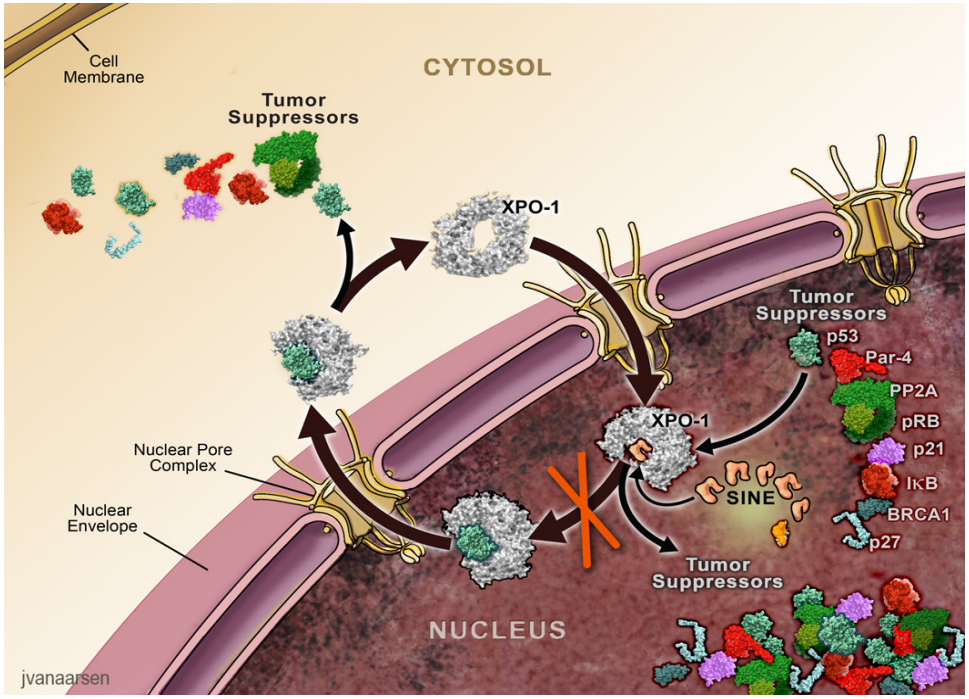
[1]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada
[2]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ
[3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
[4]Gabrail Cancer Center, Canton, OH
[5]Copenhagen University Hospital, Copenhagen, Denmark
[6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[7]The Ohio State University Comprehensive Cancer Center, Columbus, OH
[8]Sarah Cannon Research Institute, Nashville, TN
[9]Karyopharm Therapeutics Inc, Natick, MA
[10]Ozmosis Research, Toronto, ON, Canada

Presenter Disclosures

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** None
- **Stock Ownership:** None
- **Honoraria: Hoffman LaRoche, Janssen, Celgene, Lundbeck, Seattle Genetics**
- **Research Funding: Leukemia and Lymphoma Society**
- **Expert Testimony:** None
- **Other Remuneration:** None

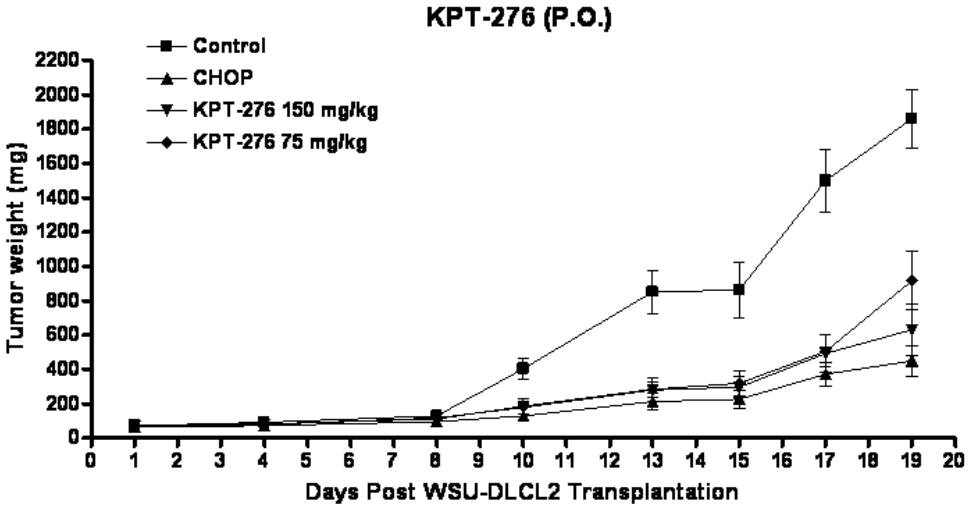
Selective Inhibitors of Nuclear Export (SINE)

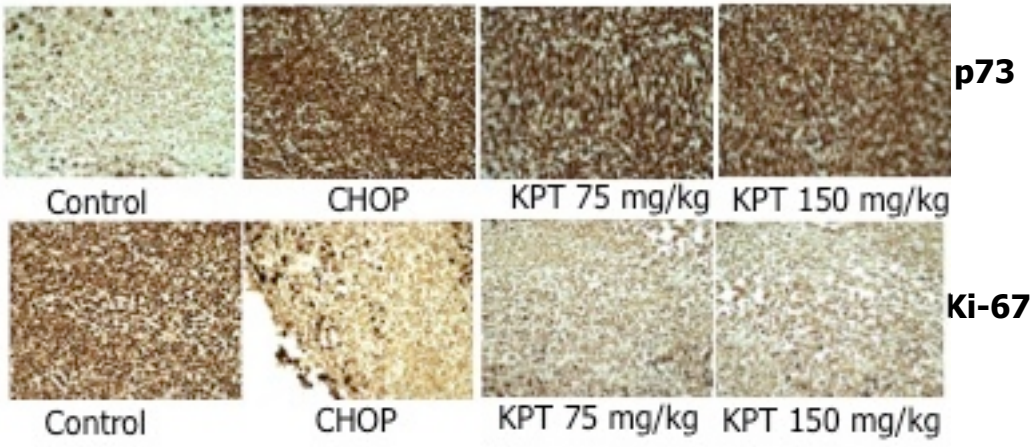
- Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export
- Exportin 1 (XPO1, CRM1) is the *only* nuclear exporter of most TSPs
- XPO1 is elevated in Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL) and other hematological malignancies

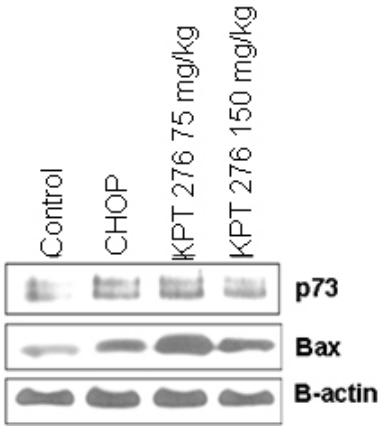


- Selinexor (KPT-330) is a covalent, oral selective inhibitor of nuclear export (SINE) XPO1 antagonist that forces nuclear retention and activation of *multiple* TSPs
- Selinexor shows robust anti-cancer activity in multiple preclinical models of NHL and CLL
- First in class, first in human phase 1 study of oral Selinexor (NCT01607892)

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

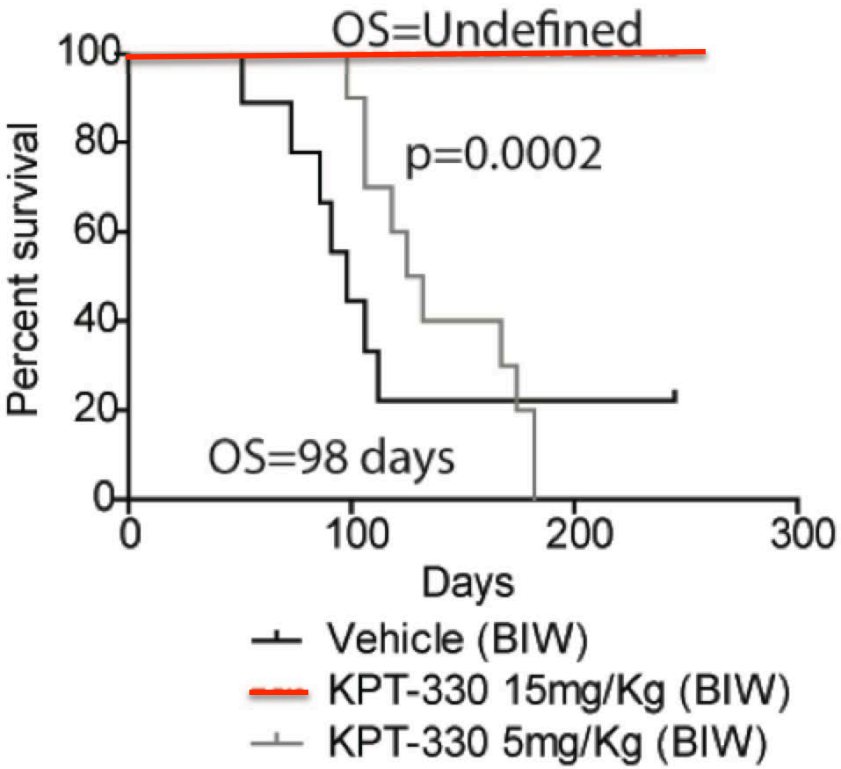


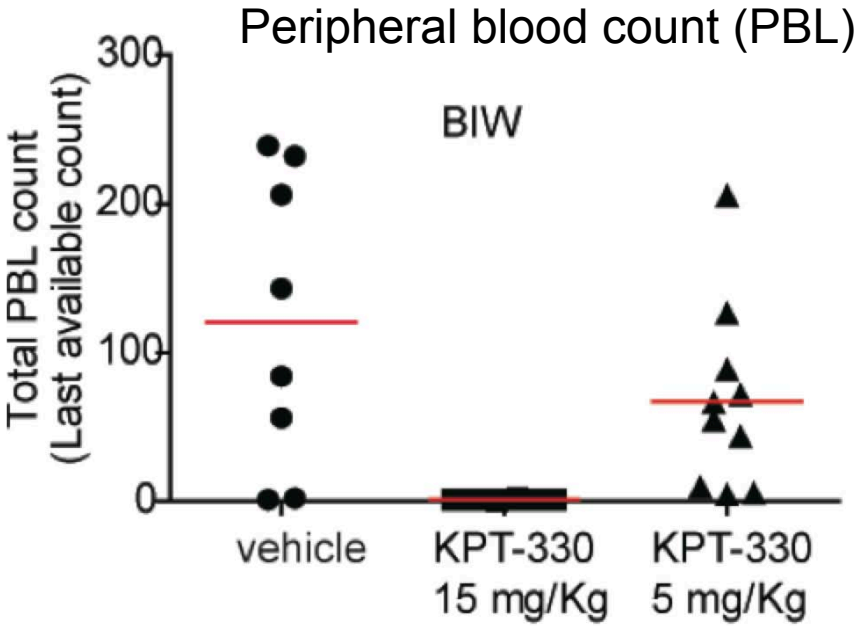




*Azmi 2013 *Department of Pathology, Wayne State University, Detroit, Michigan*

KPT-330: Effects on TCL-1 CLL Leukemograft Model

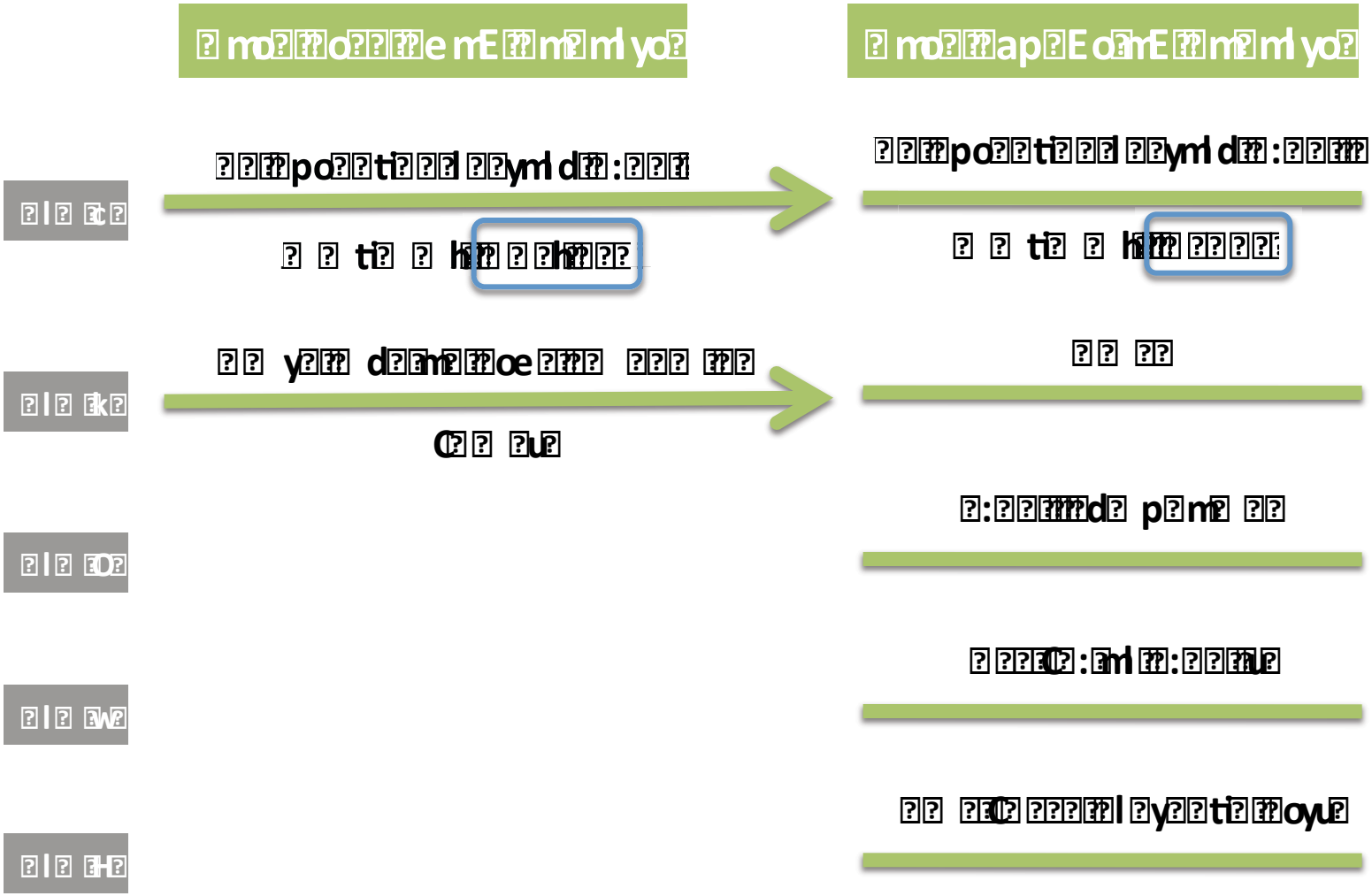




TCL1-SCID mice (N=10 each group) treated orally with: KPT-330 5 or 15 mg/kg or vehicle control twice per week (BIW; Monday and Tuesday). Treatment was initiated 14 days post engraftment

*Lapalombella 2012 *Department of Internal Medicine, The Ohio State University, Columbus Ohio*

KPT-330 Phase 1 Haematological Malignancies Study Design (NCT01607892)



KPT-330 Ph1 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; conformation of RP2D of KPT-330

- KPT-330 dosing
  - Oral on days 1, 3, 5 or days 1, 3 of each week
  - Doses 3mg/m^2 – 45mg/m^2

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

KPT-330 Ph1: 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

KPT-330 Ph1 Study: Patient Characteristics

Characteristic	N=30
Median age (range)	65 years (32-79)
Male /Female	19 Males : 11 Females
Median prior lines of treatment (range)	4.5 (1-11)
ECOG performance status, 0/1	9 : 21
Non-Hodgkin's Lymphoma	
-Follicular	6 Patients
-Mantle Cell	3 Patients
-Diffuse Large B Cell (DLBLC)	11 Patients
-Transformed	2 Patients
Chronic Lymphocytic Leukemia (CLL)	4 Patients
Richter's Syndrome	4 Patients

KPT-330 Ph1 Study: Dose Levels, DLT and MTD

Cohort #	Dose Level (mg/m^2)	Doses per cycle	DLT Evaluable Patients (n=28)	Patients with DLT	Dose Limiting Toxicity
1	3	10	2	0	
2	6	10	3	0	
3	12	10	5	0	
4	16.8	10	7	1	MM: Grade 4 thrombocytopenia (pt continued on therapy >1 year)
5	23	10	7	1	FL: Grade 4 thrombocytopenia (pt continued on therapy 4 months)
6	30	10	5	0	
7	35	8	3	0	
8	45	8	2	0	Ongoing
Expansion	35	8	14	–	DLBCL, MM, WM

All patients in Arm1 (NHL, CLL, MM and WM) were included for DLT evaluation

KPT-330 Ph1 Study: Hematological Drug Related Adverse Events

AE NAME	GRADE	Selinexor (KPT-330) Dose Levels (mg/m^2)								All N=30
		3	6	12	16.8	23	30	35	45	
Hematological		N=1	N=1	N=3	N=2	N=6	N=6	N=8	N=3	
Thrombocytopenia	Grade 1	--	--	--	1 (50%)	--	--	--	1 (33%)	7%
	Grade 2	--	--	--	--	--	1 (17%)	--	--	3%
	Grade 3	--	--	1 (33%)	--	--	2 (33%)	--	--	10%
	Grade 4	--	--	--	--	2 (33%)	1 (17%)	1 (12.5%)	1 (33%)	17%
Neutropenia	Grade 1	--	--	--	--	1 (17%)	--	--		3%
	Grade 2	--	--	--	--	--	--	--	1 (33%)	3%
	Grade 3	--	1 (100%)	1 (33%)	--	--	4 (67%)	1 (12.5%)	--	23%
	Grade 4	--	--	--	--	--	--	2 (25%)	--	7%
Anemia	Grade 1	--	--	1 (33%)	--	--	--	--	--	3%
	Grade 2	--	--	--	1 (50%)	1 (17%)	1 (17%)	--	1 (33%)	13%

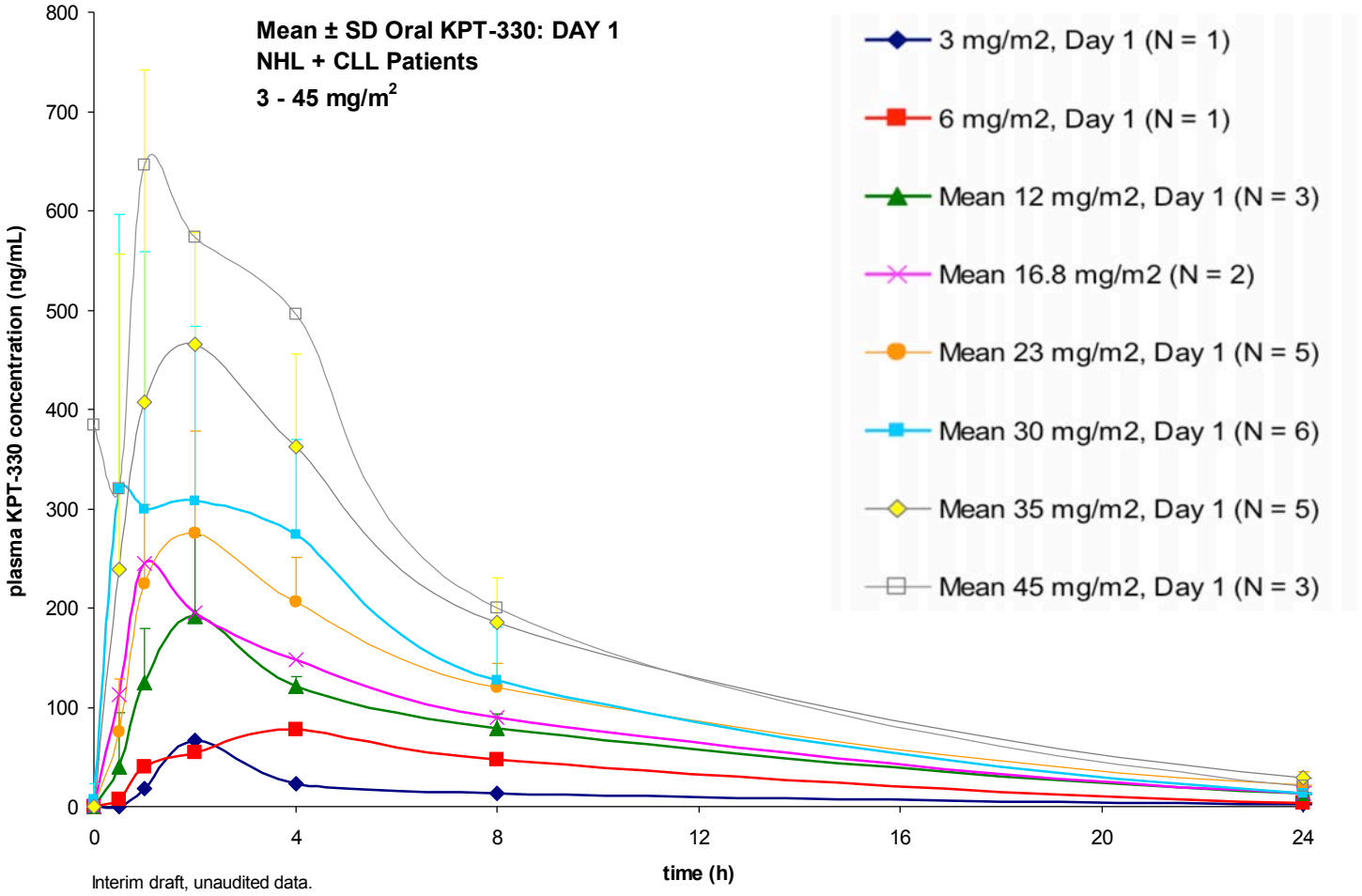
KPT-330 related AEs occurring in ≥ 2 patients

KPT-330 Ph1 Study:
Non Hematological Drug Related Adverse Events

AE NAME	GRADE	Selinexor (KPT-330) Dose Levels (mg/m^2)								All N=30
		3	6	12	16.8	23	30	35	45	
Gastrointestinal, Constitutional, and Others		N=1	N=1	N=3	N=2	N=6	N=6	N=8	N=3	
Anorexia	Grade 1	1 (100%)	--	1 (33%)	--	1 (17%)	3 (50%)	2 (25%)	2 (67%)	33%
	Grade2	--	1 (100%)	1 (33%)	1 (50%)	1 (17%)	--	2 (25%)	1 (33%)	23%
Nausea	Grade 1	1 (100%)	--	2 (67%)	1 (50%)	2 (33%)	3 (50%)	5 (62.5%)	2 (67%)	53%
	Grade2	--	1 (100%)	--	--	--	1 (17%)	--	1 (33%)	10%
Fatigue	Grade 1	1 (100%)	--	1 (33%)	--	--	1 (17%)	4 (50%)	1 (33%)	27%
	Grade2	--	1 (100%)	--	1 (50%)	1 (17%)	--	2 (25%)	1 (33%)	20%
	Grade 3	--	--	--	--	1 (17%)	2 (66%)	--	--	10%
Vomiting	Grade 1	--	1 (100%)	--	--	2 (33%)	2 (33%)	3 (37.5%)	1 (33%)	30%
	Grade2	--	--	--	--	--	1 (17%)	--	1 (33%)	7%
Diarrhea	Grade 1	--	1 (100%)	1 (33%)	1 (50%)	1 (17%)	2 (50%)	4 (50%)	--	33%
	Grade2	--	--	--	--	--	1 (17%)	--	--	3%
Weight loss	Grade 1	--	1 (100%)	1 (33%)	--	--	1 (17%)	--	--	10%
	Grade2	--	--	1 (33%)	--	--	--	--	--	3%
Malaise	Grade 1	--	1 (100%)	--	1 (50%)	--	--	--	--	7%
	Grade2	--	--	1 (33%)	--	--	--	--	--	3%
Dizziness	Grade 1	--	--	--	--	1 (17%)	--	1 (12.5%)	1 (33%)	10%
Hyponatremia	Grade 1	--	--	--	1 (50%)	--	--	1 (12.5%)	1 (33%)	10%
Blurred vision	Grade 1	--	--	--	1 (50%)	--	--	2 (25%)	--	10%
	Grade2	--	--	--	--	--	1 (17%)	--	--	3%

KPT-330 related AEs occurring in ≥ 2 patients

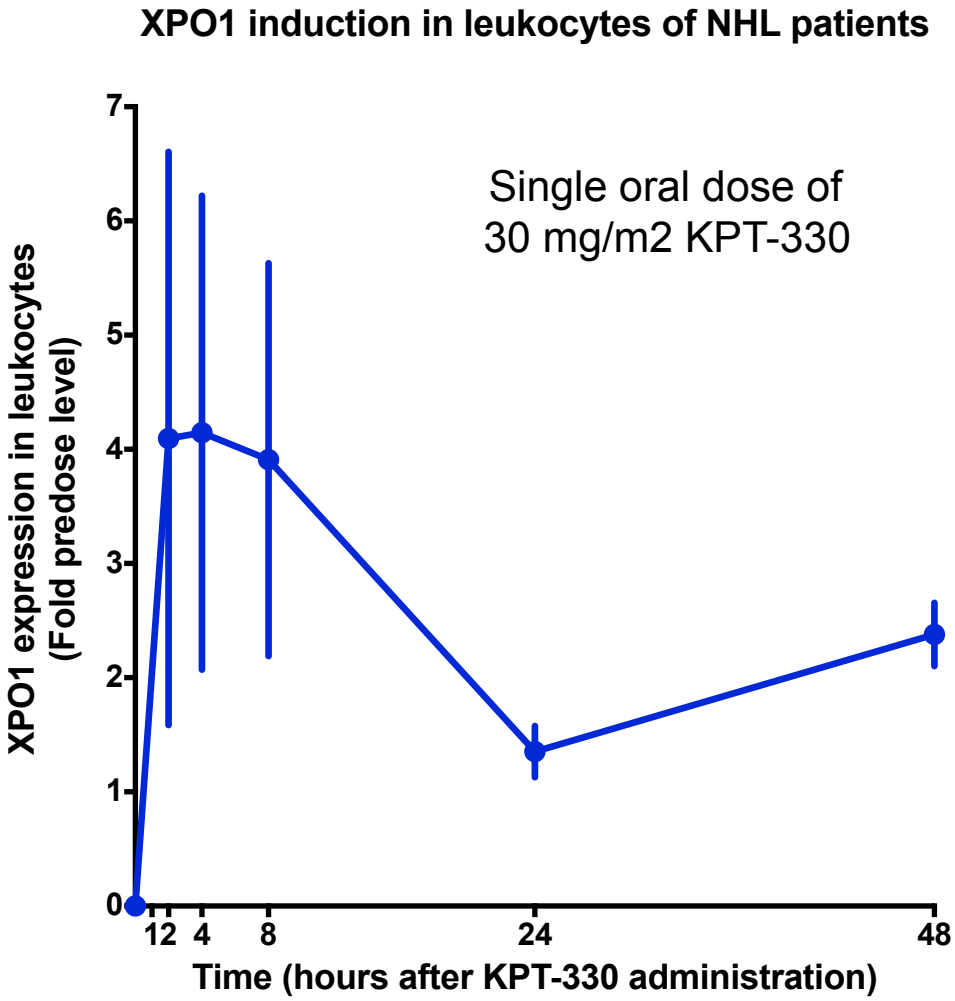
KPT-330 Ph1 Study: Pharmacokinetics



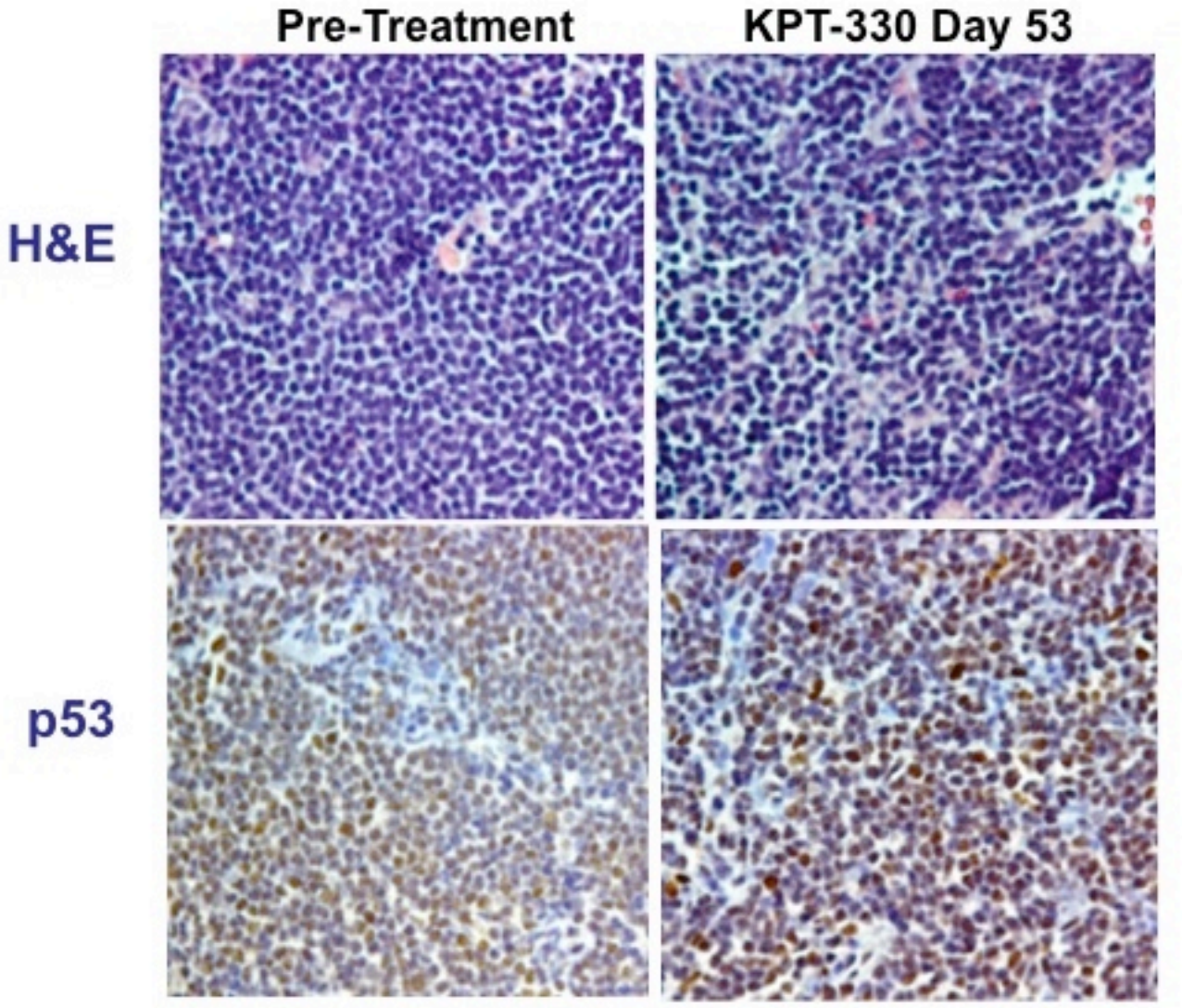
- Oral absorption of KPT-330 was rapid, with high volume of distribution
- The terminal half life ~ 5 –7 hours and independent of dose.
- Plasma KPT-330 exposure dose proportional across 3 - 35 mg/m^2 dose range
- No evidence of accumulation

KPT-330 Ph1 Study: Changes in XPO1 mRNA in Leukocytes

- XPO1 mRNA was measured in leukocytes from NHL patients using qRT-PCR
- Selinexor induced XPO1 expression at least 2-fold in 88% (15/17) of NHL patients
- XPO1 induction was time dependent and sustained for at least 48 h



KPT-330 Induced Nuclear Localization in Patient Tumor Cells (paired biopsies)

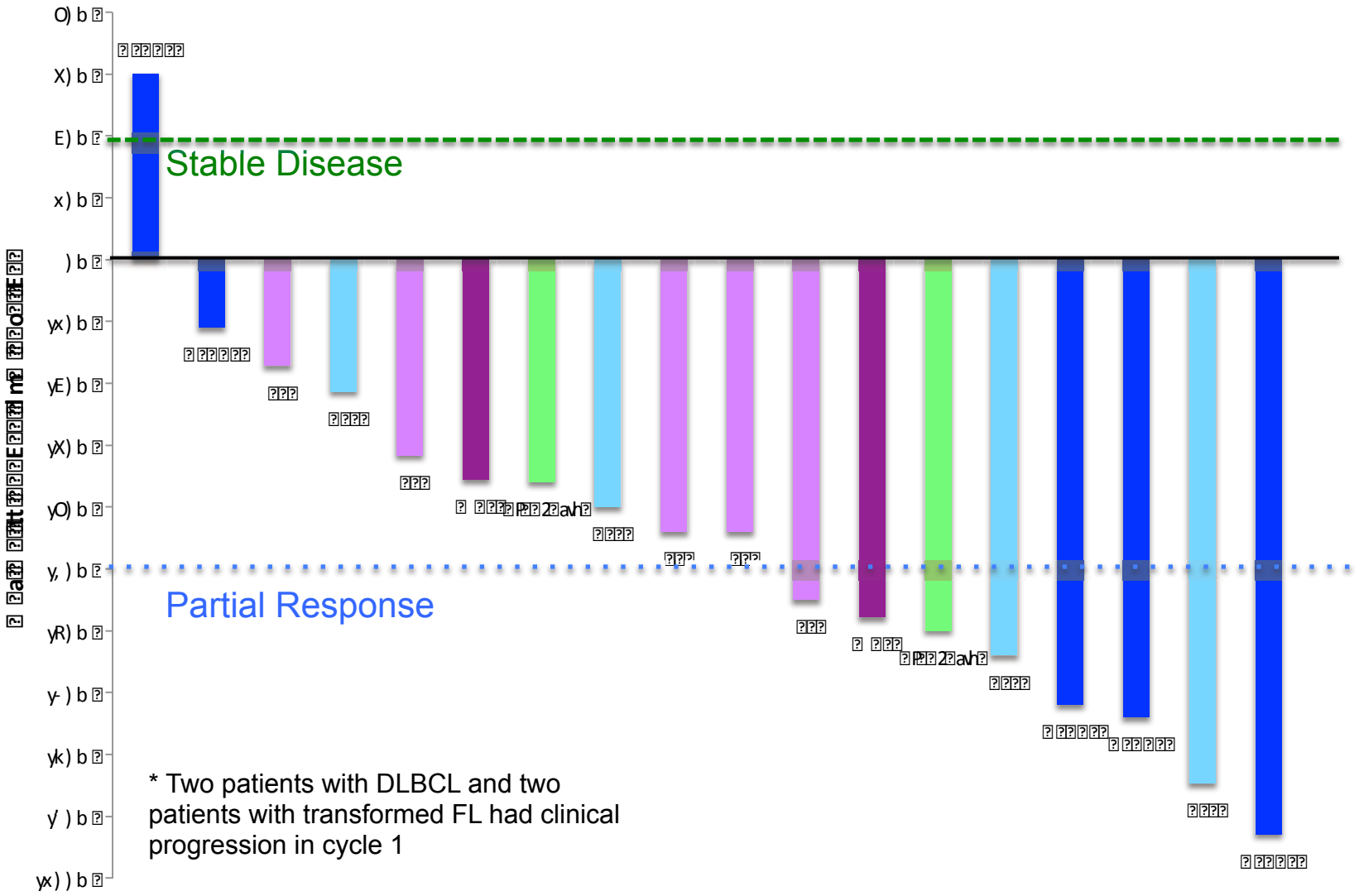


Lymph node biopsies from an MCL patient PMH-40-022 (23 mg/m^2) pre treatment and 53 days post treatment show enrichment of normal lymph node cells and nuclear localization of the TSP p53. The patient stayed on the trial for 144 days with 35% reduction in target lymph nodes on CT (Stable Disease) until withdrawing consent.

KPT-330 Ph1 Study: Responses in Heavily Pretreated CLL & NHL

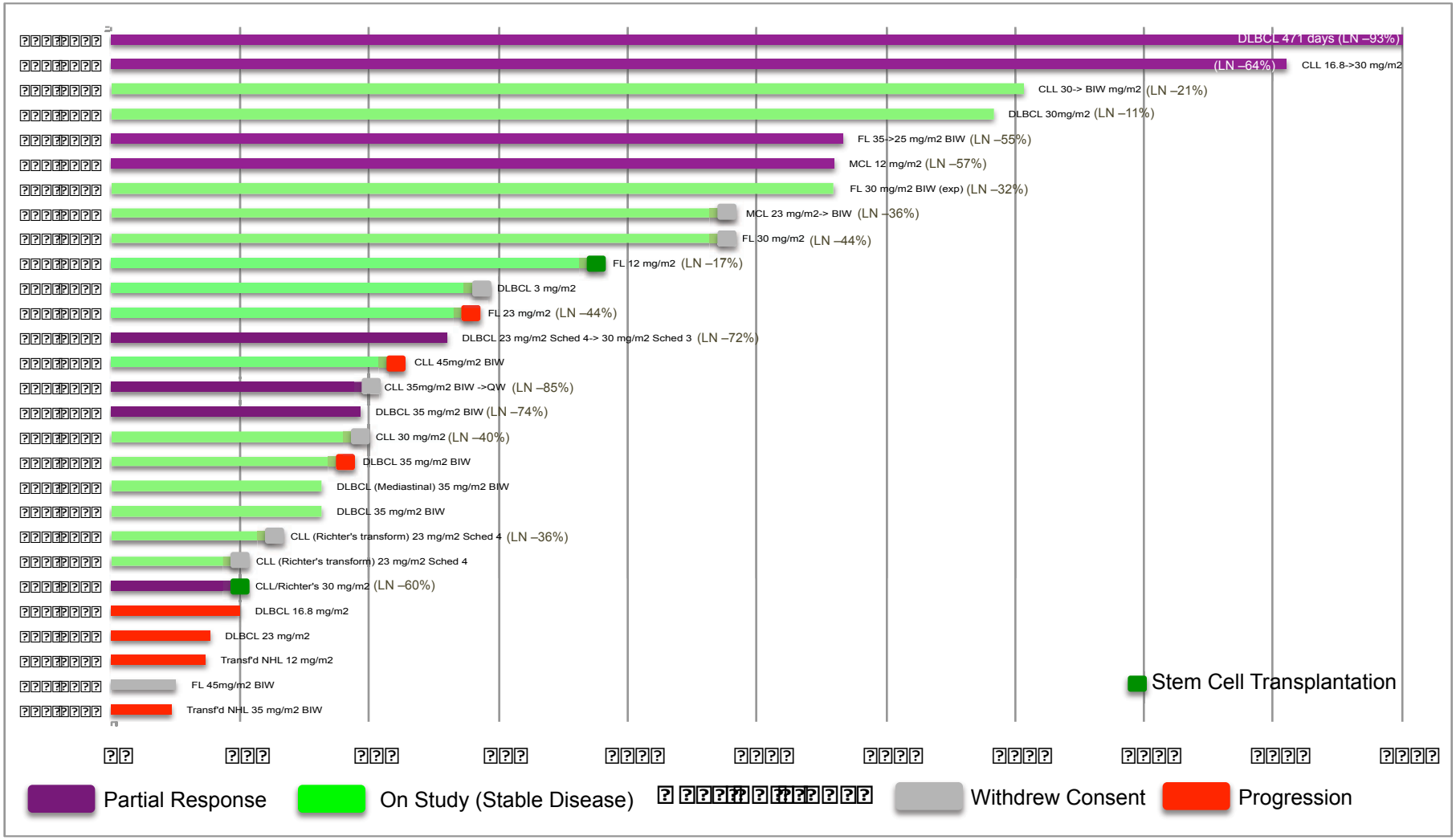
Responses in NHL/CLL/Ricther's Syndrome Patients as of 4-Dec-2013							
Cancer	**Number of Pts Evaluated**	**Total PRs and SDs (%)**	**PR (%)**	**SD (%)**	**PD**	**WC**	**NE**
CLL	4	4 (100%)	2 (50%)	2 (50%)	--	--	--
Richter's Syndrome	4	4 (100%)	1 (25%)	3 (75%)	--	--	--
NHL							
DLBCL	11	10 (91%)	3 (27%)	5 (45%)	2 (18%)	--	1 (9%)
MCL	3	2 (67%)	1 (33%)	1 (33%)	--	--	1 (33%)
FL	6	5 (83%)	1 (17%)	4 (66%)	--	1 (17%)	--
Transformed	2	--	--	--	2 (100%)	--	--
Total	**30**	**24 (80%)**	**8 (27%)**	**15 (50%)**	**4 (13%)**	**1 (3.3%)**	**2 (6.7%)**

KPT-330 Ph1 Study: Maximal % Change in Lymph Node from Baseline



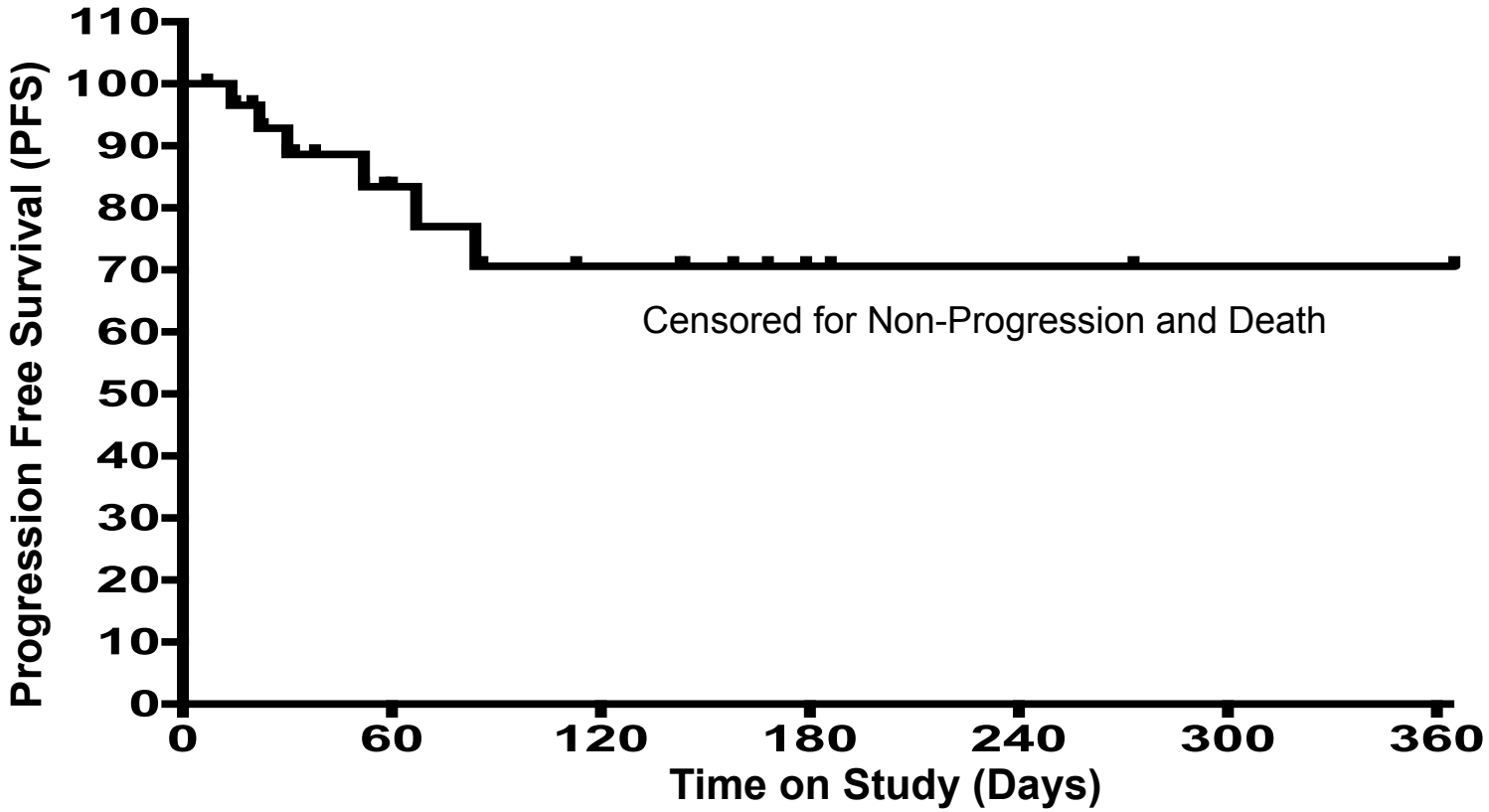
* Two patients with DLBCL and two patients with transformed FL had clinical progression in cycle 1

KPT-330 Ph1 : Patient Outcomes & Time on Study (n=28)



* 2 patients were non-evaluable

KPT-330 Ph1 : Progression Free Survival



# Days On Study	7	15	20	23	30	32	38	52	58	60	86	113	143	144	158	168	179	186	273	445
# Pts On Study	29	27	26	22	19	18	17	15	14	13	10	9	8	6	5	4	3	2	1	0
# Pts At Risk	29	28	27	24	22	21	20	18	17	16	15	14	13	11	10	9	8	7	6	5
Details	1	2	3	3,5,5	6,4,2	5	2	5	2	2	2	4	5	3,5	5	5	5	5	2	2

Notes: 1= WC death unrelated 2= WC low grade tox 3= WC infection 4= Transplant 5= On Study 6= PD

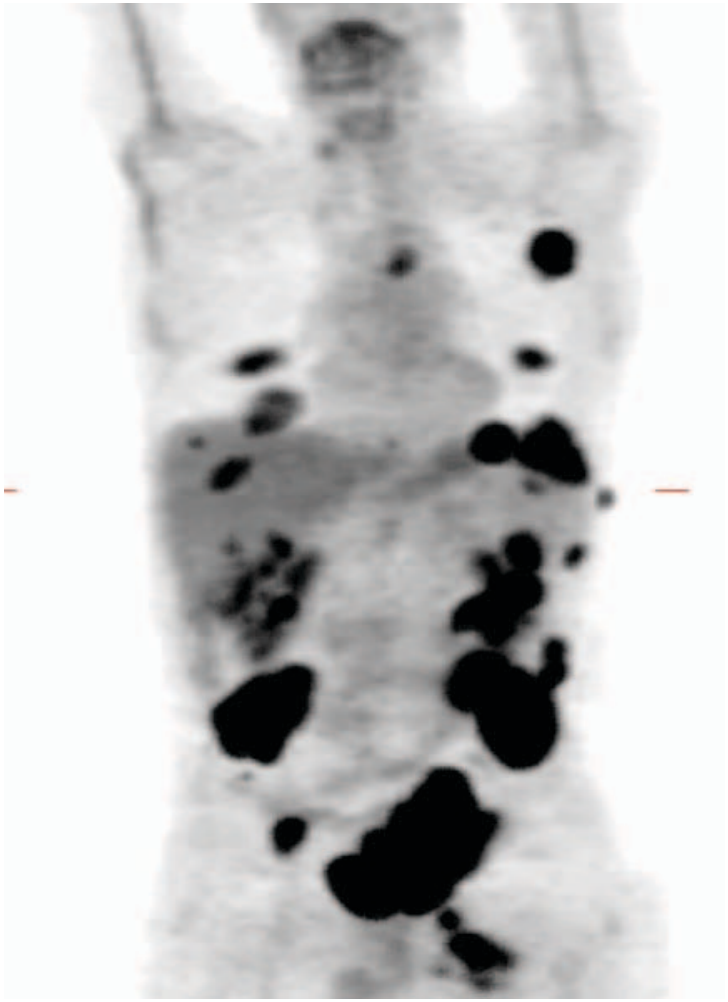
Case Study: Patient 040-003: Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

- **53 year old man with Primary Refractory DLBCL (Dec 2010)**
- Stage 4, IPI2 (elevated LDH), bulky disease
- Refractory (PD) to primary therapy and transplant
- Salvage radiation to abdominal mass, PD to salvage (GDP)
- Dec 2011-Aug 2012 – 20mg prednisone + weekly XRT
  - Marked peripheral edema (3+) due to abd/pelvic mass, pancytopenia

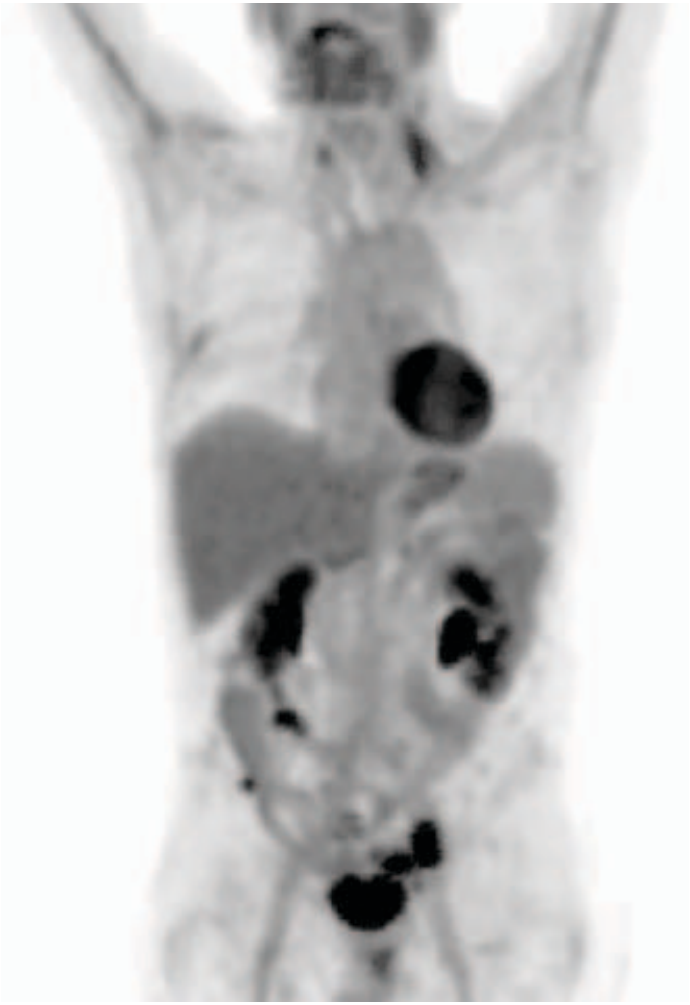
- Response in Cycle 2; currently Cycle 16
  - Began Selinexor Aug 20 2012: PR after Cycle 2 (67% response)
  - 93% response on 12mg/m^2 after Cycles 12 - 16
  - Marked reduction in peripheral edema
  - Minimal side effects, continues on single agent Selinexor

Patient 040-003 DLBCL

Baseline PET/CT



Cycle 12 PET/CT (–93%)



Case Study 040-027: BTK Inhibitor Refractory CLL with Richter's (DLBCL) Transformation

- Patient with CLL treated initially Jan 2010 with FCR
- Recurred Dec 2010, treated with Bendamustine-Rituxan
- Ofatumumab Feb 2011 (PD)
- CHOP April 2011 (PD)
- Revlimid + Flavoperidol Jul 2011 (NR)
- Ibrutinib (BTK Inhibitor) Feb 2012 – Feb 2013 then PD with Richter's Transformation
- Received Oxaliplatin, AraC, Fludarabine, Rituxan x 1 then PD
- Began KPT-330 30mg/m^2 (10X/cycle) – 60% PR in Cycle 1; main side effect Grade 2 fatigue, anorexia
- Following marked response to KPT-330, sent to transplant and T-cell vaccine (experimental)

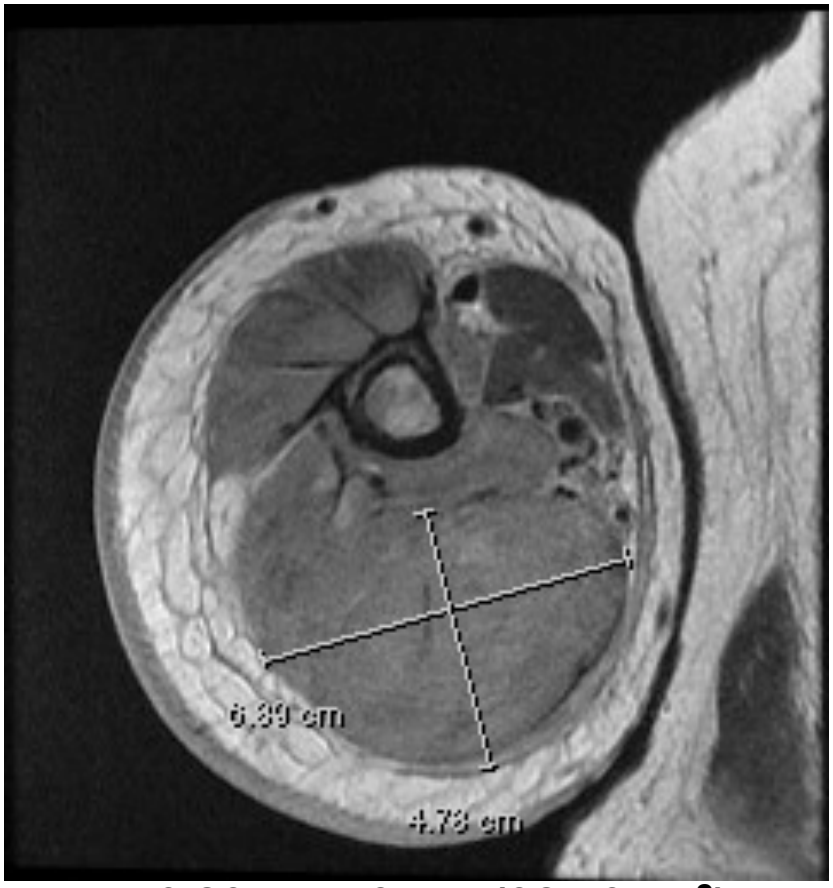
Case Study: Patient 040-046: Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

- 73 year old man with Refractory DLBCL (Feb 2012)
- Stage 4, bulky disease, possible CNS involvement
- CHOP-R initial therapy + intrathecal (CNS) metho-trexate + radiation to R arm with relapse in 10 months
- R-ICE treatment (Jan-Feb 2013) with relapse within 7 months
- Pain, marked edema in R arm (massive lesion)

- Sept 17, 2013 initiates Selinexor 20mg/m^2 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

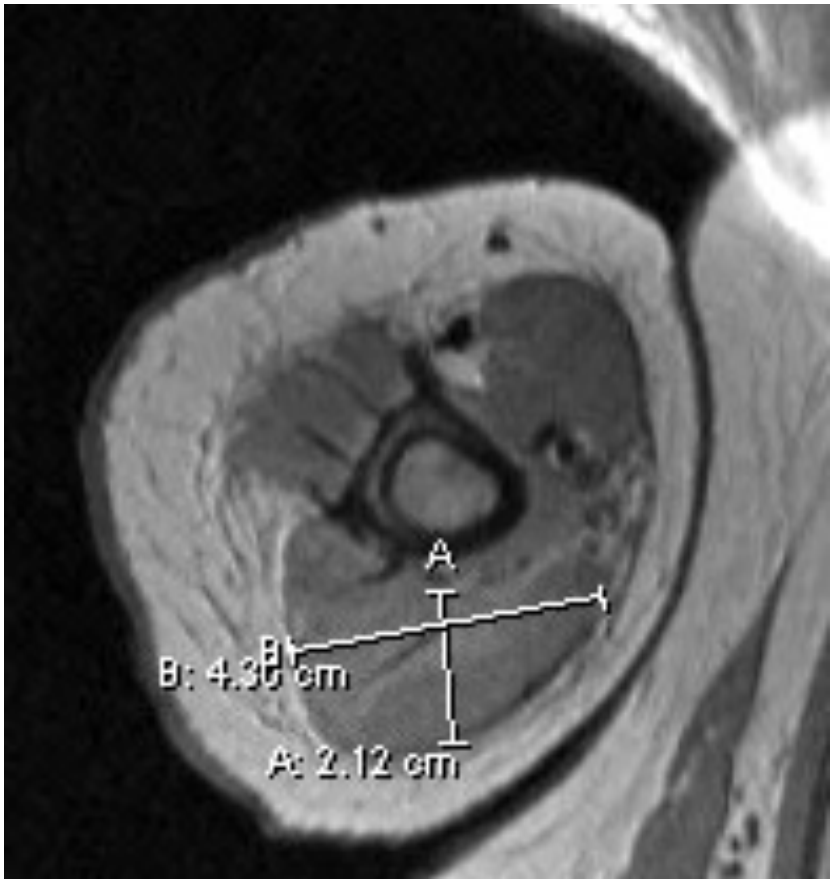
Rel/Ref DLBCL 040-046:
Rapid Partial Response (PR), bulky R arm lesion

R Arm Baseline: Sept 16, 2013



6.89 x 4.73 cm (32.59cm^2)

Cycle 1: October 13, 2013



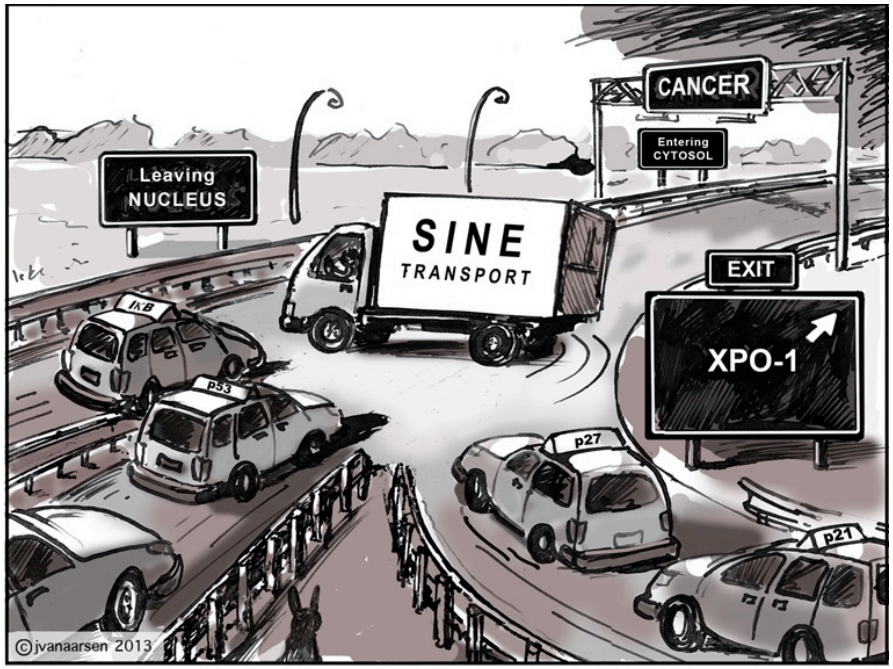
4.30 x 2.12 cm (9.12 cm^2)

Conclusions

- Novel, oral SINE Selinexor (KPT-330) can safely be given as monotherapy to patients with advanced NHL/CLL
  - Main toxicities: fatigue, anorexia, nausea, thrombocytopenia
  - MTD has not been reached; currently dosing at 45mg/m^2 BIW
  - Patients remaining on single agent Selinexor >9 months
- Selinexor has favorable PK and PD characteristics
- Signs of single-agent anti-tumor activity in heavily pre-treated patients with durable cancer control >9 months
- Expansion cohort in DLBCL (and MM) is ongoing, with future trials in Richter's syndrome and DLBCL planned

Acknowledgments

- We would like to thank:
  - Patients and their families
  - Investigators, co-investigators and the study teams at each participating center
    - Princess Margaret Cancer Centre, Toronto
    - Rigshospitalet, Copenhagen
    - Moffitt Cancer Centre, Tampa
    - Dana Farber Cancer Institute
    - Gabrail Cancer Center Research
    - Hackensack University Hospital
    - Sarah Cannon Research Institute
    - The Ohio State University
    - Tom Baker Cancer Centre
    - Washington University; St Louis, MO



The study was sponsored by Karyopharm Therapeutics Inc.