The Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) Demonstrates Broad and Durable Clinical Activity in Relapsed / Refractory Non Hodgkin's Lymphoma

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Presenter Disclosures

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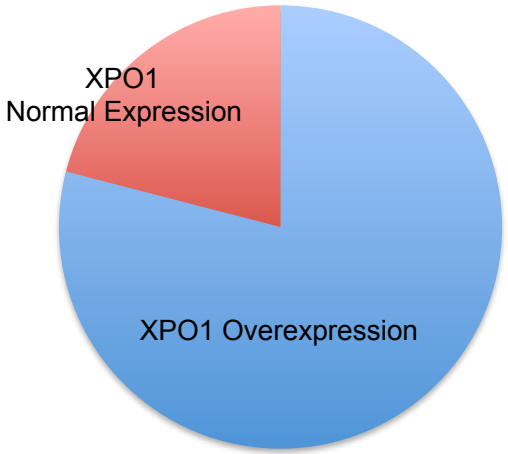
Employee, Speakers Bureau	N/A

Oral Selinexor as Novel Therapy for NHL

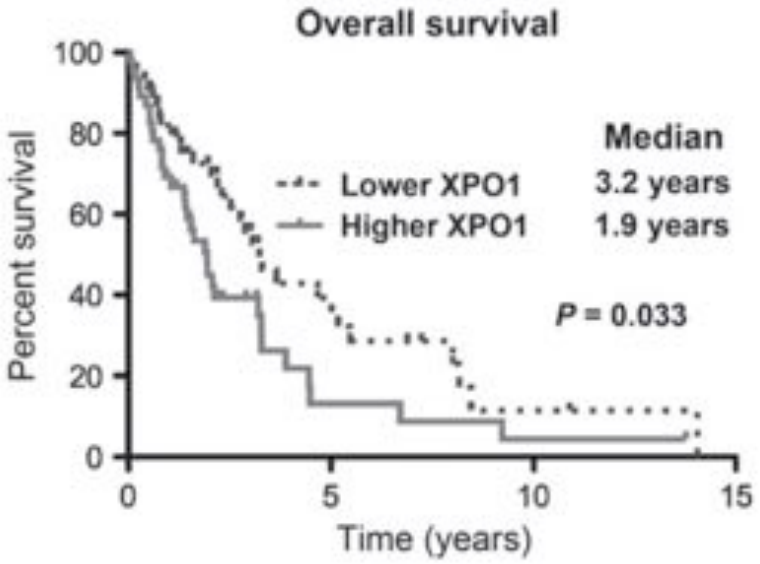
- Exportin 1 (XPO1/Crm1) is the major nuclear export protein with >200 protein and a few RNA cargos
- XPO1 is overexpressed in many hematological and solid tumor cancers and correlates with poor prognosis or resistance to chemotherapy

XPO1 overexpression in DLBCL cell lines and primary specimens
(Kuruvilla et al. (2014) EHA 19th Annual Congress)



XPO1 protein expression in 62 primary DLBCL samples

Poorer prognosis in XPO1 overexpressing MCL
(Yoshimura et al. (2014) Cancer Sci 105: 795)



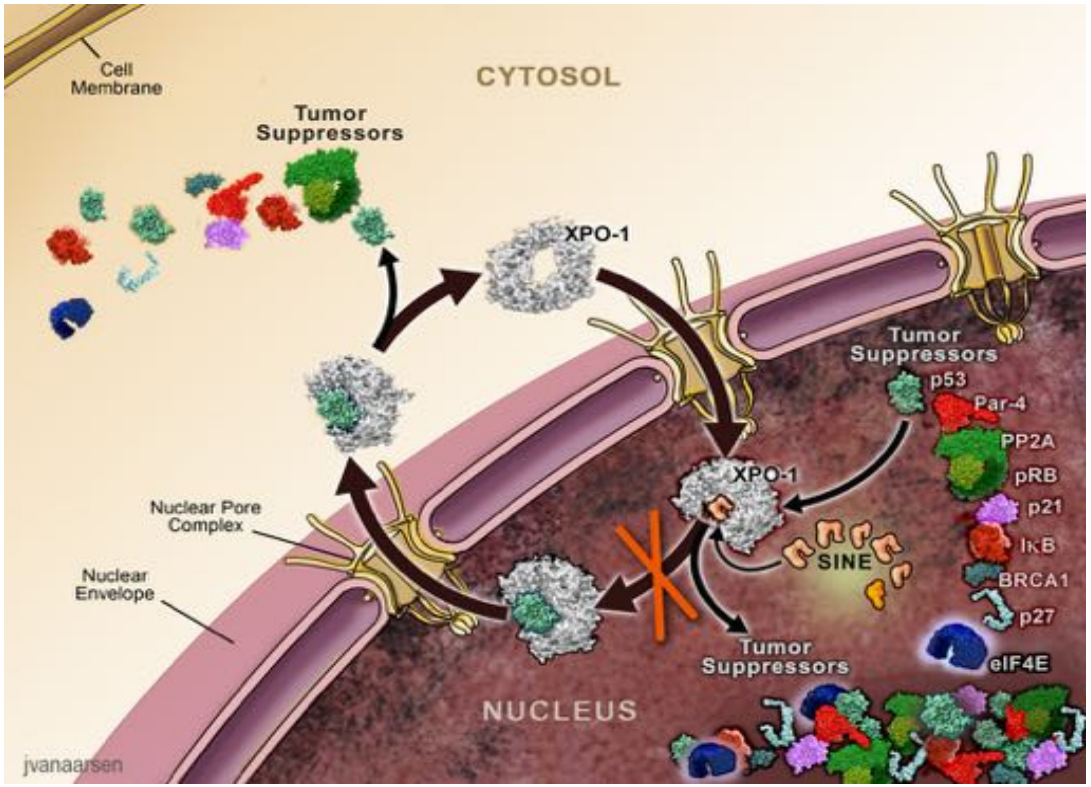
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)

- Novel, small molecule selective inhibitor of XPO1
- Oral drug given 1x, 2x, or 3 times per week
- No known drug-drug interactions through CYP450s
- Potent anti-lymphoma effects in vitro and in vivo in NHL models
- Anti-tumor activity in ongoing Phase I and II studies in advanced hematologic and solid tumors

Selinexor

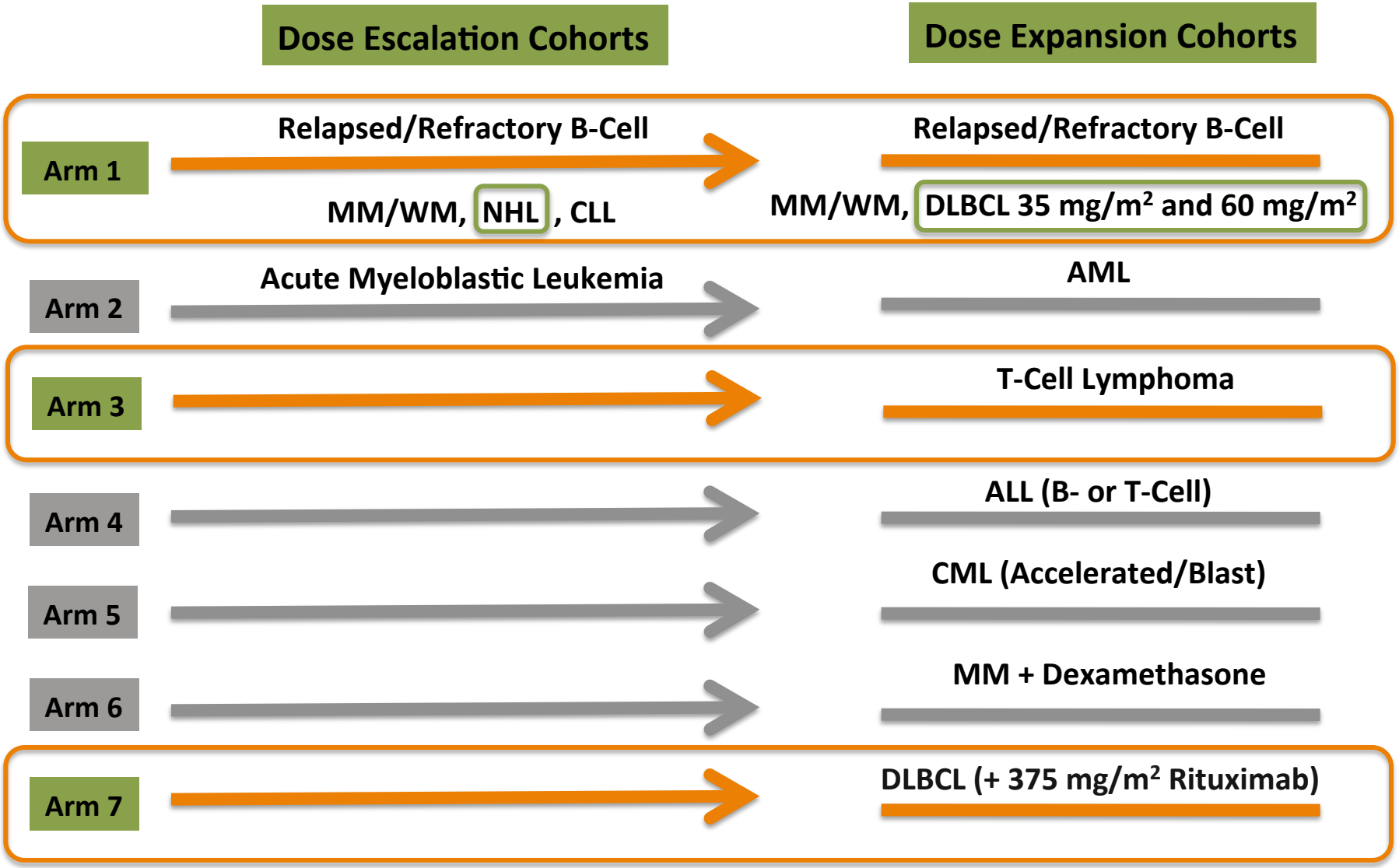
Selinexor is a Rational Therapy for NHL

- Selinexor interferes with activity of proteins known to play critical roles in NHL
  - Reduces expression of the proto-oncogene proteins c-myc, Bcl-2, Bcl-6, Mdm2, BTK, Cyclin D and survivin for which overexpression correlates with poor prognosis
  - Blocks NF-κB activation, which is required for ABC DLBCL cell survival
  - Reactivates p53, for which mutation is associated with poor prognosis



- Selinexor shows robust anti-cancer activity in multiple preclinical models of NHL, including canines with spontaneous lymphoma, largely independent of genotype

Selinexor Phase 1 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, dehydration or diarrhea while taking optimal supportive medications
  - Grade 3 fatigue ≥5 days while taking supportive care
  - Grade 3 AST or ALT elevation lasting longer than 7 days
- **Hematologic:**
  - Grade 4 neutropenia ≥7 days
  - Febrile neutropenia
  - Grade ≥3 thrombocytopenia associated with bleeding

Selinexor Phase 1 Study: Patient Characteristics

Characteristics	N* = 71
Mean Age (Range)	63 (23 – 79)
Male to Female	43 : 28
Mean Prior Treatment Regiments (Range)	3 (1–12)
ECOG Performance Status (0:1:2)	24 : 45 : 02
Non Hodgkin's Lymphoma (NHL)	
-Aggressive B-Lymphoma (DLBCL, Follicular Grade 3b, Transformed)	DLBCL N=31, Trans N=11, Follicular Grade 3b N=1
-Follicular Lymphoma & Other Indolent	10 Patients
-Mantle Cell	4 Patients
-T Cell Lymphoma	5 Patients
-Burkitt's Lymphoma	1 Patient
-Richter's Transformation	8 Patients

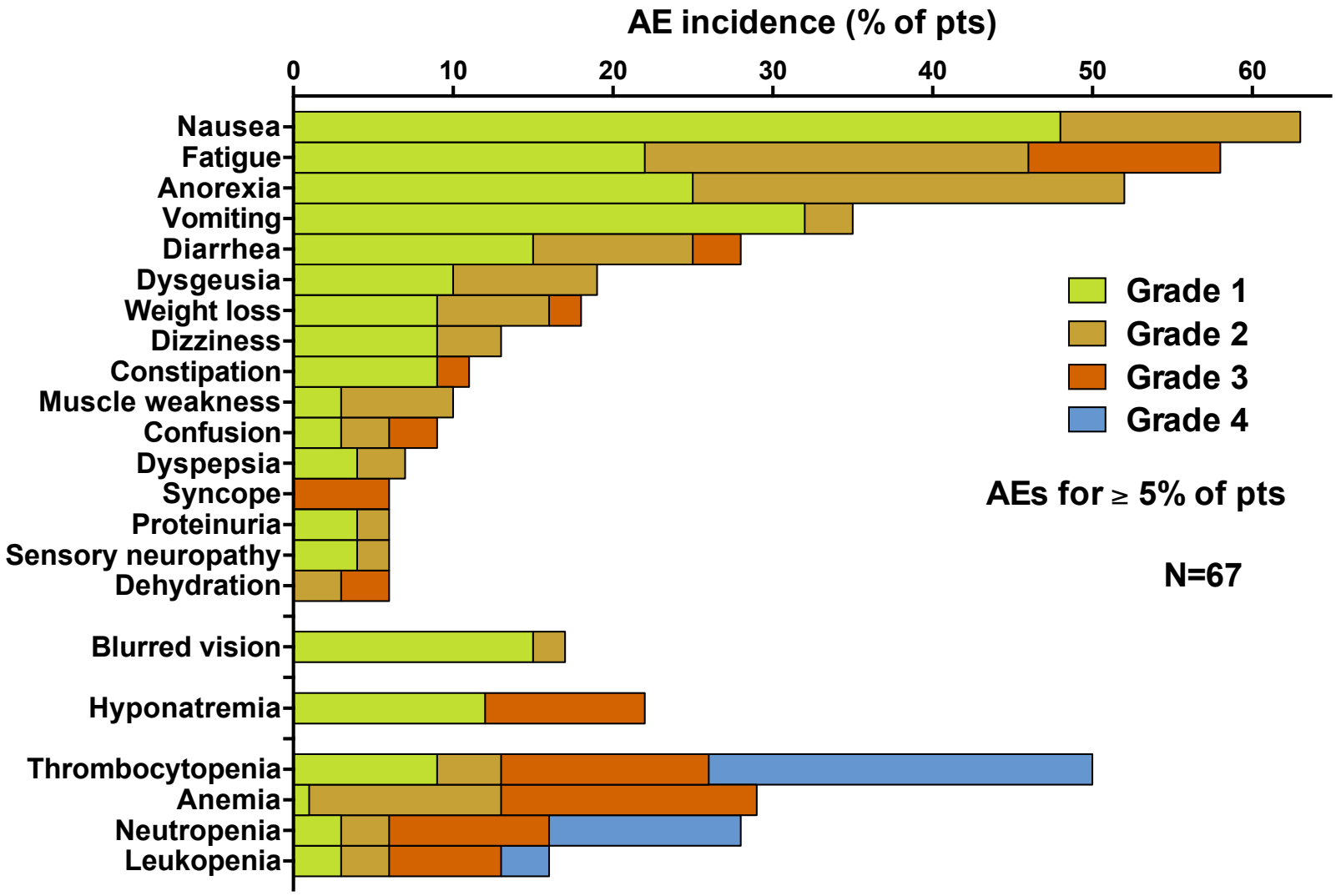
* As of 1-December-2014

Selinexor Phase 1 Study: Doses, DLT and MTD

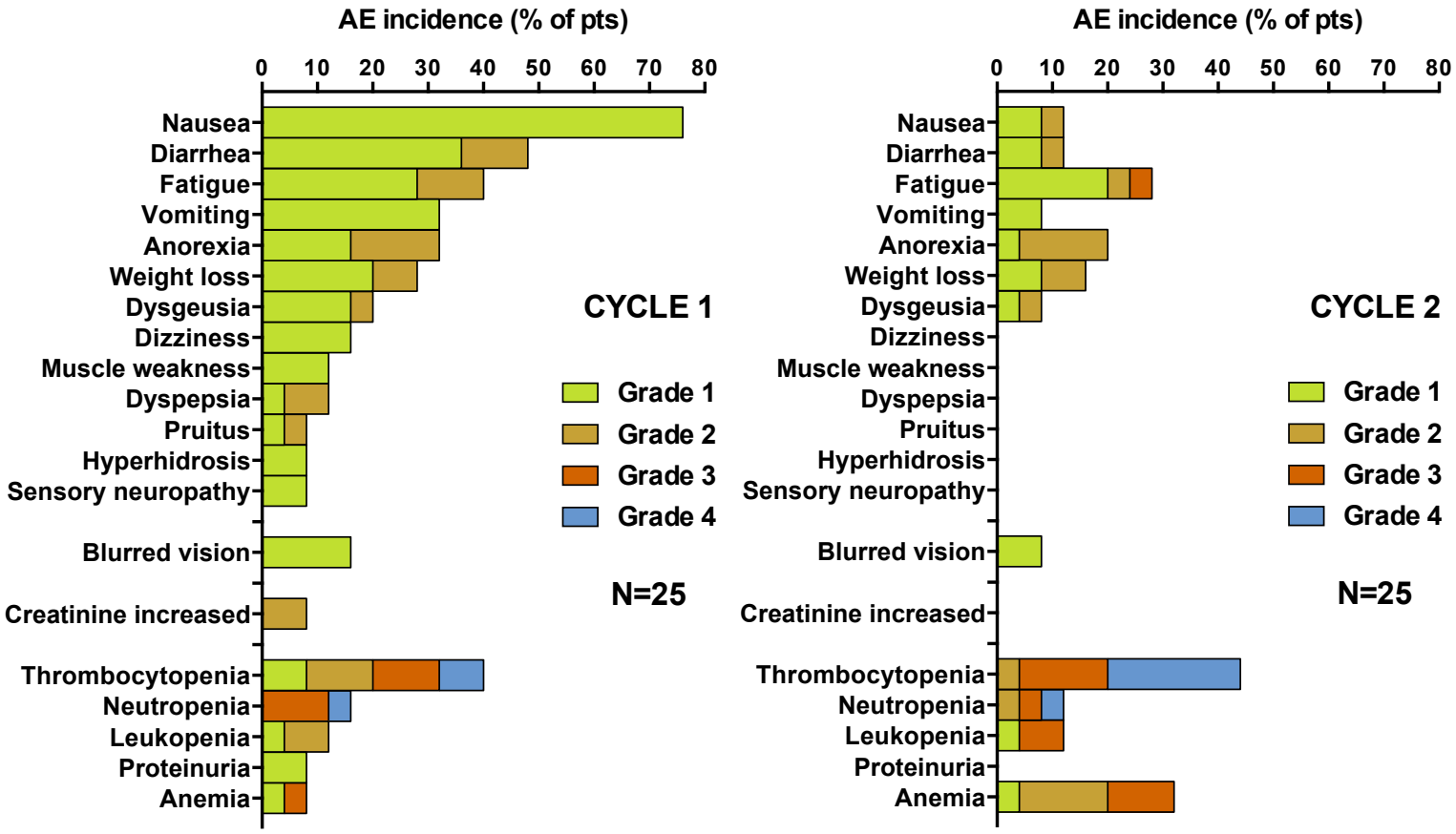
- **10 Cohorts Evaluated:**
  - Doses Ranging from 3 – 80 mg/m^2
- **3 DLTs* Have Been Seen (Only in 10 doses/cycle schedule):**
  - Dose Level: 16.8 mg/m^2; MM pt with Grade 4 thrombocytopenia
  - Dose Level: 23 mg/m^2; FL pt with Grade 4 thrombocytopenia
  - Dose Level: 30 mg/m^2; CLL pt with Grade 2 fatigue, pt missed 3 doses
- **Expansion Cohort 1**
  - 35 mg/m^2; DLBCL – MM – WM patients
- **Expansion Cohort 2**
  - 60 mg/m^2; DLBCL patients

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

Selinexor Phase 1 Study: Drug Related AEs

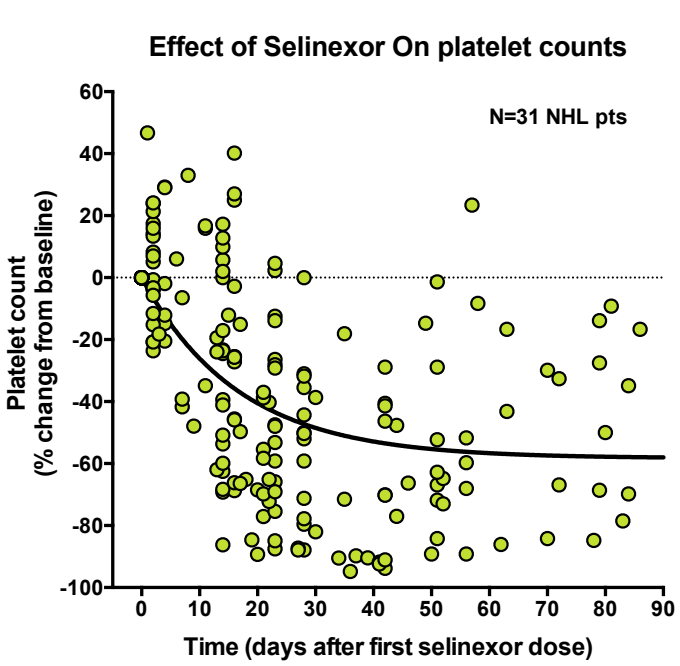


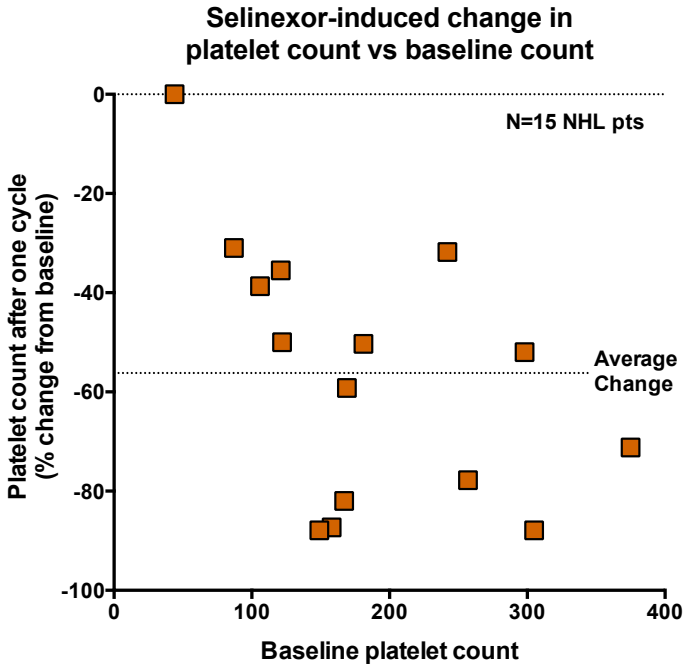
Selinexor Phase 1 Study: Common AEs By Cycle



- Possibly or probably drug-related AEs in the 25 NHL that made it through at least Cycle 2
- AEs (other than hematological) are substantially reduced after Cycle 1

Selinexor Phase 1 Study: Effects on Platelet Count



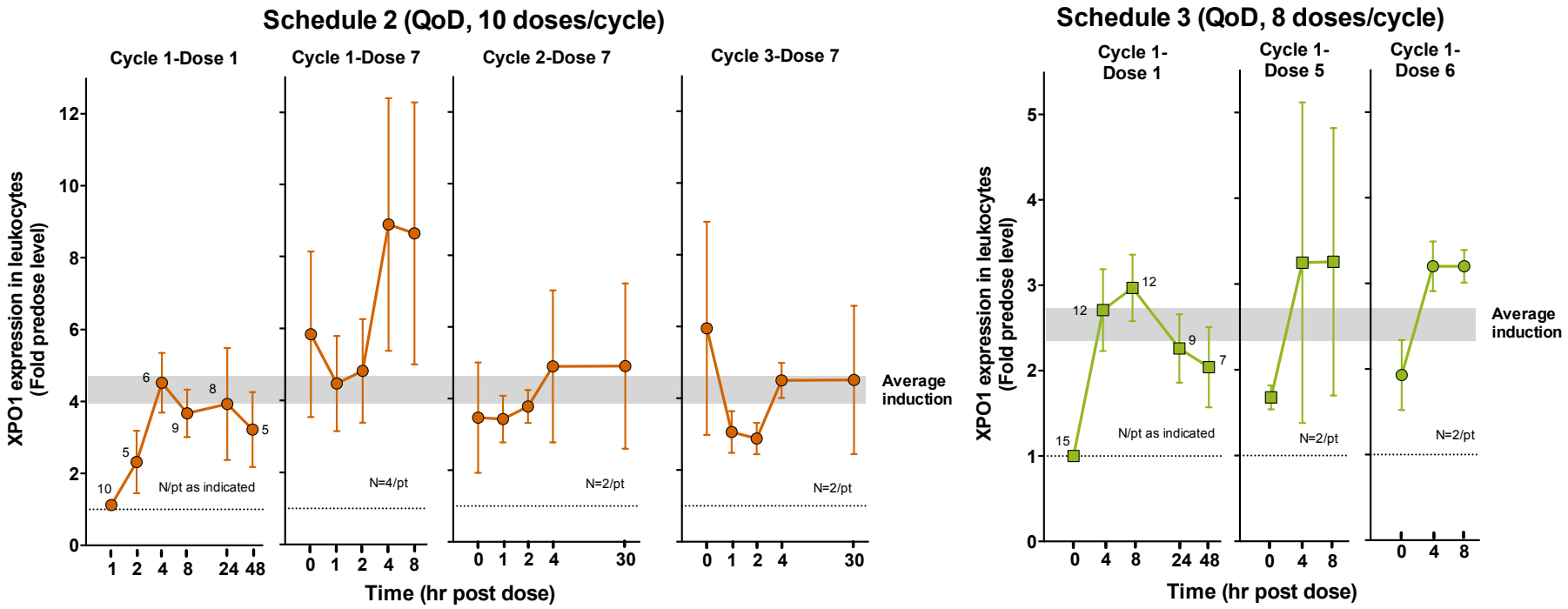


Data from pts maintained at a set dose from the start (3-80 mg/m^2, QOD x2-3/wk), over the period of platelet count measurement.

- Selinexor induced ~50% decrease in platelet count over the first cycle, without further significant loss over subsequent cycles
- Platelet loss is due to inhibition of megakaryocyte progenitor maturation*
- Platelet loss percentage was independent of baseline platelet count
- TPO agonist or IL-11 treatment can be effective at increasing platelet count

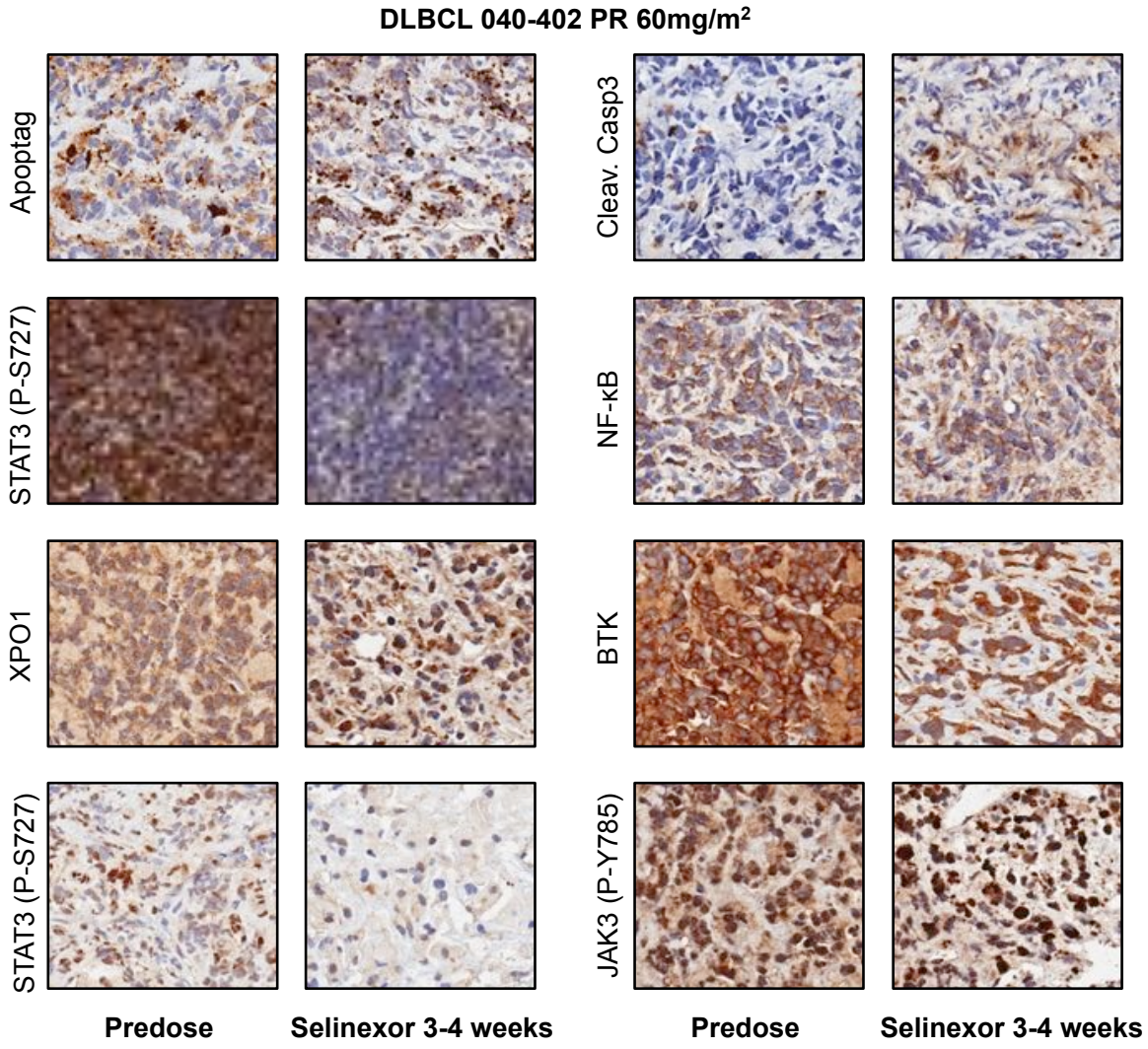
*See Poster: “Selinexor-Induced Thrombocytopenia Results from the Inhibition of Megakaryocyte …” Abstract No. 1458, ASH 2014

Selinexor Phase 1 Study: XPO1 expression in PBMCs



- Selinexor induces XPO1 gene expression in circulating leukocytes that reaches a maximal effect 4 hr after the first dose.
- Leukocyte XPO1 induction is maintained by 10 QoD doses/cycle, but is not maintained with 8 QoD doses/cycle
- Provides pharmacodynamic basis for partial recovery/better tolerability with less intensive 8 QoD doses/cycle

Selinexor Phase 1 Study: Primary Tumor IHC



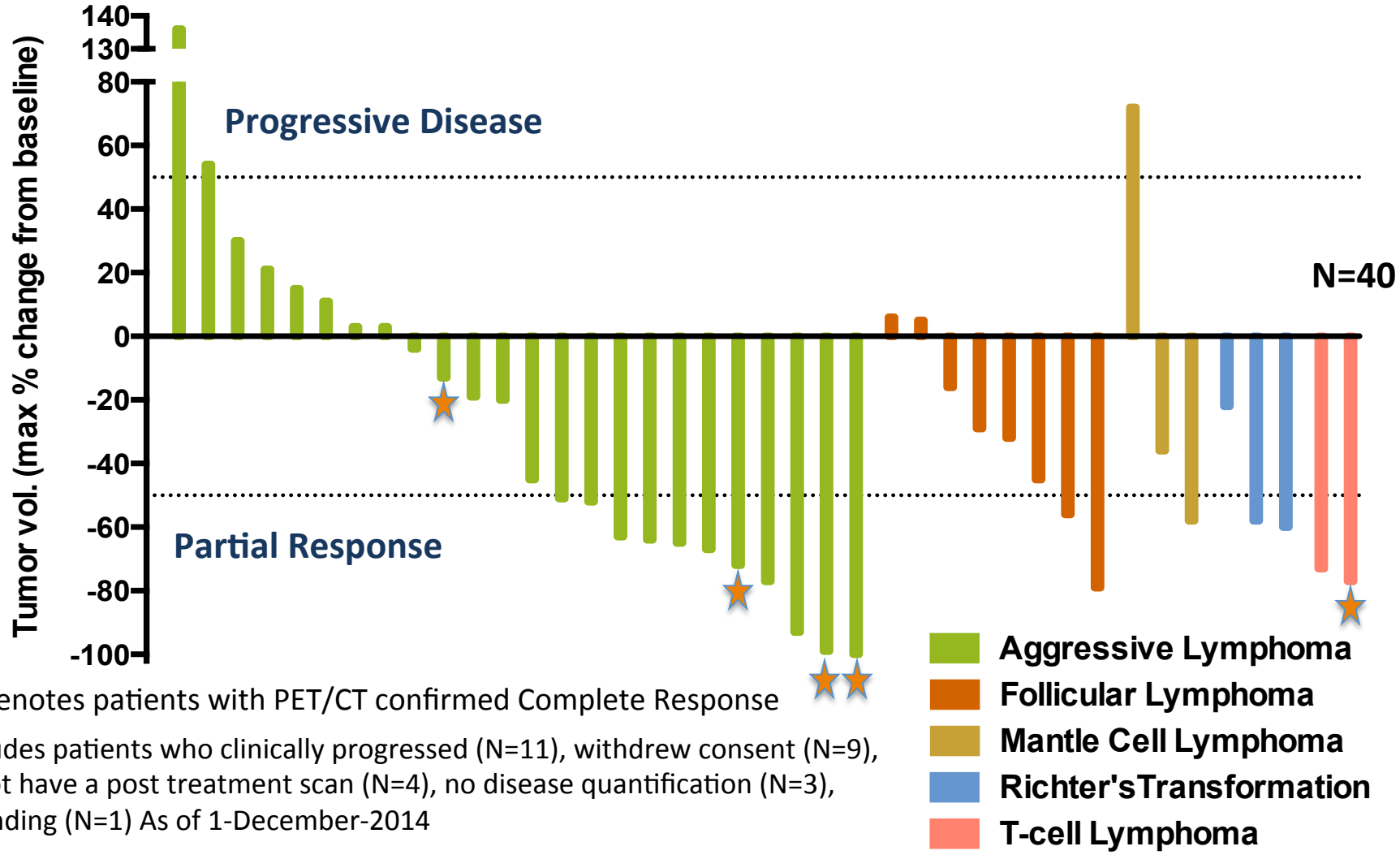
- Immunohistochemical assessment of DLBCL tumor specimens from a patient with a partial response to selinexor
- Increased apoptosis (Apoptag/ Cleaved Casp3)
- Reduction in expression of NF-κB and variety of oncoproteins (BTK, p-STAT-3, p-JAK3) relevant to NHL

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

Cancer Type	Selinexor Dose (mg/m^2)	N*	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
Aggressive B-NHL (DLBCL, FLgrd3b, Transformed)	≤ 20	4	1 (25%)	--	1 (25%)	1 (25%)	2 (50%)
	20 – 50	19	7 (37%)	4 (21%)	3 (16%)	5 (26%)	7 (37%)
	≥ 60	10	4 (40%)	--	4 (40%)	4 (40%)	2 (20%)
Follicular & Other Indolent NHL	≤ 30	4	--	--	--	4 (100%)	--
	≥ 35	4	2 (50%)	--	2 (50%)	1 (25%)	1 (25%)
Burkitt's Lymphoma	≥ 60	1	--	--	--	--	1 (100%)
Mantle Cell Lymphoma	≤ 30	2	1 (50%)	--	1 (50%)	1 (50%)	--
	≥ 35	1	--	--	--	--	1 (100%)
T-Cell Lymphoma	≤ 30	2	1 (50%)	--	1 (50%)	1 (50%)	--
	≥ 35	1	1 (100%)	1 (100%)	--	--	--
Richter's Transformation	≤ 30	3	1 (33%)	--	1 (33%)	2 (67%)	--
	≥ 35	1	1 (100%)	--	1 (100%)	--	--
TOTAL		52	19 (37%)	5 (10%)	14 (27%)	19 (37%)	14 (27%)

ORR=Overall Response Rate, CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease
1 patient is pending response; 15 patients were not evaluable for response (Responses as of 1-December-2014)

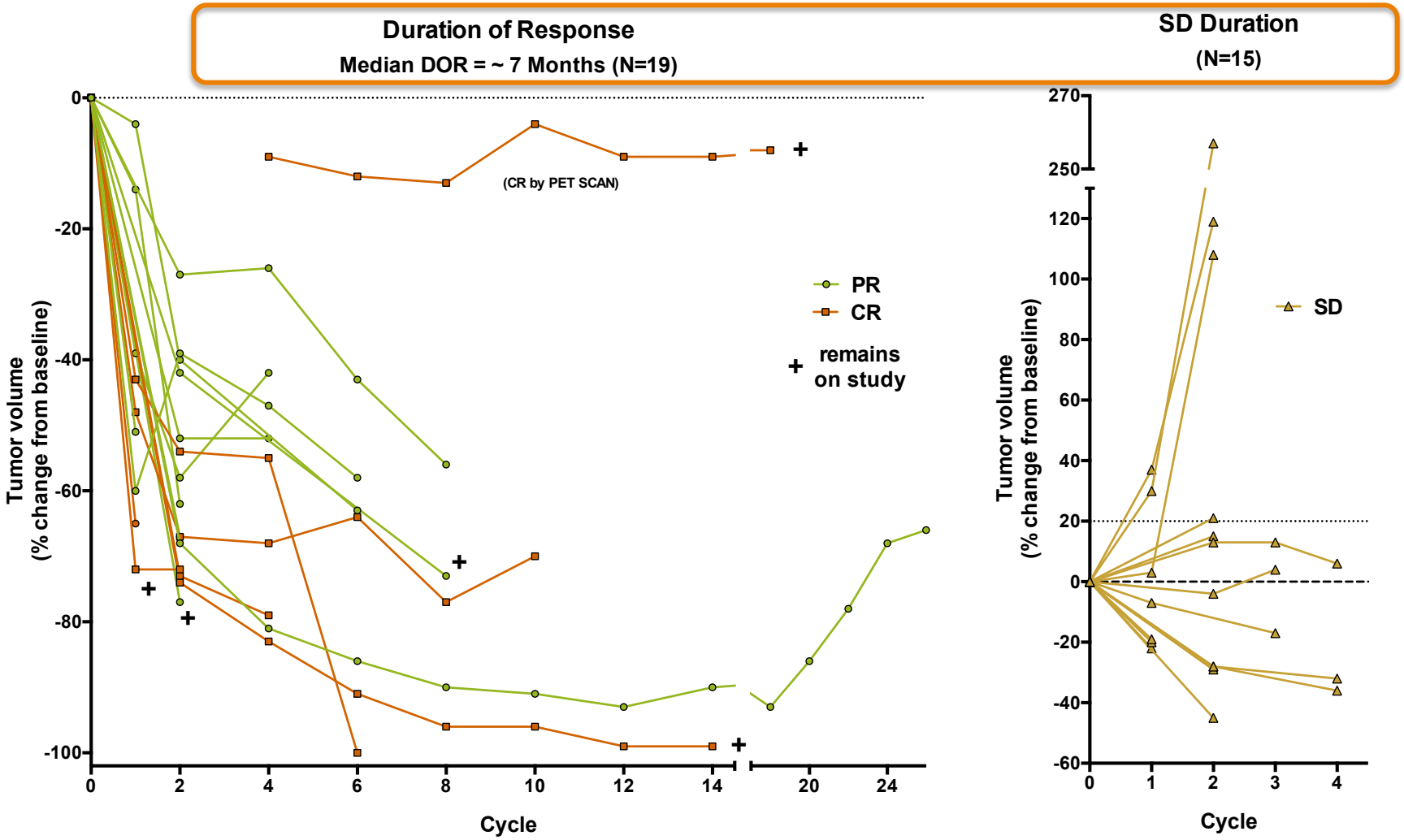
Selinexor Phase 1 Study: Evaluable Patients* Maximal % Change in Lymph Node from Baseline



★ Denotes patients with PET/CT confirmed Complete Response

*Excludes patients who clinically progressed (N=11), withdrew consent (N=9), did not have a post treatment scan (N=4), no disease quantification (N=3), or pending (N=1) As of 1-December-2014

Selinexor Phase 1 Study: Duration of Disease Control



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

Responses in Diffuse Large B-Cell Patients as of 1-December-2014							
Type	**N**	**DCR (%)**	**ORR (%)**	**CR (%)**	**PR (%)**	**SD (%)**	**PD (%)**
GCB	11	9 (82%)	4 (36%)	1 (9%)	3 (27%)	5 (45%)	2 (18%)
Non GCB	5	4 (80%)	2 (40%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)

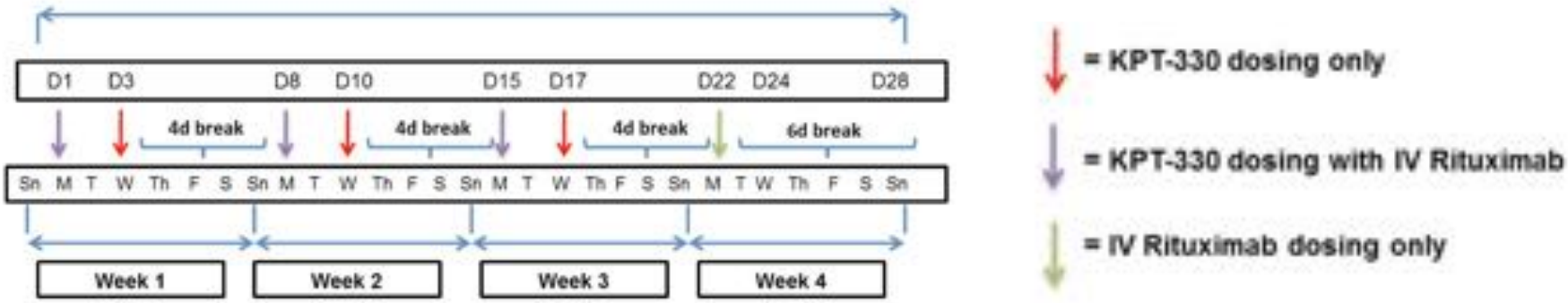
Subtyping was available for 16 evaluable patients

Patients with "Double Hit" DLBCL as of 1-December-2014				
Patient ID	**Best Response**	**% Reduction in Lymph Nodes**	**Days on Study**	**Prior Therapies**
046	**CR**	73% (PET Negative)	429+	**CHOP-R, RICE**
058	**PD**	--	57	**CHOP-R, RICE**
072	**PR**	-65%	214	**R-CHOP, Benda, RICE, DHAP-R, BEAM**
086	**SD**	-45%	104	**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 (+ patient remains on study)

Selinexor Phase 1 Study: Rituximab Combo

- **ARM 7:** Patients receive a combination of selinexor with rituximab
  - Dosing Scheme Below:



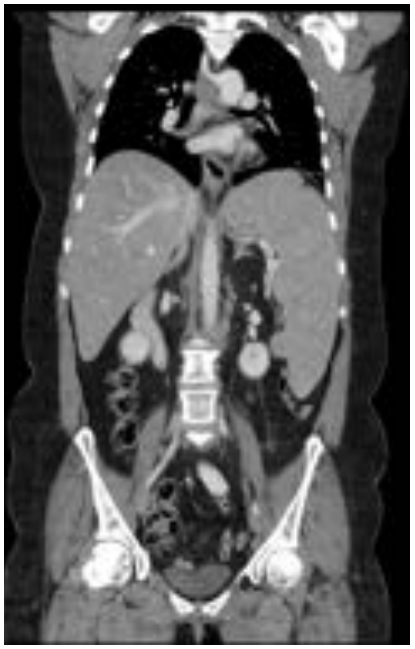
- Three patients have been enrolled on **ARM 7** thus far
  - Cohort 1: 45 mg/m^2 selinexor + 375 mg/m^2 rituximab has cleared DLT evaluation
  - Responses include **1** Partial Response (55% Reduction) and **2** Progressive Disease
- Cohort 2: 60 mg/m^2 selinexor + 375 mg/m^2 rituximab is currently enrolling

Case Study: Patient 040-050: Refractory DLBCL : Complete Response

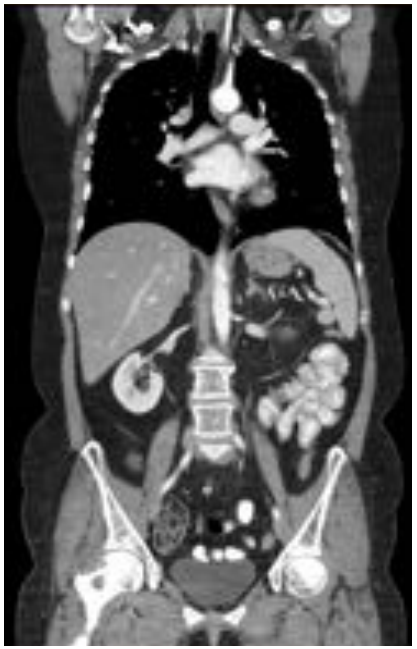
- 51 year old female – DLBCL
- March 2006 – Stage IV DLBCL R-CHOPX6
- Jan 2010 – Relapse Stage IV DLBCL GDPX2 and Autologous SCT – Maintenance Rituximab (NCIC CTG LY12 RCT)
- April 2011 – Relapse in Neck – Radiation
- Jan 2012 – Relapse in Neck – steroids
- Feb 2012 – PD in Neck – Panabinostat X6 cycles RPh2
- Jul 2013 – Relapse – steroids

Selinexor Treatment

- October 7, 2013, initiates Selinexor 35 mg/m^2
- MRI: 74% reduction in cycles 1 & 2
- PET CT negative Cycle 12, : CR

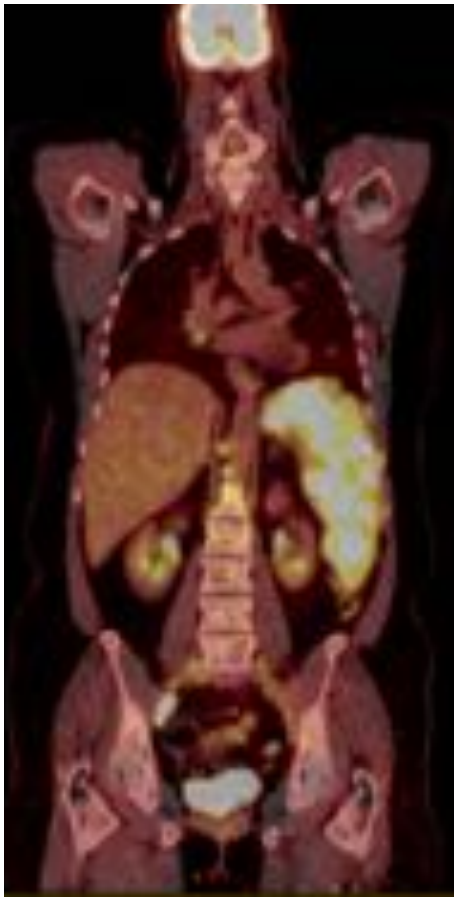


Baseline

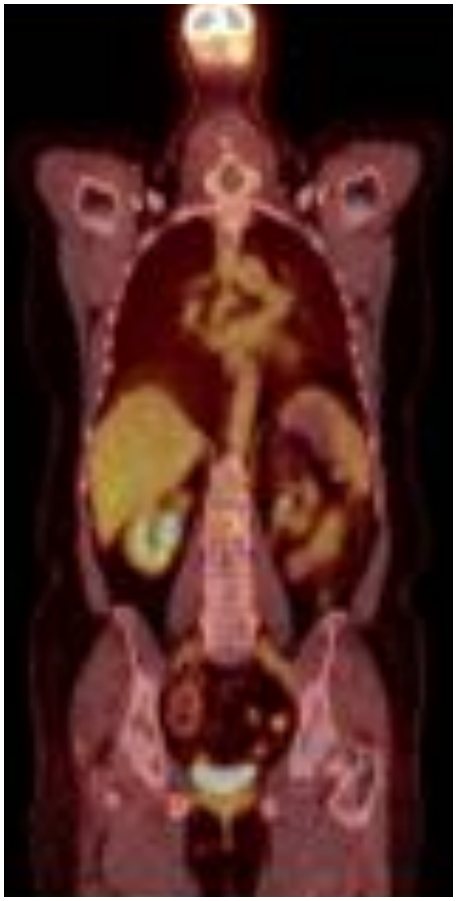


Cycle 12

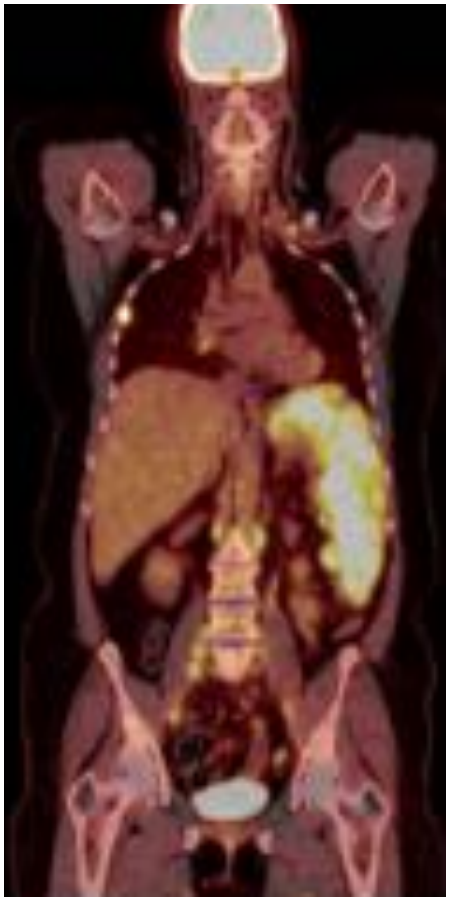
Rel/Ref DLBCL 040-050: PET Confirmed Complete Response



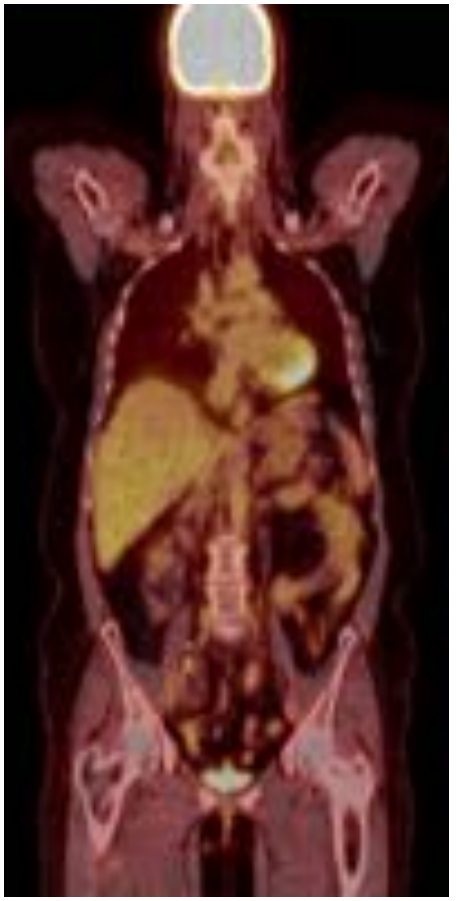
Baseline



Cycle 14



Baseline



Cycle 14

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
- Selinexor has favorable PK and PD characteristics
- Single-agent anti-tumor activity across all NHL types with durable cancer control >9 months; median DOR ~ 7 months
- Marked activity across GCB, nonGCB, and Double-Hit DLBCL
- Further evaluation of selinexor in NHL is currently enrolling in two separate Phase 2 Studies:
  - DLBCL – SADAL: randomized study of selinexor + low dose dexamethasone **(NCT02227251)**
  - Richter's Transformation – SIRRT: open label study with selinexor monotherapy **(NCT02138786)**

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