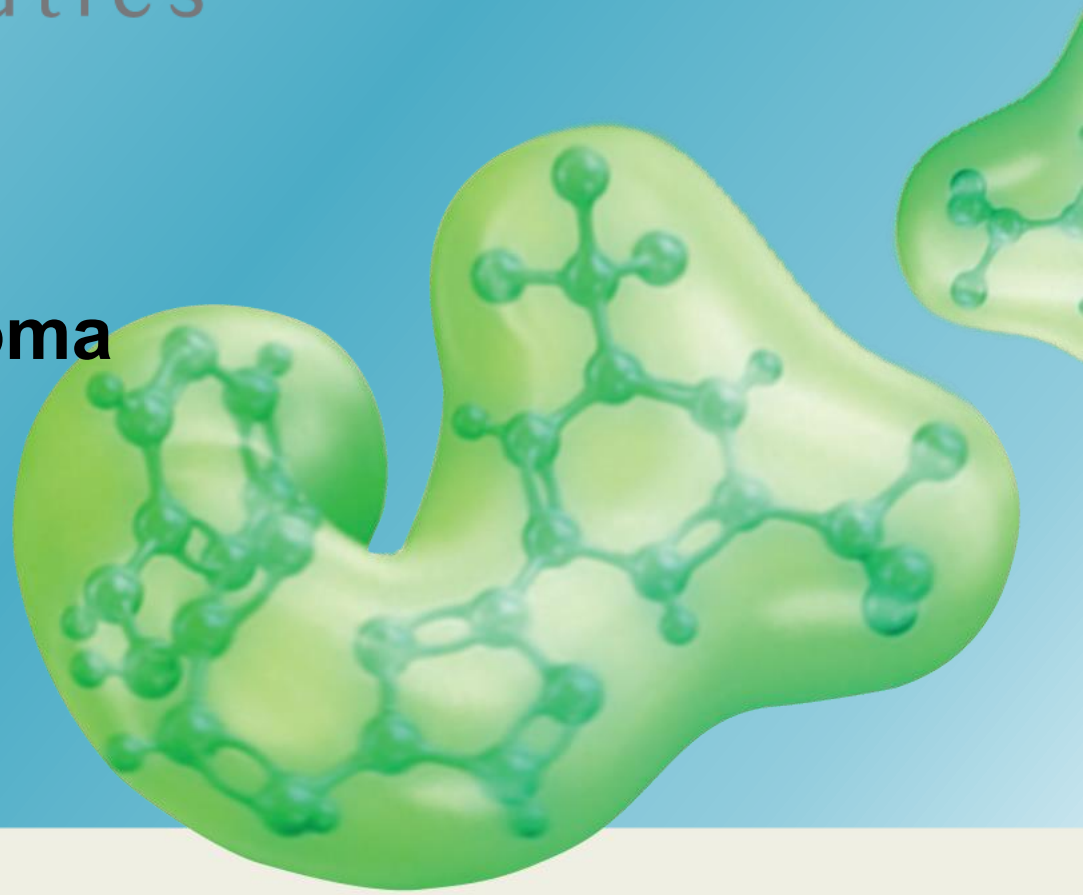
Karyopharm Therapeutics

Nuclear Export Inhibition: Selinexor in Non-Hodgkin's Lymphoma

10 May 2016, Bologna Italy

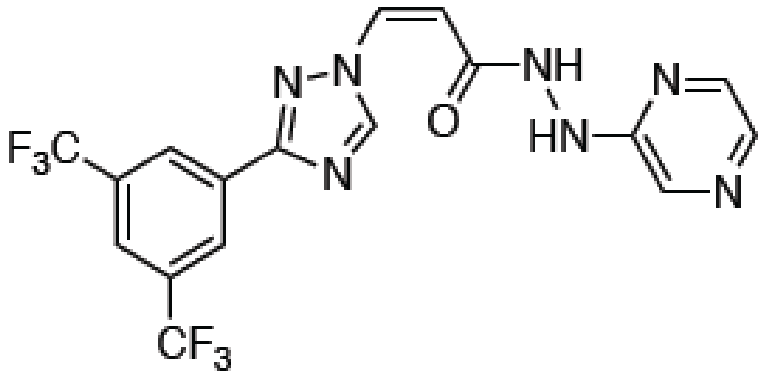


Targeting Disease at the Nuclear Pore

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

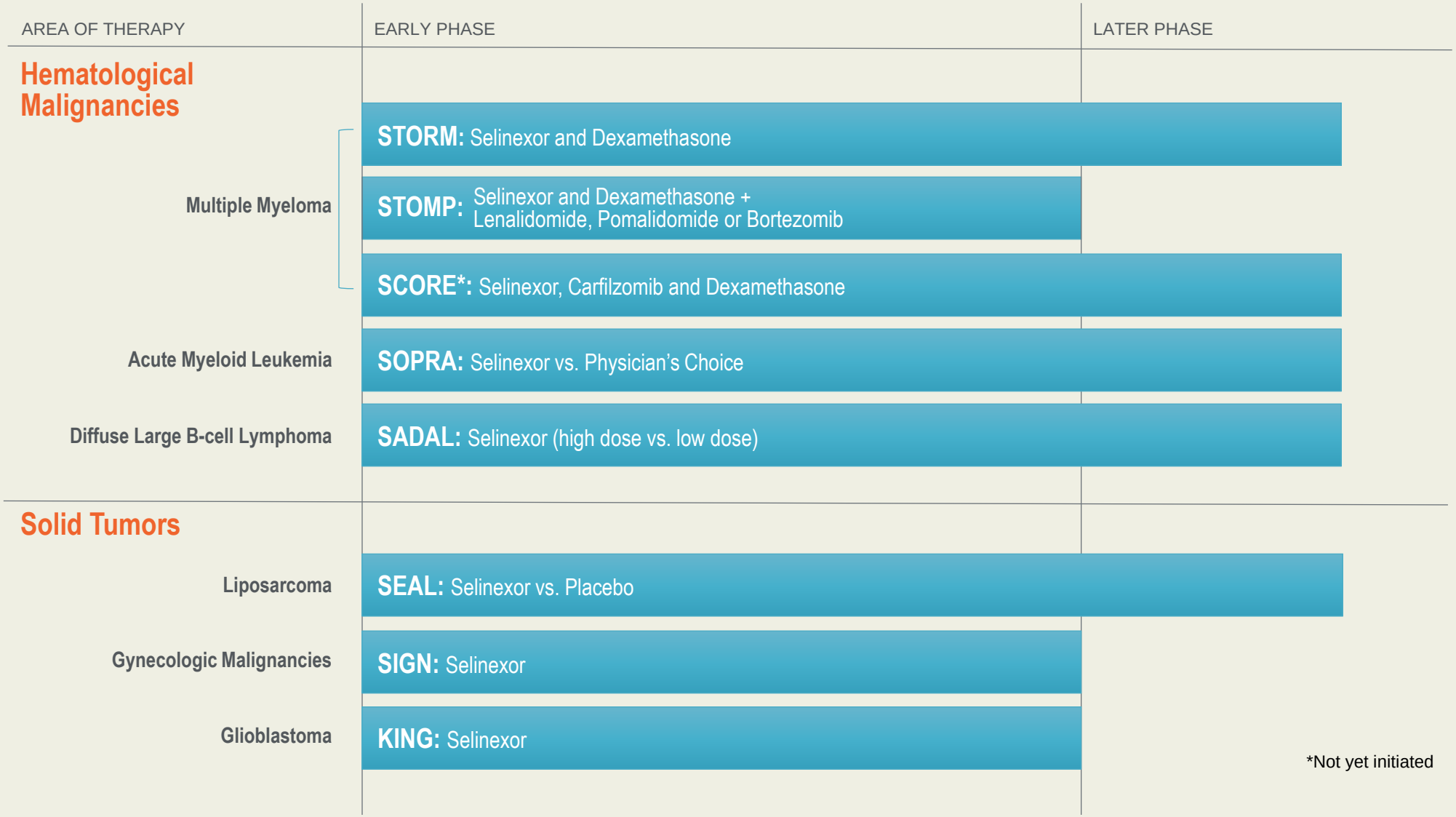
- Novel, small molecule selective inhibitor of XPO1
- Oral drug administered 1-2 times (day 1,3) per week
- No known drug-drug interactions
- Over 1500 patients treated with selinexor alone and in combination across many tumor types
- Anti-tumor activity in ongoing studies in advanced hematologic and solid tumors
- Main side effects (anorexia, nausea, fatigue, platelet reductions) manageable with standard supportive care, including steroids
- Treatment >2 years is feasible without cumulative or organ-specific toxicities

Selinexor

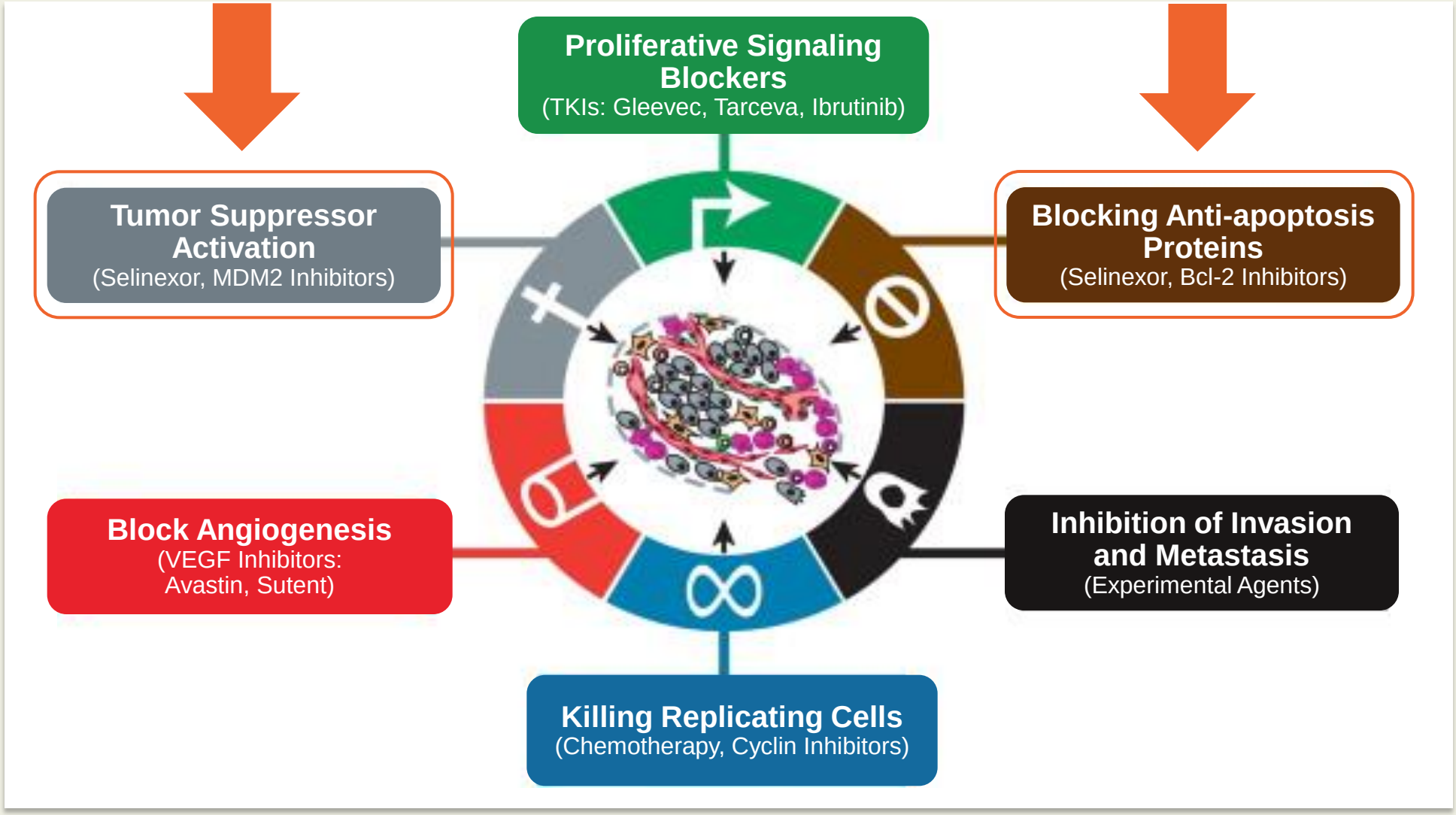


MW = 443 D

Oral SINE Compound: Selinexor (KPT-330)



SINE™ Compounds Target the Hallmarks of Cancer* Through Unique Dual Pathways

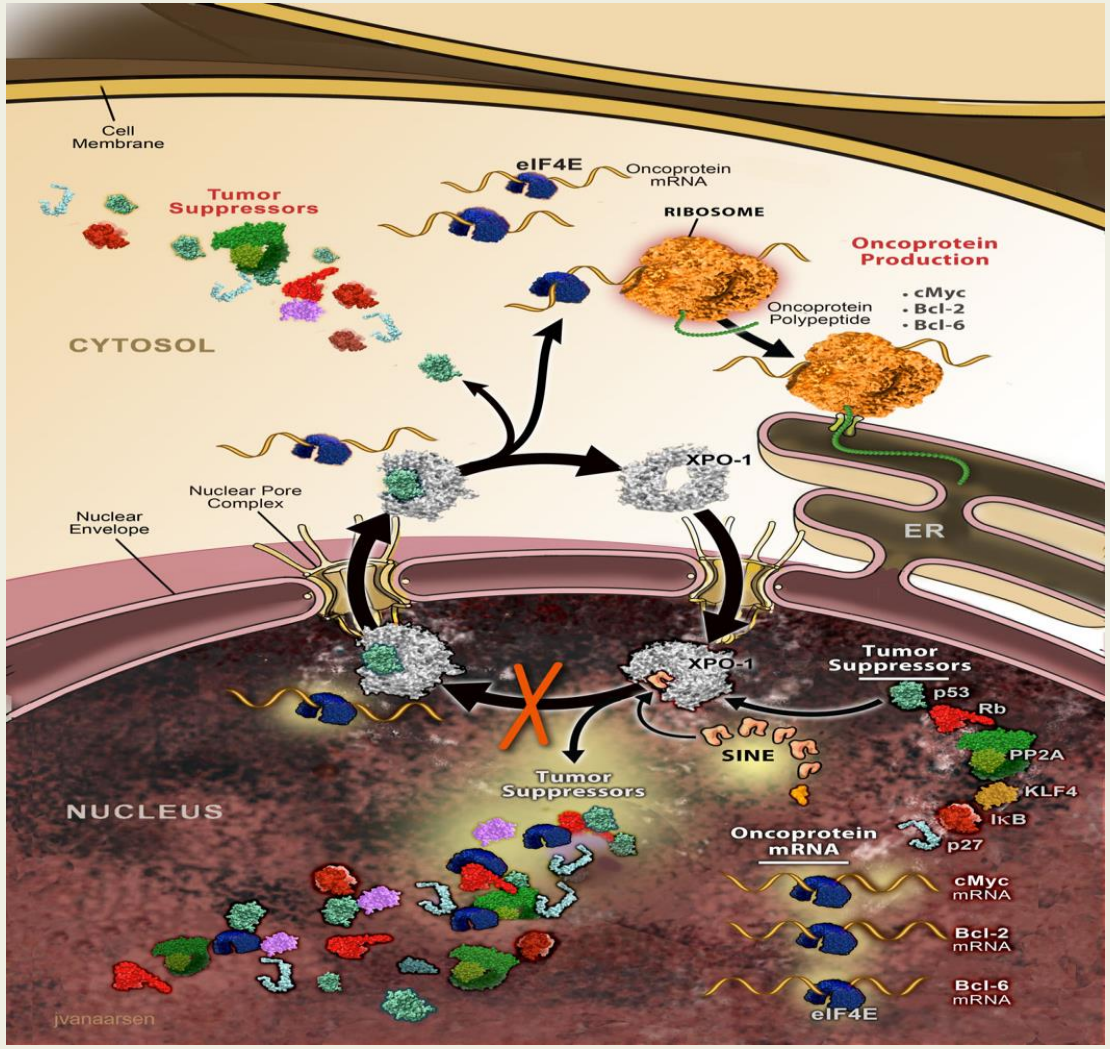


*Based on: Hanahan & Weinberg 2012, Cell, volume 144, issue 5 2011 646 - 674

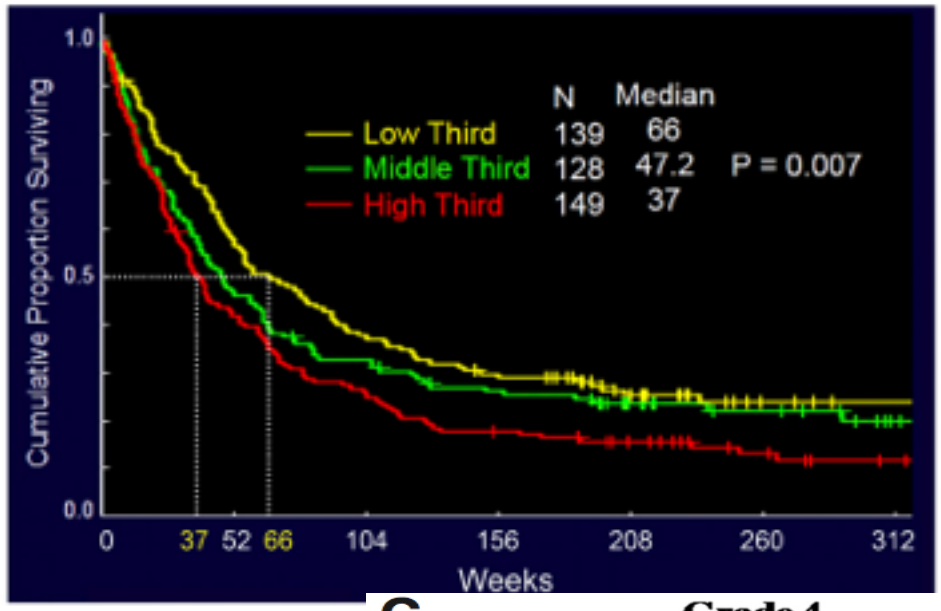
Selinexor Mechanism of Action

Video Link: http://karyopharm.com/sinetm-technology/overview/

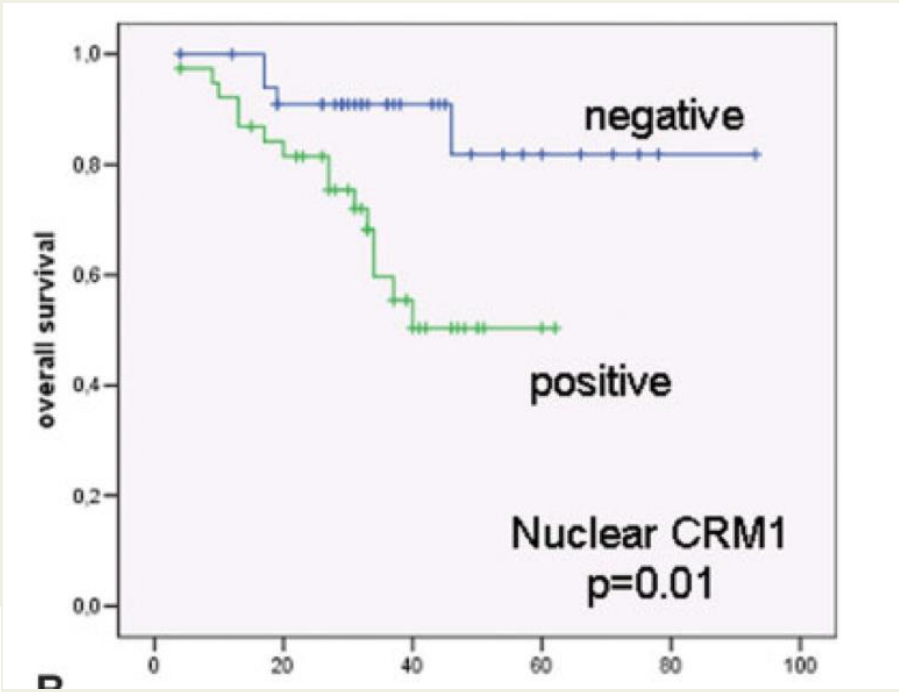
- XPO1 (CRM1) is one of 8 nuclear export proteins
  - Carries ~300 cargoes from nucleus to cytoplasm including the major Tumor Suppressor Proteins (TSPs) and eIF4E (cap-binding protein)
- By blocking XPO1, Selinexor augments TSPs and reduces oncoproteins known to play critical roles in NHL
  - Forces nuclear retention and activation of TSPs p53, IκB, FOXO, etc
  - Reduces expression of oncoproteins c-myc, Bcl-2, Bcl-6, Mdm2, BTK, Cyclin D and survivin
  - Blocks NF-κB activation, which is required for ABC DLBCL cell survival
  - In p53-mutant DLBCL, induces p73 and other TSPs to induce apoptosis
- Selinexor shows robust anti-cancer activity in multiple preclinical models of NHL, including dogs with spontaneous B- or T cell lymphoma, largely independent of genotype (including p53 mutant models)



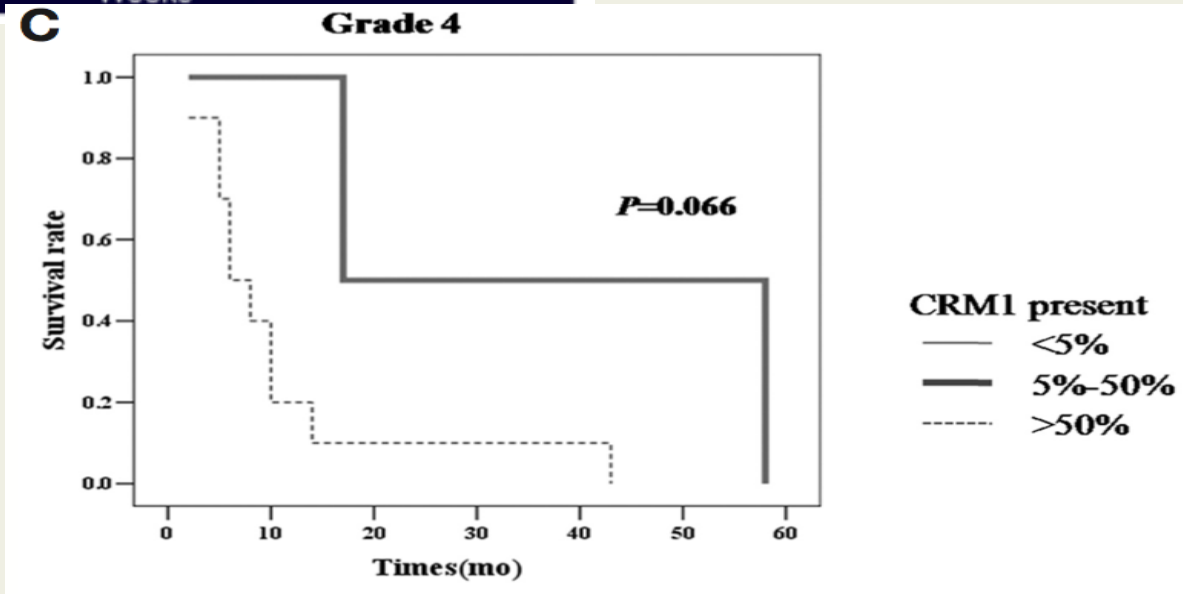
XPO1 Is Overexpressed in Cancer and Usually Correlates with Disease Stage or Poor Prognosis (Cont'd)



AML (Kojima 2013)



Glioblastoma (Shen 2009)

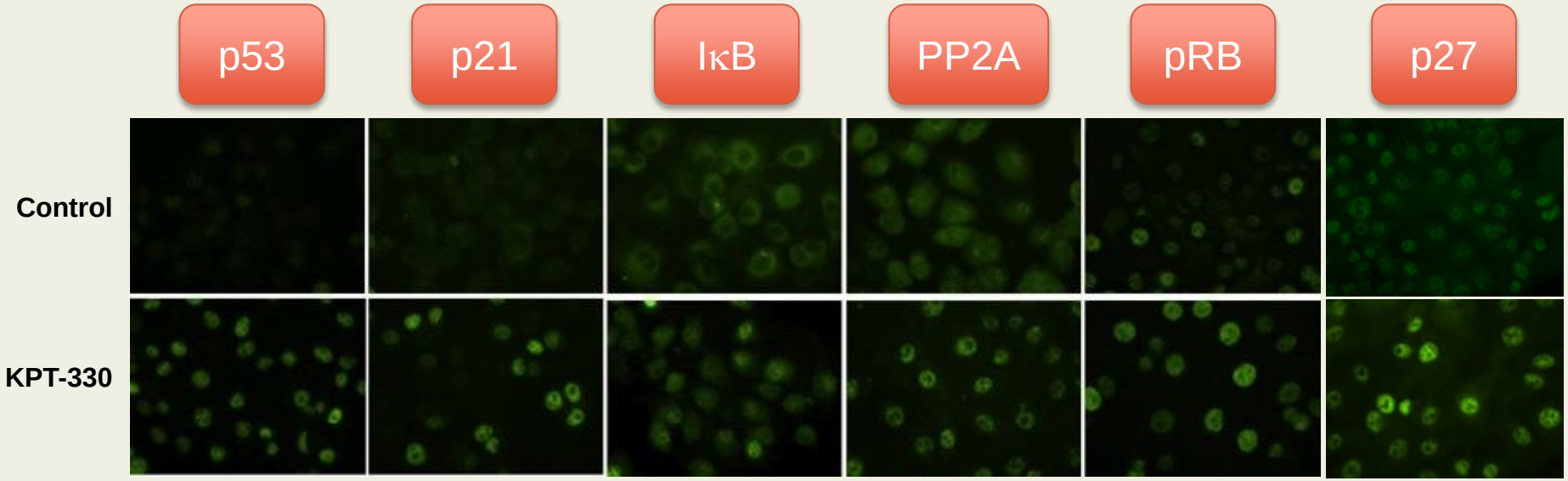


Ovarian (Noske 2008)

Selinexor Forces Nuclear Retention, Increases Nuclear Levels of, and Activates Many TSPs

XPO1 Inhibition

Forced Nuclear Retention & Activation by Blocking Nuclear Export



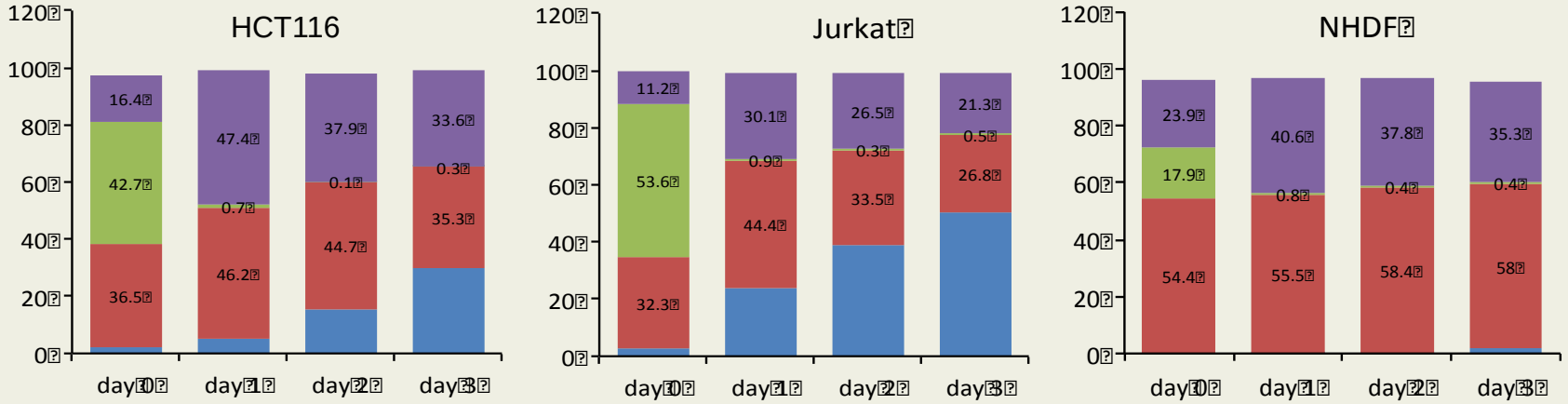
Tumor cells show very low levels and/or cytoplasmic location of their TSPs
KPT-330 increases the total level *and* nuclear location of multiple TSPs

Data Presented at ASCO 2014

SINEs Induce Cell Cycle Arrest and Apoptosis in Cancer Cells

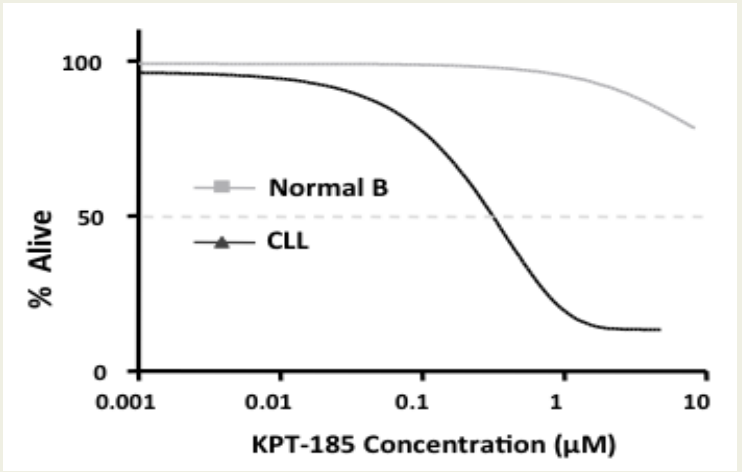
Apoptosis is induced in cancer cell lines, but not in normal cells independent of cycling

A. Colon Cancer (K-ras^{mut}) **B. T-ALL** **C. Normal Human Fibroblasts**

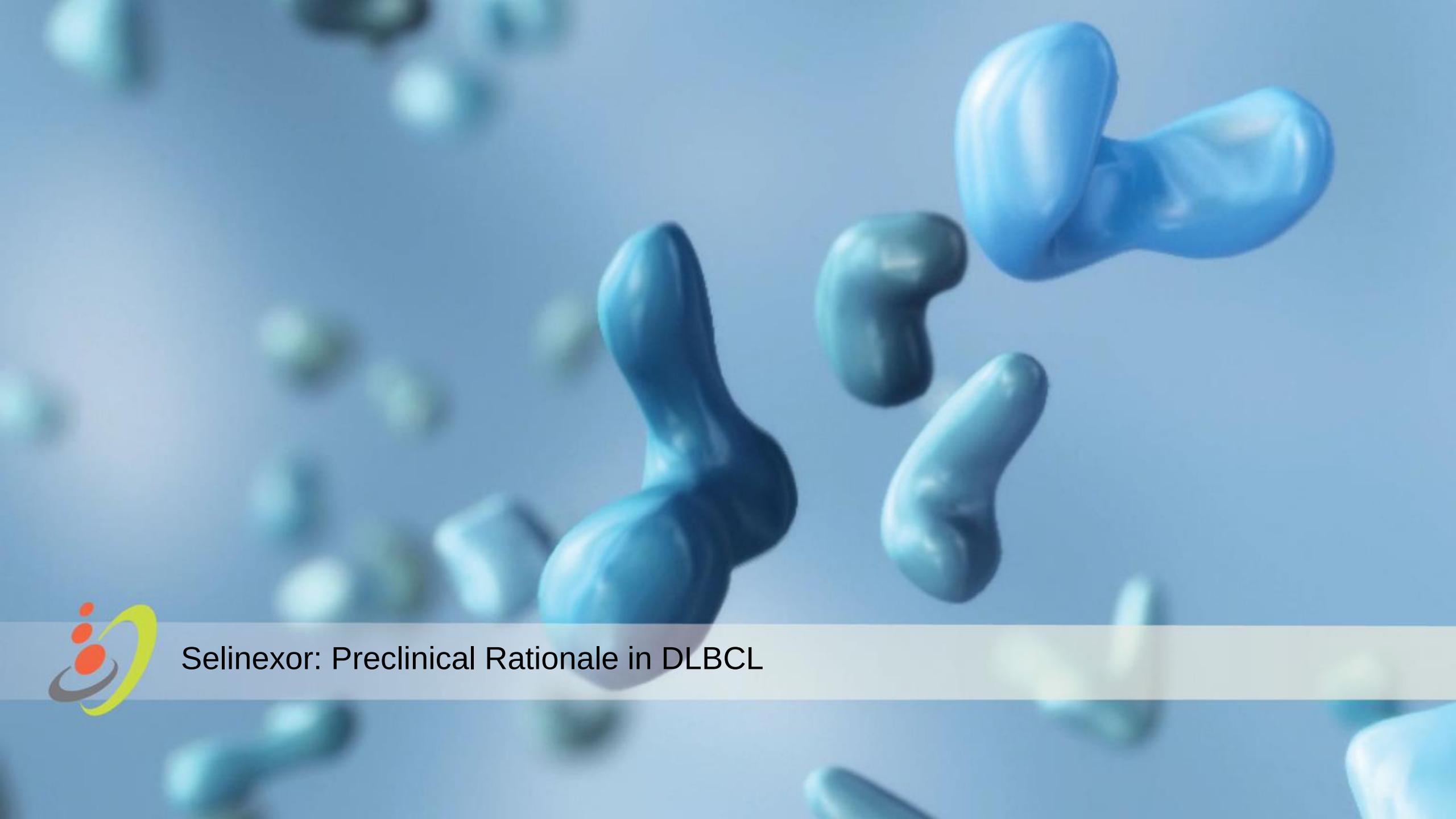


A-C. Treatment with KPT-330 for 0-3 days

D. Human B-CLL and Normal Peripheral B Lymphocytes



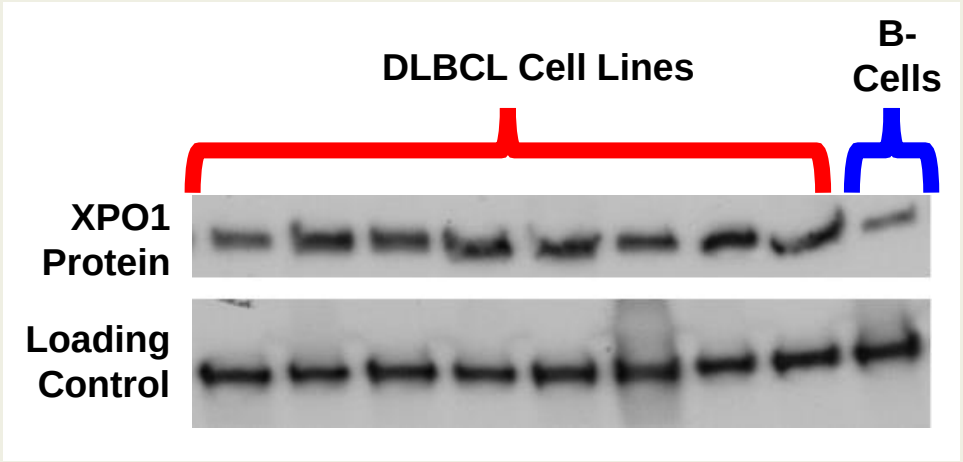
Lapalombella et al. 2012; ASCO 2014



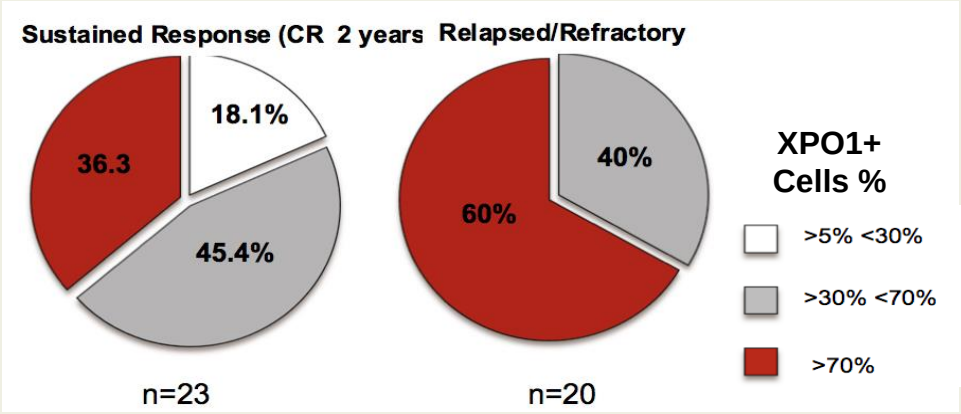
Selinexor: Preclinical Rationale in DLBCL

XPO1 is Highly Expressed in DLBCL; Inhibition of XPO1 with Selinexor Induces Cell Death

A XPO1 expression in 7 DLBCL cell lines



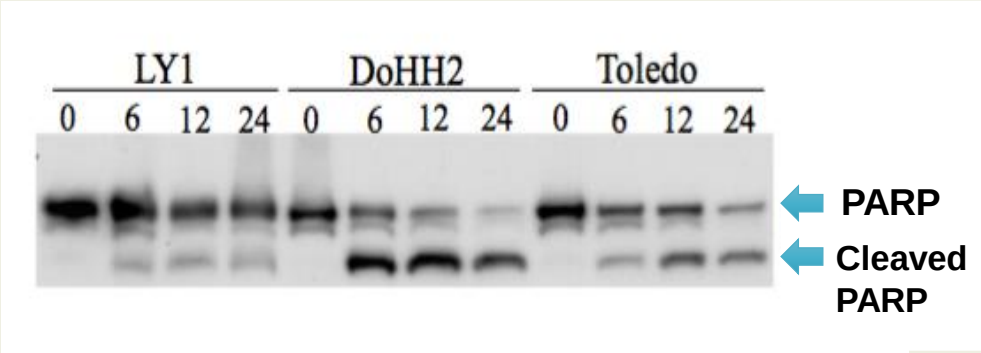
B XPO1 Expression is High in R/R DLBCL



C

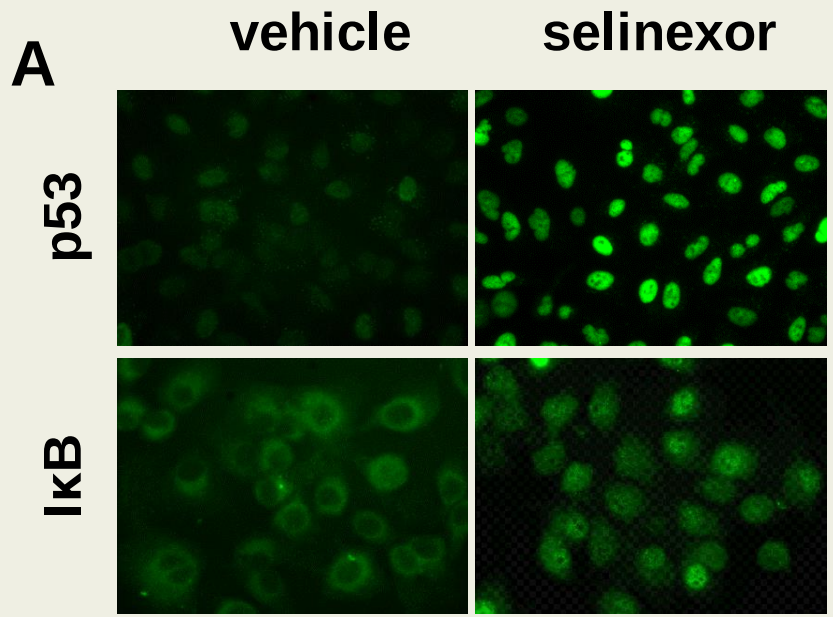
DLBCL Cell Line	Type	Trans-locations	IC_{50} (nM) 48 hrs
OCI-Ly7	GCB	MYC	9.5
DoHH2	GCB DH	BCL2, MYC	13.6
SUDHL4	GCB DH	BCL2, MYC	510
OCI-Ly10	ABC		665
TMD8	ABC DH	BCL6, MYC	402
SUDHL6	GCB	BCL2	745
SC-1	GCB	BCL2	>1000
HBL1	ABC		>1000
WSU-DLCL	NA		>1000
VAL	NA		>1000

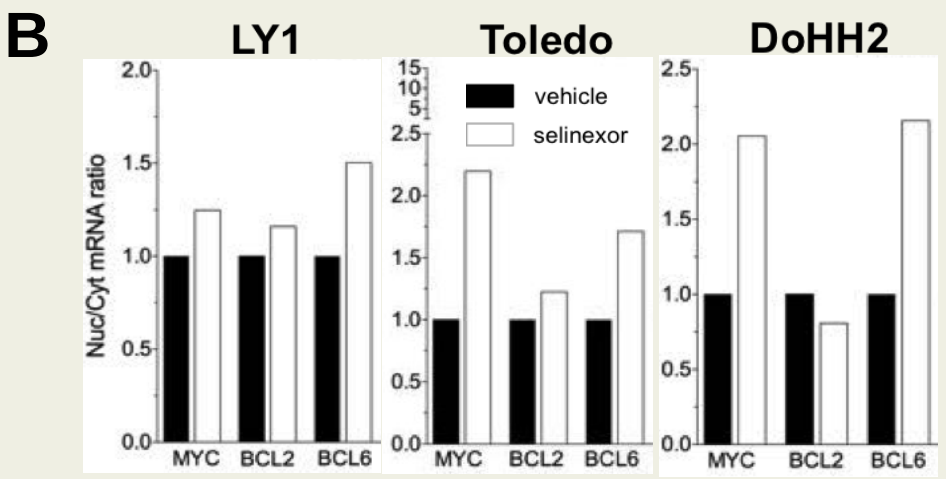
D Selinexor Induces PARP Cleavage

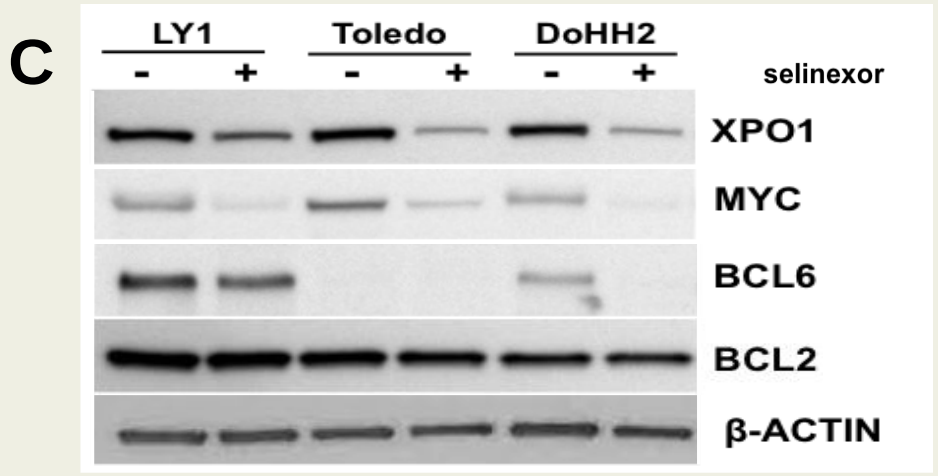


Kuruvilla and Cherchietti 2014 EHA, Kuruvilla and Cherchietti 2015 EHA

Selinexor Dual Effects: Induces Nuclear Retention of TSPs and Oncogene mRNAs





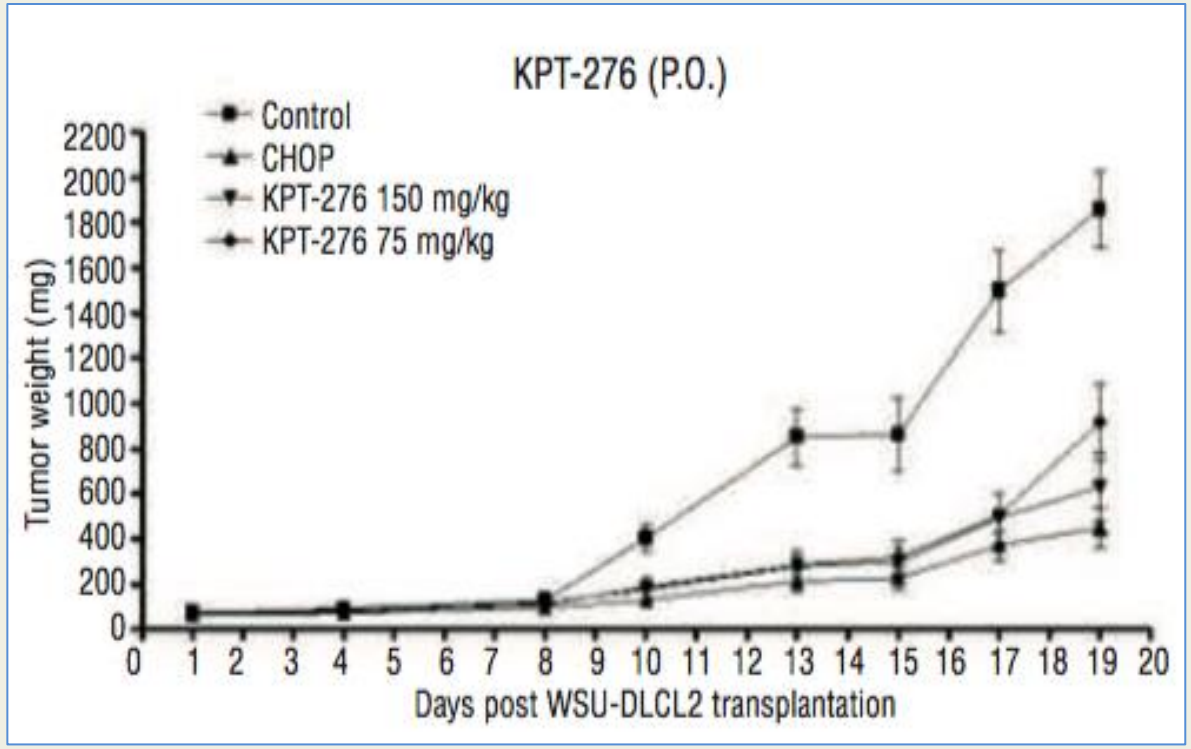


(A) Selinexor (1 μM) induced nuclear retention of tumor suppressor p53 and NF-κB inhibitor IκB in cell culture after 4 h

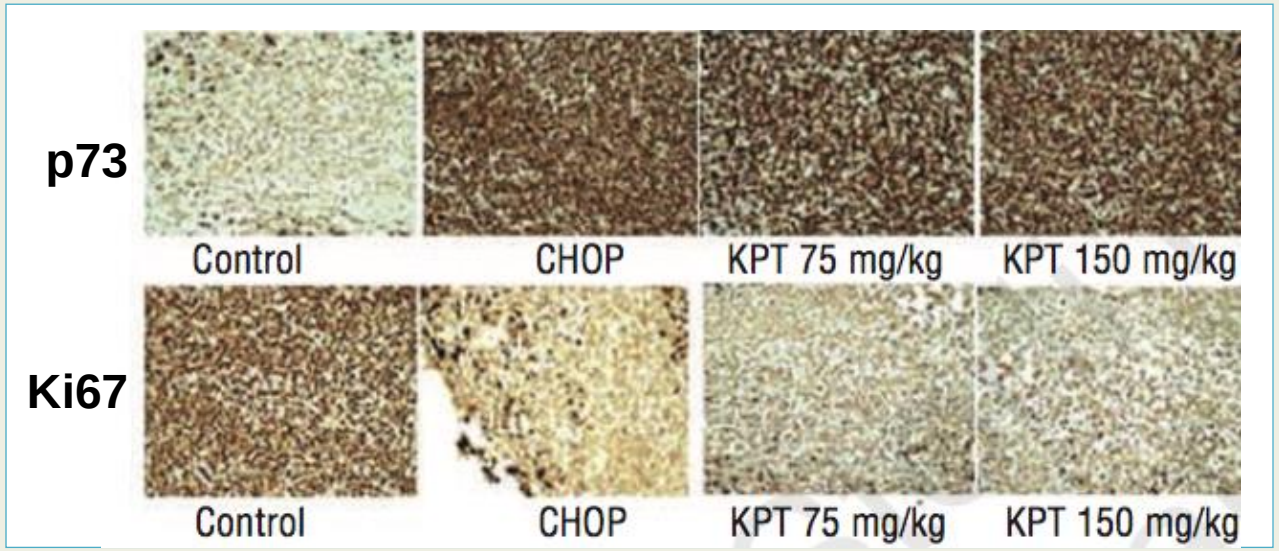
(B) And (C) Selinexor (0.5 μM) induced nuclear retention of mRNA for MYC and BCL6 and reduced their protein expression after 24 h in DLBCL cell lines (Marullo et al. Cancer Res August 1, 2015 75; LB-062)

Kuruvilla and Cherchietti 2014 EHA, Kuruvilla and Cherchietti 2015 EHA

Oral SINE XPO1 Inhibitors Are Active in p53-mutant DLBCL

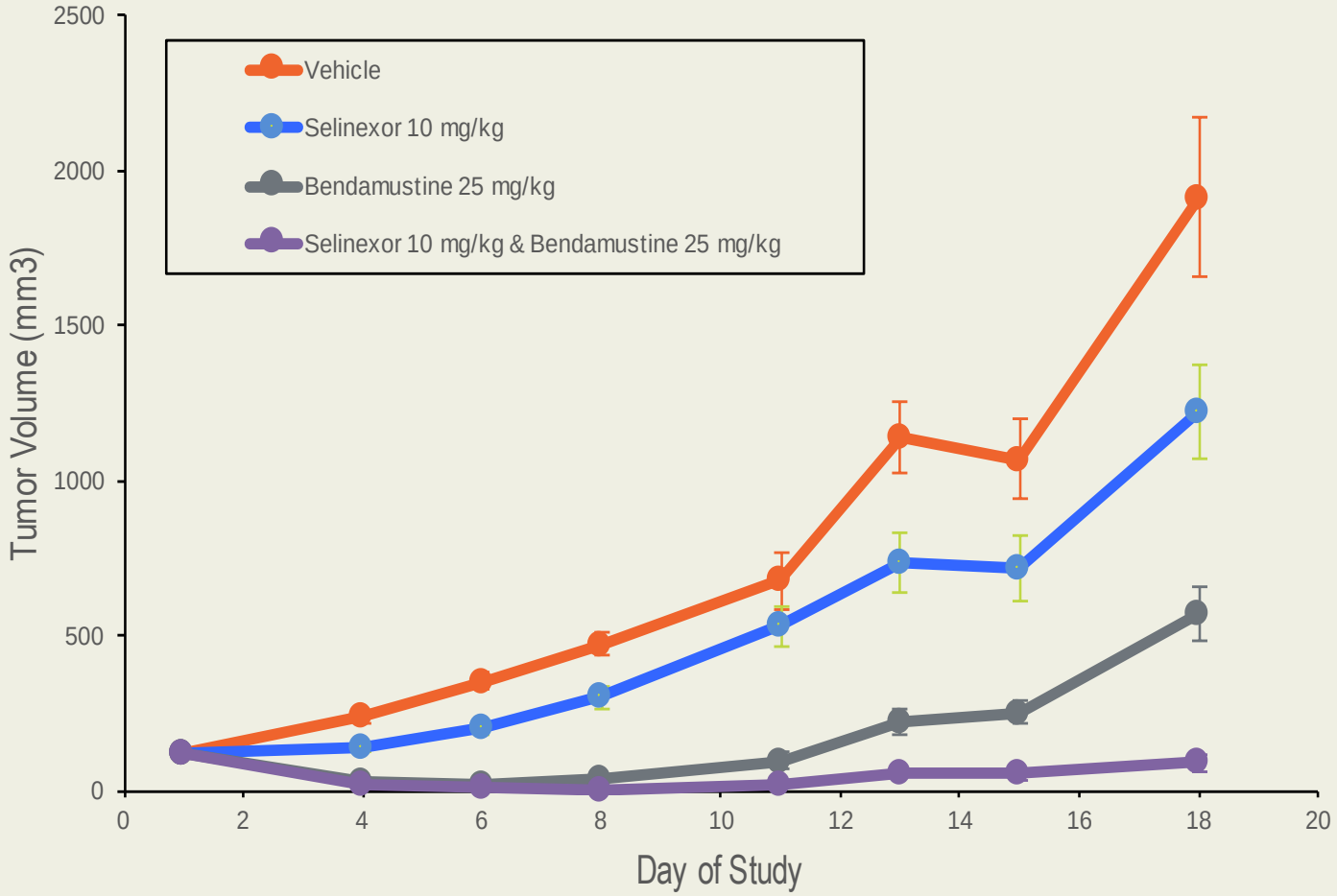


WSU-DLCL2 p53-mutant DLBCL



Azmi et al., *Haematologica*, 2013

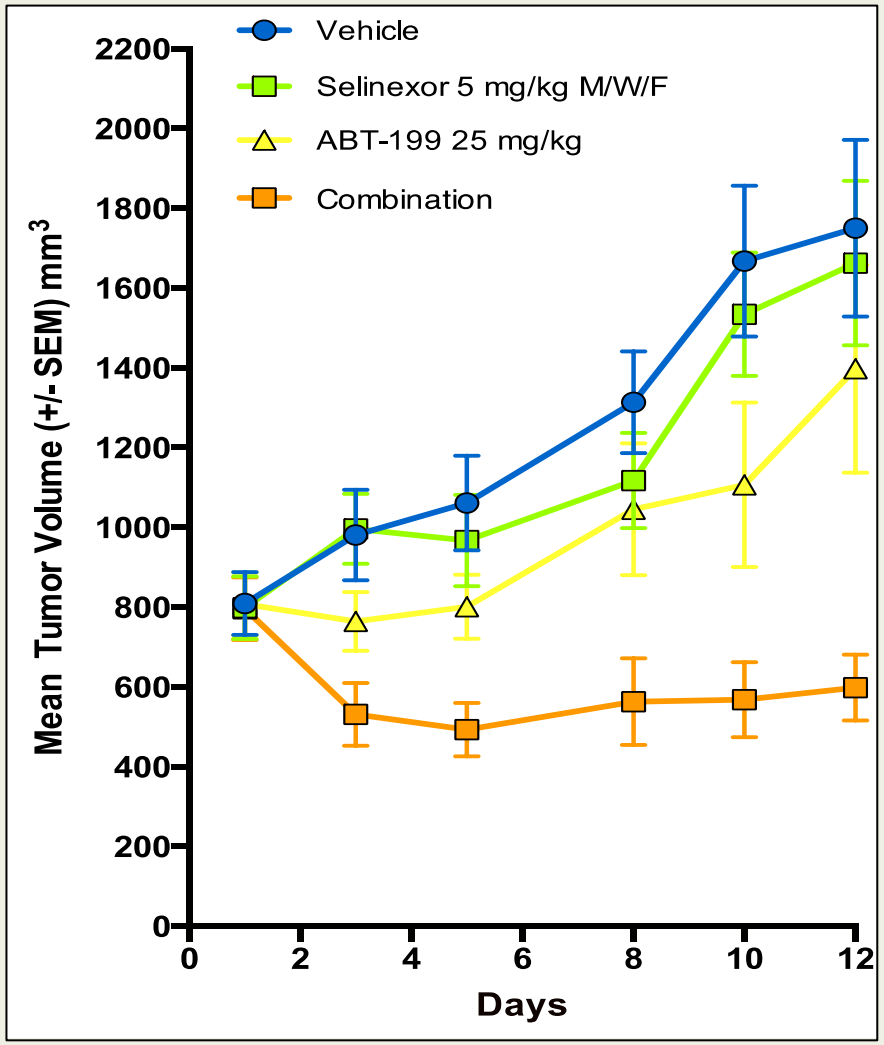
Additive Growth Inhibitory Effect of Selinexor-Bendamustine Combination: DoHH2-Derived Xenografts



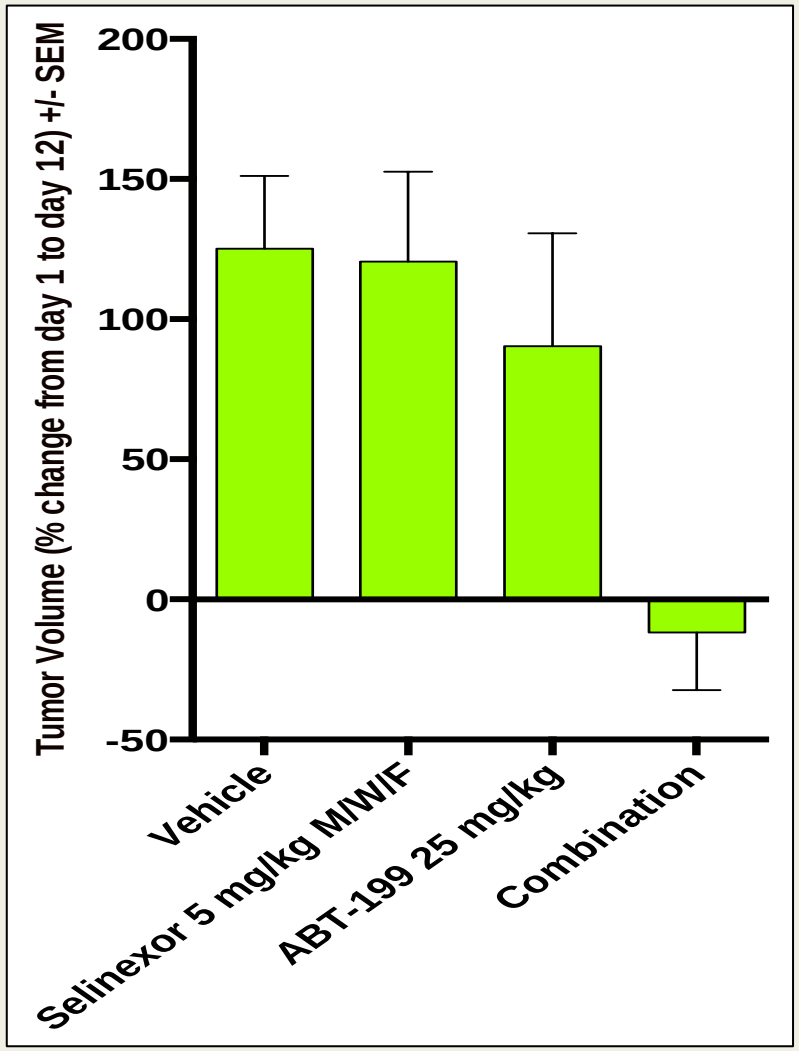
Treatment	% TGI (day 18)
Selinexor	37
Bendamustine	86
Combination	107

Elloul and Friedlander 2016 AACR

Selinexor and Venetoclax (BLC2 Inhibitor) Synergize Against Large DoHH2 (GCB) DLBCL Xenografts



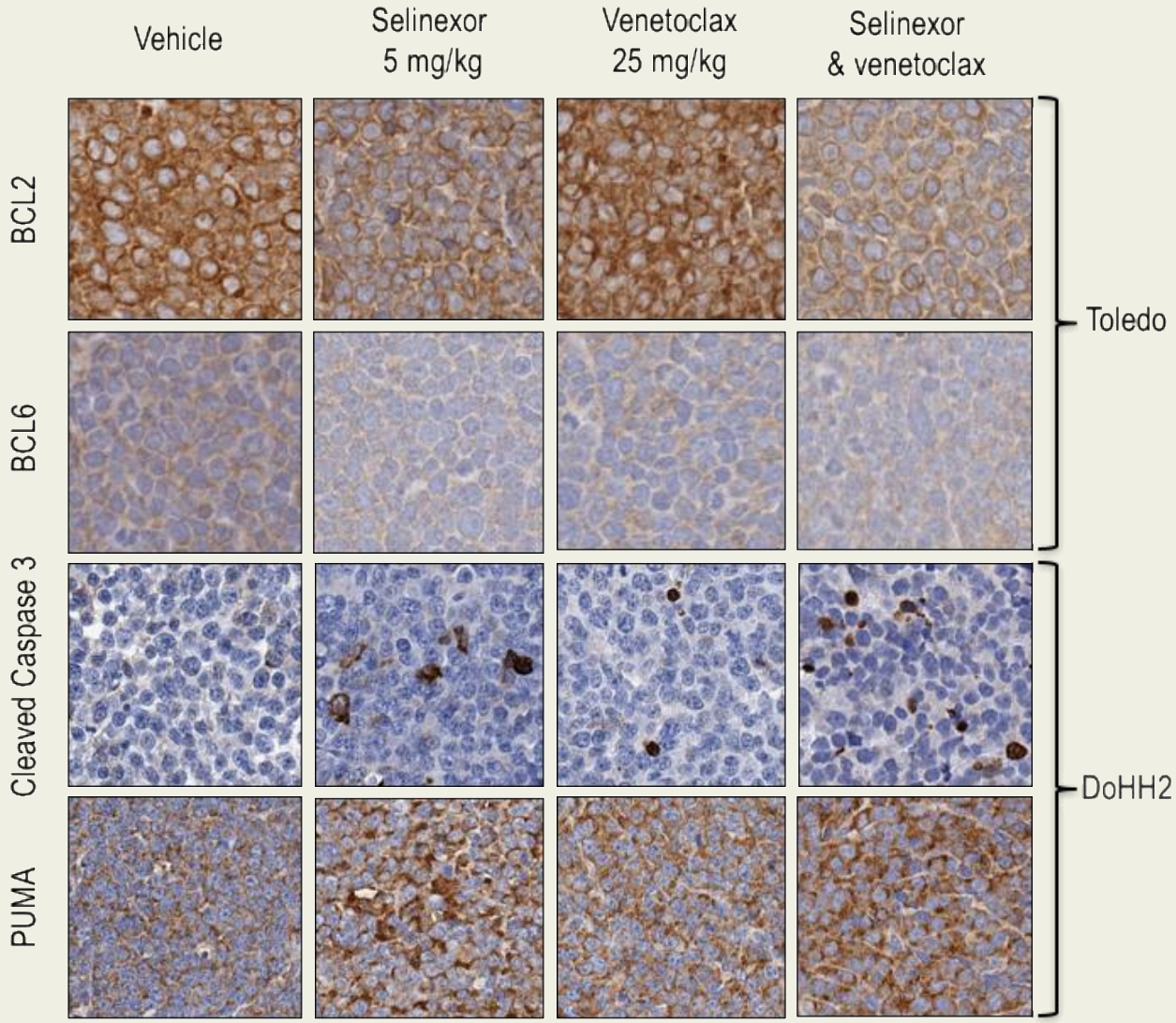
Mean initial tumor volume: 802 mm^3



Elloul and Friedlander 2016 AACR

Down Regulation of BCL2, BCL6 and Induction of Apoptosis in Selinexor-Venetoclax Treated DLBCL Xenograft models

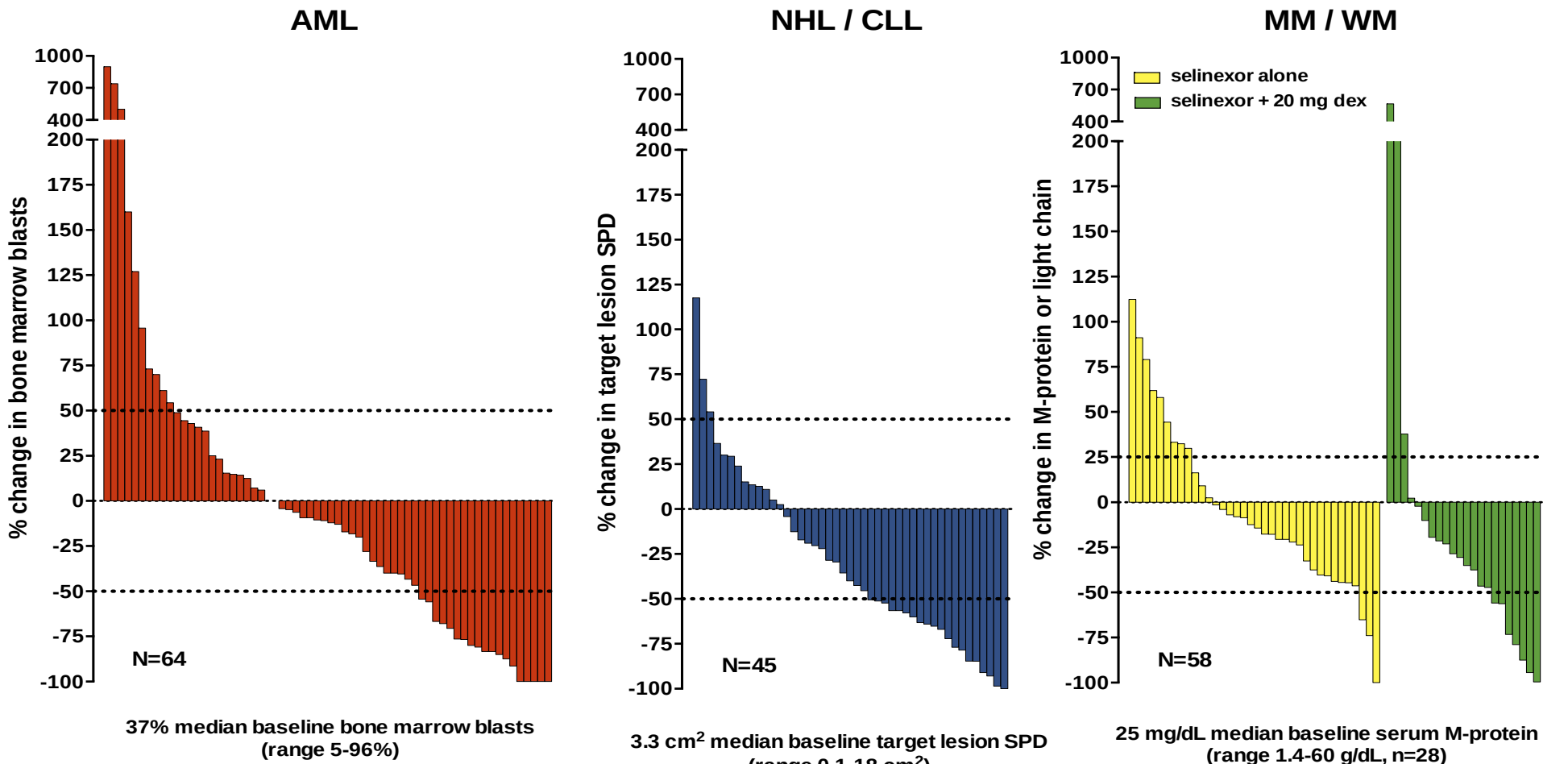
The effects of selinexor and venetoclax alone or in combination on BCL2, BCL6 and apoptosis-related proteins in Toledo- and DoHH2-derived DLBCL xenografts were determined by IHC.



Elloul and Friedlander 2016 AACR

Selinexor: Phase 1 in Hematological Malignancies – Focus on DLBCL

Selinexor Phase 1: Broad Single Agent Activity



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, FL3b, 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%)
Richter's Transformation	≤ 30	3	1 (33%)	--	1 (33%)	2 (67%)	--
	≥ 35	1	1 (100%)	--	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%)	--	--	--
Burkitt's Lymphoma	≥ 60	1	--	--	--	--	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

Best Responses in Patients with R/R DLBCL

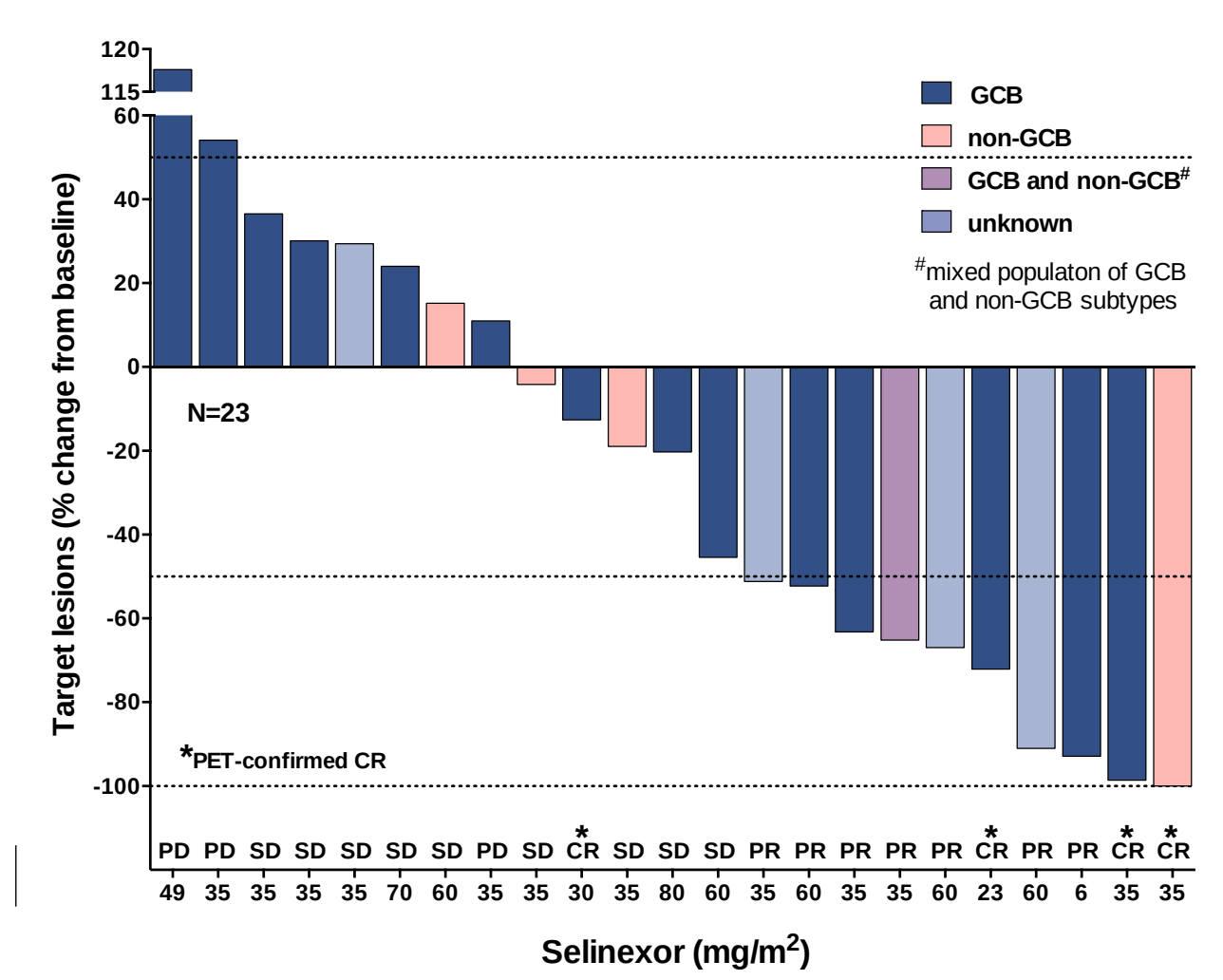
- 31% ORR and 51% DCR for all 39 evaluable DLBCL patients (42 patients total in study)
- **43% ORR and 71% DCR for evaluable DLBCL patients on study ≥ 1 month**
- ORR and DCR are comparable across DLBCL origin or subtype
- Duration of response was >9 months
- Responses were also observed in “double-hit” DLBCL

Category		Total Evaluable	ORR	CR	PR	SD	PD	DCR
All Patients		39*	**31%**	4 (10%)	8 (21%)	8 (21%)	19 (49%)	51%
Patients on study ≥ 1 Month		28	**43%**	4 (14%)	8 (29%)	8 (29%)	8 (29%)	71%
Origin	De novo	28	**25%**	3 (11%)	4 (14%)	6 (21%)	15 (54%)	46%
	Transformed	11	**45%**	1 (9%)	4 (36%)	2 (18%)	4 (36%)	64%
Subtype	GCB	14	**43%**	3 (21%)	3 (21%)	5 (36%)	3 (21%)	79%
	non-GCB	4	**25%**	1 (25%)	--	3 (75%)	--	100%

All patients

*Three patients were non-evaluable for response due to consent withdrawal with lack of disease assessment prior to one cycle on study.
Responses (as of 1-June-2015) were adjudicated according to the *International Working Group Response Criteria for Non-Hodgkin’s Lymphoma (NHL) 2007* based on interim unaudited data. ORR=Objective Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, DCR=Disease Control Rate (CR+PR+SD) GCB=Germinal Center B Cell. GCB/non-GCB subtypes were not defined for all patients.

Maximal Change in Target Lesions



16 evaluable patients had <u>no</u> **or** <u>estimated</u> tumor measurements, including:

- 14 PD with clinical progression and no scans,
- 1 SD with no measureable disease and,
- 1 PR with an estimated decrease in lesion size of 50%, who subsequently went to transplant.

- Note: most patients with responses had >14 week systemic therapy-free interval before initiating single-agent selinexor

Best Responses in DLBCL with Translocations

Translocations		Total Evaluable	ORR	CR	PR	SD	PD	DCR
All	**any translocation**	14	**43%**	2 (14%)	4 (29%)	2 (14%)	6 (43%)	57%
Triple Hit	**MYC/BCL2/BCL6**	1	**--**	--	--	--	1 (100%)	--
Double Hit	**MYC/BCL2**	4	**75%**	1 (20%)	2 (40%)	--	1 (40%)	75%
Single Hit	**BCL2 or MYC**	9	**33%**	1 (11%)	2 (22%)	2 (22%)	4 (44%)	56%

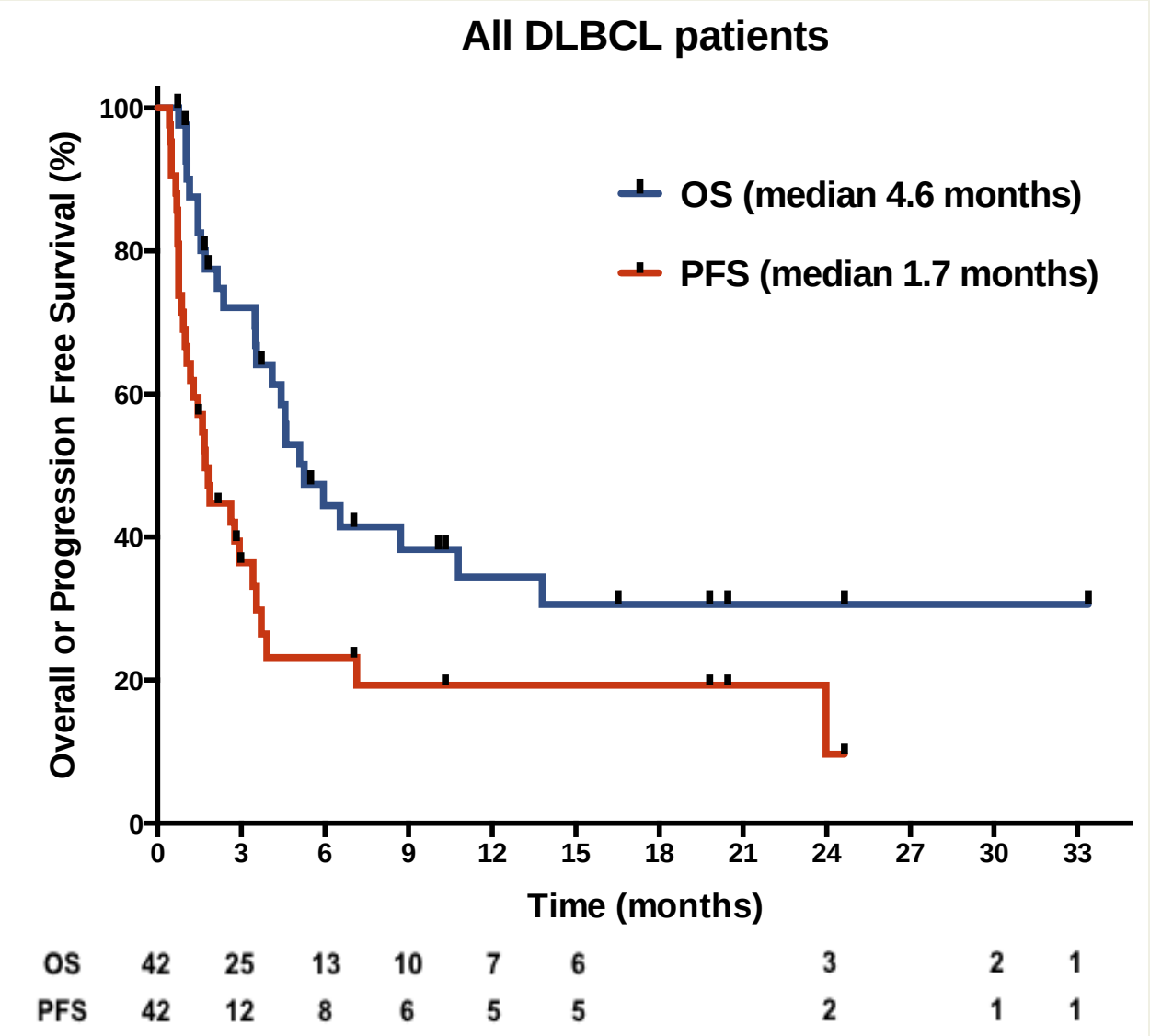
Responses (as of 1-June-2015) were adjudicated according to the *International Working Group Response Criteria for Non-Hodgkin's Lymphoma (NHL) 2007* based on interim unaudited data. ORR=Objective Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, DCR=Disease Control Rate (CR+PR+SD). Single hit patients include 1 MYC and 8 BCL2 translocations.

Patients with Objective Responses in Double, or Single Hit DLBCL*

Patient ID	Translocation(s)	Best Response	% Change in Target Lesions	Days on Study	Prior Therapy Regimens
046	MYC/BCL2	CR	-73%[a]	589	R-CHOP, RICE
072	MYC/BCL2	PR	-63%	214	R-CHOP, Benda, RICE
432	MYC/BCL2	PR	-50%[b]	91 (transplant)	R-CHOP, RICE, Ofa-Etop-Ifo
050	BCL2	CR	-100%[a]	602+	R-CHOP, Etop-Cyclo, R-GDP, Panob
003	BCL2	PR	-93%	729	R-CHOP, R-DHAP, BEAM, GDP
402	BCL2	PR	-52%	119	R-CHOP, R-GDP

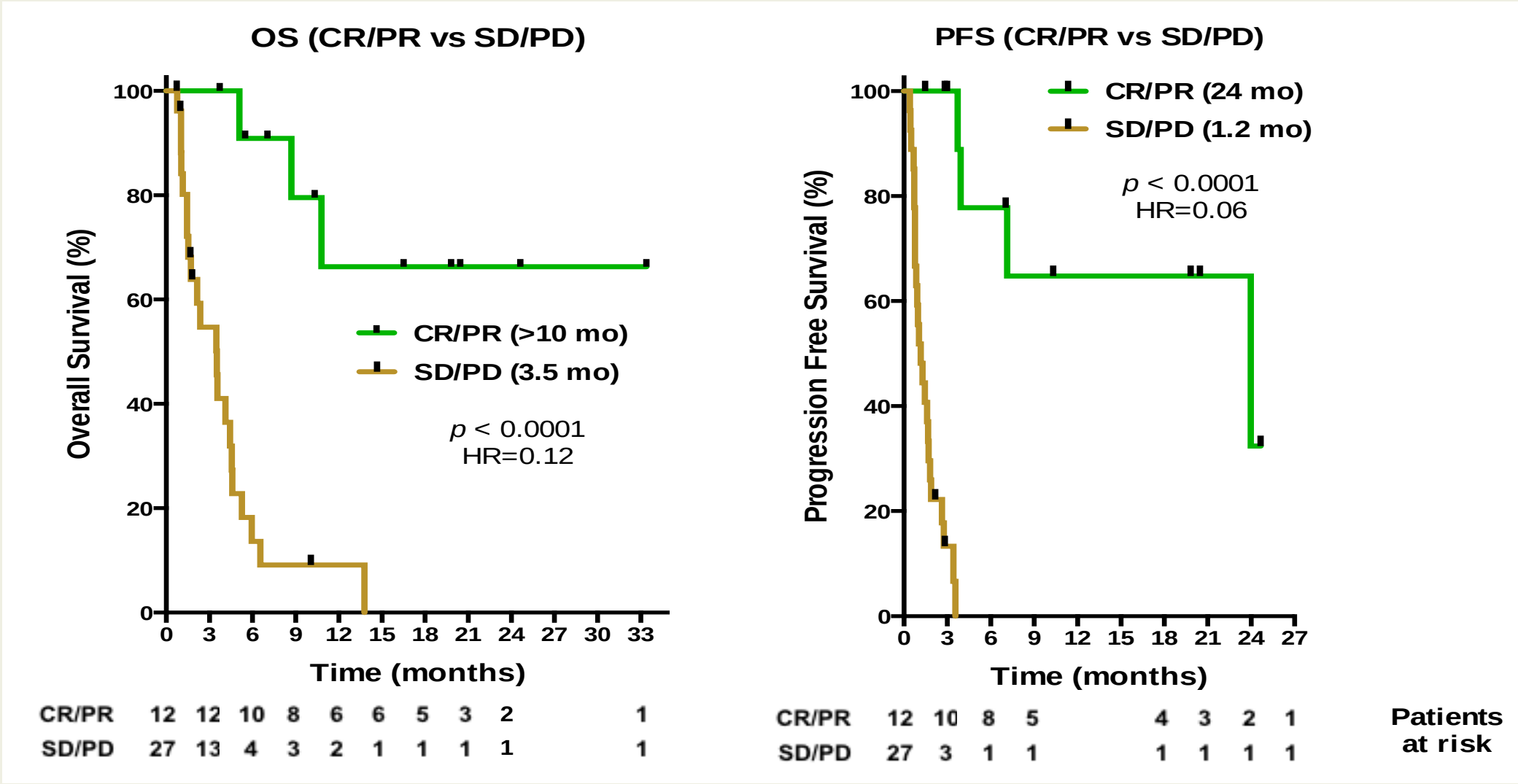
*as of 1-June-2015; + patient still on therapy; [a]PET-negative; [b]estimated

Overall and Progression Free Survival in DLBCL



Garzon et al., EHA 2015

OS and PFS are Increased in Responders



Garzon et al., EHA 2015

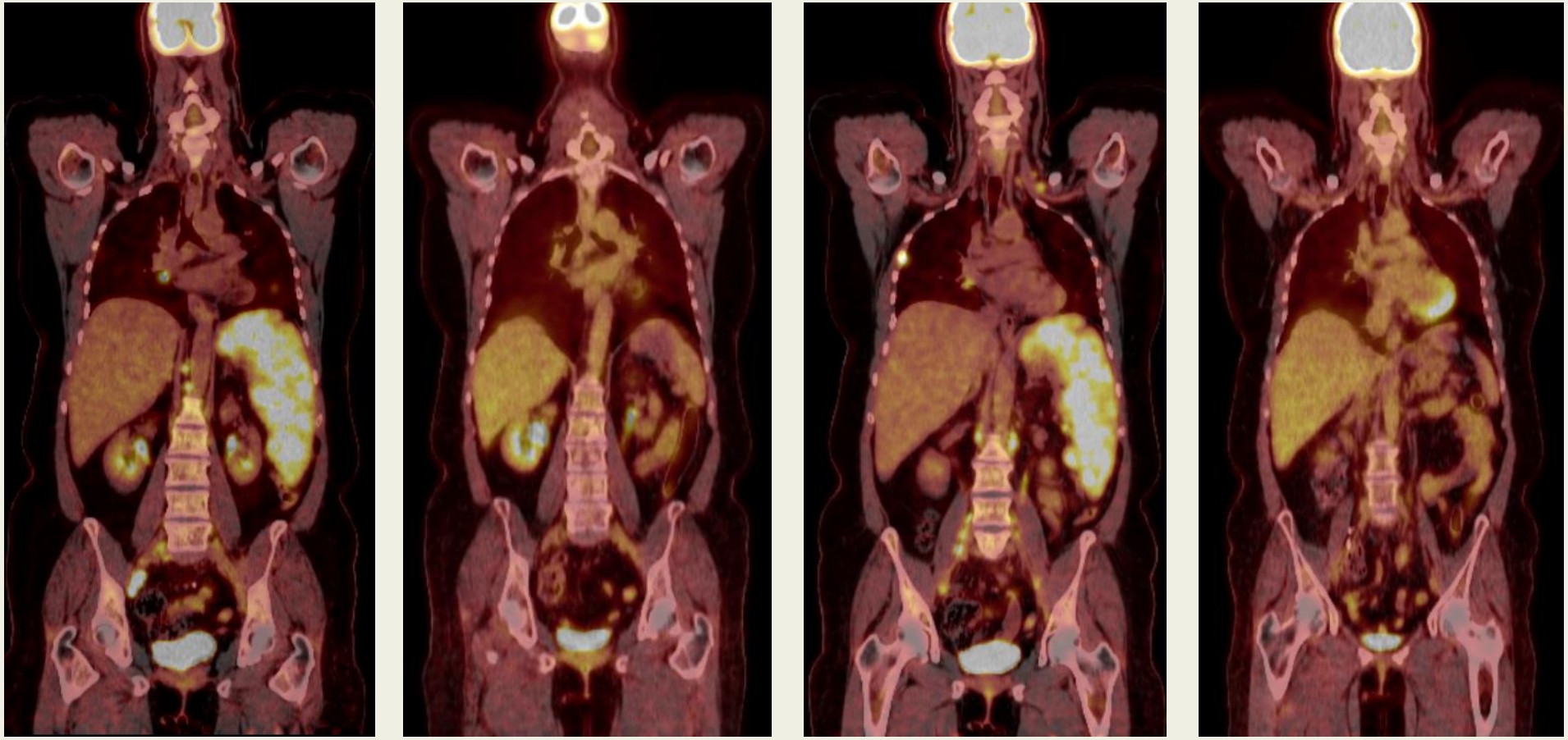
Patient Case Study: Relapsed DLBCL – Complete Response

- 51 year old female – DLBCL
- March 2006 – Stage IV DLBCL R-CHOP (x6)
- Jan 2010 – Relapse Stage IV DLBCL GDP (x2) 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) 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
- Continued on Selinexor monotherapy (**18+** months) prior to single lesion increasing PET signal
- Dose re-escalated and patient remains in strong, durable PR >2 years

Relapsed DLBCL: PET Confirmed Complete Response

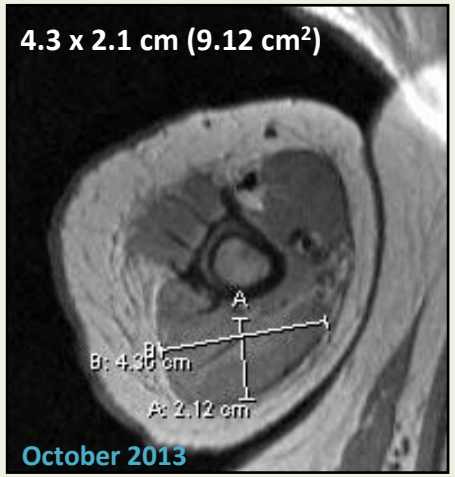


Baseline | Cycle 14 | Baseline | Cycle 14

Prolonged Complete Response in DH-GCB-DLBCL

Relapsed DLBCL (Feb 2012) – "Double Hit" / GCB

- Age 73, Stage 4, bulky disease, possible CNS involvement
- R-CHOP initial therapy + intrathecal MTX and radiation to right arm
- Relapse after 10 months
- R-ICE treatment with relapse within 7 months
- Pain, marked edema, and massive lesion in right arm (essential immobile)
- Plan for amputation of arm in absence of successful treatment



Selinexor 20 mg/m² BIW (Sept 2013)

- Clinical improvement in 2 weeks with marked reduction in arm edema and pain
  Side effects managed with supportive care; dose increased Cycle 3 to 30mg/m² BIW
- Complete remission (PET negative and biopsy negative for tumor)
- Remains disease free after >2.5 years; currently off therapy (1 May 2016)

Phase 1 DLBCL Summary

- No standard regimen exists for relapsed/refractory DLBCL following failure of two immunochemotherapy regimens *(NCCN Guidelines 2014)*
- In 42 (39 evaluable) patients with heavily pretreated relapsed / refractory DLBCL, (3 median prior treatment regimens) selinexor monotherapy showed significant anti-cancer activity, with the majority of responses in patients with >14 week therapy-free interval
- Most common selinexor-related AEs in DLBCL patients were low grade nausea, anorexia, fatigue, vomiting and higher grade thrombocytopenia and anemia
- Responses to selinexor are seen in GCB and ABC subtypes, and in DH disease
- Objective responses to selinexor are durable and correlate with improved OS and PFS, suggesting that these responses are associated with clinical benefit
- Two of the four patients with CR are off therapy and remain in CR >2.5 years after initiation of selinexor; one additional patient with CR continues on therapy with single node showing PET-activity

SADAL (Selinexor Against Diffuse Aggressive Lymphoma)
Phase 2b Trial in *Relapsed* DLBCL

SADAL: Ongoing Randomized Trial (potential for Accelerated Approval)

- Relapsed / Refractory ≥3rd line (≥14 weeks since last systemic therapy)
- **Randomized 1:1 to twice-weekly single-agent selinexor 60mg vs. 100mg**
- At least 50% of patients with GCB-DLBCL
- Targeting ~200 patients
- Primary endpoint: overall response rate
- Data readout anticipated in mid-2017

Preparations for Phase 3 Study

- Selinexor+Rituximab+Chemotherapy vs. Rituximab+Chemotherapy alone
- Combinations for 3rd, 2nd and 1st Line Phase 1/2 Studies to Initiate 2016
- Phase 3 studies planned for 2017

Selinexor + R-ICE in R/R Aggressive NHL:

A Phase I Investigator Sponsored Trial of Selinexor (KPT-330) and Rituximab, Ifosfamide, Carboplatin and Etoposide in Patients with Relapsed or Refractory Aggressive B-Cell Lymphomas (Dr. P. Martin)

Conclusions

- Selinexor is a first-in-class, oral, SINE compound with broad anti-cancer activity
  - ↑↑ Tumor Suppressor Protein (TSP) activity by forced nuclear retention
  - ↓↓ eIF4E-dependent oncoproteins by nuclear mRNA sequestration
- Recommended phase 2 dose is 60-80 mg twice weekly
- Main side effects are nausea, anorexia, fatigue, and thrombocytopenia
  - manageable with supportive care and/or dose reduction / interruption
- Can be given for prolonged periods (>1-2 years) without major organ toxicities or cumulative toxicities
- Can combine with chemotherapy, proteasome inhibitors and other agents with minimal increased toxicities
- TSP reactivation and oncoprotein reduction could be a key foundation for many other types of anti-cancer therapy

Thank you very much