Patients with Heavily Pretreated Diffuse Large B-Cell Lymphoma (DLBCL) Who Respond to Oral Selinexor Therapy Show Prolonged Survival: Updated Phase I Results

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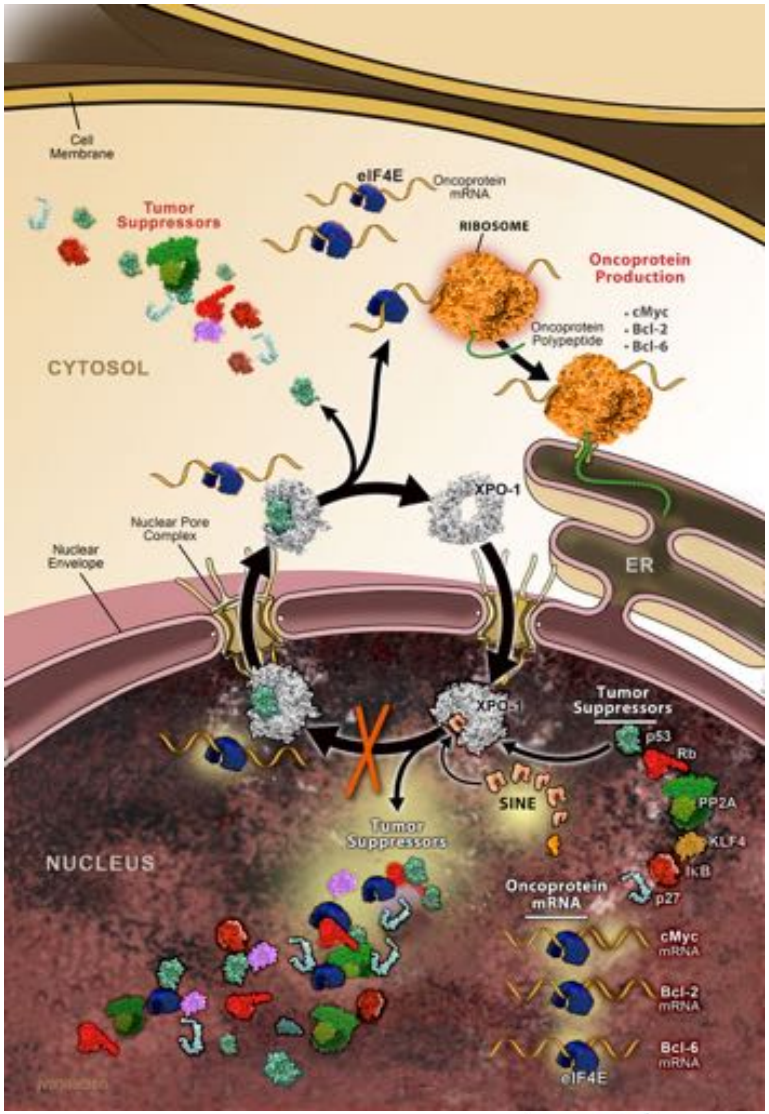
Selinexor – Mechanism of Action

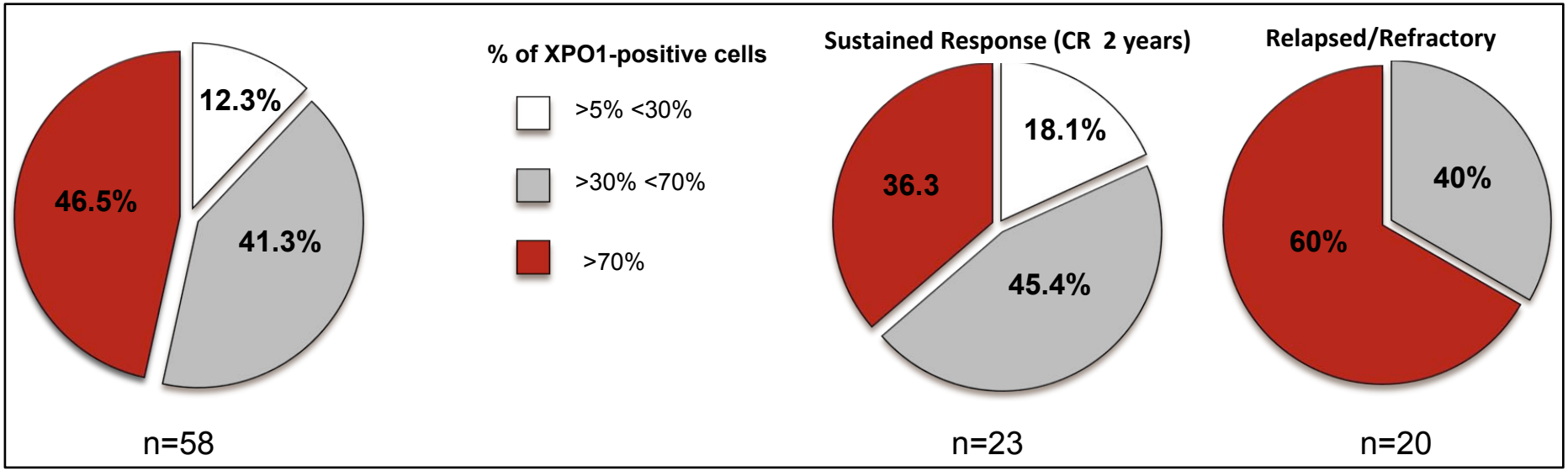
- The nuclear export protein Exportin 1 (XPO1) is overexpressed in all types of malignant lymphoma, including DLBCL
- Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that inhibits XPO1 to force nuclear retention of tumor suppressors and other proteins integral to tumorigenesis
- Selinexor interferes with proteins known to play critical roles in DLBCL
  - Reduces Myc, Bcl2 and Bcl6 protein through forced nuclear retention of eIF4E
    - Overexpression and translocations of Myc, Bcl2 and Bcl6 lead to more aggressive DLBCL
  - Blocks NF-κB activation through nuclear retention of IκB
    - NF-κB activation is important for DLBCL ABC subtype survival



Exportin 1 (XPO1) Expression in DLBCL

XPO1 Expression in DLBCL Tissues (by IHC)

XPO1 Expression in Chemo-sensitive and Chemo-refractory DLBCL Patient Cells

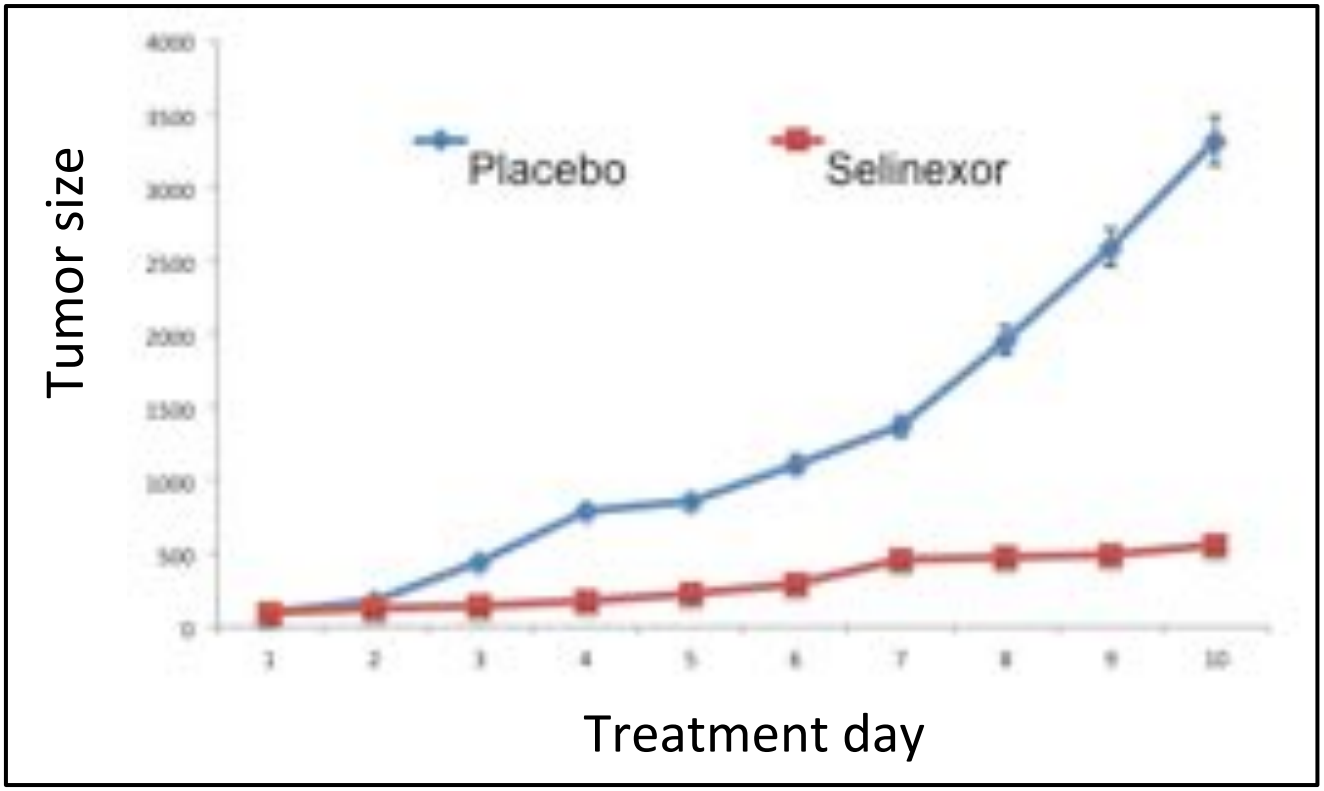


- XPO1 is highly expressed in DLBCL, specially in chemo relapsed/refractory cases with 60% of patients having >70% XPO1 positive cells

Marullo et al AACR 2015

In Vivo Pharmacology

Patient-Derived Xenograft of "Triple Hit" DLBCL



Triple hit PDX was transplanted into mouse flank. 10 mg/kg selinexor was administered twice weekly. Tumor size was greatly reduced with selinexor treated as compared to placebo.

Unpublished data from Leandro Cerchietti, Cornell University

Selinexor Study Design – NCT01607892

- Phase 1 dose escalation study of the safety, PK, & PD of selinexor in patients with advanced hematological malignancies
- Primary Objective
  - Evaluate the safety and tolerability of selinexor and determine the Recommended Phase 2 Dose (RP2D) for hematological malignancies
- Secondary Objective
  - Anti-tumor response in patients with advanced hematological malignancies according to the International Working Group Response Criteria for Non-Hodgkin's Lymphoma (NHL) 2007
- Treatment Scheme
  - 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 (~ 5 mg – 136 mg)
- 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

Study Design: NCT01607892

DOSE ESCALATION	DOSE EXPANSION
Non-Hodgkin's Lymphoma (NHL)	DLBCL 35 mg/m^2 (~60 mg) DLBCL 60 mg/m^2 (~100 mg) T-Cell Lymphomas 40 mg/m^2 (~68 mg)
Multiple Myeloma (MM)	MM 35 mg/m^2 (~60 mg) MM 45 (60) mg/m^2 (~77 (102) mg) + Low Dose Dex
Acute Myeloid Leukemia (AML)	AML 40 mg/m^2 (~68 mg)

Patient Characteristics

DLBCL Patient Characteristics	N* = 42
De-Novo Patients Enrolled	31
Transformed Patients Enrolled	11
Patients ≥ 1 Month on Study	29
Median Age (Range)	61 (30 – 82)
Male : Female	24 : 18
Median Prior Treatment Regimens (Range)	3 (1 – 9)
ECOG Performance Status (0:1:2)	12 : 29 : 01
Neutrophils >1000/µL and Platelets >30,000/µL	31

* As of 1-June-2015

Data are from treatment with doses of 3-80 mg/m^2

Selinexor - Related Adverse Events in DLBCL Patients

Selinexor Related Adverse Events					
AE TERM	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total N=42**
Gastrointestinal					
Nausea	56%	14%	**2%**	--	72%
Anorexia	33%	28%	**2%**	--	63%
Vomiting	40%	2%	--	--	42%
Diarrhea	19%	12%	**5%**	--	35%
Dysgeusia	12%	12%	--	--	23%
Dyspepsia	7%	5%	--	--	12%
Constipation	9%	--	--	--	9%
Constitutional	--	--	--	--	
Fatigue	23%	23%	**14%**	--	60%
Weight loss	9%	7%	**5%**	--	21%
Dehydration	--	5%	**2%**	--	7%
Hematologic	--	--	--	--	
Thrombocytopenia	9%	2%	**16%**	**30%**	58%
Anemia	--	9%	**19%**	**2%**	30%
Neutropenia	5%	2%	**12%**	**9%**	28%
Leukopenia	2%	--	**7%**	**7%**	16%
Lymphocytopenia	--	2%	**7%**	--	9%
Purpura	5%	--	--	--	5%
Epistaxis	5%	--	--	--	5%

Selinexor Related Adverse Events					
AE TERM	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total N=42**
Biochemical	--	--	--	--	
Hyponatremia	19%	--	**7%**	--	26%
Proteinuria	2%	2%	--	--	5%
Serum amylase increased	--	2%	**2%**	--	5%
Creatinine increased	--	5%	--	--	5%
AST increased	5%	--	--	--	5%
ALT increased	5%	--	--	--	5%
Ocular	--	--	--	--	
Blurred vision	23%	2%	--	--	26%
Cataract	--	--	**5%**	--	5%
Flashing lights	5%	--	--	--	5%
Other	--	--	--	--	
Dizziness	12%	5%	--	--	16%
Confusion	2%	2%	**5%**	--	9%
Peripheral sensory neuropathy	5%	2%	--	--	7%
Gait disturbance	2%	2%	**2%**	--	7%
Syncope	--	--	**5%**	--	5%
Generalized muscle weakness	5%	7%	--	--	12%
Abdominal pain	2%	2%	--	--	5%
Headache	5%	--	--	--	5%
Hypotension	2%	--	**2%**	--	5%
Hot flashes	2%	2%	--	--	5%

- Most common related AEs in DLBCL patients are Grade 1/2 constitutional and GI (nausea, anorexia, fatigue, vomiting) and higher Grade 3/4 thrombocytopenia and to a lesser extent anemia

Best Responses in DLBCL patients

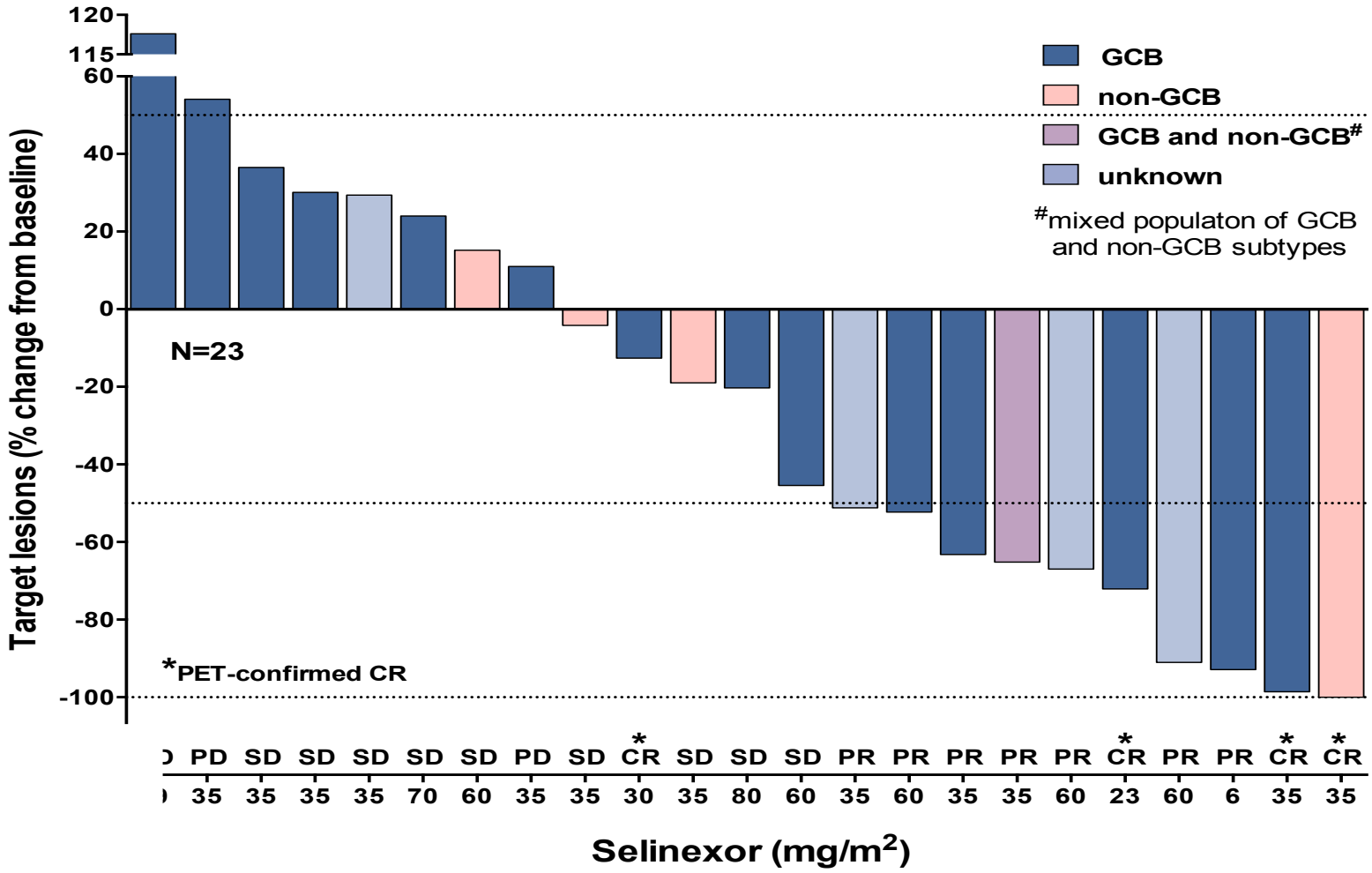
Category		Total Evaluable	ORR	CR	PR	SD	PD	DCR
All Patients		39*	**31%**	4 (10%)	8 (21%)	8 (21%)	19 (49%)	51%
Patients on study ≥ 1 Month		28	**43%**	4 (14%)	8 (29%)	8 (29%)	8 (29%)	71%
Origin	De novo	28	**25%**	3 (11%)	4 (14%)	6 (21%)	15 (54%)	46%
	Transformed	11	**45%**	1 (9%)	4 (36%)	2 (18%)	4 (36%)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

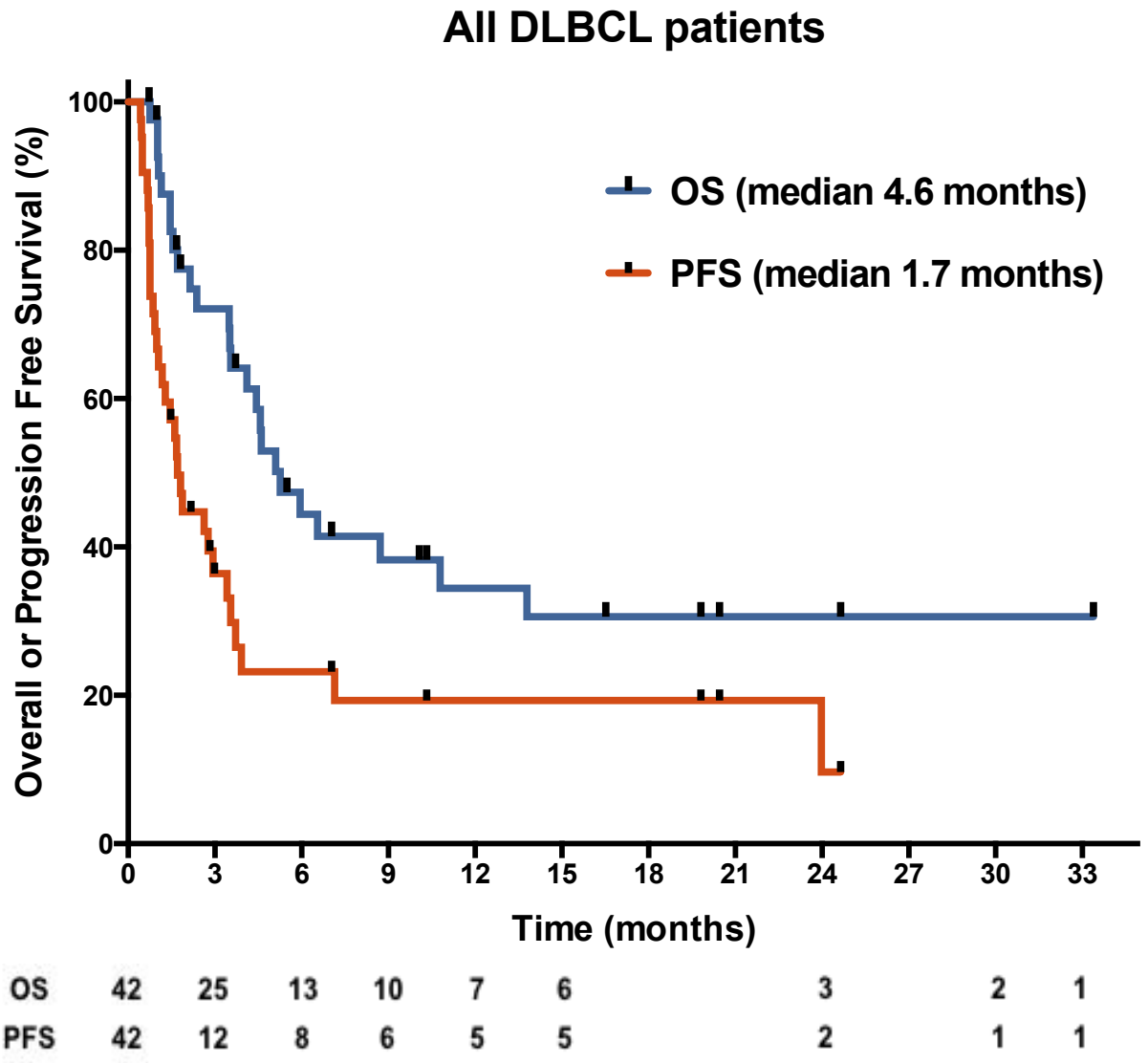
- 31% ORR and 51% DCR for all evaluable DLBCL patients
- **43% ORR and 71% DCR for evaluable DLBCL patients on study ≥ 1 month**
- ORR and DCR are comparable across DLBCL origin or subtype
- Duration of response was >9 months
- Responses were also observed in "double-hit" DLBCL

Maximal Change in Target Lesions



16 evaluable patients had no or estimated 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.

Overall and Progression Free Survival in DLBCL



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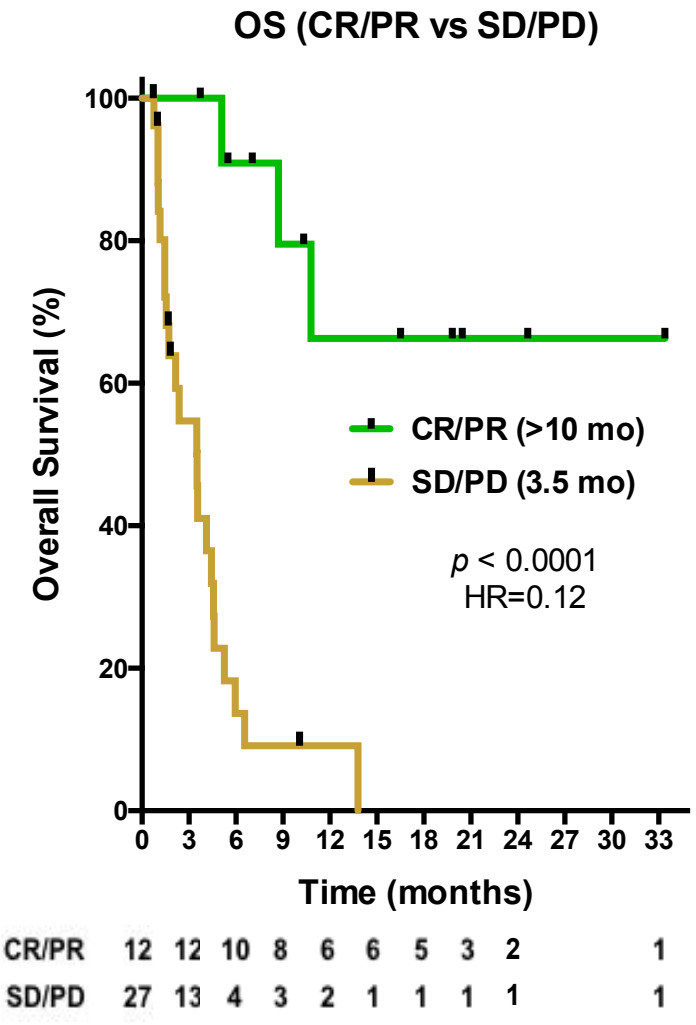
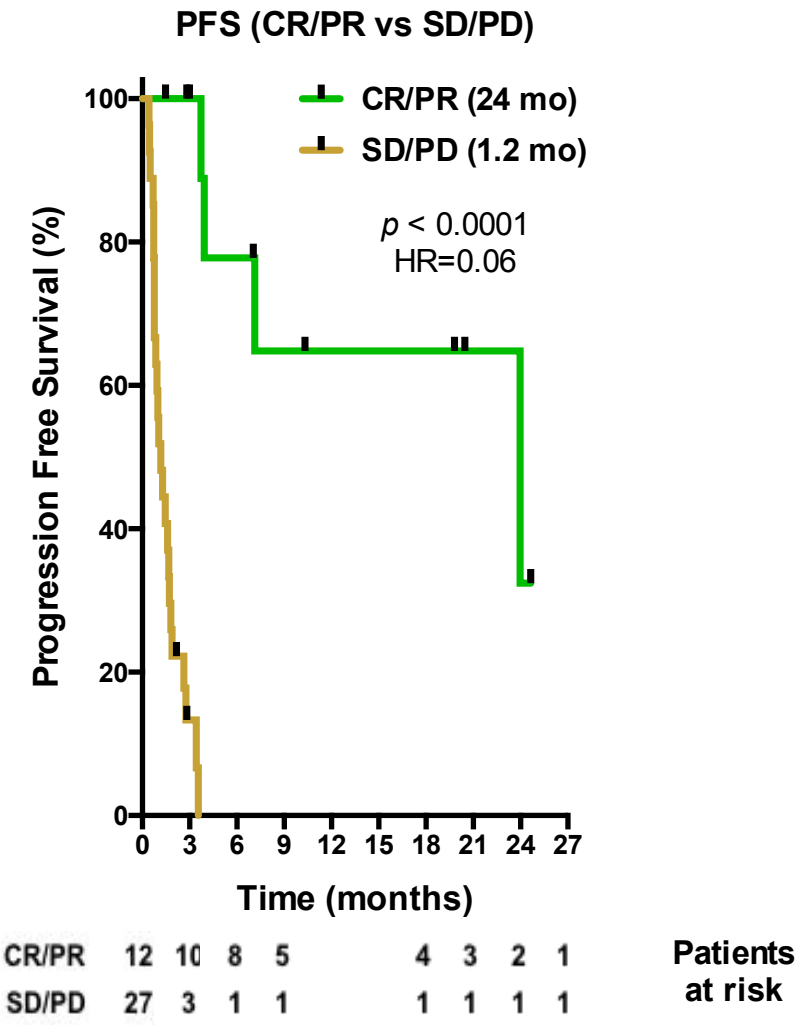
OS and PFS are Increased in Responders





Overall and Progression Free Survival in DLBCL

Survival Endpoint	Patients	All		On Study ≥ 1 mo	
		N	Median	N	Median
OS	All	42	4.6 mo	29	6.0 mo
	CR/PR	12	>10 mo	12	>10 mo
	SD/PD	27	3.5 mo	17	3.5 mo
PFS	All	29	1.7 mo	29	3.6 mo
	CR/PR	12	24 mo	12	24 mo
	SD/PD	17	1.2 mo	17	1.7 mo

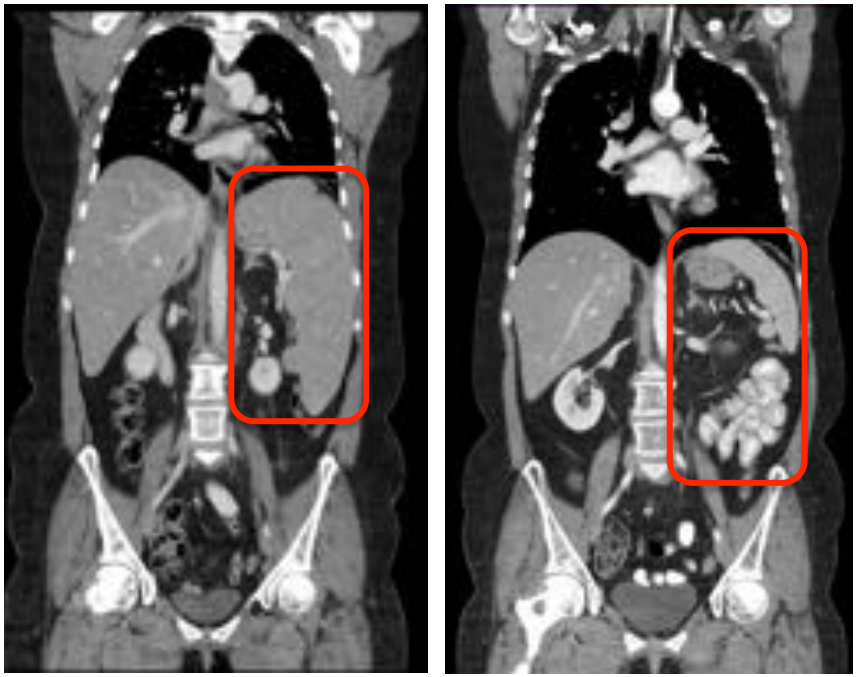
- For patients on study ≥ 1 month, OS and PFS was improved to **6.0** and **3.6** months respectively as compared to all patients OS and PFS of **4.6** and **1.7** months

Patient Case Study: Refractory 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) cycles RPh2
- Jul 2013 – Relapse – steroids

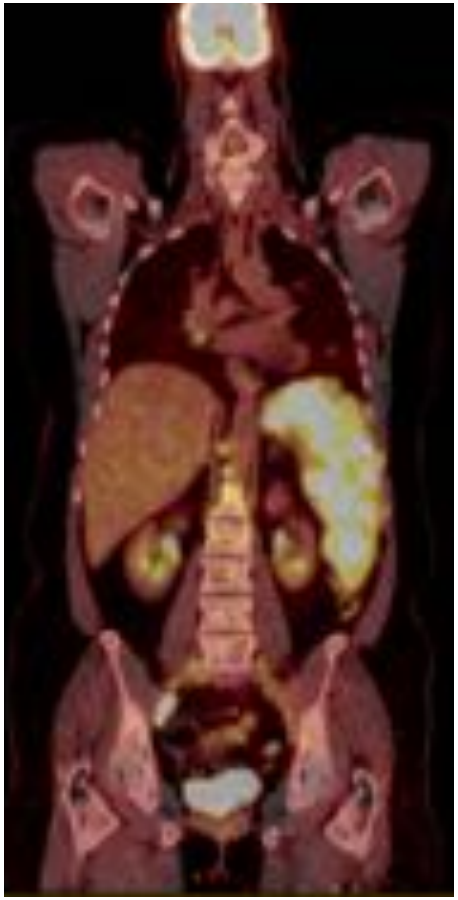
Selinexor Treatment

- October 7, 2013, initiates selinexor 35 mg/m^2
- MRI: 74% reduction in cycles 1 & 2
- PET CT negative Cycle 12, : CR
- Continues on selinexor monotherapy (**20+** months)

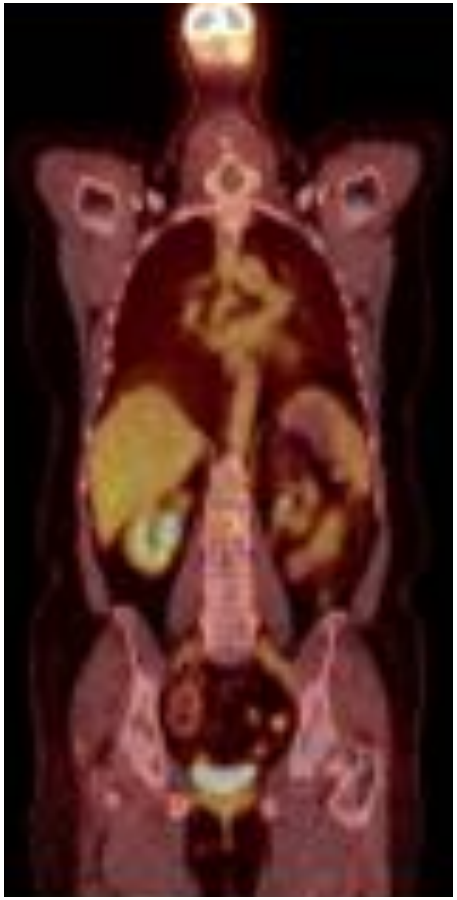


Baseline **Cycle 12**

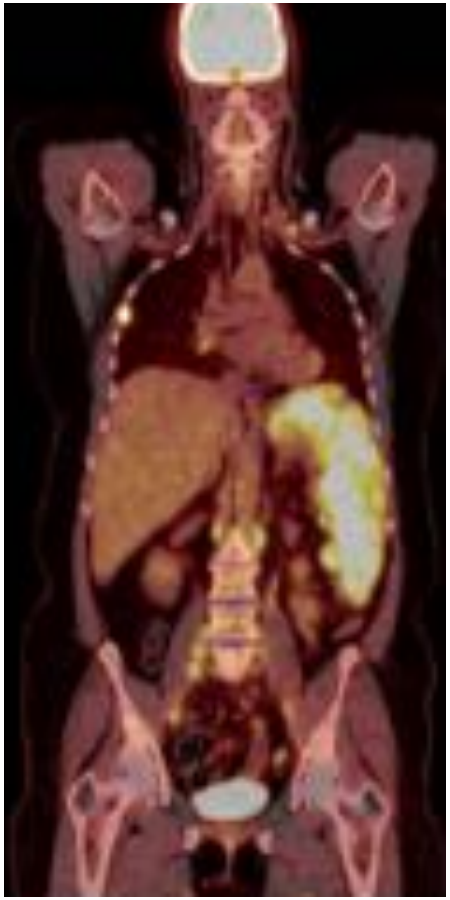
Refractory DLBCL: PET Confirmed Complete Response



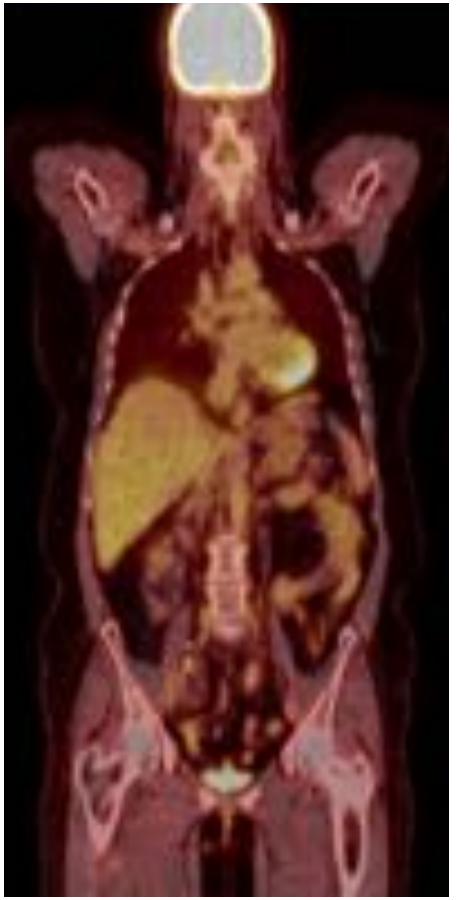
Baseline



Cycle 14



Baseline



Cycle 14

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Conclusions

- No standard regimen exists for relapsed/refractory DLBCL following failure of two immunochemotherapy regimens *(NCCN Guidelines 2014)*
- In 39 evaluable patients with heavily pretreated relapsed / refractory DLBCL, (3 median prior treatment regimens) selinexor monotherapy showed significant anti-cancer activity
- Most common selinexor-related AEs in DLBCL patients were lower grade constitutional and GI (nausea, anorexia, fatigue, vomiting) and higher grade thrombocytopenia and anemia that respond to supportive care
- Responses to selinexor are seen in both GCB and non-GCB subtypes
- Objective responses to selinexor are durable and correlate with improved OS and PFS, suggesting that these responses are associated with clinical benefit
- A Phase 2 of selinexor monotherapy (60 mg vs 100 mg) in patients with heavily pretreated DLBCL is ongoing and combination studies are being initiated

Phase 2 : SADAL Study

Based on data from Phase 1; A Phase 2 study of selinexor monotherapy was designed for patients with DLBCL:

SADAL – Selinexor Against Diffuse Aggressive Lymphoma

Ongoing Randomized Trial for Accelerated Approval

- Relapsed / Refractory ≥3rd line
- Twice-weekly randomized selinexor 1:1: selinexor 60 mg vs. selinexor 100 mg
- ≥50% of patients with GCB-DLBCL
- Initiated December 2014, ~ 200 patients to be enrolled
- Primary Endpoint: Overall Response Rate
- Data read out anticipated, late 2016