

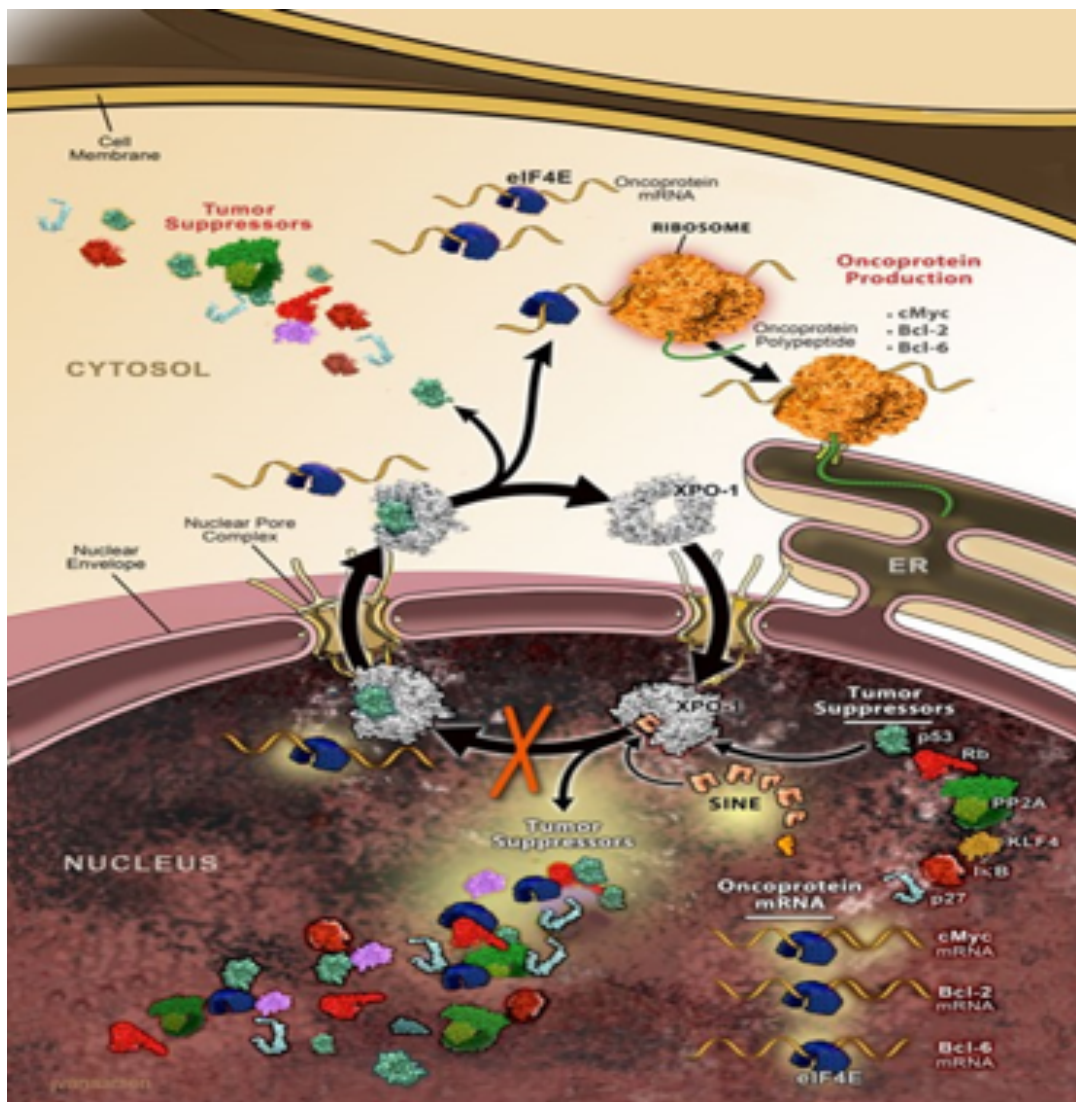
A Phase 2b Randomized Study of Selinexor in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) Demonstrates Durable Responses in both GCB and Non-GCB subtypes

**Poster CT132
Abstract 8539**

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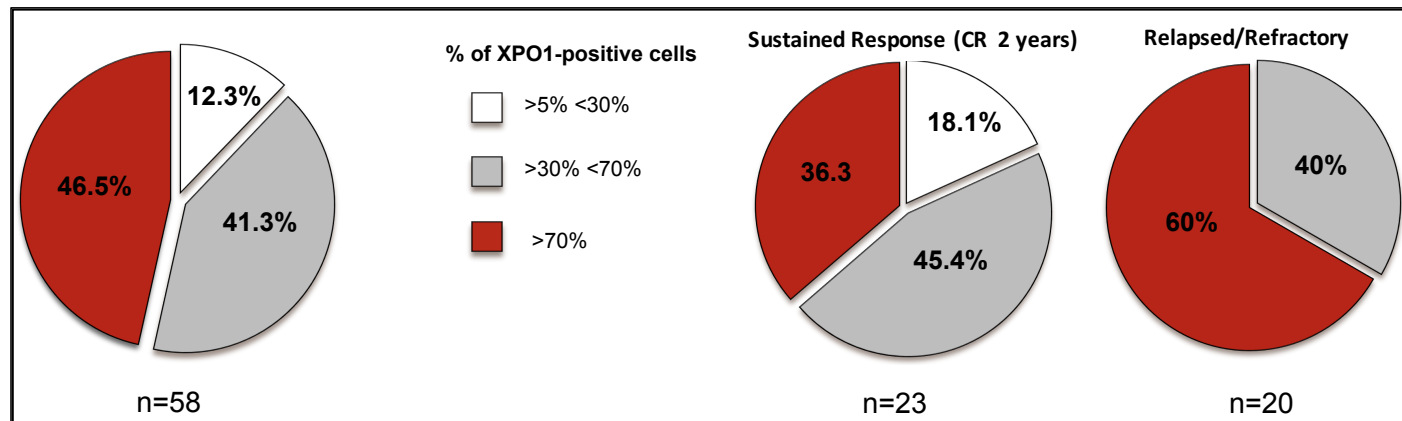
Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs) and eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, MDM2 and cyclins)
- Selinexor, an oral selective inhibitor of XPO1-mediated nuclear export (SINE), reactivates multiple TSPs and reduces oncoproteins known to play critical roles in NHL
 - Blocks NF- κ B activation through I κ B nuclear retention and other mechanisms
 - In p53-mutant DLBCL, locks p73 and other TSPs in the nucleus and induces apoptosis
- Selinexor has demonstrated single agent activity in patients with heavily pretreated refractory NHL
- Selinexor shows anti-cancer activity in multiple preclinical models of NHL, including in mouse xenografts and in dogs with spontaneous B- or T-cell lymphoma, independent of genotype (including p53 mutant models)

Pre-Clinical / *In Vivo* Activity

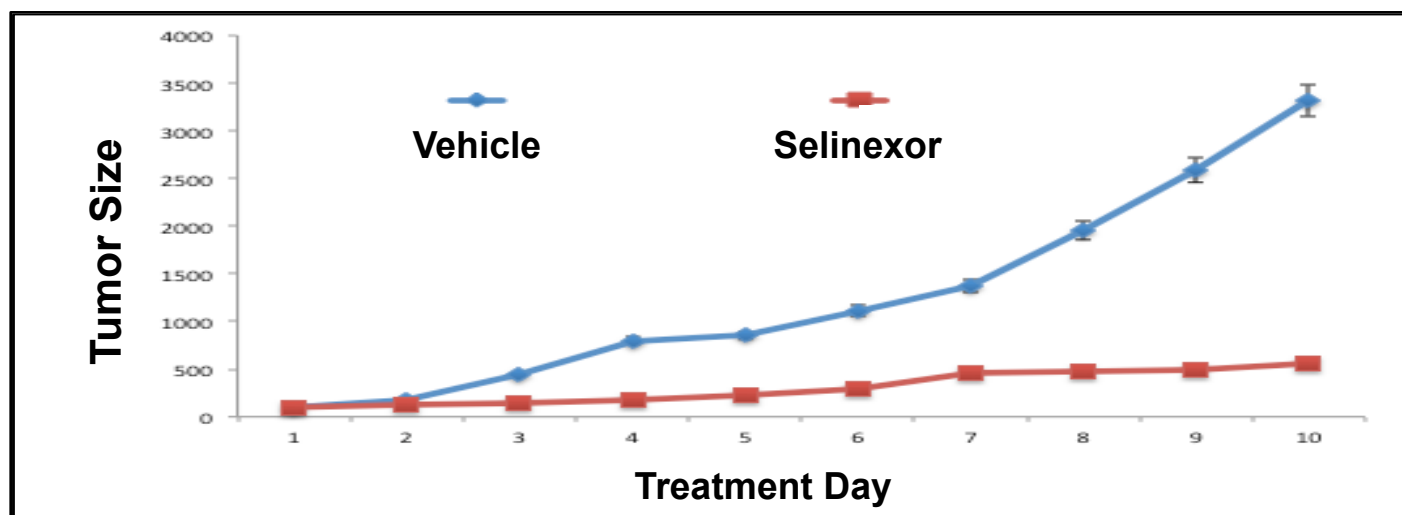
A XPO1 Expression in DLBCL Tissues (by IHC)



A) XPO1 is highly expressed in DLBCL, particularly in chemo-relapsed/refractory cases with 60% of DLBCL having >70% XPO1 positive cells (*Marullo AACR 2015*)

B Patient-Derived Xenograft of “Triple Hit” DLBCL

B



B) Triple hit PDX was transplanted into mouse flank. 10 mg/kg selinexor was administered twice weekly. Tumor size was significantly reduced after selinexor treatment as compared to placebo. (*Cerchietti, unpublished*)

SADAL Study Design

- **Selinexor Against Diffuse Aggressive Lymphoma (SADAL)** – A Phase 2B open label, randomized study comparing 60 mg vs. 100 mg single agent oral selinexor in patients with relapsed/refractory diffuse large B-Cell lymphoma (DLBCL)
 - Stratified by DLBCL subtype (GCB or non-GCB); with at least 50 GCB patients in each arm
- **Objectives:**
 - Primary: Overall Response Rate (ORR)
 - Secondary: Duration of response (DOR), disease control rate (DCR), overall survival (OS), and safety for each arm independently
- **Main Inclusion/Exclusion Criteria:**
 - Patients ≥ 18 years with clinical or radiographic evidence of progressive DLBCL, having received 2–5 prior treatment regimens
 - ≥ 14 weeks from last prior therapy
 - Excluded ANC $< 1000/\text{mm}^3$ or platelets $< 75,000/\text{mm}^3$
- **Dosing Schemes:**
 - 60 mg or 100 mg selinexor twice weekly (days 1 and 3 each week) of each 28 day cycle

SADAL Patient Characteristics

SADAL Patient Characteristics	60 mg	100 mg
Patients Enrolled as of March 1, 2017 (N=72)	37	35
Median Age, Years (range)	71 (38 – 87)	68 (32 – 82)
Males : Females	24 M : 13 F	23 M : 12 F
GCB Subtype	18 (49%)	18 (51%)
Non-GCB Subtype	19 (51%)	17 (49%)
Median Dose Received	56 mg	80 mg
Median Prior Regimens (range)	3 (2 – 5)	3 (2 – 5)
-Prior Stem Cell Transplant	10 (27%)	16 (46%)
-Median Prior Lines of anti-CD20 Antibodies (range)	2 (1 – 5)	2 (1 – 4)
R-IPI Risk (<i>Sehn 2007</i>)		
-High Risk	5 (14%)	4 (11%)
-High Intermediate Risk	16 (43%)	14 (40%)
-Low Intermediate Risk	11 (30%)	13 (37%)
-Low Risk	5 (14%)	2 (6%)
-Unknown	-	2 (6%)

SADAL Safety – Related Adverse Events (N=72)

AE Term	60 mg N=37				100 mg N=35			
	Grade 1/2	Grade 3	Grade 4	Total	Grade 1/2	Grade 3	Grade 4	Total
Gastrointestinal								
Nausea	20 (54%)	1 (3%)	--	21 (57%)	13 (37%)	3 (9%)	--	16 (46%)
Anorexia	15 (41%)	1 (3%)	--	16 (43%)	15 (43%)	4 (11%)	--	19 (54%)
Vomiting	14 (38%)	--	--	14 (38%)	10 (29%)	1 (3%)	--	11 (31%)
Diarrhea	8 (22%)	1 (3%)	--	9 (24%)	8 (23%)	2 (6%)	--	10 (29%)
Altered Taste	4 (11%)	--	--	4 (11%)	1 (3%)	--	--	1 (3%)
Constipation	3 (8%)	--	--	3 (8%)	3 (9%)	--	--	3 (9%)
Constitutional								
Fatigue/Asthenia	19 (51%)	4 (11%)	--	23 (62%)	15 (43%)	8 (23%)	1 (3%)	24 (69%)
Weight Loss	10 (27%)	--	--	10 (27%)	11 (31%)	--	--	11 (31%)
Malaise	1 (3%)	--	--	1 (3%)	4 (11%)	--	--	4 (11%)
Hematologic								
Thrombocytopenia	3 (8%)	7 (19%)	5 (14%)	15 (41%)	8 (23%)	7 (20%)	9 (26%)	24 (69%)
Anemia	7 (19%)	5 (14%)	--	12 (32%)	7 (20%)	4 (11%)	--	11 (31%)
Neutropenia	3 (8%)	4 (11%)	2 (5%)	9 (24%)	2 (6%)	4 (11%)	3 (9%)	9 (26%)
Leukopenia	--	2 (5%)	1 (3%)	3 (8%)	1 (3%)	--	1 (3%)	2 (6%)
Other								
Hyponatremia	1 (3%)	2 (5%)	--	3 (8%)	1 (3%)	5 (14%)	--	6 (17%)
Dyspnea	3 (8%)	--	--	3 (8%)	--	2 (6%)	--	2 (6%)
Pyrexia	1 (3%)	2 (5%)	--	3 (8%)	2 (6%)	--	--	2 (6%)
Insomnia	2 (5%)	1 (3%)	--	3 (8%)	3 (9%)	--	--	3 (9%)
Vision Blurred	2 (5%)	--	--	2 (5%)	3 (9%)	--	--	3 (9%)
Dizziness	1 (3%)	--	--	1 (3%)	7 (20%)	--	--	7 (20%)

Related Adverse Events: The most common related adverse effects (AEs) across both dosing groups were: fatigue, thrombocytopenia, nausea, anorexia, and vomiting. These were managed with dose interruptions/reductions, and/or standard supportive care. Grade 3/4 fatigue (26% v 11%), thrombocytopenia (46% v 32%), and anorexia (11% v 3%) were higher in the 100 mg arm as compared to the 60 mg arm. The median dose delivered was 56 mg on the 60 mg arm, 80 mg on the 100 mg arm.

SADAL Efficacy – Independent Central Radiological Review (N=63)

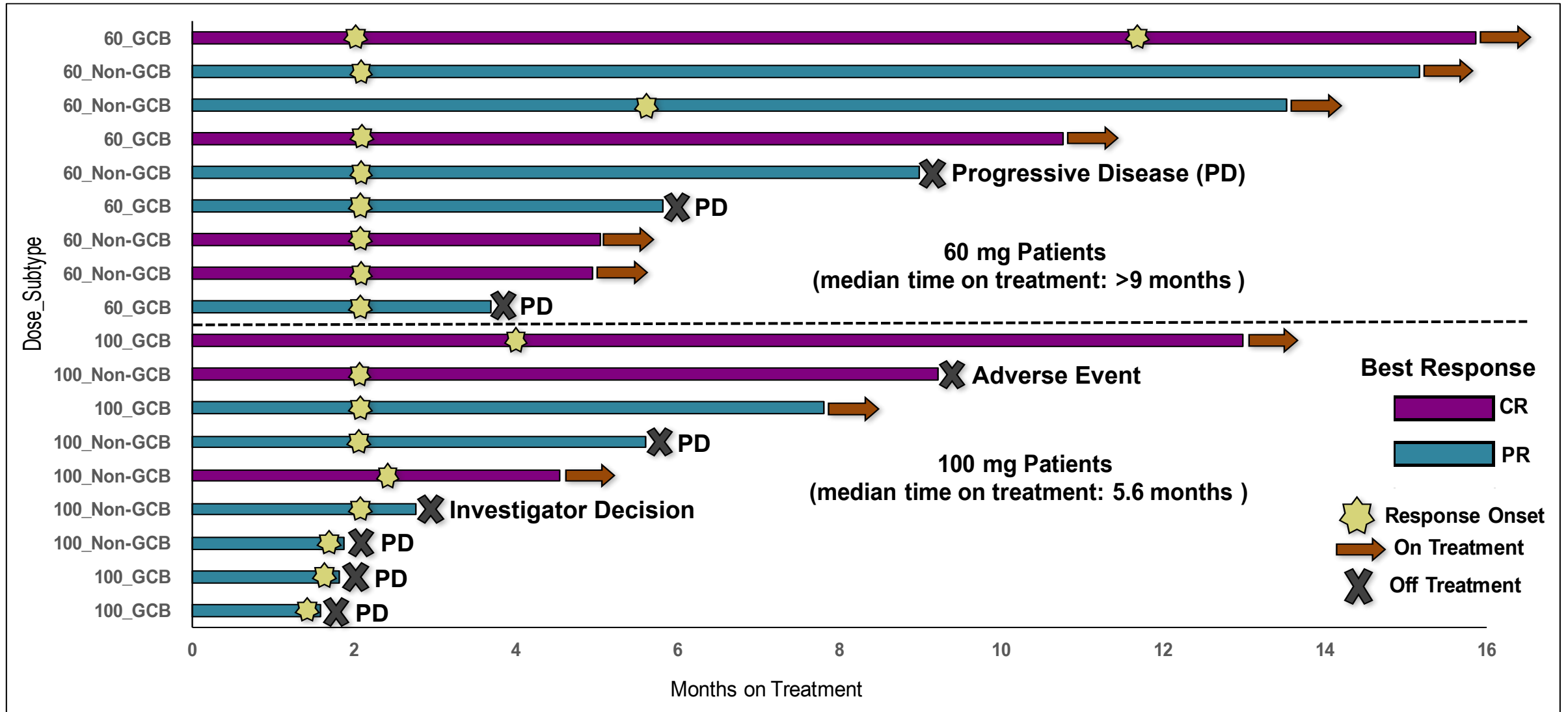
Best Responses[†] in the First 63 Patients as of March 1, 2017

Category	N	ORR (%)	DCR (%)	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)
All Patients	63	18 (28.6%)	27 (42.9%)	7 (11.1%)	11 (17.5%)	9 (14.3%)	29 (46.0%)	7 (11.1%)
60 mg	32	9 (28.1%)	12 (37.5%)	4 (12.5%)	5 (15.6%)	3 (9.4%)	17 (53.1%)	3 (9.4%)
100 mg	31	9 (29.0%)	15 (48.4%)	3 (9.7%)	6 (19.4%)	6 (19.4%)	12 (38.7%)	4 (12.9%)
GCB – Subtype	32	8 (25.0%)	14 (43.8%)	3 (9.4%)	5 (15.6%)	6 (18.8%)	13 (40.6%)	5 (15.6%)
Non-GCB – Subtype	31	10 (32.3%)	13 (41.9%)	4 (12.9%)	6 (19.4%)	3 (9.7%)	16 (51.6%)	2 (6.5%)

[†]Responses were adjudicated according to the Lugano Classification (*Cheson, 2014*) by an independent central radiological review committee. ORR=Overall Response Rate (CR+PR), DCR=Disease Control Rate (CR+PR+SD), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Non-evaluable. Responses are based on interim unaudited data as of March 1, 2017 for the first 63 patients (of 72 total patients).

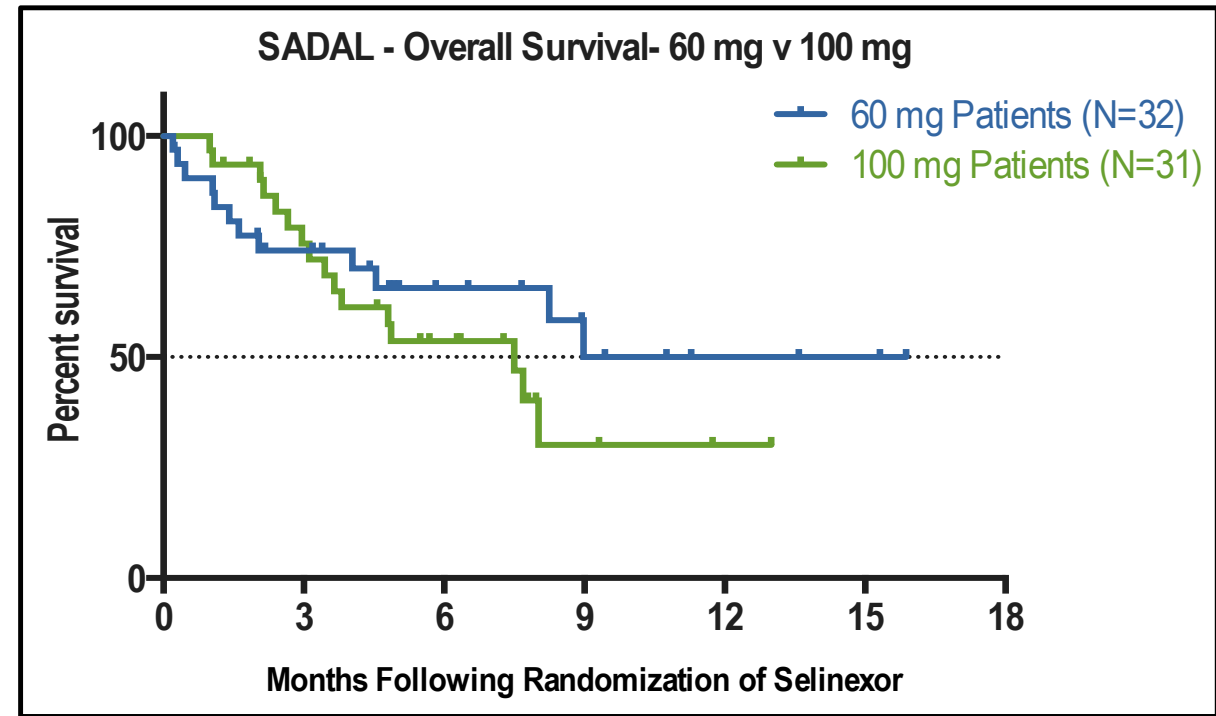
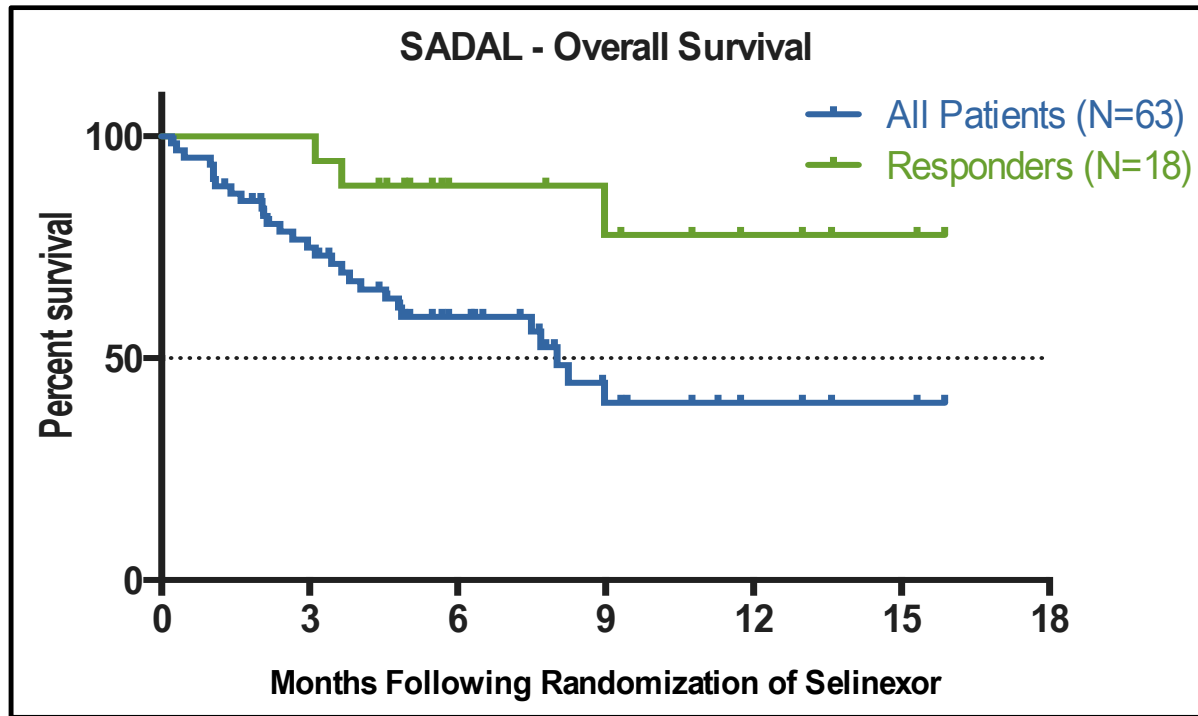
Overall response rate as determined by an independent central radiological review

Responders (N=18) – Independent Central Radiological Review



Among responders in the 60 mg arm the median time on treatment was >9 months (**median DOR >7 months**) with a follow up of 13 months. Nine responders in total remain on treatment including 6 patients with a CR. The median time to onset of response was ~2 months (i.e., at the first response evaluation).

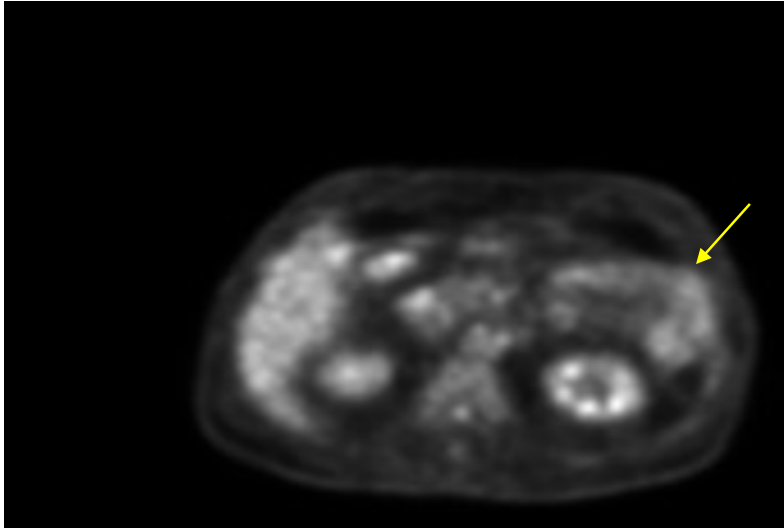
SADAL Efficacy – Overall Survival



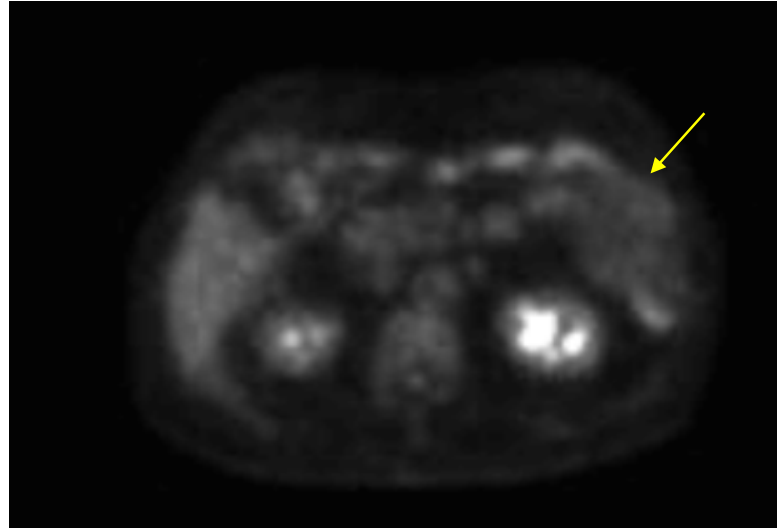
Median overall survival among all patients was 8 months (consistent with published data in this population), undefined among responders, undefined for patients treated at 60 mg, and 7.5 months for patients treated at 100 mg

SADAL Efficacy – Case Report

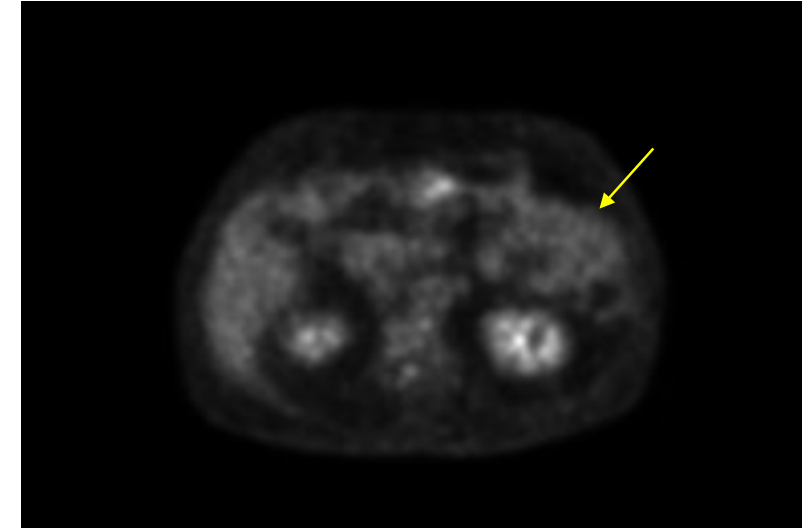
Baseline



Cycle 3: mPR



Cycle 13: mCR



PET/CT images from a 55 year old male, GCB subtype, with 2 prior treatment regimens (*R-CHOP* x 6 cycles (SD); *R-Gemcitabine-Lenalidomide* (*R-Gem-L*) x 3 cycles (SD)). After 2 cycles of selinexor 60 mg po twice weekly, patient achieved a metabolic partial response, and after 10 more cycles, patient achieved a metabolic complete response (CR). The patient continues on treatment >15 months with a CR.

Summary and Conclusions

- Selinexor is a novel oral therapy with single agent activity against both GCB and non-GCB (ABC) relapsed/refractory DLBCL
- In this heavily pretreated, older population, the most common AEs are: fatigue, thrombocytopenia, nausea, anorexia, and vomiting, mainly grades 1 and 2
- Response rates are similar between the 60 and 100 mg dose groups, but the lower dose of 60 mg is better tolerated than the 100 mg dose
 - Patients treated at 60 mg have fewer dose interruptions/modifications than patients at 100 mg
 - An amendment is underway to discontinue dosing on the 100 mg arm
 - Up to an additional 90 patients will be enrolled in the 60 mg arm
- Selinexor monotherapy shows activity with relapsed/refractory DLBCL with a centrally confirmed ORR of 28.6% and a median DOR >7 months in the 60 mg arm including prolonged CRs
 - Responses were rapid with a median time to response of 2 months
- In this difficult to treat, older population, selinexor could represent a new oral option for patients whose disease is unlikely to respond to further chemotherapy or targeted agents