Single Agent Oral Selinexor Demonstrates Deep and Durable Responses in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) in Both GCB and Non-GCB Subtypes: The Phase 2b SADAL Study

Abstract 1677

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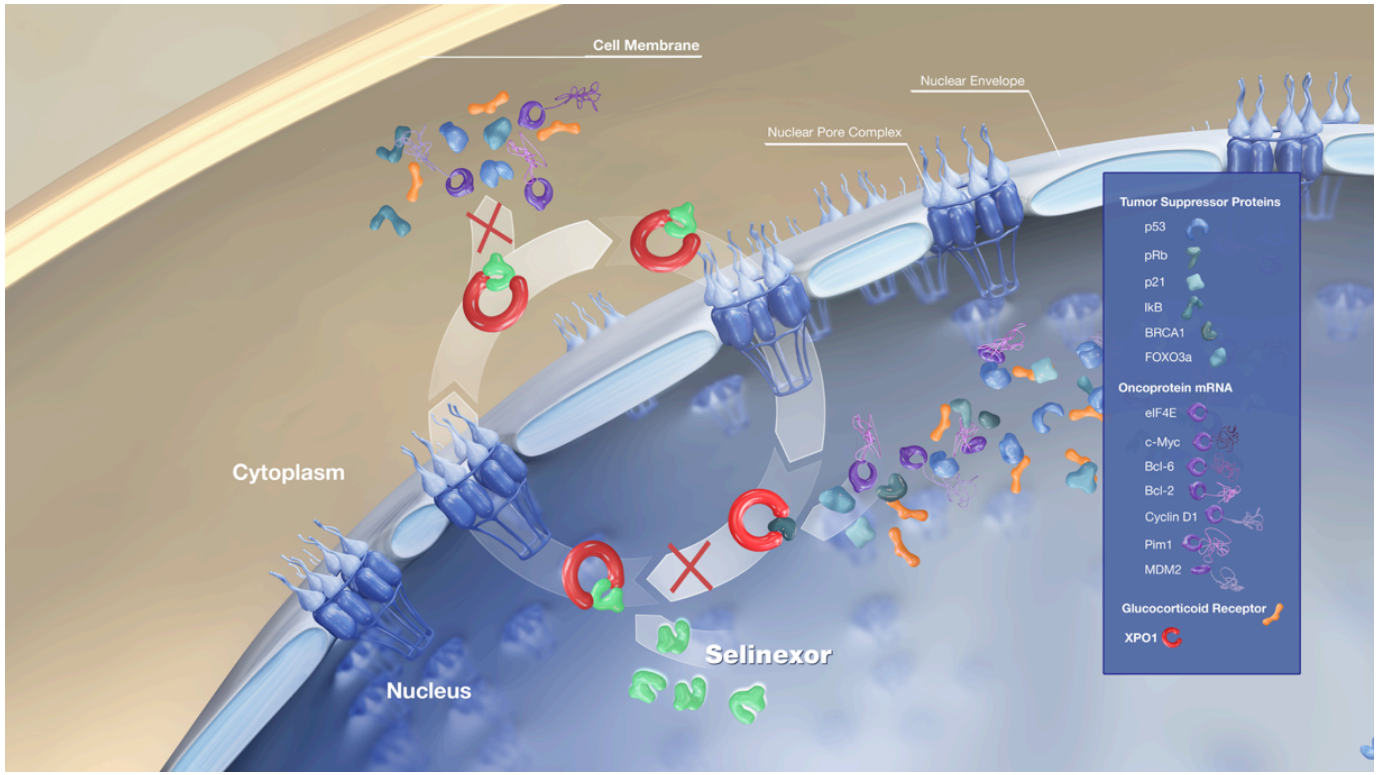
Selinexor: Mechanism of Action



- **Exportin 1 (XPO1)** is the major nuclear export protein for:
  - Tumor suppressor proteins (TSPs, e.g., p53, IκB and FOXO)
  - eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
- **Selinexor** is an oral selective **XPO1** inhibitor; preclinical data supports that XPO1 inhibition:
  - Reactivates multiple TSPs relevant to NHL, including p53, p21, IκB and FOXO
  - Promotes the nuclear localization of eIF4e, which is overexpressed in most B-cell lymphomas (*Kodali 2011*)
  - Reduces c-Myc, Bcl-2, and Bcl-6 levels (*Kuruvilla 2014; Schmidt 2013*)

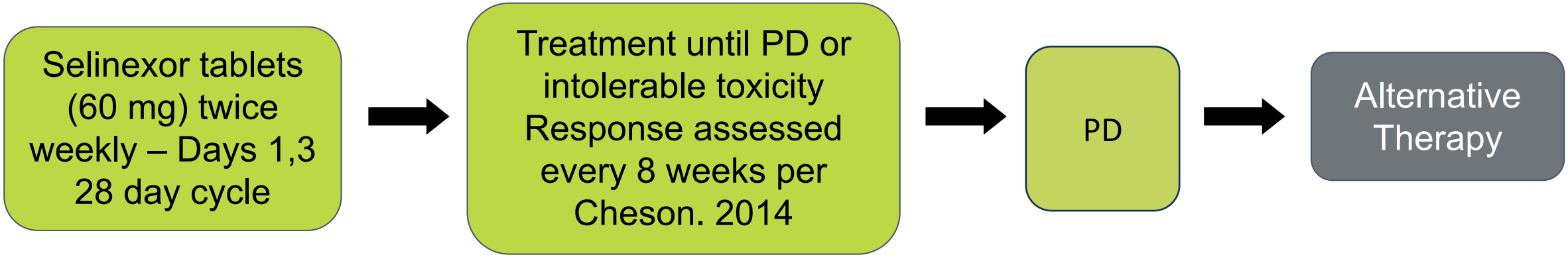
mRNA, messenger Ribonucleic Acids; IkB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; FOXO, forkhead box; eIF4e, eukaryotic translation initiation factor 4E; BCL-xL, B-cell Lymphoma-extra Large; NHL, Non-Hodgkin Lymphoma; Bcl2, B-cell Lymphoma 2; Bcl6, B-cell Lymphoma 6.

SADAL Study Design

- **S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma (**SADAL**) is an open-label, randomized Phase 2B study comparing 60 mg vs. 100 mg single agent oral selinexor in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)
- **Objectives:**
  - **Primary Endpoint:** overall response rate (ORR) as determined by an Independent Central Radiological Review (ICRR), using the Lugano Classification
  - **Secondary Endpoints:** duration of response (DOR), overall survival (OS), safety
- **Patient Population:**
  - Patients, ≥18 years, with histologically confirmed, transformed or de novo DLBCL, with documented evidence of disease progression
  - Patients must not be eligible for high-dose chemotherapy with autologous stem cell transplantation rescue
- **Modified Intent to Treat (mITT) Population:**
  - All patients who were randomized to the 60 mg Arm under protocol version 6.0 (and enrolled under protocol versions 7.0 or higher) that received at least 1 dose of selinexor. The mITT group included patients who discontinued selinexor due to toxicity, disease progression, or died from any cause. This population was the primary analysis population and was used for primary, secondary, and exploratory analyses of efficacy. Data presented will focus on the mITT.

SADAL Study Design Cont.

- **Main Inclusion / Exclusion Criteria:**
  - Two (2) – 5 prior treatment regimens, patients achieving a CR or PR on most recent prior therapy must have an 8 week washout period prior to enrollment
  - Patients whose most recent systemic therapy did not induce a CR or PR must have ≥14 weeks washout period prior to Cycle 1 Day 1
  - ANC >1000 cells/mm^3, platelet count >75,000/mm^3, hemoglobin >10 g/dL
  - Patients with known central nervous system lymphoma or meningeal involvement were excluded
- **Study Schematic:**



SADAL, Selinexor Against Diffuse Aggressive Lymphoma; CR, Complete Response; PR, Partial Response; ANC, Absolute Neutrophil Count; PD, Progressive Disease.

SADAL Patient Characteristics

SADAL Patient Characteristics (mITT)	N
Enrolled* as of November 15, 2018	129
Median Age, Years (range)	67 (35–87)
Males : Females	76 M : 53 F
Median Years from DLBCL Diagnosis (range)	2.1 (<1–16.2)
de novo DLBCL : Transformed DLBCL : Unknown	**97** (75%) : **30** (23%) : **2** (2%)
GCB Subtype : Non-GCB Subtype : Unclassified	**60** GCB : **63** Non-GCB : **5** Unclassified
Median Prior Treatment Regimens (range)	**2 (1–6)**
-Prior Transplant	40 (31%)
Revised-International Prognostic Index (Sehn, 2007)	
-Very Good	3 (2%)
-Good	58 (45%)
-Poor	59 (46%)
-Unknown	9 (7%)

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; mITT, modified Intent-To-Treat; N, Number; M, Males; F, Females; GCB, Germinal Center B-Cell like.

*Two patients enrolled (1 patient with follicular lymphoma (subtype not included above), 1 patient with CNS involvement) did not meet eligibility criteria and are excluded from efficacy analysis

SADAL Treatment Related Adverse Events in ≥10% of Patients

AE Term	Selinexor 60 mg BIW mITT population (N=128*)				
Hematologic	**Grade 1 (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Total (N=128)**
Thrombocytopenia	7 (5.5%)	11 (8.6%)	29 (22.7%)	16 (12.5%)	**63 (49.2%)**
Anemia	6 (4.7%)	16 (12.5%)	13 (10.2%)	1 (0.8%)	**36 (28.1%)**
Neutropenia	1 (0.8%)	6 (4.7%)	17 (13.3%)	9 (7.0%)	**33 (25.8%)**
Gastrointestinal					
Nausea	29 (22.7%)	27 (21.1%)	8 (6.3%)	--	**64 (50.0%)**
Anorexia	19 (14.8%)	19 (14.8%)	3 (2.3%)	--	**41 (32.0%)**
Vomiting	24 (18.8%)	3 (2.3%)	2 (1.6%)	--	**29 (22.7%)**
Diarrhea	16 (12.5%)	8 (6.3%)	4 (3.1%)	--	**28 (21.9%)**
Altered Taste	12 (9.4%)	3 (2.3%)	--	--	**15 (11.7%)**
Constipation	11 (8.6%)	2 (1.6%)	--	--	**13 (10.2%)**
Constitutional					
Fatigue	18 (14.1%)	16 (12.5%)	12 (9.4%)	--	**46 (35.9%)**
Asthenia	7 (5.5%)	11 (8.6%)	3 (2.3%)	--	**21 (16.4%)**
Weight Loss	13 (10.2%)	14 (10.9%)	--	--	**27 (21.1%)**

Treatment Related Adverse Events as of November 1, 2018

- No related Grade 5 AEs were reported in the mITT population
- *One patient (without any reported related AEs) was recently enrolled and not included in total N

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; AE, Adverse Events; BIW, twice weekly; mITT, modified Intent-To-Treat; N, Number.

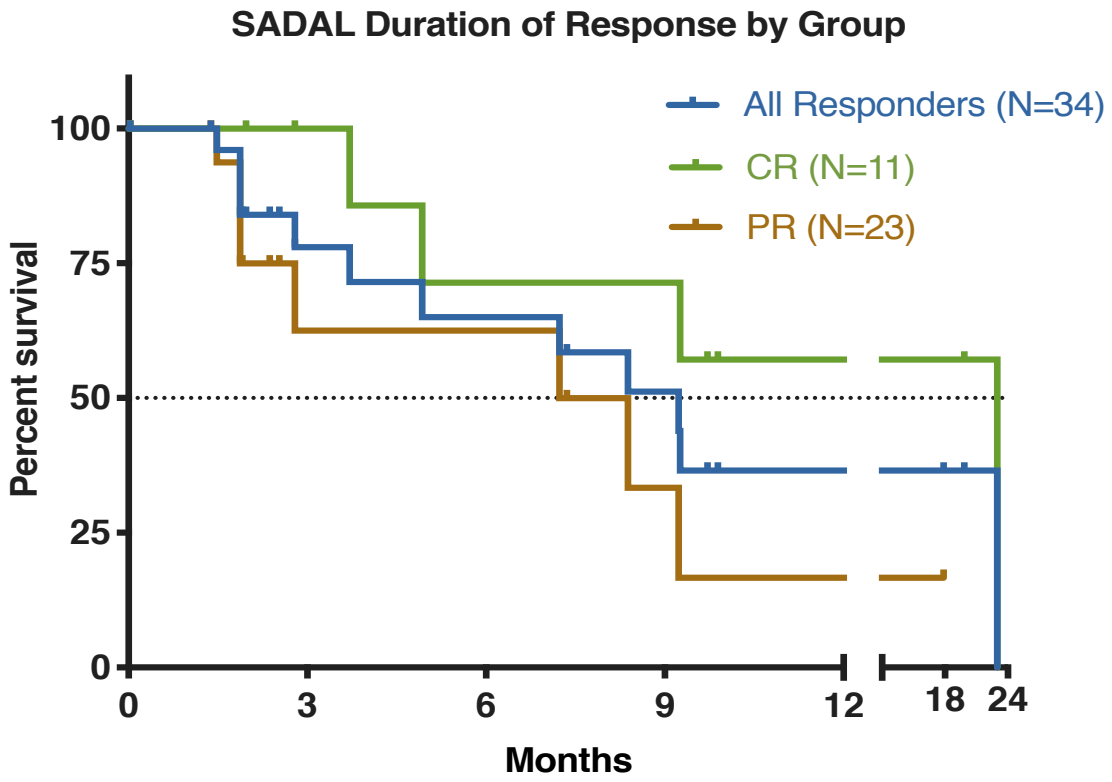
SADAL Efficacy

Best Responses† in Evaluable SADAL mITT Patients as of November 15, 2018							
Category	**N**	**ORR (%)**	**CR (%)**	**PR (%)**	**SD (%)**	**PD/NR (%)**	**Pending***
All Patients	115	**34 (29.6%)**	11 (9.6%)	23 (20.0%)	8 (7.0%)	73 (63.5%)	12
GCB Subtype	53	**18 (34.0%)**	5 (9.4%)	13 (24.5%)	5 (9.4%)	30 (56.6%)	6
Non-GCB Subtype	57	**12 (21.1%)**	6 (10.5%)	6 (10.5%)	3 (5.3%)	42 (73.7%)	6
Unclassified Subtype	5	**4 (80.0%)**	--	4 (80.0%)	--	1 (20.0%)	--

†Responses were adjudicated according to the Lugano Classification, Cheson 2014 by an Independent Central Radiological Review. ORR=Overall Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NR=No Response Recorded. *Pending patients are currently on treatment but have not yet had a response assessment, not included in total N. Responses as of November 15, 2018 based on interim unaudited data.

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; mITT, modified Intent-To-Treat; N, Number; ORR, Overall Response Rate; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; NR, No Response recorded; GCB, Germinal Center B-Cell like.

SADAL Duration of Response



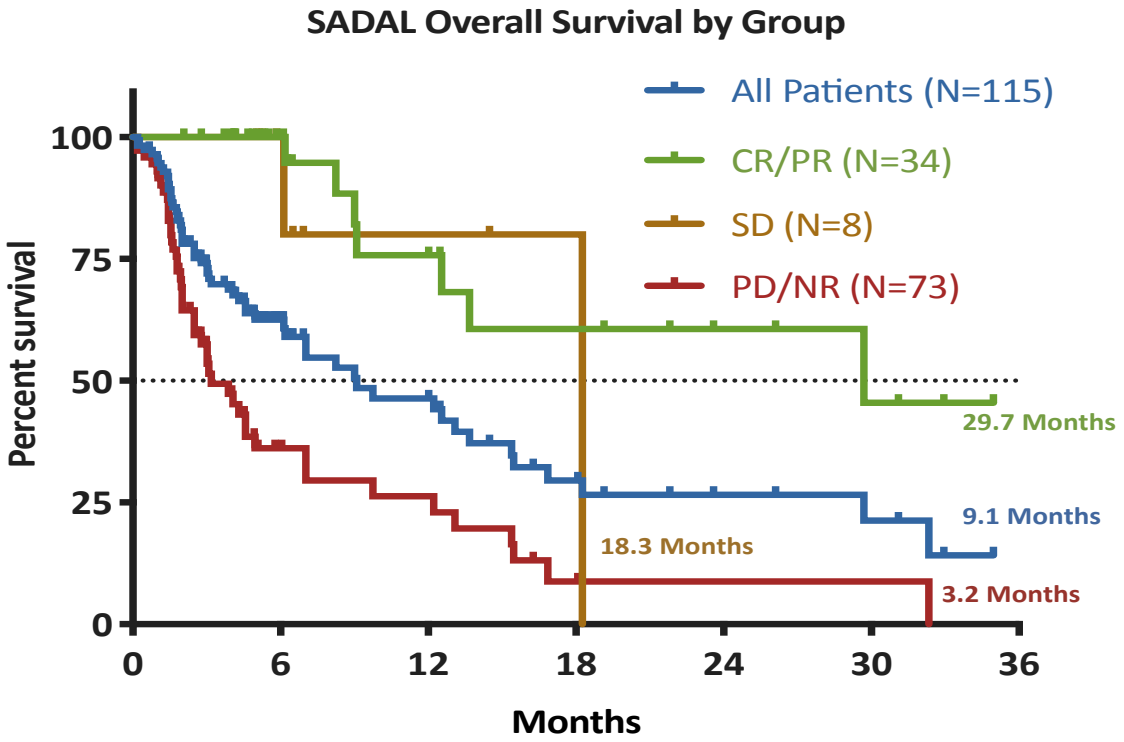
Patients at Risk	Months	0	1.9	2.8	3.7	4.9	7.4	9.2	9.9	17.9	19.8	23.0
	All Responders	**34**	24	14	12	11	9	7	4	3	2	1
	CR Patients	**11**	--	8	7	6	--	--	3	--	2	1
	PR Patients	**23**	15	6	--	--	4	2	--	1	--	--

A) Among responders (N=34) the median duration of response (DOR) was **9.2** months overall. CR patients (N=11) had a median DOR of **23.0 months** (7 of 11 CR patients still on treatment). PR patients (N=23) had a median DOR of **7.8 months**.

Category	Median DOR	95% CI
All Responders	9.2 Months	(4.9, 23.0)
CR Patients	23.0 Months	(4.9, 23.0)
PR Patients	7.8 Months	(2.8, NE)

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; CR, Complete Response; N, Number; PR, Partial Response; CI, Confidence limits.

SADAL Overall Survival



B) The median overall survival was **9.1** months in all patients, **29.7** months in CR/PR patients (27 out of 34 CR/PR patients censored), and **3.2** months in PD/NR patients.

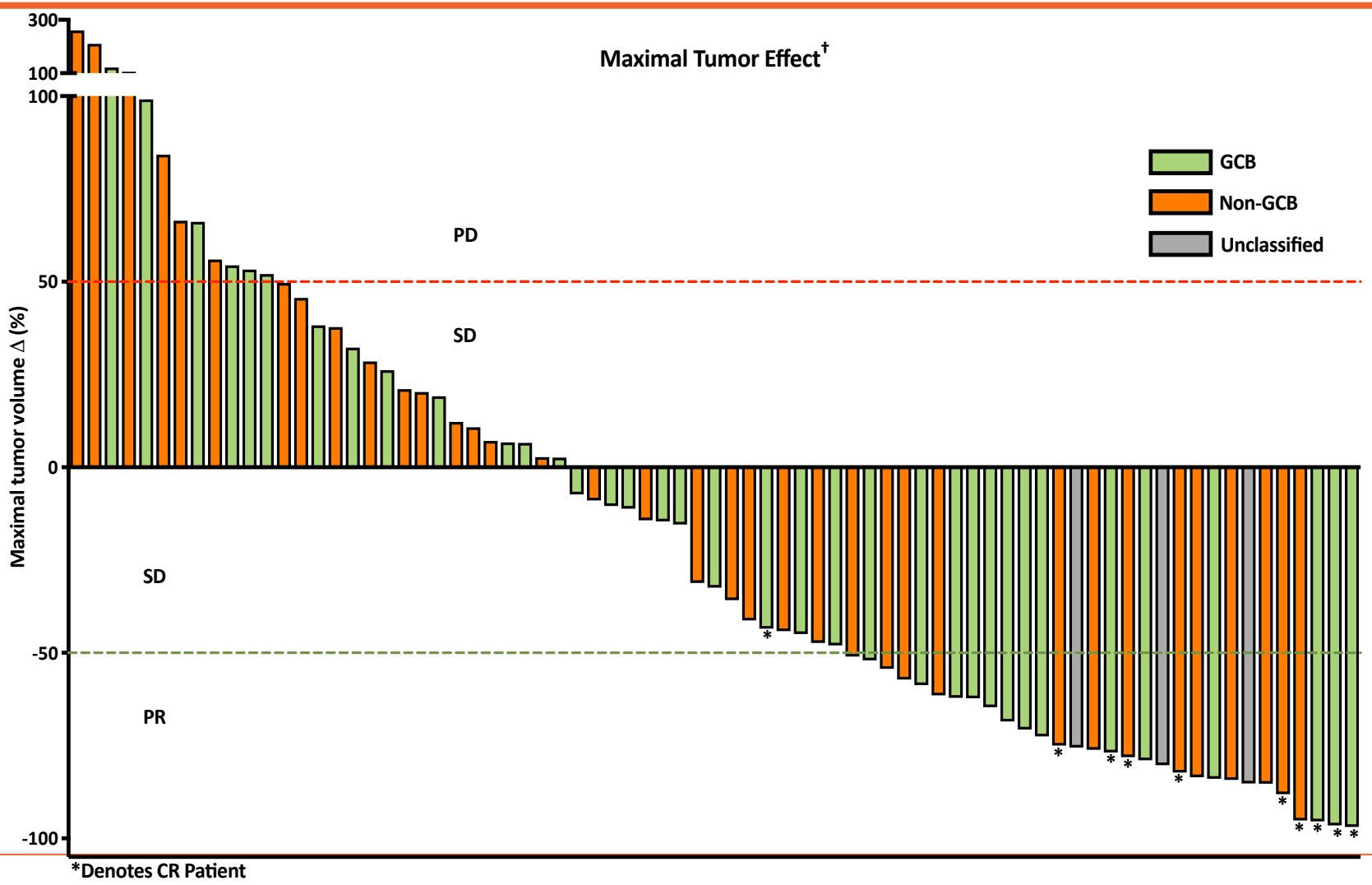
Patients at Risk

Months	0	2.8	3.2	5.0	6.9	9.1	12.0	14.5	16.9	18.3	21.8	23.6	26.1	29.7	32.3	35.0
All Patients	**115**	74	65	46	29	24	22	16	12	10	8	7	6	5	3	1
CR/PR Patients	**34**	--	--	--	--	13	12	--	--	--	7	6	5	4	--	1
SD Patients	**8**	--	--	8	3	--	--	2	--	1	--	--	--	--	--	--
PD/NR Patients	**73**	33	25	--	--	--	--	--	3	--	--	--	--	--	1	--

Category	Median OS	95% CI
All Patients	9.1 Months	(6.2, 15.4)
CR/PR Patients	29.7 Months	(12.6, NE)
SD Patients	18.3 Months	(NE, NE)
PD/NR Patients	3.2 Months	(2.5, 7.0)

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; CR, Complete Response; N, Number; PR, Partial Response; CI, Confidence limits.

SADAL Tumor Effect



C) Forty-six patients with a post-baseline response reading had reductions in tumor burden. †Changes in anatomical tumor burden shown for all patients. Metabolic changes not shown.

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; GCB, Germinal Center B-Cell like; SD, Stable Disease; PR, Partial Response; PD, Progressive Disease.

SADAL Summary and Conclusions

Selinexor is an oral, first-in-class investigational treatment with a novel mechanism of action inhibiting XPO1

SADAL is pivotal phase 2b study of single agent selinexor in patients with relapsed/refractory DLBCL who are not eligible for high-dose chemotherapy with autologous stem cell transplantation rescue

- **Single Agent Oral Selinexor Demonstrates Deep and Durable Responses in R/R DLBCL** :
  - ORR of **29.6%**; including a **9.6%** CR Rate (7 out of 11 CR patients still on treatment)
    - Responses were seen in GCB (**34.0%**) and non-GCB (**21.1%**) subtypes
  - Median DOR of **9.2** months; **23.0** months in CR patients; **7.8** months in PR patients
  - Median OS of **9.1** months overall; **29.7** months in patients CR/PR

Side effects were manageable, transient and consistent with known selinexor side effect profile

- Most common AEs mainly G1/2: nausea (50.0%); anorexia (32.0%), fatigue (35.9%); and asthenia (16.4%)
- Most common G3/4 AEs: thrombocytopenia (35.2%); neutropenia (20.3%), and anemia (10.9%)

Responses to selinexor in this patient population are encouraging and highlight the potential of selinexor as a new treatment option for relapsed / refractory DLBCL

SADAL, Selinexor Against Diffuse Aggressive Lymphoma; G3/4, Grade 3/4; AEs, Adverse Events; ORR, Overall Response Rate; DLBCL, Diffuse Large B-cell Lymphoma, CR, Complete Response; GCR, Germinal Center B-Cell like; DOR, Duration Of Response; PR, Partial Response; OS, Overall Survival.