A Phase 2b Study of Selinexor in Patients with Relapsed / Refractory Diffuse Large B-Cell Lymphoma: SADAL trial

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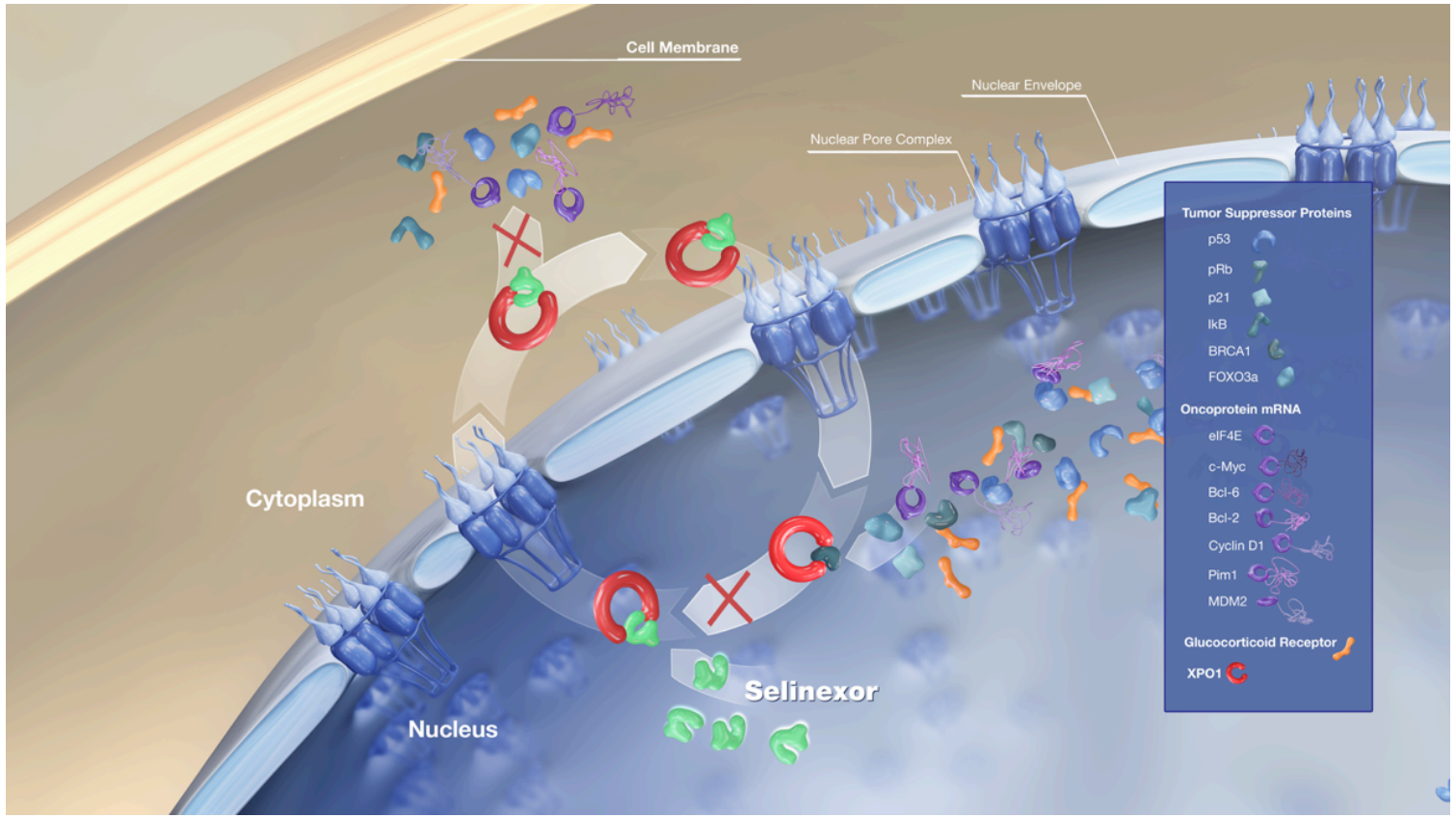
Selinexor: Mechanism of Action



Exportin 1 (XPO1 or CRM1) mediates the nuclear export of proteins, mRNAs, rRNAs, snRNAs and impacts

- **Tumor suppressor proteins** (p53, IκB, FOXO etc.)
- **eIF4E** (Translational initiation factor) bound oncogenic mRNAs (c-Myc, Bcl-xL, cyclins etc.)

Selinexor is an oral selective **XPO1** inhibitor; preclinical data support that XPO1 inhibition:

- Reactivates multiple TSPs relevant to NHL, (p53, p21, IκB, FOXO etc.)
- Disrupts localization of eIF4e (overexpressed in most B-cell lymphomas[1]
- Reduces c-Myc, Bcl-2, and Bcl-6 levels[2-3]

1. Kodali 2011 2. Kuruvilla 2014 3. Schmidt 2013

SADAL: Study Design

Single Agent Oral Selinexor in Patients with Relapsed / Refractory DLBCL

Selinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma (**SADAL**): An Open-label, Phase 2b study

Patient Population
- Patients with de novo or t-DLBCL
- Relapsed or Refractory DLBCL
- Not eligible for ASCT

Main Inclusion / Exclusion
- 2 – 5 prior treatment regimens
- Platelet count >75,000/mm^3
- Cr Cl <30 ml/min – excluded

Oral Selinexor
60 mg twice-weekly
Days 1, 3 – 28 day cycle

→

Treatment until PD or intolerable toxicity;
Response assessed every 8 weeks per *Cheson 2014*

→

mITT Population for all Analysis and Safety
(≥Protocol Version 6 patients)

Objectives:

- **Primary Endpoint**: Overall response rate (ORR): Independent Central Radiological Review (ICRR); Lugano Classification (2014)
- **Secondary Endpoints**: Duration of response (DOR), Overall survival (OS), Safety

Modified Intent to Treat (mITT) Population: All patients who were randomized to the **60 mg Arm**

SADAL: Patient Characteristics

Characteristic	N
Enrolled* as of April 3, 2019	**127**
Median Age, Years (Range)	**67** (35–87)
Males (%) : Females (%)	**75** (59%) : **52** (41%)
Median Years from DLBCL Diagnosis (Range)	**2.6 yrs** (<1–26.2)
De novo DLBCL : Transformed DLBCL : Unknown	**96** (76%) : **30** (24%) : **1** (<1%)
GCB Subtype : Non-GCB Subtype : Unclassified	**59** GCB : **63** Non-GCB : **5** Unclassified
Median Prior Treatment Regimens (Range)	**2 (1–6)**
Prior Transplantation	39 (31%)

SADAL: Treatment-Related Adverse Events

AE Term	Selinexor 60 mg BIW mITT Population (N=127)				
Hematologic	**Grade 1 (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Total (N=127)**
Thrombocytopenia	6 (4.7)	10 (7.9)	35 (27.6)	15 (11.8)	**66 (52.0)**
Anemia	3 (2.4)	18 (14.2)	16 (12.6)	1 (0.8)	**38 (29.9)**
Neutropenia	1 (0.8)	6 (4.7)	17 (13.4)	9 (7.1)	**33 (26.0)**
Gastrointestinal					
Nausea	31 (24.4)	28 (22.0)	8 (6.3)	--	**67 (52.8)**
Anorexia	20 (15.7)	19 (15.0)	5 (3.9)	--	**44 (34.6)**
Vomiting	25 (19.7)	6 (4.7)	2 (1.6)	--	**33 (26.0)**
Diarrhea	14 (11.0)	8 (6.3)	4 (3.1)	--	**26 (20.5)**
Dysgeusia	12 (9.4)	3 (2.4)	--	--	**15 (11.8)**
Constipation	10 (7.9)	4 (3.1)	--	--	**14 (11.0)**
Constitutional					
Fatigue	19 (15.0)	17 (13.4)	12 (9.4)	--	**48 (37.8)**
Asthenia	5 (3.9)	11 (8.7)	3 (2.4)	--	**19 (15.0)**
Weight Loss	10 (7.9)	17 (13.4)	--	--	**27 (21.3)**

- No related Grade 5 AEs were reported in the mITT population
- Side effects were generally reversible and managed with dose modifications and/or standard supportive care

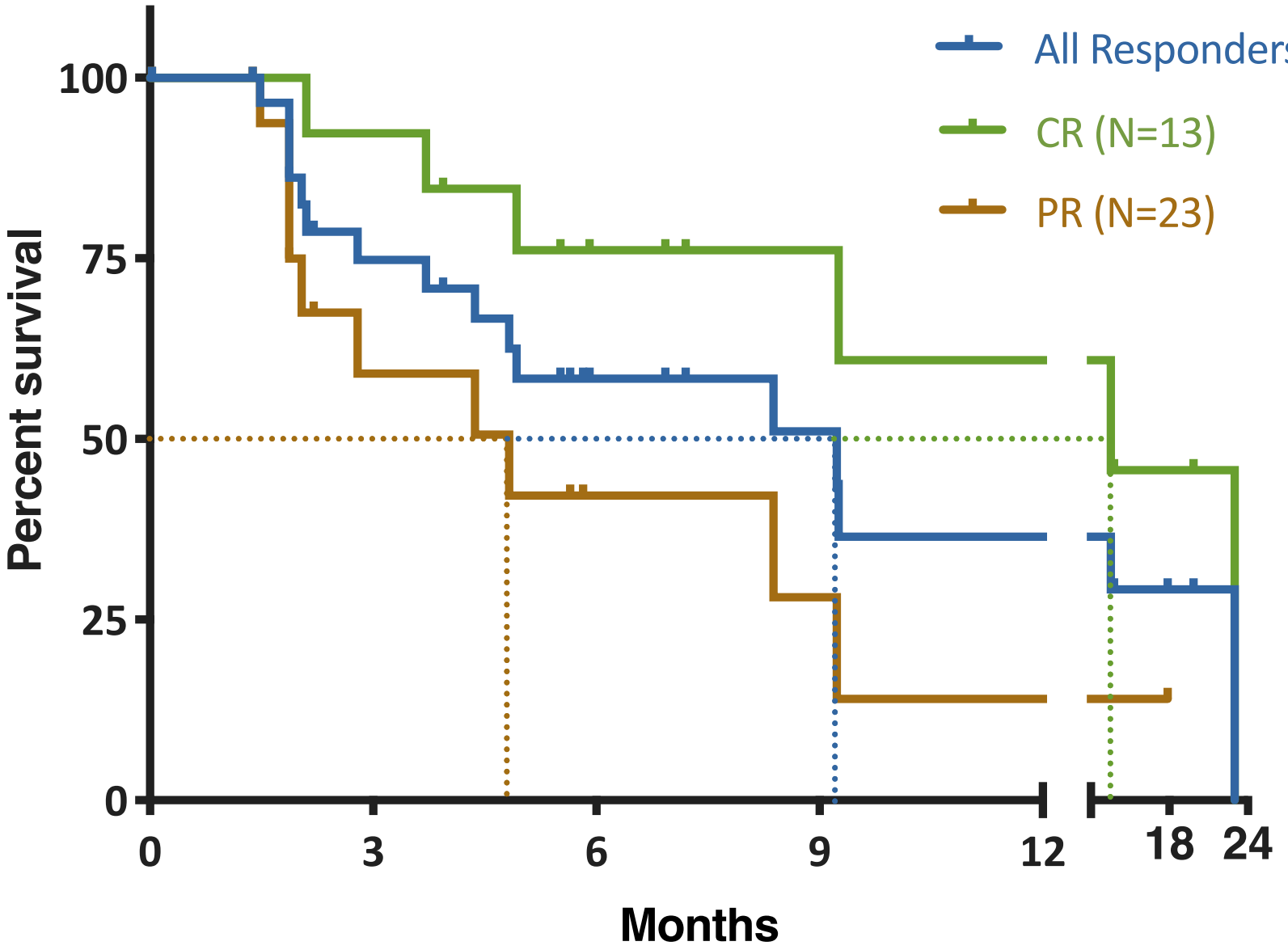
SADAL: Response Rates

Best Responses† in Evaluable patients as of April 3, 2019						
Category	**N**	**ORR (%)**	**CR (%)**	**PR (%)**	**SD (%)**	**PD/NR (%)**
All Patients	127	**36 (28.3%)**	**13 (10.2%)**	23 (18.1%)	11 (8.7%)	80 (63.0%)
GCB Subtype	59	**20 (33.9%)**	**7 (11.9%)**	13 (22.0%)	7 (11.9%)	32 (54.2%)
Non-GCB Subtype	63	**13 (20.6%)**	**5 (7.9%)**	8 (12.7%)	3 (4.8%)	47 (74.6%)
Unclassified	5	**3 (60.0%)**	**1 (20.0%)**	2 (40.0%)	1 (20.0%)	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. Responses as of April 3, 2019 based on interim unaudited data.

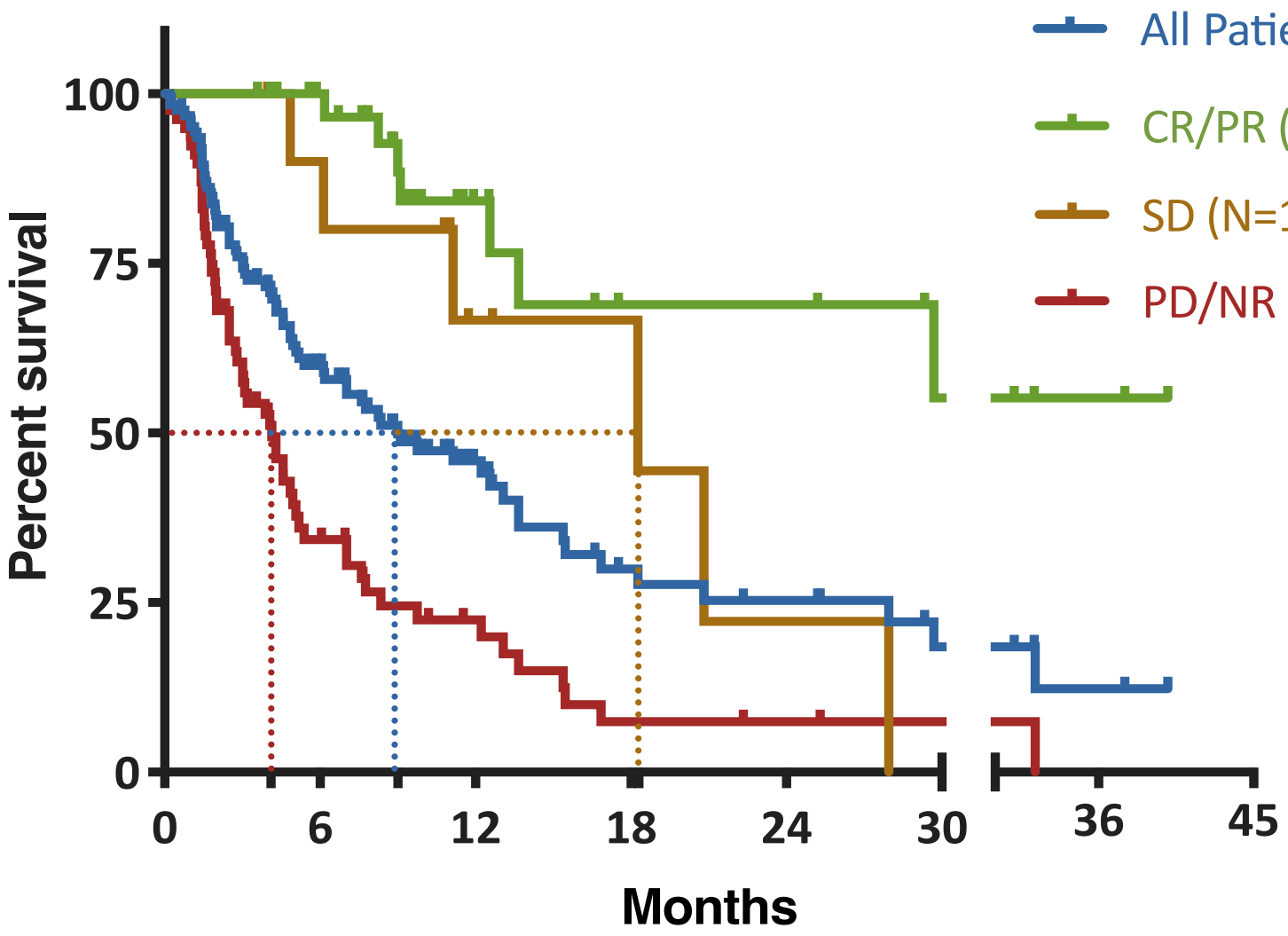
- **Median time to response: 1.8 months (range: 1.5 – 6.4)**

SADAL: Duration of Response



Category	Median DOR (months)	95% CI
All Responders	9.2	(4.8 – 23.0)
CR Patients	13.5	(9.3 – 23.0)
PR Patients	4.8	(2.0 – NE)

SADAL: Overall Survival

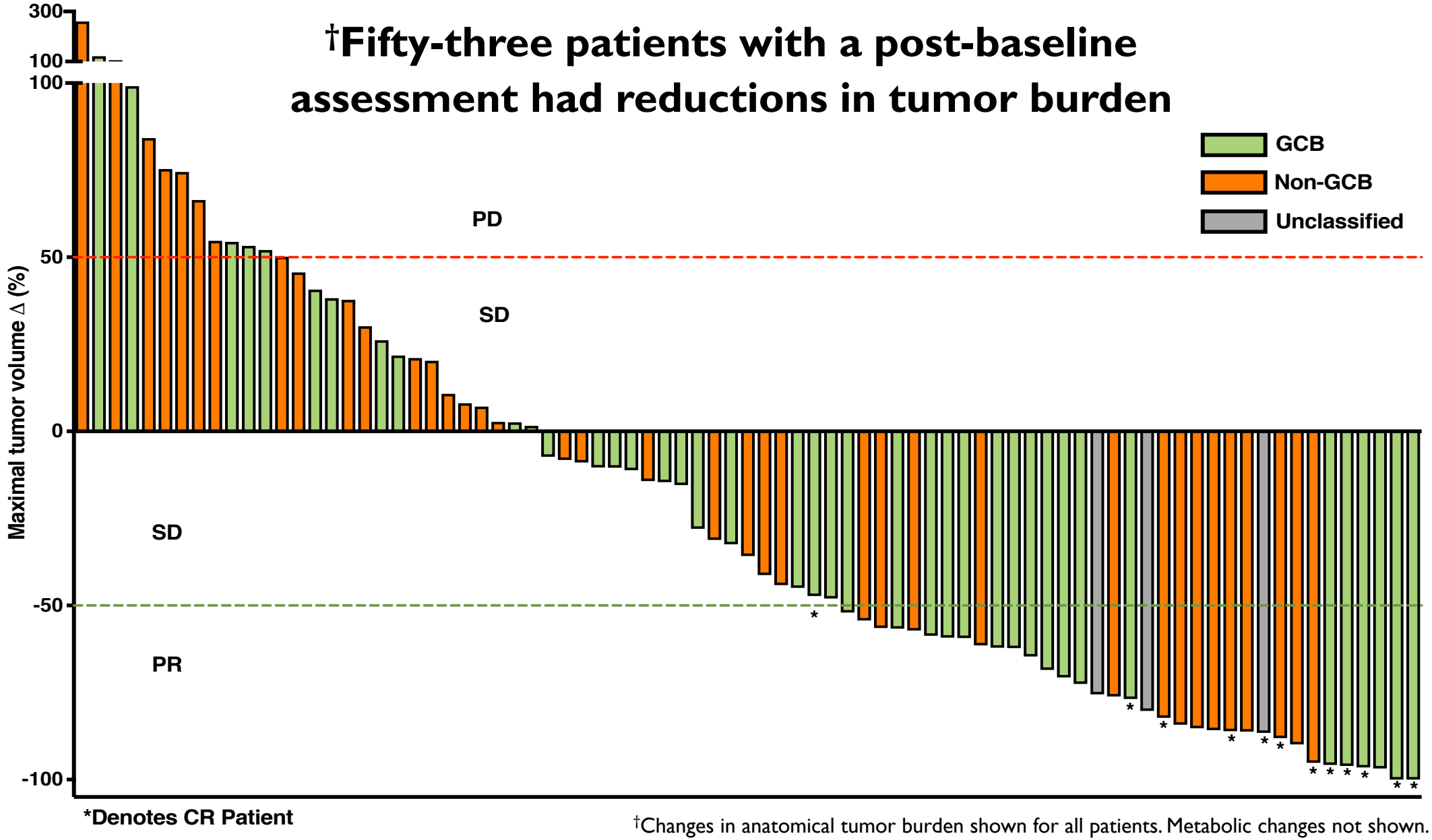


Category	Median OS (months)	95% CI
All Patients	9.0	(6.2 – 13.7)
CR/PR Patients	Not Reached	(13.7 – NE)
SD Patients	18.3	(11.1 – 28.0)
PD/NR Patients	4.1	(3.0 – 5.2)

Median follow-up of 11 months

SADAL: Tumor Responses: Anatomical

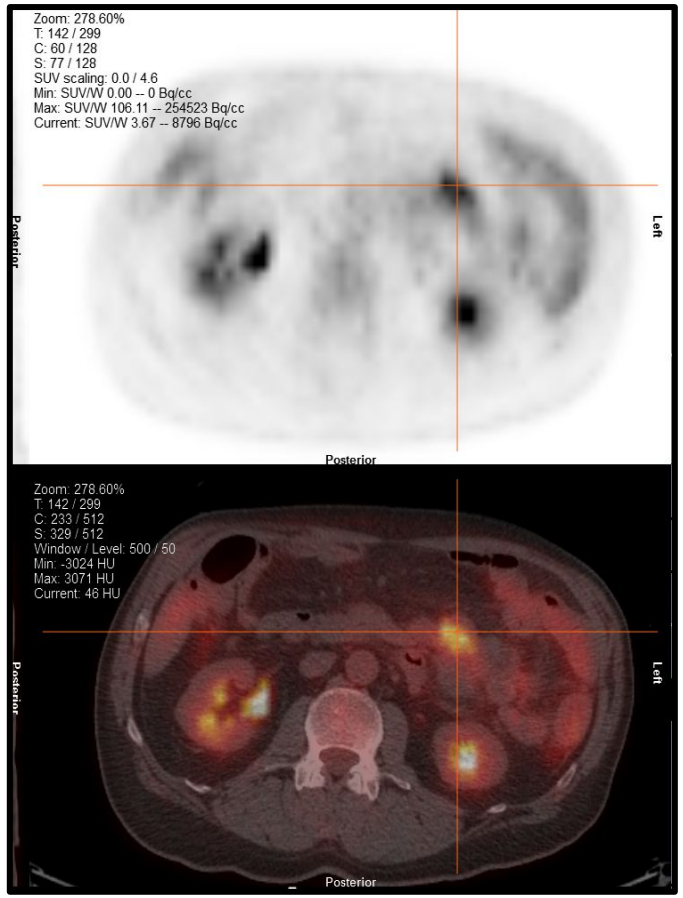
†Fifty-three patients with a post-baseline assessment had reductions in tumor burden



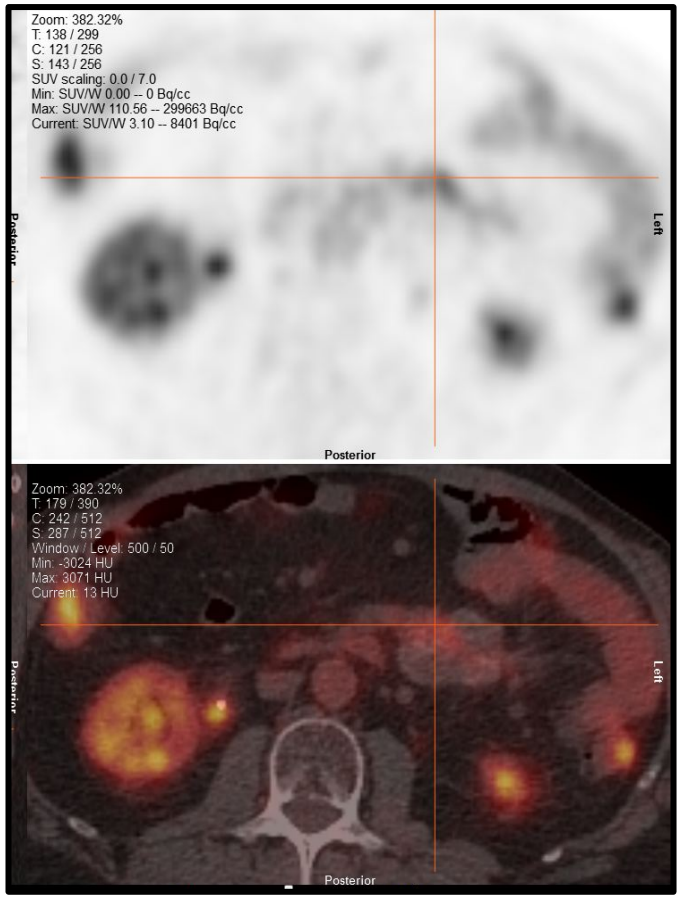
†Changes in anatomical tumor burden shown for all patients. Metabolic changes not shown.

SADAL: Patient Case Study* (1)

Baseline



8 Months Post-Tx



- Male 55 yrs, with GCB-DLBCL; Bulky abdominal mass; Primary Refractory
- Progressed 3 weeks post 6 x R-CHOP; Poor response to 2 x Gemcitabine based salvage regimen

- Anatomic PR after 4 months
- **Complete metabolic response after 8 months of selinexor:**

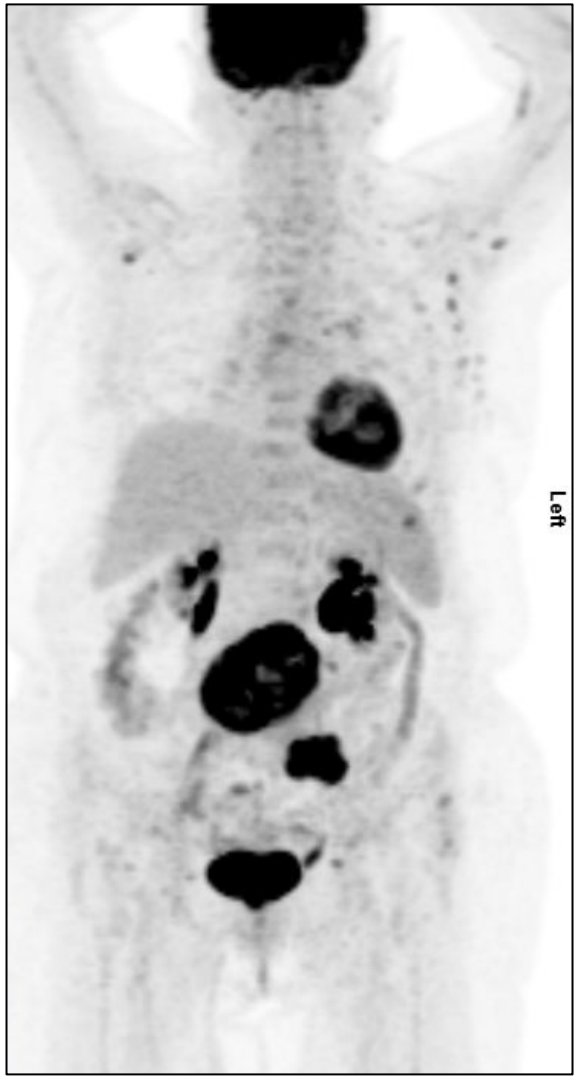
- Currently on selinexor 60 mg once a week

Remains in remission: >30 months

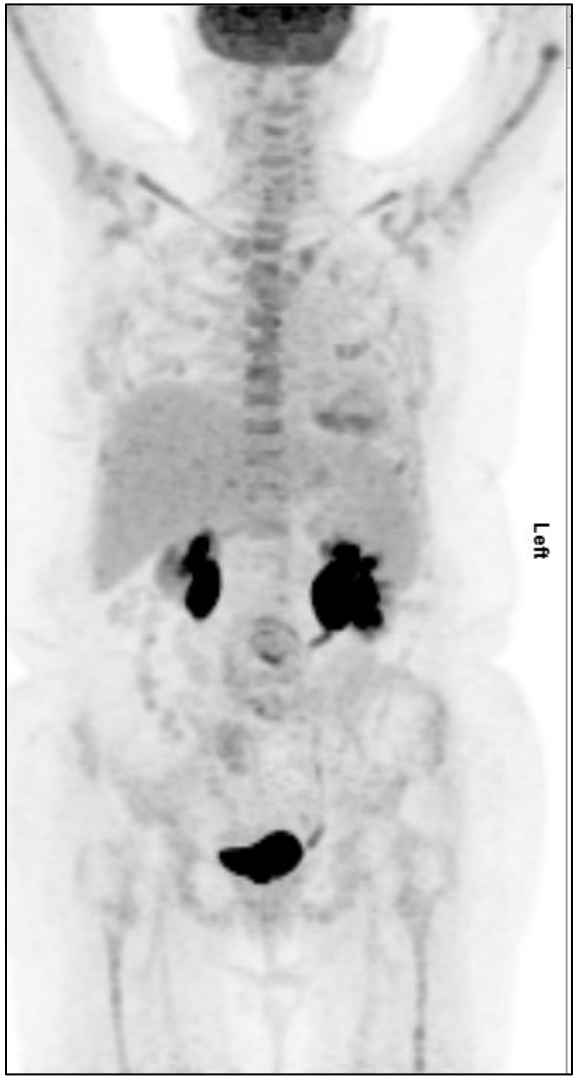
*Results in one patient are not indicative of results in the study population

SADAL: Patient Case Study* (2)

Baseline



9 Months Post-Tx



- Female, 76 yrs, Transformed DLBCL with 3 lines of prior therapy
- 6 months of Selinexor: Anatomic PR
- 9 months of selinexor: **Complete metabolic response**
- Selinexor stopped for >28 days for unrelated AE – Off study

*Results in one patient are not indicative of results in the study population

SADAL: Summary and Conclusions

Single Agent Oral Selinexor Demonstrates Deep and Durable Responses in R/R DLBCL an area of unmet need

- ORR of **28.3%** — **10.2%** CR Rate; ORR: GCB **33.9%**, non-GCB: **20.6%**
- Median DOR of **9.2** months — DOR: **13.5** months in CR patients
- Median OS of **9.0** months — Not yet reached in patients CR/PR

Side effects were expected and managed with appropriate supportive care and/or dose modifications

- Most common AEs mainly G1/2: Nausea, Fatigue, Anorexia, and Vomiting
- Limited G3/4 AEs: Thrombocytopenia, Anemia, and Neutropenia

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- **Single agent oral selinexor, if approved, may be a new treatment option for patients with relapsed or refractory DLBCL**
- **Further evaluation of selinexor in combinations is ongoing**

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