Abstract # EP-1260

Survival Among Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) Treated with Single Agent Selinexor in the SADAL Study

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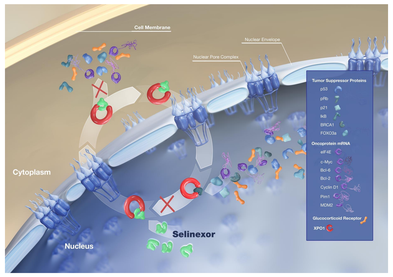
Introduction

Diffuse Large B-Cell Lymphoma (DLBCL)

- DLBCL is typically treated with multi-agent chemotherapy plus an anti-CD20 monoclonal antibody leading to cure in ~50-60% of patients.
- Another 20-40% of patients with relapsed/refractory disease may be cured with chemotherapy with autologous stem cell transplantation (ASCT), but only a minority of patients are candidates for this intensive therapy.
- Patients with disease refractory to multiple therapies have a very poor prognosis, highlighting the need for novel treatments for this patient population.

Selinexor – A Selective Inhibitor of Nuclear Export

- Exportin 1 (XPO1) is the most well characterized nuclear export protein and mediates export of tumor suppressor proteins (TSP, e.g., p53, p21, IkB and FOXO) and many growth regulatory proteins (e.g., c-Myc, Bcl-xL, cyclins), cell cycle arrest, and apoptosis of cancer cells.
- XPO1 XPO1 is over expressed in DLBCL and high levels of XPO1 correlate with poor outcomes
  - Inhibition of XPO1 prevents export of TSP from the nucleus
  - In cancer cells with damaged DNA, accumulation of TSPs in the nucleus reinitiates and amplifies their pro-apoptotic function
  - Normal cells resume normal activity after transient XPO1 inhibition due to intact DNA



- Selinexor has been approved by the FDA in combination with dexamethasone (Sd) for patients with relapsed/refractory multiple myeloma.[1]
- In a Phase 1 study of patients with heavily pre-treated DLBCL, single agent selinexor demonstrated an overall response rate (ORR) of 32% with complete response in 9.3%

Methods

Selinexor Treatment of Diffuse Large B-cell Lymphoma: SADAL Study

- The SADAL (Selinexor Against Diffuse Aggressive Lymphoma) study was an open-label Phase 2b study in which patients with previously treated, pathologically confirmed *de novo* DLBCL, or DLBCL transformed from previously diagnosed indolent lymphoma, with a performance status of ≤ 2 and having received at least 2 prior therapies were enrolled.[2]
- Selinexor (60 mg) was administered orally on days 1 and 3 weekly until disease progression or unacceptable toxicity.

We performed analyses of the SADAL study to determine if there are differences in overall survival and safety among patients stratified by disease status, age, DLBCL subtype, ASCT, and response to last prior therapy.

Results

Table 1. Patient Demographics and Disease Characteristics

	N=134
Age (years), median (range)	67 (35-91)
≥70 years (%)	60 (44.8)
Male, n(%) Female, n (%)	79 (59.0) : 55 (41.0)
Time since DLBCL diagnosis, years, median (range)	2.6 (0.1, 26.2)
Weeks since last disease progression event, median (range)	7.3 (1.9, 406.3)
DLBCL type, n (%)	
De novo DLBCL	103 (76.9)
Transformed DLBCL	31 (23.1)
DLBCL subtype, n (%)	
GCB	63 (47.0)
non-GCB	66 (49.3)
Unclassified	5 (3.7)
Double Hit/Triple Hit DLBCL, n (%)	
Yes	2 (1.5)
No	81 (60.4)
Missing	51 (38.1)
Prior ASCT therapy for DLBCL, n (%)	
Yes	40 (29.9)

Efficacy in the mITT population (n=134)

- Single agent oral selinexor showed a 29.1% ORR in 134 patients with previously treated, *de novo* DLBCL, or DLBCL transformed from indolent lymphoma, after two lines of chemo-immunotherapy.
- The median overall survival in the mITT population was 9.0 months (95% CI: 6.2, 13.7), with a median follow-up time of 14.8 months.
- Deaths occurred in 79 patients (59%)

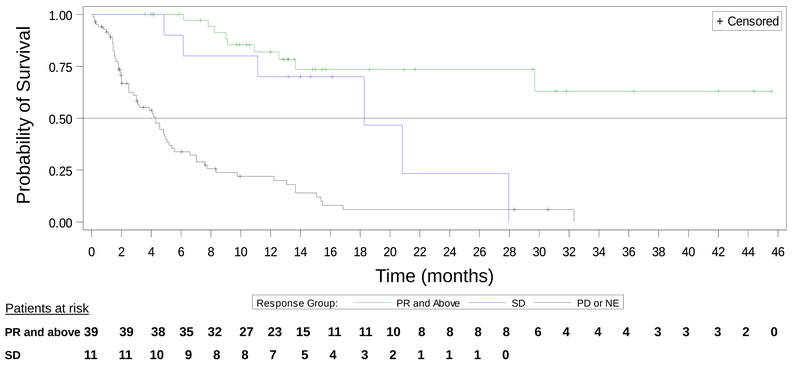


Table 2. Overall Survival by Subgroup

		Overall Survival median (months), 95% CI	HR (95% CI)
Disease response	Complete response (n=18)	NR (29.7, NR)	
	Partial response (n=21)	NR (12.6, NR)	
	Stable disease (n=11)	18.3 (11.1, 28.0)	
	Progressive disease or not evaluable (n=84)	4.3 (3.0, 5.4)	
Age	<70 years (n=74)	11.1 (5.4, 28.0)	0.72 (0.5, 1.1)
	≥70 years (n=60)	7.8 (6.1, 13.7)	
DLBCL subtype	GCB (n=63)	9.0 (5.0, 15.5)	0.95 (0.6, 1.5)
	Non-GCB (n=66)	8.3 (5.4, 16.9)	
Prior ASCT Status	Prior ASCT (n=40)	10.9 (7.0, NR)	0.72 (0.4, 1.2)
	No prior ASCT (n=94)	7.8 (4.9, 13.7)	
Last prior therapy	Not refractory (n=30)	13.7 (6.6, NR)	0.8 (0.5, 1.4)
	Refractory (n=96)	8.3 (5.2, 13.7)	

NR, not reached

Table 3. Treatment-Related Adverse Events (all Grades, incidence ≥20%)

Adverse Event	mITT (n=134) N (%)
Thrombocytopenia	72 (53.7)
Nausea	69 (51.5)
Fatigue	50 (37.3)
Decreased appetite	46 (34.3)
Anemia	44 (32.8)
Neutropenia	41 (30.6)
Vomiting	35 (26.1)
Weight decreased	29 (21.6)
Diarrhea	28 (20.9)
Serious Adverse Events	28 (20.9)
Dose Reduction	60 (44.8)
Discontinuation	23 (17.2)

The AE profile was comparable between patients who are ≥70 years of age and patients under 70 years of age with similar incidence of serious adverse reactions (49% vs 47%), adverse events leading to discontinuation (19% vs 16%) and fatal adverse reactions (n=3 [5%] vs n=2 [3%]).

Conclusions

- **Single agent selinexor demonstrated a 9 month median overall survival benefit in a patient population in which survival is expected to be <6 months per historical control.[3]**
- **OS benefit was observed in patients regardless of age, DLBCL subtype, prior ASCT therapy, or refractory status.**
- **Randomized studies with selinexor in combination with other anti-DLBCL agents are warranted.**

References

[1]Chari, A. et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N Engl J Med*. 2019 Aug 22;381(8):727-738.

[2]Kalakonda, N. et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm multinational phase 2 trial. *Lancet Hematology*. (In press)

[3]Crump, M. et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017 Oct 19;130(16):1800-1808.

Disclosures: This study was sponsored by Karyopharm Therapeutics.