Effect of Age on the Efficacy and Safety of Single Agent Oral Selinexor in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL): Subset Analysis from the SADAL Pivotal Phase 2b Study

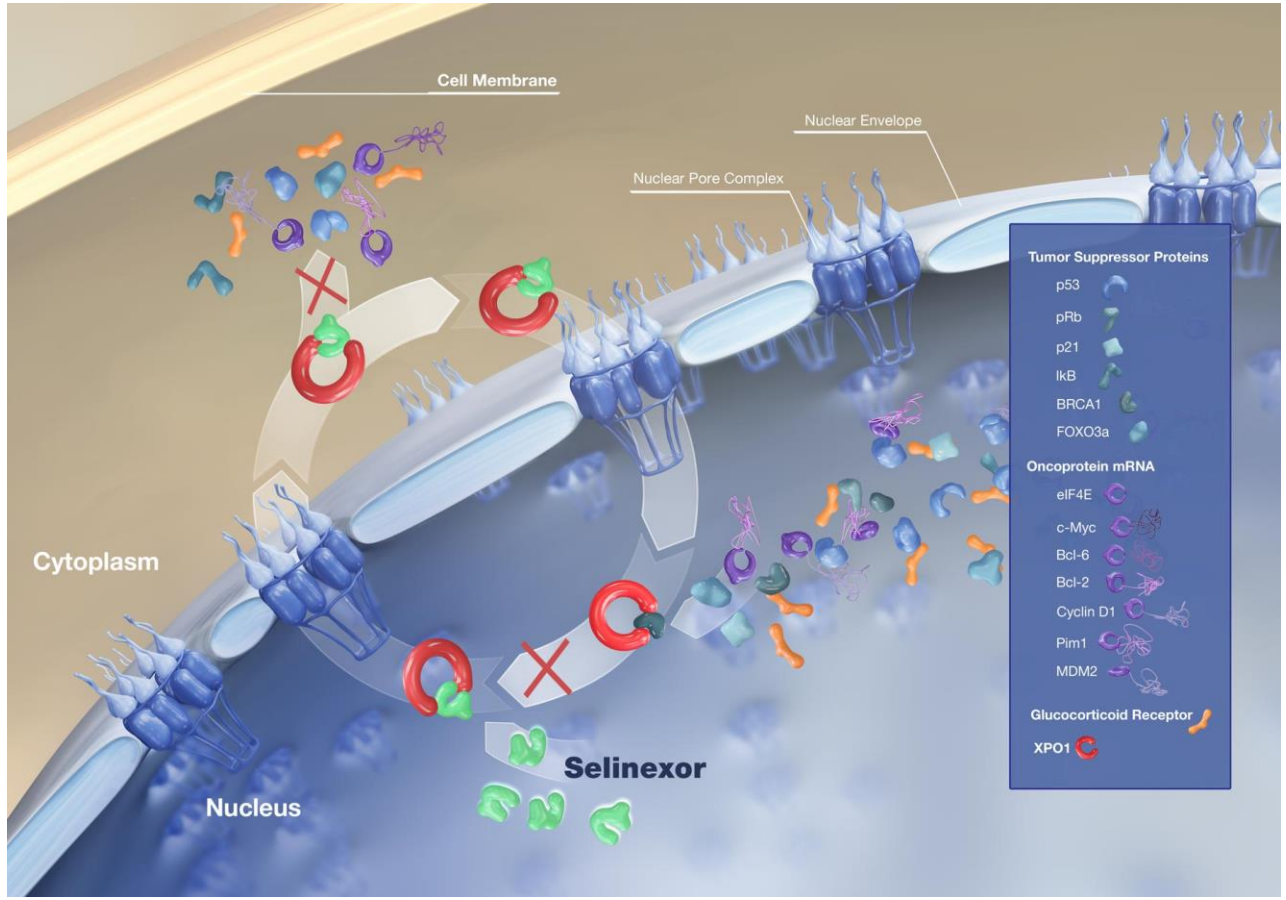
Marie Maerevoet[31] , Michael W. Schuster[1], Miguel A Canales[2,3], Jason Westin[4], Josée M Zijlstra[5], George A Follows[6], Reem Karmali[7], Nagesh Kalakonda[8], Andre H. Goy[9], Rene-Olivier Casasnovas[10], Joost Vermaat[11], Eric Van Den Neste[12], Sylvain Choquet[13], Catherine Thieblemont[14], Federica Cavallo[15], Maria de Fatima De La Cruz[16], Brian T. Hill[17], Herve Tilly[18], Shireen Kassam[19], Reda Bouabdallah[20], Ulrich Jaeger[21], Ronit Gurion[22], Paolo Caimi[23], Peter Martin[24], Andrew Davies[25], Sonali M. Smith[26], Graham P. Collins[27], Fritz Offner[28], Gilles Salles[29], Xiwen Ma[30], Kelly Corona[30], Jean-Richard Saint-Martin[30], Anita A. Joshi[30], Kamal Chamoun[30], Hongwei Wang[30], Jatin J. Shah[30], Sharon Shacham[30], Michael G Kauffman[30]

[1]Stony Brook University, Stony Brook, NY; [2]La Paz University Hospital, Madrid, Spain; [3]Hematology and Hemotherapy Unit, La Paz University Hospital-IdiPAZ, Madrid, Spain; [4]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Amsterdam UMC, Vrije Universiteit, Cancer Center, Amsterdam, Netherlands on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON /LLPC; [6]Addenbrooke's Hospital, Cambridge, United Kingdom; [7]Division of Hematology Oncology, Northwestern University, Chicago, IL; [8]University of Liverpool, Liverpool, United Kingdom; [9]Division of Lymphoma, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [10]Hématologie Clinique and INSERM 1231, CHU Dijon, Dijon, France; [11]Department of Hematology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands; [12]Cliniques universitaires Saint-Luc, Brussels, BEL; [13]Hospital Pitie Salpetriere, Paris, France; [14]APHP, Hôpital Saint-Louis, Hémato-oncologie, Université de Paris, Paris Diderot, Paris, France; [15]Department of Molecular Biotechnologies and Health Sciences, Division of Hematology, University of Torino, Torino, Italy; [16]Hospital Universitario Virgen del Rocio, Sevilla, Spain;[17]Taussig Cancer Institute, Department of Hematology and Medical Oncology, Cleveland Clinic Foundation, Cleveland, OH; [18]Centre Henri Becquerel, Rouen, France; [19]King's College Hospital, London, United Kingdom; [20]Institut Paoli-Calmettes, Marseille, France[21]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, AA, Austria; [22]Rabin Medical Center, Petah Tikva, Israel; [23]University Hospitals Cleveland Medical Center, Cleveland, OH; [24]Weill Cornell Medicine-New York Presbyterian Hospital, New York, NY; [25]Cancer Research UK Centre/Experimental Cancer Medicines Centre, University of Southampton, Southampton, United Kingdom; [26]Department of Oncology, University of Chicago, Chicago, IL; [27]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [28]University Hospital Ghent, Gent, Belgium; [29]Centre Hospitalier Lyon-Sud, Lyon, France; [30]Karyopharm Therapeutics, Newton, MA; [31]Institut Jules Bordet, Brussels, Belgium

Conflict of Interest Disclosure

There are no relationships to disclose

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export and Reactivates Tumor Suppressor Proteins

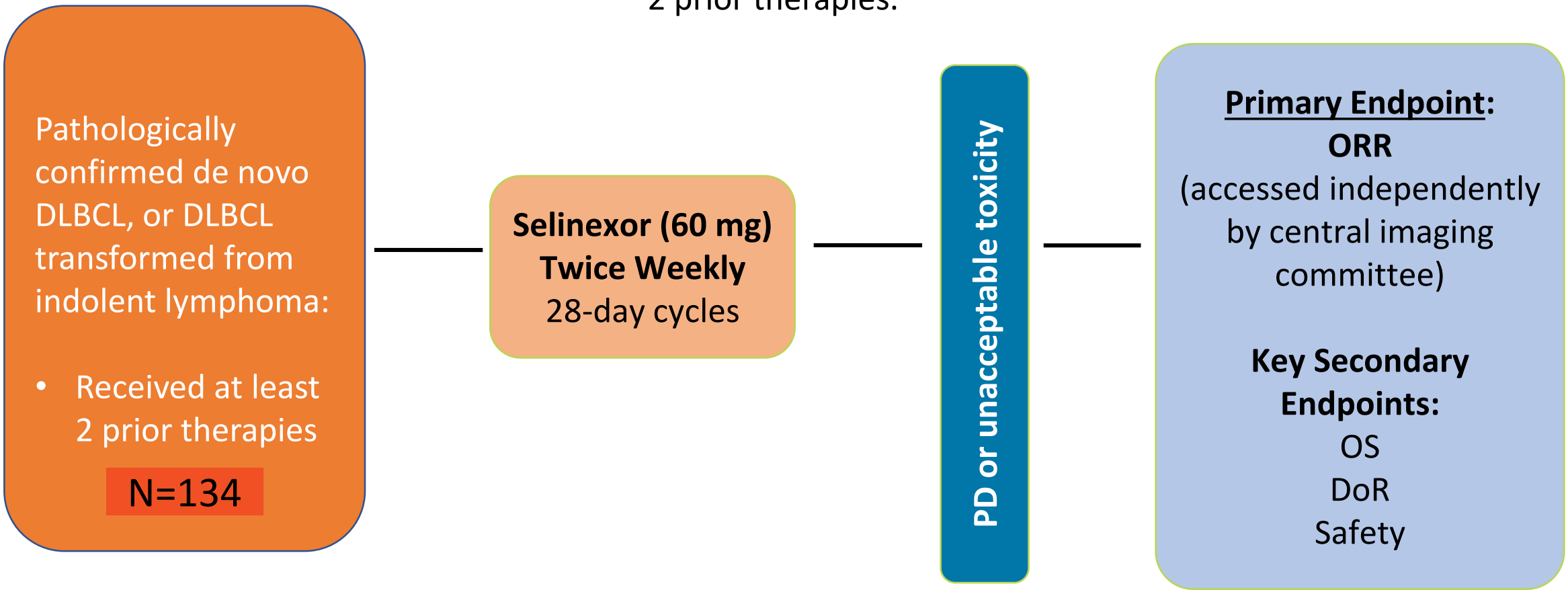


- Selinexor selectively binds and inactivates exportin 1 (XPO1)
  - Forcing the **nuclear retention and reactivation of cell cycle regulators** such as p53, FOXO, IkB, and Rb
  - **Reducing oncoproteins** known to play critical roles in NHL (c-Myc, Bcl2, Bcl6, BclXL)
  - XPO1 overexpression in DLBCL **correlates with poor prognosis**
  - Selinexor in combination with dexamethasone (Sd) has been approved by the FDA for patients with relapsed / refractory multiple myeloma.

Single agent oral Selinexor is approved by the FDA for the treatment of patients with relapsed or refractory DLBCL, de novo or transformed from follicular lymphoma after ≥2 prior therapies

SADAL Trial Design

SADAL Trial: The SADAL (Selinexor Against Diffuse Aggressive Lymphoma) study was a multi-center, open-label Phase 2b study which enrolled patients with previously treated, pathologically confirmed de novo DLBCL, or DLBCL transformed from previously diagnosed indolent lymphoma, and having received at least 2 prior therapies.



DoR = duration of response, OS = overall survival, PD = progressive disease, ORR= overall response rate.

SADAL Overall Efficacy Results

	Response per IRC [a], (n=134)	Median DOR per IRC, months (95% CI)[c] (n=39)
Overall Response Rate (ORR)[b], (95% CI)	**39 (29.0)** (22.0, 38.0)	**9.3** (4.9, NE)
Complete Response (CR), n (%)	18 (13.0)	23.0 (10.4, NE)
Partial Response (PR), n (%)	21 (15.7)	4.4 (1.9, NE)
Stable Disease (SD), n (%)	11 (8.2)	--
Progressive Disease (PD) / Not Evaluable (NE), n (%)	84 (62.7)	--

- Median time to PR or better: 8.1 weeks (range: 6.7 – 16.4)

a. Responses were adjudicated according to the Lugano 2014 Criteria (Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068. doi: 10.1200/JCO.2013.54.8800) by an Independent Radiologic Committee (IRC) and confirmed by an Independent Oncologist Reviewer. The Deauville criteria (a 5-point scale) was used to grade response using PET-CT. PET-CT results were prioritized over CT results.
b. Includes CR + PR.
c. Median follow up 11.1 months
XPOVIO® [package insert]. Cambridge, MA: Karyopharm Therapeutics, Inc.; 2020; Unpublished data.

Methods: SADAL Subset Analysis based on Age

We performed post-hoc analyses of the SADAL study to determine if there are differences in efficacy and safety among patients by age groups, defined as patients: <65 years old vs ≥65 years old.

Total Patients Enrolled	N=134
<65 years old	N=52 (39%)
≥65 years old	N=82 (61%)

Baseline and Disease Characteristics by Age Group

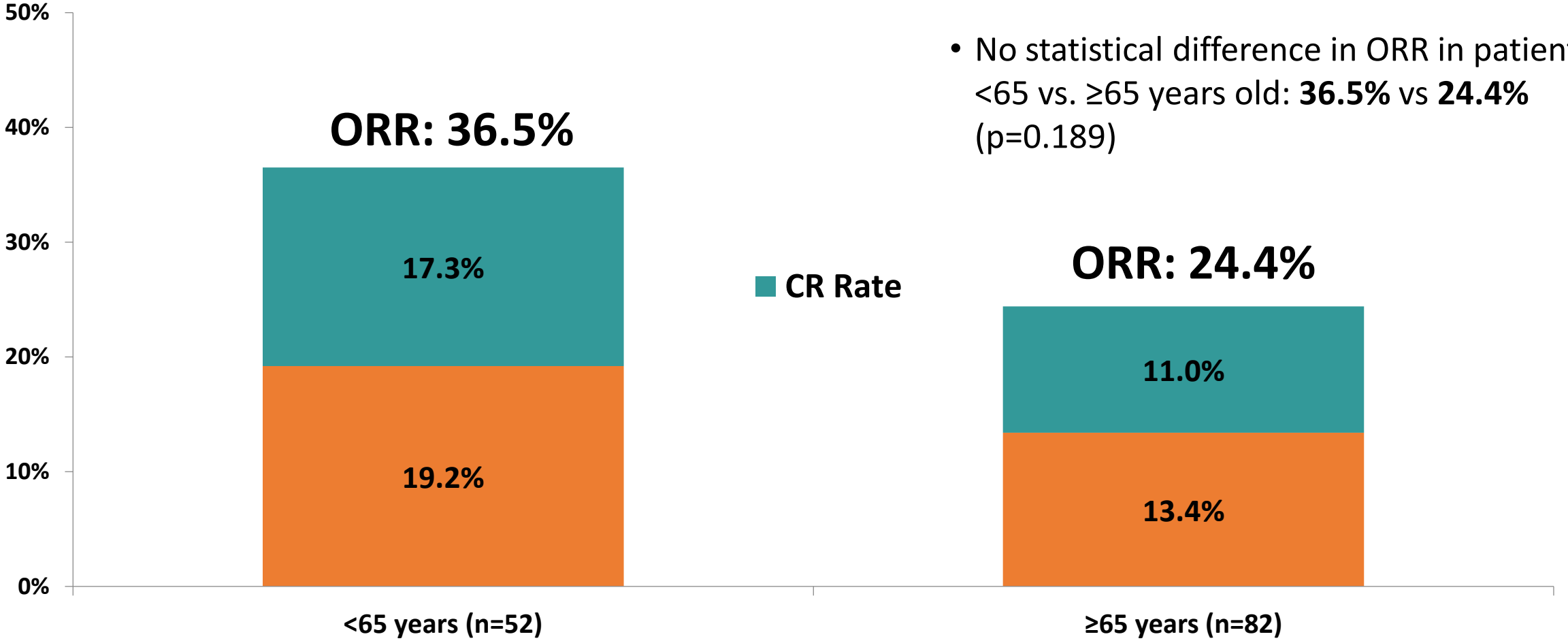
	Age <65 years (n=52)	Age ≥65 years (n=82)
Median Age, Years (range)	**57** (35, 64)	**73** (65, 91)
Age Category, n (%)		
18 – 50	**8** (15.4)	--
51 – 64	**44** (84.6)	--
65 – 74	--	**49** (59.8)
≥75	--	**33** (40.2)
Male, n (%)	**32** (61.5)	**47** (57.3)
Female, n (%)	**20** (38.5)	**35** (42.7)
DLBCL Type, n (%)		
De novo	**43** (82.7)	**60** (73.2)
Transformed	**9** (17.3)	**22** (26.8)
DLBCL Subtype, n (%)		
GCB	**28** (53.8)	**35** (42.7)
non-GCB	**21** (40.4)	**45** (54.9)
Non-Classified	**3** (5.8)	**2** (2.4)
Number of Prior Regimens, Median (range)	**2** (2-5)	**2** (2-5)
Prior ASCT, n (%)	**32** (61.5)	**31** (37.8)

Related Adverse Events, ≥10% Overall

Adverse Events, ≥10% overall	<65 years (n=52)	≥65 years (n=82)
Thrombocytopenia	31 (59.6)	41 (50.0)
Nausea	24 (46.2)	45 (54.9)
Fatigue	17 (32.7)	33 (40.2)
Decreased Appetite	18 (34.6)	28 (34.1)
Anemia	19 (36.5)	25 (30.5)
Neutropenia	17 (32.7)	24 (29.3)
Vomiting	9 (17.3)	26 (31.7)
Weight Decreased	7 (13.5)	22 (26.8)
Diarrhea	7 (13.5)	21 (25.6)
Asthenia	6 (11.5)	15 (18.3)
Constipation	7 (13.5)	7 (8.5)
Dizziness	5 (9.6)	8 (9.8)
Patients with ≥1 Serious Adverse Event	**6 (11.5)**	**22 (26.8)**

- The incidence of treatment-related AEs was comparable between both groups: The most common grade ≥3 AEs in <65 vs ≥65 year olds were thrombocytopenia (42.3% vs 39.0%), nausea (3.8% vs 7.3%), and fatigue (5.8% vs 13.4%). Treatment-related serious AEs occurred in 11.5% of patients <65 (n=6) and 26.8% ≥65 (n=22). Treatment discontinuations due to AEs occurred at a lower incidence in the <65 group compared with ≥65 (3.8% vs 11.0%).

Efficacy – ORR, DOR, OS



- No statistical difference in ORR in patients <65 vs. ≥65 years old: **36.5%** vs **24.4%** (p=0.189)

Age Group	n	DOR, median (months)	OS, median (months)
<65 Years	52	**9.7**	**13.7**
≥65 Years	82	**9.2**	**7.8**

Conclusions

- In patients with relapsed / refractory DLBCL who were **≥65 years old had similar clinical benefit to those <65 years old when treated with oral selinexor**.
  - There was no statistical difference in ORR in patients <65 vs ≥65 years old: **36.5% vs 24.4%** (p=0.189). The complete response (CR) rates were **17.3% and 11%** (p=0.431), respectively.
  - Median **DOR** was similar at **9.7 months** in the <65 compared to **9.2 months** in the ≥65 year old patients.
  - Selinexor is effective in de novo DLBCL (26.2% ORR) or transformed lymphoma patients (38.7% ORR)
- The incidence of treatment-related AEs was comparable between patients <65 and ≥65 years old

Selinexor is approved, and an active convenient oral option for patients with relapsed DLBCL including older patients