



Universiteit  
Leiden  
The Netherlands

## **Comparison of the effectiveness and safety of the oral selective inhibitor of nuclear export, selinexor, in diffuse large B cell lymphoma subtypes**

Casasnovas, R.O.; Follows, G.; Zijlstra, J.M.; Vermaat, J.S.P.; Kalakonda, N.; Choquet, S.; ...  
; Goy, A.

### **Citation**

Casasnovas, R. O., Follows, G., Zijlstra, J. M., Vermaat, J. S. P., Kalakonda, N., Choquet, S., ... Goy, A. (2022). Comparison of the effectiveness and safety of the oral selective inhibitor of nuclear export, selinexor, in diffuse large B cell lymphoma subtypes. *Clinical Lymphoma, Myeloma And Leukemia*, 22(1), 24-33. doi:10.1016/j.clml.2021.07.017

Version: Publisher's Version

License: [Licensed under Article 25fa Copyright Act/Law \(Amendment Taverne\)](#)

Downloaded from: <https://hdl.handle.net/1887/3564980>

**Note:** To cite this publication please use the final published version (if applicable).

# Comparison of the Effectiveness and Safety of the Oral Selective Inhibitor of Nuclear Export, Selinexor, in Diffuse Large B Cell Lymphoma Subtypes

Rene-Olivier Casasnovas,<sup>1</sup> George Follows,<sup>2</sup> Josee M. Zijlstra,<sup>3</sup> Joost S.P. Vermaat,<sup>4</sup> Nagesh Kalakonda,<sup>5</sup> Sylvain Choquet,<sup>6</sup> Eric Van Den Neste,<sup>7</sup> Brian Hill,<sup>8</sup> Catherine Thieblemont,<sup>9,10</sup> Federica Cavallo,<sup>11</sup> Fatima De la Cruz,<sup>12</sup> John Kuruvilla,<sup>13</sup> Nada Hamad,<sup>14</sup> Ulrich Jaeger,<sup>15</sup> Paolo F. Caimi,<sup>16</sup> Ronit Gurion,<sup>17,18</sup> Krzysztof Warzocha,<sup>19</sup> Sameer Bakhshi,<sup>20</sup> Juan-Manuel Sancho,<sup>21</sup> Michael Schuster,<sup>22</sup> Miklos Egyed,<sup>23</sup> Fritz Offner,<sup>24</sup> Theodoros P. Vassilakopoulos,<sup>25</sup> Priyanka Samal,<sup>26</sup> Matthew Ku,<sup>27</sup> Xiwen Ma,<sup>28</sup> Kamal Chamoun,<sup>28</sup> Jatin Shah,<sup>28</sup> Miguel Canales,<sup>29</sup> Marie Maerevoet,<sup>30</sup> Sharon Shacham,<sup>28</sup> Michael G. Kauffman,<sup>28</sup> Andre Goy<sup>31</sup>

## Abstract

**The phase 2b, open-label, multicenter SADAL study evaluated single agent oral selinexor, a selective inhibitor of nuclear export (SINE) compound, in patients with diffuse large B cell lymphoma (DLBCL) after  $\geq 2$  lines of systemic therapy. Similar activity was observed in GCB- and non-GCB DLBCL with a trend to higher response rates in DLBCL transformed from follicular lymphoma. Lower response rates were observed in double expressor DLBCL; higher response rates were observed in patients with baseline hemoglobin  $\geq 10$  g/dL and normal levels of C-MYC or BCL-2 expression (51%). Overall, strong single agent activity with selinexor were observed in patients with relapsed/refractory DLBCL.**

**Background:** The SADAL study evaluated oral selinexor in patients with relapsed and/or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior lines of systemic therapy. In this post-hoc analysis, we analyzed the outcomes of the SADAL study by DLBCL subtype to determine the effects of DLBCL subtypes on efficacy and tolerability of

<sup>1</sup>Hématologie Clinique and INSERM 1231, CHU Dijon Bourgogne, Dijon, France

<sup>2</sup>Addenbrooke's Hospital, Cambridge, United Kingdom

<sup>3</sup>Amsterdam University Medical Center, Vrije Universiteit, Cancer Center, Amsterdam, The Netherlands

<sup>4</sup>Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>University of Liverpool, Liverpool, United Kingdom

<sup>6</sup>Hôpital Pitié Salpêtrière, Paris, France

<sup>7</sup>Cliniques Universitaires Saint-Luc, Brussels, Belgium

<sup>8</sup>Cleveland Clinic, Cleveland, OH

<sup>9</sup>AP-HP, Hôpital Saint-Louis, Hématologie-oncologie, DMU DHI, Paris, France

<sup>10</sup>Université de Paris, Paris, France

<sup>11</sup>Department of Molecular Biotechnologies and Health Sciences, Division of Hematology, University of Turin, Turin, Italy

<sup>12</sup>Hospital Universitario Virgen del Rocío, Sevilla, Spain

<sup>13</sup>Princess Margaret Cancer Center, Toronto, Canada

<sup>14</sup>St Vincent's Hospital Sydney, Darlinghurst, NSW, Australia

<sup>15</sup>Medical University of Vienna, Vienna, Austria

<sup>16</sup>UH Seidman Cancer Center, Cleveland, OH

<sup>17</sup>Institute of Hematology, Rabin Medical Center, Petah Tikva, Israel

<sup>18</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

<sup>19</sup>Instytut Hematologii i Transfuzjologii, Warsaw, Poland

<sup>20</sup>Dr. B. R. A. Institute Rotary Cancer Hospital, New Delhi, India

<sup>21</sup>Hospital Universitari Germans Trias I Pujol, Barcelona, Spain

<sup>22</sup>Stony Brook University Hospital Cancer Center, New York, NY

<sup>23</sup>Teaching Hospital Kaposi Mór, Kaposvár, Hungary

<sup>24</sup>Ghent University Hospital, Ghent, Belgium

<sup>25</sup>Department of Haematology, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece

<sup>26</sup>Institute of Medical Sciences & SUM Hospital, Odisha, India

<sup>27</sup>St. Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia

<sup>28</sup>Karyopharm Therapeutics, Newton, MA

<sup>29</sup>Hospital Universitario La Paz, Madrid, Spain

<sup>30</sup>Institute Jules Bordet, Brussels, Belgium

<sup>31</sup>Hackensack University Medical Center, Hackensack, NJ

Submitted: Apr 20, 2021; Revised: Jul 11, 2021; Accepted: Jul 16, 2021; Epub: 22 July 2021

Address for correspondence: Rene-Olivier Casasnovas, MD, Hématologie Clinique and INSERM 1231, CHU Dijon, Dijon, France  
E-mail contact: [olivier.casasnovas@chu-dijon.fr](mailto:olivier.casasnovas@chu-dijon.fr)

selinexor. **Patients and Methods:** Data from 134 patients in SADAL were analyzed by DLBCL subtypes for overall response rate (ORR), overall survival (OS), duration of treatment response, progression-free survival, and adverse events rate. **Results:** ORR in the entire cohort was 29.1%, and similar in patients with germinal center (GCB) versus non-GCB DLBCL (31.7% vs. 24.2%,  $P = 0.45$ ); transformed DLBCL showed a trend towards higher ORR than *de novo* DLBCL: 38.7% vs. 26.2% ( $P = 0.23$ ). Despite similar prior treatment regimens and baseline characteristics, patients with DLBCL and normal C-MYC/BCL-2 protein expression levels had a significantly higher ORR (46.2% vs. 14.8%,  $P = 0.012$ ) and significantly longer OS (medians 13.7 vs. 5.1 months, hazard ratio 0.43 [95% CI, 0.23-0.77],  $P = 0.004$ ) as compared with those whose DLBCL had C-MYC and BCL-2 overexpression. Among patients who had normal expression levels of either C-MYC or BCL-2 and baseline hemoglobin levels  $\geq 10$ g/dL, ORR was 51.5% ( $n = 47$ ), with median OS of 15.5 months and median PFS of 4.6 months. Similar rates of adverse events were noted in all subgroups. **Conclusions:** Overall, single agent oral selinexor showed strong responses in patients with limited treatment alternatives regardless of germinal center B-cell type or disease origin.

*Clinical Lymphoma, Myeloma and Leukemia*, Vol. 22, No. 1, 24–33 © 2021 Elsevier Inc. All rights reserved.

**Keywords:** DLBCL subtypes, Relapsed/refractory DLBCL, Treatment response, XPO1, Salvage therapy, De novo and transformed DLBCL

## Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 30%-35% of NHL cases.<sup>1</sup> The standard first-line therapy for DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP),<sup>2-4</sup> however, 10% of patients have primary refractory disease and 30%-40% relapse.<sup>3, 5</sup> Patients with refractory or relapsed disease who are fit are usually treated with salvage chemotherapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT).<sup>3, 4</sup> However, ~50% of patients cannot undergo ASCT due to inadequate response to salvage chemotherapy, age, or other comorbidities.<sup>6</sup> Notably, over half of patients who undergo ASCT ultimately relapse.<sup>7</sup>

In 2000, Alizadeh et al<sup>8</sup> identified two main DLBCL molecular subtypes reflecting 2 distinct cells of origin: germinal center B-cell-like (GCB) and activated B cell (ABC)-like, also called non-GCB. Patients with GCB DLBCL have more favorable outcomes than those with non-GCB DLBCL when treated with standard immunochemotherapy.<sup>9, 10</sup> Alongside the classification by cell of origin, additional molecular and genetic subtypes have been identified. Double-hit lymphoma (DHL) and triple-hit lymphoma (THL), which occur in approximately 8% of patients, present with concurrent chromosomal translocations of *MYC* and *BCL-2* and/or *BCL-6* genes.<sup>1, 3</sup> These phenotypes are mainly found in patients identified with GCB DLBCL.<sup>11</sup> On the other hand, expression of *both* C-MYC and BCL-2 proteins (double expression [DE]) occurs in 20%-30% of DLBCL patients, primarily in the non-GCB subset. All of these (DHL/THL, DE) have been shown to indicate a poor prognosis with chemotherapy.<sup>12, 13</sup>

Selinexor is an oral selective inhibitor of nuclear export (SINE) compound that binds covalently to cysteine 528 in the cargo binding pocket of the nuclear exporter Exportin 1 (XPO1) and inhibits its activity.<sup>14-16</sup> This inhibition results in the accumulation of tumor suppressor proteins in the nucleus of malignant cells and blocks the translation of mRNAs of many oncogenes which drive cell proliferation, leading to cell cycle arrest and, in cells with

damaged DNA including DLBCL cells, apoptosis.<sup>14-18</sup> Selinexor in combination with low-dose dexamethasone  $\pm$  bortezomib is approved by the United States Food and Drug Administration (FDA) for adult patients with multiple myeloma who have received at least one prior therapy.<sup>19</sup> In June 2020, selinexor was granted accelerated approval by the FDA for adult patients with previously treated DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. This approval was based on the SADAL phase 2b, open-label, multicenter study<sup>20</sup> that showed an overall response rate (ORR) of 29.1% (39/134; 95% CI 21.6–37.6), with 13.4% of patients achieving a complete response and 15.7% a partial response.<sup>21</sup> In this exploratory post-hoc analysis, we analyzed the outcomes of the SADAL study by DLBCL subtype to determine the effects of DLBCL subtypes on efficacy and tolerability of selinexor. We also sought a specific subpopulation of heavily pretreated patients with DLBCL who were most likely to have a significant response (partial or complete response) on single agent oral selinexor.

## Patients and Methods

### Study design and participants

SADAL was a phase 2b, open-label, multi-center study in 59 sites in 19 countries.<sup>20</sup>

A total of 134 patients were included in the study. Detailed inclusion and exclusion criteria were previously described.<sup>20</sup> In brief, patients were included in the study if they were 18 years or older, had pathologically confirmed *de novo* DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma, an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2, progressed after 2 to 5 lines of previous therapy or were not candidates for ASCT, had measurable disease according to the 2014 Lugano criteria,<sup>22</sup> and an estimated life expectancy of 3 months. Patients whose most recent systemic anti-DLBCL therapy induced a partial response or complete response had to have at least 60 days or more elapsed since the end of that therapy. All other patients, had to have at least 98 days elapsed since the end of their most recent systemic anti-DLBCL therapy. Exclusion criteria included

# Effectiveness of selinexor in DLBCL subtypes

known central nervous system lymphoma, meningeal involvement, or creatinine clearance less than 30 mL/min.

The study was approved by the local institutional review board or independent ethics committee at each study center and all patients provided an informed consent before enrollment. The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The trial is registered with ClinicalTrials.gov, NCT02227251.

## Treatment

Oral selinexor (60 mg) was administered on days 1 and 3 of each week for a 4 week cycle until disease progression, death, or unacceptable toxicities. All patients were required to receive 8 mg of ondansetron (or equivalent) before the first dose of selinexor and continued two to three times daily, as needed. Additional supportive care was provided at the discretion of the investigator per institutional guidelines or the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.

## Assessment of disease activity

DLBCL status was assessed by positron emission tomography (PET) and computed tomography (CT) (or PET and magnetic resonance imaging [MRI]) every 8 weeks ( $\pm 1$  week). Disease activity was assessed according to the revised 2014 Lugano criteria for response assessment of lymphoma<sup>22</sup> by independent central review and separately according to investigator assessments. An independent oncologist reviewed the clinical data and confirmed the best responses, their duration and disease progression. Patients removed from study based on progressive disease confirmed by the central imaging laboratory were followed up for survival.

## Determination of DLBCL subtypes

DLBCL subtype classification was performed by Cancer Genetics Inc. (Rutherford, NJ, USA). Data on DLBCL cell of origin (GCB or non-GCB) was determined for 111 patients from fresh or archival tumor biopsy samples and analyzed by immunohistochemistry (IHC) based on the Hans<sup>23</sup> and Taly<sup>24</sup> algorithms. The cell of origin status of an additional 18 patients without a biopsy was determined according to pathology reports provided by investigators on samples collected previously. Five additional patients were not evaluable due to missing data. Therefore, data on cell of origin was available for 129 of 134 patients included in the SADAL study.

To determine DHL/THL status, fluorescent in-situ hybridization was done to detect the translocation or rearrangement status of *C-MYC* and *BCL-2* genes.

C-MYC and BCL-2 protein expression levels were determined by IHC. For this analysis, information on protein expression was available for 79 patients. The overexpression status of these marker genes was defined based on the percentage of positively stained cells by IHC staining. C-MYC overexpression was defined as more than 40% of tumor cells stained positive for C-MYC. BCL-2 overexpression was defined as more than 50% of tumor cells stained positive for BCL-2. These cutoff lines are based on the 2016 Revision of the World Health Organization Classification of Lymphoid Neoplasms.<sup>1</sup>

## Safety assessments

Safety was monitored by assessing adverse events, concomitant medications, laboratory parameters, physical examinations, vital signs, weight, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram, and ophthalmic examinations. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) at every visit.

## Outcomes

In the current analyses we describe the outcomes of patients with GCB vs. non-GCB DLBCL (as specified in the study protocol). In addition, we performed an exploratory post-hoc analysis to compare the outcomes of patients with *de novo* vs. transformed DLBCL; and DE vs. non-DE.

The primary endpoint, ORR, was defined as the proportion of patients who had either a CR or PR according to the 2014 Lugano criteria.<sup>22</sup> Additional endpoints included the duration of response (DOR), defined as the duration of time from first occurrence of CR or PR until the first date that disease progression was documented; progression-free survival (PFS), defined as the duration of time from enrolment until progression or death due to any cause; and overall survival (OS), defined as the duration of time from enrolment until death due to any cause.

## Statistical Analysis

Summary statistics were computed for each of the DLBCL subtypes. Continuous variables were summarized by number, mean, standard deviation, minimum, median, and maximum and sum, and categorical variables were summarized by frequencies and percentages. A 2 sided 95% exact confidence interval (CI) is presented for ORR. The chi-squared test was used to compare proportions between subgroups. For time-to-event variables, the Kaplan–Meier method was used for descriptive summaries. The log-rank test and Cox proportional hazards model were used for comparing DLBCL subtypes. Two proportion z-test was used to test two group proportions. SAS (version 9.4) was used for statistical analyses.

## Results

A total of 134 patients were included in the analysis. Patient baseline characteristics are shown in Table 1. The median age in all subgroups was 65 years or above. The majority had ECOG performance status 0 to 1. Approximately 30% of patients in all subgroups had prior radiotherapy. At baseline, most patients had platelet count equal to or above 150 ( $10^9/L$ ), hemoglobin equal to or above 100 g/L, and creatinine clearance equal to or above 60 mL/min.

Most patients (103/134, 76.9%) had *de novo* DLBCL. Sixty-three patients (63/134, 47.0%) had GCB and 66 patients (66/134, 49.3%) had the non-GCB subtype. One patient had DHL and another had THL and both had *de novo* DLBCL of the GCB subtype. All patients with transformed DLBCL had a history of follicular lymphoma. Seventy-eight patients with evaluable biopsies had overexpression of at least one oncoprotein: C-MYC or BCL-2 or BCL-6 (Table 2). Twenty-seven patients (20.2%) had DE DLBCL. DE constituted 15.9% (10/63) of patients with GCB

**Table 1** Baseline Demographics and Clinical Characteristics of the Study Population

Characteristic	GCB n = 63	Non-GCB n = 66	De Novo n = 103	Transformed n = 31	Doubleexpressors n = 27	Nondouble expressors n = 52
Median age, years (range) <sup>a</sup>	67.0 (44, 91)	69.5 (35, 87)	67.0 (35, 91)	69.0 (48, 82)	65.0 (47, 86)	69.5 (35, 87)
Sex n (%)						
Female	28 (44.4)	25 (37.9)	38 (36.9)	17 (54.8)	8 (29.6)	25 (48.1)
Male	35 (55.6)	41 (62.1)	65 (63.1)	14 (45.2)	19 (70.4)	27 (51.9)
Median time since DLBCL diagnosis, years (range) <sup>b</sup>	2.4 (0.1, 26.2)	2.7 (0.5, 16.2)	2.4 (0.3, 26.2)	3.0 (0.1, 15.9)	2.1 (0.5, 12.5)	3.0 (0.5, 26.2)
Median number of prior systemic treatment regimens for DLBCL (range) <sup>c</sup>	2 (2, 5)	2 (2, 5)	2 (2, 5)	2 (2, 4)	2 (2, 5)	2 (2, 4)
Refractory to the most recent systemic treatment regimen for DLBCL <sup>d</sup>	45 (71.4)	48 (72.7)	76 (73.8)	20 (64.5)	21 (77.8)	37 (71.2)
Relapsed status to the first systemic treatment regimen for DLBCL, n (%)						
Refractory or Relapse < 1 Year	30 (47.6)	37 (56.1)	57 (55.3)	14 (45.2)	14 (51.9)	24 (46.2)
Relapse ≥ 1 Year	22 (34.9)	23 (34.8)	32 (31.1)	14 (45.2)	9 (33.3)	24 (46.2)
Unknown	11 (17.5)	6 (9.1)	14 (13.6)	3 (9.7)	4 (14.8)	4 (7.7)
Prior ASCT therapy for DLBCL, n (%)	25 (39.7)	13 (19.7)	32 (31.1)	8 (25.8)	6 (22.2)	17 (32.7)
Relapse status to the last ASCT therapy for DLBCL, n/prior ASCT therapy (%) <sup>e</sup>						
Refractory or Relapse <1 Year	14/25 (56.0)	8/13 (61.5)	19/32 (59.4)	4/8 (50)	4/6 (66.7)	9/17 (52.9)
Relapse ≥ 1 Year	8/25 (32.0)	4/13 (30.8)	9/32 (28.1)	4/8 (50)	2/6 (33.3)	6/17 (35.3)
Unknown	3/25 (12.0)	1/13 (7.7)	4/32 (12.5)	0	0	2/17 (11.8)
Prior radiotherapy	20 (31.7)	21 (31.8)	33 (32.0)	9 (29.0)	10 (37.0)	18 (34.6)
ECOG performance status, n (%)						
0	25 (39.7)	27 (40.9)	42 (40.8)	15 (48.4)	14 (51.9)	24 (46.2)
1	32 (50.8)	29 (43.9)	50 (48.5)	11 (35.5)	10 (37.0)	26 (50.0)
2	6 (9.5)	9 (13.6)	10 (9.7)	5 (16.1)	2 (7.4)	2 (3.8)
3	0	1 (1.5)	1 (1.0)	0	1 (3.7)	0
Creatinine clearance (ml/min) at Baseline, n (%)						
<30	2 (3.2)	1 (1.5)	2 (1.9)	1 (3.2)	0	0
30- <60	13 (20.6)	20 (30.3)	27 (26.2)	7 (22.6)	9 (33.3)	11 (21.2)
≥60	48 (76.2)	45 (68.2)	74(71.8)	23 (74.2)	18 (66.7)	41 (78.8)

(continued on next page)

Table 1 (continued)

Characteristic	GCB n = 63	Non-GCB n = 66	De Novo n = 103	Transformed n = 31	Doubleexpressors n = 27	Nondouble expressors n = 52
Hemoglobin (g/L) at baseline, n (%)						
80- <90	1 (1.6)	0	1 (1.0)	0	0	0
90- <100	6 (9.5)	6 (9.1)	10 (9.7)	2 (6.5)	3 (11.1)	5 (9.6)
≥100	56 (88.9)	60 (90.9)	92 (89.3)	29 (93.5)	24 (88.9)	47 (90.4)
Platelet count (10 <sup>9</sup> /L) at Baseline, n (%)						
50- <100	3 (4.8)	6 (9.1)	6 (5.8)	3 (9.7)	2 (7.4)	3 (5.8)
100- <150	14 (22.2)	17 (25.8)	29 (28.2)	3 (9.7)	8 (29.6)	11 (21.2)
≥150	46 (73.0)	43 (65.2)	68 (66.0)	25 (80.6)	17 (63.0)	38 (73.1)
Lactic acid dehydrogenase > 2xULN at Baseline, n (%)	9 (14.3)	7 (10.6)	13 (12.6)	4 (12.9)	6 (22.2)	3 (5.8)
Selinexor treatment						
Median treatment with selinexor, weeks (range)	10 (1- 193)	8 (1- 183)	9 (1-193)	10 (1-58)	8 (1, 78)	15 (1, 124)
Total selinexor dose received, mg (range)	1080 (60-15960)	900 (60-12840)	900 (60-15960)	960 (120-5120)	760 (120, 5540)	1280 (60, 10320)
Median of average selinexor dose/week, mg (range)	96 (48-180)	101.5 (48-140)	101.1 (48-140)	95 (57-180)	105 (48, 135)	86.7 (48, 140)
Average selinexor dose/week, mg, mean (SD)	94.9 (26.9)	96.8 (23.1)	96.5 (23.8)	93.2 (27.6)	97.4 (23.9)	90.3 (23.7)
Dose reductions, n (%)	28 (44.4%)	33 (50.0%)	50 (48.5%)	15 (48.4%)	14 (51.9%)	32 (61.5%)
Dose interruptions, n (%)	40 (63.5%)	43 (65.2%)	64 (62.1%)	22 (71.0%)	19 (70.4%)	37 (71.2%)

Abbreviations: ASCT = autologous stem cell transplantation; ECOG = Eastern Cooperative Oncology Group performance status; GCB

<sup>a</sup> Age at first dose of study drug

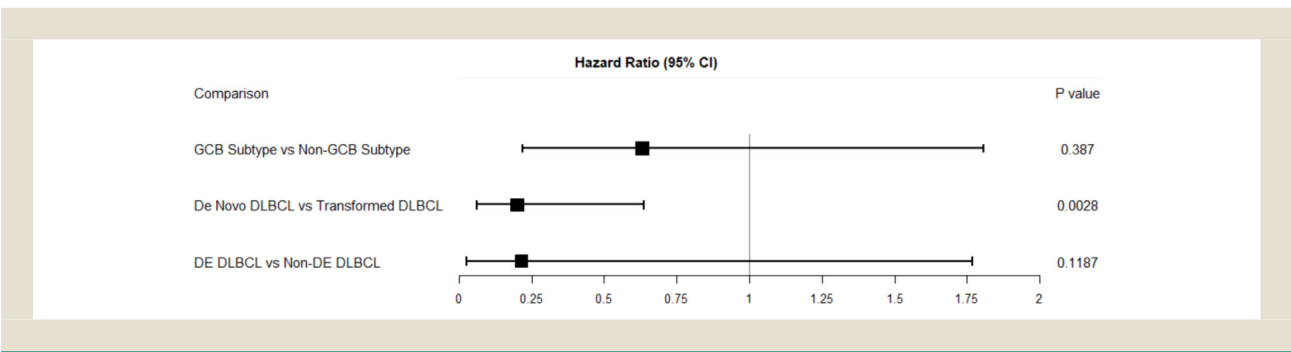
<sup>b</sup> At the time of signing the informed consent

<sup>c</sup> analysis of the number of prior systemic regimens included both systemic chemo- and targeted therapies and radiotherapies

<sup>d</sup> Defined as best response ≤SD or progressive disease <6 months (if not ASCT) or <12 months (if ASCT) from the most recent systemic treatment regimen for DLBCL

<sup>e</sup> The percentage calculated out of those who received prior ASCT

**Figure 1** Duration of response by DLBCL subtype  
 CI = confidence interval, DE = double expressors, DLBCL= diffuse large B cell lymphoma, GCB = Germinal Center B-Cell like.



**Table 2** Immunostaining Results of the Study Population

Biomarker	MYC n (%)	BCL-2 n (%)	BCL-6 n (%)
Positive	46 (34.3%)	53 (39.6%)	88 (65.7%)
Negative	50 (37.3%)	12 (8.9%)	14 (10.4%)
Unknown	38 (28.4%)	69 (51.5%)	32 (23.9%)

Note: Positive cutoff for biomarkers MYC (≥ 40%), BCL-2 (≥ 50%), BCL-6 (≥ 30%)

DLBCL, 25.8% (17/66) of patients with non-GCB DLBCL, 23.3% (24/103) of patients with *de novo* DLBCL, and 9.7% (3/31) of patients with transformed DLBCL.

**Selinexor treatment during the study**

Among all DLBCL subtypes analyzed, patients who were non-DE received the highest median total dose and had the longest median treatment with selinexor (15 weeks). Average selinexor dose/week was similar among the subtypes analyzed (Table 1).

**Efficacy and safety of selinexor by cell of origin subtype**

Comparison between GCB and non-GCB DLBCL subtypes did not show significant differences in the efficacy parameters: ORR was 31.7% for GCB and 24.2% for non-GCB DLBCL (P = 0.45), corresponding to median DORs of 23 and 9.3 months (P = 0.39), respectively (Figure 1). PFS for GCB and non-GCB were 3.6 months (95% CI, 1.9-9.0) and 2.1 months (95% CI 1.9-3.8), respectively (P = 0.105) (Figure 2), and OS for GCB and non-GCB were 9.0 months (95% CI, 5.0-15.5) and 8.3 months (95% CI 5.4-16.9), respectively (P = 0.836) (Figure 3).

The median durations of treatment were 10 (1-193) and 8 (1-193) weeks for GCB and non-GCB DLBCL, respectively. As shown in Table 3, the most common hematological treatment emergent adverse events (TEAEs) were thrombocytopenia (63.5% and 56.1% for GCB and non-GCB, respectively) and anemia (42.9% and 42.4% for GCB and non-GCB, respectively). The most common non-hematological TEAEs were nausea (49.2% and 60.61% for GCB and non-GCB, respectively) and fatigue (46.0% and 50.0% for GCB and non-GCB, respectively). Approximately 20% of patients died within 30 days following termination of treatment

most of them due to progressive disease: 11 of 13 with GCB DLBCL and 10/13 with non-GCB DLBCL; no treatment-related TEAEs resulted in death.

**Efficacy and safety of selinexor by DLBCL disease origin**

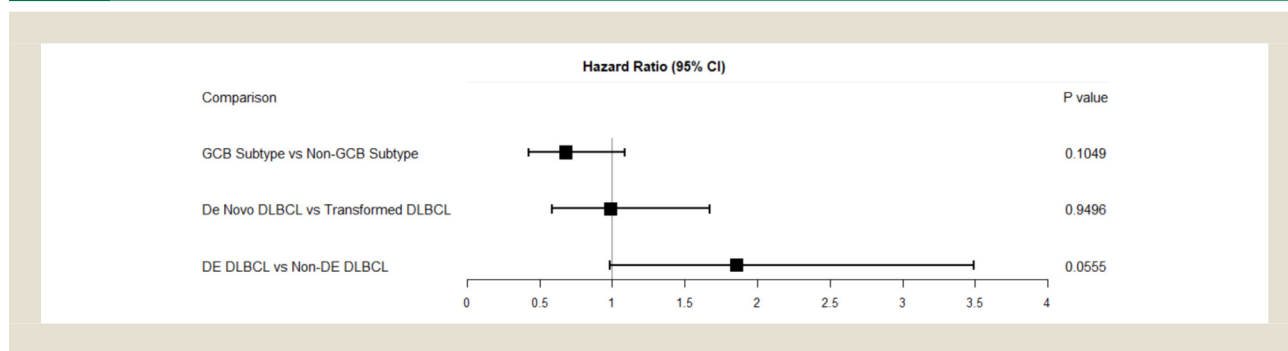
The median age and number of prior therapies of patients with *de novo* versus transformed DLBCL were 67.0 and 2 versus 69.0 and 2, respectively, making it unlikely that age or number of prior therapies significantly impacted the efficacy outcomes between these two groups. While the ORR was not statistically different in patients with *de novo* DLBCL compared to transformed DLBCL (26.2% vs. 38.7%, P = 0.234), the median DOR was significantly longer in patients with *de novo* DLBCL (23 months [95% CI 9.7-not reached] vs. 4.4 months [95% CI 2.0-9.2]) with a HR of 0.2 (95% CI 0.06-0.64, P = 0.003; Figure 1). PFS and OS were similar in both subtypes: PFS for *de novo* versus transformed DLBCL were 2.1 months (95% CI, 1.9-4.0) vs. 3.7 months (95% CI 2.1-7.0, P = 0.950; Figure 2), and OS for *de novo* vs. transformed DLBCL were 7.8 months (95% CI, 5.6-13.7) vs. 12.6 months (95% CI 5.2-not reached, P = 0.798; Figure 3). Similar to the TEAEs observed for the GCB and non-GCB subtypes, the most common hematological TEAEs for *de novo* and transformed DLBCL were thrombocytopenia (63.1% and 54.8%) and anemia (39.8% and 51.6%), while the most common non-hematological TEAEs were nausea (54.4% and 64.5%) and fatigue (47.6% and 45.2%) (Table 3).

**Efficacy and safety of selinexor according to double expression**

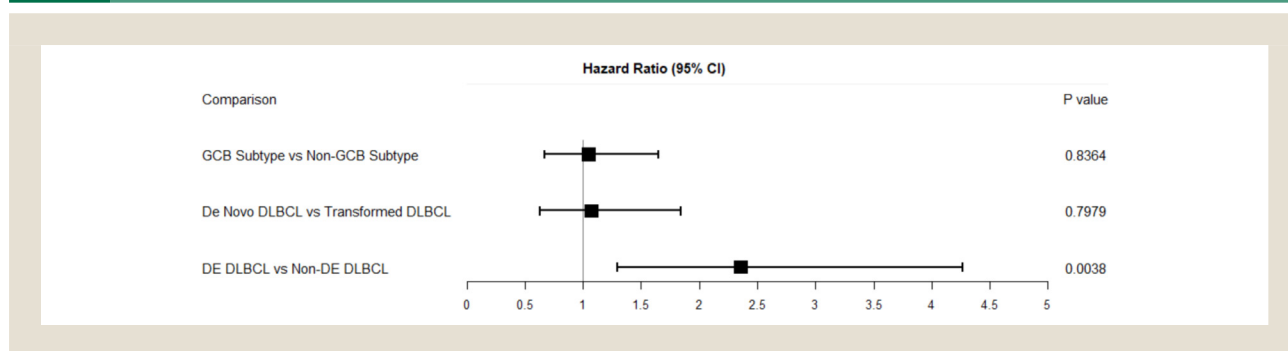
DLBCL which was not DE was associated with a significantly higher ORR than DE disease (46.2% vs.14.8%, P = 0.012), significantly longer median OS (13.7 months [95% CI, 11.1-32.3] vs. 5.1 months [95% CI, 3.0, 15.1], P = 0.004) with a HR of 0.43 (95% CI, 0.23-0.77; Figure 3), and showed a trend for longer median PFS (4.6 months [95% CI 3.7-11.1] vs. 1.8 months [95% CI 1.6-11.5], P = 0.056; Figure 2). Median DOR in patients with non-DE disease was 9.2 months (95% CI 4.8-23) but was not reached in patients with DE disease due to the small number of responders in this group (Figure 1). The most common hematological and non-hematological adverse events were similar to those of the subtypes above (Table 3).

## Effectiveness of selinexor in DLBCL subtypes

**Figure 2** Progression-free survival by DLBCL subtype  
CI = confidence interval, DE = double expressors, DLBCL= diffuse large B cell lymphoma, GCB = Germinal Center B-Cell like.



**Figure 3** Overall survival by DLBCL subtype  
CI = confidence interval, DE = double expressors, DLBCL= diffuse large B cell lymphoma, GCB = Germinal Center B-Cell like.



In order to further identify a population that may optimally respond to single agent selinexor, we explored other baseline variables and their impact on ORR (multivariate analysis could not be done due to the low numbers of cases/events). The analysis revealed that among patients who had normal levels of *either* C-MYC or BCL-2 and baseline hemoglobin levels  $\geq 10\text{g/dL}$ , ORR was 51.5% (n = 47), with median OS of 15.5 months (95% CI, 12.6-not reached) and median PFS of 4.6 months (95% CI, 3.8-11.1).

### Discussion

The SADAL study evaluated the effect of selinexor treatment in patients with relapsed/refractory (R/R) DLBCL who had received at least two previous lines of therapy and whose disease had progressed after ASCT therapy or were ineligible for ASCT.<sup>20</sup> The study showed an ORR of 29.1% (95% CI 21.6–37.6). Here we evaluated whether the efficacy and tolerability of selinexor are affected by DLBCL subtype. Our analysis showed that selinexor has similar ORR in patients with GCB and non-GCB DLBCL and in patients with *de novo* or transformed subtypes; DOR was significantly longer for *de novo* disease and this was not due to preponderance of GCB disease in the transformed group. Among patients with DE lymphoma, 37% (10/27) had GCB DLBCL and 63% (17/27) had non-GCB DLBCL. DE has been reported to be more common in non-GCB DLBCL<sup>1, 13</sup> and therefore it has been suggested that DE may mediate effects on prognosis of patients with non-GCB.

However, in the current analysis, there were no significant differences in the efficacy parameters of patients with GCB and non-GCB. Patients with DE DLBCL fared more poorly (ORR 14.8%) than all other subtypes analyzed with the shortest PFS and OS. One patient had DHL and the other had THL both of them were classified as GCB DLBCL. Analysis of safety showed similar rates of adverse events among all subgroups analyzed.

In the SADAL study, selinexor was administered as oral daily monotherapy, allowing convenient administration without the need for hospital admission. Comparison of the results of this study to other studies that reported treatment of R/R DLBCL with monotherapy show similar ORRs; however, most of these studies were in patients with less heavily pretreated disease than those enrolled in SADAL. Some of these studies also compared efficacy by lymphoma subtype. Adult patients with R/R B-cell NHL who had received at least one prior rituximab-containing regimen and were treated with tafasitamab showed an ORR of 26%;<sup>25</sup> Patients with R/R DLBCL with a previous history of ASCT who were treated with lenalidomide monotherapy had an ORR of 28%.<sup>26</sup> The ORR of single agent lenalidomide in patients with DLBCL after  $\geq 2$  prior therapies was 27.5% without difference between GCB and non-GCB subtypes.<sup>27</sup> Similarly, treatment with lenalidomide monotherapy in the observational real-world evidence RE-MIND study showed a best ORR of 34.2% in R/R DLBCL transplant-ineligible patients after 2 to 3 prior therapies.<sup>28</sup> Lenalidomide



**Table 3** Treatment Emergent Adverse Events by DLBCL Subtype

Treatment emergent adverse events	GCB n = 63	Non-GCB n = 66	De Novo n = 103	Transformed n = 31	Double expressors n = 27
<b>Thrombocytopenia</b>					
Any grade	40 (63.5)	37 (56.1)	65 (63.1)	17 (54.8)	20 (74.1)
Grade ≥3	29 (46.0)	28 (42.4)	46 (44.7)	15 (48.4)	13 (48.1)
<b>Anemia</b>	27 (42.9)	28 (42.4)	41 (39.8)	16 (51.6)	12 (44.4)
Any grade	27 (42.9)	28 (42.4)	41 (39.8)	16 (51.6)	12 (44.4)
Grade ≥3	16 (25.4)	13 (19.7)	23 (22.3)	6 (19.4)	7 (25.9)
<b>Neutropenia</b>					
Any grade	16 (25.4)	24 (36.4)	31 (30.1)	11 (35.5)	7 (25.9)
Grade ≥3	10 (15.9)	22 (33.3)	23 (22.3)	11 (35.5)	6 (22.2)
<b>Blurred Vision</b>					
Any grade	7 (11.1)	3 (4.5)	8 (7.8)	3 (9.7)	1 (3.7)
Grade ≥3	0	0	0	0	0
<b>Nausea</b>					
Any grade	31 (49.2)	40 (60.6)	56 (54.4)	20 (64.5)	15 (55.6)
Grade ≥3	6 (9.5)	2 (3.0)	5 (4.9)	3 (9.7)	1 (3.7)
<b>Diarrhea</b>					
Any grade	25 (39.7)	19 (28.8)	33 (32.0)	13 (41.9)	6 (22.2)
Grade ≥3	2 (3.2)	1 (1.5)	1 (1.0)	3 (9.7)	0
<b>Vomiting</b>					
Any grade	20 (31.7)	18 (27.3)	31 (30.1)	7 (22.6)	6 (22.2)
Grade ≥3	1 (1.6)	1 (1.5)	1 (1.0)	1 (3.2)	1 (3.7)
<b>Abdominal pain</b>					
Any grade	6 (9.5)	4 (6.1)	8 (7.8)	3 (9.7)	2 (7.4)
Grade ≥3	0	0	0	0	0
<b>Fatigue</b>					
Any grade	29 (46.0)	33 (50.0)	49 (47.6)	14 (45.2)	14 (51.9)
Grade ≥3	2 (3.2)	13 (19.7)	10 (9.7)	5 (16.1)	3 (11.1)
<b>Asthenia</b>					
Any grade	12 (19.0)	12 (18.2)	21 (20.4)	7 (22.6)	5 (18.5)
Grade ≥3	4 (6.3)	1 (1.5)	4 (3.9)	2 (6.5)	1 (3.7)
<b>Decreased Weight</b>					
Any grade	21 (33.3)	16 (24.2)	32 (31.1)	8 (25.8)	5 (18.5)
Grade ≥3	0	0	0	0	0
<b>Decreased appetite</b>					
Any grade	20 (31.7)	25 (37.9)	37 (35.9)	12 (38.7)	10 (37.0)
Grade ≥3	3 (4.8)	2 (3.0)	3 (2.9)	2 (6.5)	1 (3.7)
<b>Hyponatremia</b>					
Any grade	6 (9.5)	9 (13.6)	12 (11.7)	3 (9.7)	3 (11.1)
Grade ≥3	3 (4.8)	8 (12.1)	8 (7.8)	3 (9.7)	1 (3.7)
<b>Peripheral neuropathy</b>					
Any grade	3 (4.8)	5 (7.6)	5 (4.9)	3 (9.7)	0
Grade ≥3	0	0	0	0	0

combined with rituximab also showed an ORR of 28% in patients with R/R DLBCL.<sup>29</sup> A retrospective cohort study of 41 patients with R/R DLBCL after ≥ 1 prior therapy who were treated with ibrutinib showed an ORR of 22%;<sup>30</sup> the ORRs for GCB (n = 11) and non-GCB (n = 24) DLBCL were 18.2% and 21%, respectively (2 of 6 patients with indeterminant subtype responded). The median OS following ibrutinib monotherapy was 5.6 months for GCB and 6.3 months for non-GCB,<sup>30</sup> which is also shorter than

median OS observed for GCB and non-GCB patients in the current study (9.0 and 8.3 months, respectively). A retrospective analysis of 25 patients with R/R DLBCL DE that were treated with ibrutinib monotherapy showed an OS of 5.5 months similar to the OS of 5.1 months observed in patients with DE DLBCL treated with selinexor.<sup>31</sup> ORR for patients with R/R transformed DLBCL who were treated with ibrutinib monotherapy was 35%<sup>32</sup> compared to 38.7% in the current study. Monotherapy with loncastuximab

## Effectiveness of selinexor in DLBCL subtypes

tesirine showed an ORR of 48%, in patients with R/R DLBCL, with median PFS of 4.9 months and median OS of 9.9 months. Importantly, post hoc-analyses to further identify a population that might optimally respond to single agent selinexor showed that just over half of patients with normal expression levels of either C-MYC or BCL-2, and baseline hemoglobin levels  $\geq 10$ g/dL could be expected to respond to this treatment (ORR 51.5%). This result requires further study with prospective validation but may be useful until such data are available.

In line with the literature,<sup>33</sup> patients with DE DLBCL had a shorter PFS and OS compared to patients without those abnormalities. We could not evaluate efficacy in patients with DHL/THL because there were only 2 patients with these subtypes; neither responded. It is well established that patients with DHL or those who are DE have poor outcomes with standard chemoimmunotherapy with a worse outcome on patients with DHL than those who are DE.<sup>33–35</sup> DE and DHL are also associated with poorer outcomes after ASCT in patients with R/R DLBCL<sup>36</sup> or after allogeneic hematopoietic cell transplantation.<sup>37</sup>

Selinexor in combination with other therapies for treatment of R/R DLBCL is currently being evaluated (eg, with rituximab-gemcitabine-dexamethasone-platinum [NCT04442022], rituximab, ifosfamide, carboplatin, and etoposide [NCT02471911], Venetoclax [NCT03955783], R-CHOP [NCT03147885], and ibrutinib [NCT02303392]). It is expected that these combinations would exhibit higher activity due to synergistic effects.

This analysis is limited by the small sample size of each subgroup analyzed. Moreover, it is well documented that the correlation between immunohistochemical characterization of DLBCL using the Hans or other algorithm as compared with the subtype determined by gene expression profiling (GEP) is imperfect, so that the outcomes between GCB and non-GCB subtypes reported here may not hold if GEP were used.<sup>38–40</sup> Analyses of larger cohorts of DLBCL patients with these phenotypes and the incorporation of GEP, as well as pre-specification of the non-DE – hemoglobin  $\geq 10$  g/dL cohort will enable to confirm the efficacy of selinexor in these patient subpopulations.

Despite the importance of molecular classification of DLBCL for prognosis and personalization of therapy,<sup>41</sup> it should be remembered that at present these heavily pre-treated DLBCL patients, for whom transplant or chimeric antigen receptor T cell therapy is not an option, have limited alternatives for advanced-line treatment. Therefore, with its ease of administration including at-home dosing, clear monitoring requirements and no maximal duration of therapy, oral selinexor can be a convenient and tolerable therapy for patients with previously treated DLBCL, particularly those whose tumors do not overexpress *both* C-MYC and BCL-2/6.

### Conclusion

Single agent oral selinexor showed strong responses in previously treated DLBCL patients with limited treatment alternatives regardless of germinal center B-cell type or disease origin. Combination therapies to further increase the efficacy of selinexor are currently under investigation.

### Clinical Practice Points

- DLBCL can be classified into several subtypes by cell of origin (germinal center B-cell-like [GCB] versus non-GCB), by *de novo* disease versus transformed disease and by molecular phenotypes, which include concurrent chromosomal translocations of *MYC* and *BCL-2* and/or *BCL-6* genes (double-hit/triple-hit lymphomas), and co-overexpression of *MYC* and *BCL-2* proteins (double expressors).
- Selinexor is an oral selective inhibitor of nuclear export (SINE) that was granted accelerated approval by the FDA for adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.
- Selinexor administered as a single agent showed similar objective response rates in patients with GCB and non-GCB subtypes as well as in *de novo* versus transformed DLBCL.
- Selinexor is an effective treatment for previously treated DLBCL patients with limited treatment alternatives regardless of germinal center B-cell type or disease origin.

### Funding

Karyopharm Therapeutics was the sponsor of this study and was responsible for study design, the collection of data, analysis of data, interpretation of data, writing of the report, and the decision to submit the paper for publication. The corresponding author had full access to all data and had the final responsibility for the decision to submit for publication with the agreement of all other authors.

### Acknowledgments

Medical writing support was funded by Karyopharm Therapeutics Inc. and provided by Sharon Furman-Assaf, PhD, under close direction of the authors.

### Disclosures

R-O.C. reports advisory boards for Roche, Takeda, Bristol-Myers Squibb, Amgen, Gilead, Merck, Abbvie, and research grants from Roche and Gilead outside the submitted work. G.F. reports advisory boards/lecturing for Karyopharm, Roche, Abbvie, Janssen, and AstraZeneca. C.T. reports advisory boards for Novartis, Kite Pharma, Roche, Bristol-Myers Squibb, Amgen, Gilead, Merck, Abbvie and Incyte. J.K. reports research funding from Janssen, Roche, and AstraZeneca; honoraria from Amgen, Antengene, AstraZeneca, Bristol-Myers Squibb, Gilead, Incyte, Janssen, Karyopharm, Merck, Novartis, Pfizer, Roche, Seattle Genetics, and TG Therapeutics; consulting for Abbvie, Bristol-Myers Squibb, Gilead, Karyopharm, Merck, Roche, and Seattle Genetics; and serving on a data safety and monitoring board for Karyopharm. N.D. reports advisory boards for Novartis, Gilead, Roche, Janssen, CSL, and Antegen. U.J. reports honoraria for advisory boards for Karyopharm. P.F.C. reports research funding from ADC Therapeutics; grants from Genentech; consulting from ADC Therapeutics, Kite Pharma, Verastem Oncology, Seattle Genetics, Amgen and TG Therapeutics; and speaker's bureau from Celgene. R.G. reports consulting for Roche, Jansen, Takeda, Gilead, Medison, Novartis and Neopharm. M.S. reports personal fees from Karyopharm during the conduct of the study, and personal fees from Amgen, Abbvie,

Gilead, Takeda, Celgene, Pharmacyclics, Astellas, Verastem, Merck, Novartis, Genentech, and Seattle Genetics, outside the submitted work. M.C. reports speaking for Amgen, Janssen, Novartis, Roche, Sandoz, and Takeda; advisory boards/consulting for Bristol-Myers Squibb/Celgene, Gilead/Kite Pharma, iQone, Janssen, Karyopharm, Novartis, Roche, and Sandoz; CME support, travel and accommodation from Gilead/Kite Pharma, Janssen, Novartis, Roche, and Sandoz. X.M., K.C. J.S. and M.G.K. are employees and stockholders of Karyopharm. SS reports being employed by and owning stock in Karyopharm Therapeutics, holding patents (8999996, 9079865, 9714226, PCT/US12/048319, and 1574957) on hydrazide-containing nuclear transport modulators and uses, and holding pending patents (PCT/US12/048319, 499/2012, PI20102724, and 2012000928) on hydrazide-containing nuclear transport modulators and uses.

All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390.
2. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood*. 2015;125:22–32.
3. Sarkozy C, Sehn LH. Management of relapsed/refractory DLBCL. *Best Pract Res Clin Haematol*. 2018;31:209–216.
4. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5):v116–v125.
5. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010;116:2040–2045.
6. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184–4190.
7. Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. *Br J Haematol*. 2018;182:633–643.
8. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000;403:503–511.
9. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:1937–1947.
10. Fu K, Weisenburger DD, Choi WW, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. *J Clin Oncol*. 2008;26:4587–4594.
11. Scott DW, King RL, Staiger AM, et al. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. *Blood*. 2018;131:2060–2064.
12. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: Definition and treatment. *Cancer*. 2018;124:4622–4632.
13. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2021;384:842–858.
14. Turner JG, Dawson J, Emmons MF, et al. CRM1 Inhibition Sensitizes Drug Resistant Human Myeloma Cells to Topoisomerase II and Proteasome Inhibitors both In Vitro and Ex Vivo. *J Cancer*. 2013;4:614–625.
15. Schmidt J, Braggio E, Kortuem KM, et al. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. *Leukemia*. 2013;27:2357–2365.
16. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. *Leukemia*. 2014;28:155–165.
17. Turner JG, Marchion DC, Dawson JL, et al. Human multiple myeloma cells are sensitized to topoisomerase II inhibitors by CRM1 inhibition. *Cancer Res*. 2009;69:6899–6905.
18. Gandhi UH, Senapedis W, Baloglu E, et al. Clinical Implications of Targeting XPO1-mediated Nuclear Export in Multiple Myeloma. *Clin Lymphoma Myeloma Leuk*. 2018;18:335–345.
19. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *The Lancet*. 2020;396:1563–1573.
20. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. *Lancet Haematol*. 2020;7:e511–e522.
21. Maerevoet M, Zijlstra JM, Follows G, et al. Survival among patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) treated with single agent oral selinexor in the SADAL study. *European Hematology Association (EHA) Congress Hemasphere*. 2020;4(S1):591.
22. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068.
23. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103:275–282.
24. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. *J Clin Oncol*. 2011;29:200–207.
25. Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2018;29:1266–1272.
26. Vose JM, Habermann TM, Czuczman MS, et al. Single-agent lenalidomide is active in patients with relapsed or refractory aggressive non-Hodgkin lymphoma who received prior stem cell transplantation. *Br J Haematol*. 2013;162:639–647.
27. Czuczman MS, Trnny M, Davies A, et al. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *Clin Cancer Res*. 2017;23:4127–4137.
28. Rodgers T, Luigi Zinzani P, Marino D, et al. ABCL-135: RE-MIND: A Comparison of Tafasitamab (MOR208) + Lenalidomide (L-MIND) Versus Lenalidomide Monotherapy (Real-World Data) in Transplant-Ineligible Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma. *Clinical Lymphoma Myeloma and Leukemia*. 2020;20:S265–S266.
29. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. *Leukemia*. 2013;27:1902–1909.
30. Winter AM, Landsburg DJ, Mato AR, et al. A multi-institutional outcomes analysis of patients with relapsed or refractory DLBCL treated with ibrutinib. *Blood*. 2017;130:1676–1679.
31. Landsburg DJ, Hughes ME, Koike A, et al. Outcomes of patients with relapsed/refractory double-expressor B-cell lymphoma treated with ibrutinib monotherapy. *Blood Adv*. 2019;3:132–135.
32. Graf SA, Cassidy RD, Morris K, et al. Ibrutinib Monotherapy in Relapsed or Refractory, Transformed Diffuse Large B-cell Lymphoma. *Clin Lymphoma Myeloma Leuk*. 2021;21(3):176–181.
33. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood*. 2013;121:4021–4031 quiz 4250.
34. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012;30:3452–3459.
35. Mehta A, Verma A, Gupta G, et al. Double Hit and Double Expressor Diffuse Large B Cell Lymphoma Subtypes: Discrete Subtypes and Major Predictors of Overall Survival. *Indian J Hematol Blood Transfus*. 2020;36:627–634.
36. Herrera AF, Mei M, Low L, et al. Relapsed or Refractory Double-Expressor and Double-Hit Lymphomas Have Inferior Progression-Free Survival After Autologous Stem-Cell Transplantation. *J Clin Oncol*. 2017;35:24–31.
37. Kawashima I, Inamoto Y, Maeshima AM, et al. Double-Expressor Lymphoma Is Associated with Poor Outcomes after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2018;24:294–300.
38. Yan W-H, Jiang X-N, Wang W-G, et al. Cell-of-Origin Subtyping of Diffuse Large B-Cell Lymphoma by Using a qPCR-based. *Gene Expression Assay on Formalin-Fixed Paraffin-Embedded Tissues*. *Front Oncol*. 2020 Jun 5;10:1–10. doi:10.14694/EdBook\_AM.2015.35.e449.
39. Saad AG, Grada Z, Bishop B, et al. nCounter NanoString Assay Shows Variable Concordance With Immunohistochemistry-based Algorithms in Classifying Cases of Diffuse Large B-Cell Lymphoma According to the Cell-of-Origin. *Appl Immunohistochem Mol Morphol*. 2019;27:644–648.
40. Yoon N, Ahn S, Yong Yoo H, et al. Cell-of-origin of diffuse large B-cell lymphomas determined by the Lymph2Cx assay: better prognostic indicator than Hans algorithm. *Oncotarget*. 2017;8:22014–22022.
41. Nowakowski GS, Czuczman MS. ABC, GCB, and Double-Hit Diffuse Large B-Cell Lymphoma: Does Subtype Make a Difference in Therapy Selection? *Ann Soc Clin Oncol Educ Book*. 2015:e449–e457.