# Effect of prior therapy and disease refractoriness on the efficacy and safety of oral selinexor in patients with diffuse large B-cell lymphoma (DLBCL) a post-hoc analysis of the SADAL study

Schuster, M.; Zijlstra, J.; Casasnovas, R.O.; Vermaat, J.S.P.; Kalakonda, N.; Goy, A.; ... ; Maerevoet, M.

# Effect of Prior Therapy and Disease Refractoriness on the Efficacy and Safety of Oral Selinexor in Patients with Diffuse Large B-cell Lymphoma (DLBCL): A Post-hoc Analysis of the SADAL Study

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

## Abstract

**Patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL) have a poor prognosis and a median overall survival of less than 6 months. Outcomes and responses were evaluated in 134 patients with DLBCL administered selinexor. Our findings demonstrate that selinexor treatment in DLBCL patients can safely induce durable responses and improve outcomes regardless of prior treatments and refractory status.**

**Background:** Despite a number of treatment options, patients with diffuse large B-cell lymphoma (DLBCL) whose disease has become refractory to treatment have a poor prognosis. Selinexor is a novel, oral drug that is approved to treat patients with relapsed/refractory DLBCL. In this post hoc analysis of the SADAL study, a multinational, open-label study, we evaluated subpopulations to determine if response to single agent selinexor is impacted by number of lines of prior treatment, autologous stem cell transplant (ASCT), response to first and most recent therapies, and time to progressive disease.**Patients:** Patients (n = 134) with DLBCL after 2-5 prior therapies were enrolled in SADAL and received 60mg selinexor twice weekly. **Results:** The median overall survival was 9.0 months and median progression free survival was 2.6 months. Patients who had the best overall response rate (ORR) and disease control rate were those who had prior ASCT (42.5% and 50.0%) or responded to last line of therapy (35.9% and 43.5%). Patients with primary refractory DLBCL also showed responses (ORR 21.8%). Adverse events between subgroups were similar to the overall study population, the most common being thrombocytopenia (29.1%), fatigue (7.5%), and nausea (6.0%). **Conclusion:**

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[1]Stony Brook University Hospital Cancer Center, Stony Brook, NY
[2]Amsterdam UMC, Vrije Universiteit, Cancer Center, Amsterdam, Netherlands
[3]Hématologie Clinique and INSERM 1231, Dijon, France
[4]LUMC, Leiden, Netherlands
[5]University of Liverpool, Liverpool, United Kingdom
[6]Hackensack University Medical Center, Hackensack, NJ, United States
[7]Hôpital Pitié Salpêtrière, Paris, France
[8]Cliniques Universitaires Saint-Luc, Brussels, Belgium
[9]Cleveland Clinic, Cleveland, OH, United States
[10]APHP, Saint-Louis Hospital, Hemato-oncology, Paris, France & Diderot University, Paris, France
[11]University of Torino, Turin, Italy
[12]Hospital Universitario Virgen del Rocio, Sevilla, Spain
[13]Princess Margaret Cancer Centre, Toronto, Canada
[14]St. Vincent's Hospital Sydney, Darlinghurst, Australia
[15]Medical University of Vienna, Vienna, Austria
[16]UH Seidman Cancer Center, Cleveland, OH, United States
[17]Rabin MC, Petah Tiqwa, Israel
[18]Instytut Hematologii i Transfuzjologii, Warszawa, Poland
[19]Dr. B. R. A. Institute Rotary Cancer Hospital, New Delhi, India
[20]Hospital Universitari Germans Trias I Pujol, Barcelona, Spain
[21]Addenbrooke's Hospital, Cambridge, United Kingdom
[22]Teaching Hospital Mór Kaposi, Kaposvár, Hungary
[23]UZ Gent, Gent, Belgium
[24]Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece
[25]Institute of Medical Sciences & SUM Hospital, Odisha, India
[26]St.Vincent's Hospital Melbourne, Fitzroy, Australia
[27]Karyopharm Therapeutics, Newton, MA, United States
[28]Hospital Universitario La Paz, Madrid, Spain
[29]Institut Jules Bordet, Brussels, Belgium

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Address for correspondence: Michael Schuster, Stony Brook University Hospital Cancer Center, 3 Edmund D. Pellegrino Rd., Stony Brook, NY 11794
E-mail contact: Michael.Schuster@stonybrookmedicine.edu

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Regardless of prior therapy and disease refractory status, selinexor treatment demonstrated results consistent with its novel mechanism of action and lack of cross-resistance. Thus, single agent oral selinexor can induce deep, durable, and tolerable responses in patients with DLBCL who have recurrent disease after several chemoimmunotherapy combination regimens.

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## Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of Non-Hodgkin lymphoma (NHL) that has multiple distinct molecular subtypes.[1–3] Due to the molecular heterogeneity of DLBCL, it is difficult to identify effective treatment regimens. Standard first line of treatment for DLBCL typically consists of an anti-CD20 monoclonal antibody plus anthracycline-based chemotherapy, typically administered as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone); this induces long term remissions in 50%-70%.[4–9] Patients who relapse after, or never reach, a complete response (CR) generally receive salvage regimens consisting of different chemotherapy combinations. A subset of patients, typically younger and without significant medical comorbidities, will be eligible for intensive combination chemotherapy approaches, including salvage chemotherapy and autologous stem cell transplant (ASCT), and chimeric antigen receptor (CAR) T cell therapy; ~50% of these patients achieve at least a partial response (PR). Despite the availability of these treatments in this subset of patients, the majority of patients will experience disease progression.[10–13] However, CAR-T cell therapy, which is approved for use as a third line or later treatment in both the US and Europe, has challenges including lack of effective bridging therapies (although there may be a potential role for polatuzumab vedotin),[14] toxicity, and limited patient access due to high costs and patients' comorbidities.[15–18] Less intensive (palliative) chemotherapy[19] and/or novel agents are offered to patients who are unlikely to tolerate the intensive regimens. Patients with primary refractory DLBCL, defined as those who progress within 6 months of their initial immunochemotherapy, have especially poor outcomes.[12,20,21] Similarly, patients whose disease relapses after second line therapy, including those who relapse after ASCT (or CAR-T) therapy, have a very poor prognosis.

Exportin-1 (XPO1) is the only known transporter of the major tumor suppressor proteins (TSPs) and is overexpressed in DLBCL, correlating with poor prognosis.[22] XPO1-mediated nuclear export of TSPs inactivates their tumor suppressor function (independent of mutations), leading to unrestrained cell growth and accumulation of genomic mutations that perpetuate the neoplastic phenotype.[23] Selinexor is an oral, small-molecule selective inhibitor of XPO1-mediated nuclear export (SINE) compound.[24] Inhibition of XPO1 forces the nuclear retention and functional activation of TSPs (eg, p53, p21, I$\kappa$B, and FOXO), reductions in several oncoproteins (eg, c-Myc, Bcl-xL, cyclins), cell cycle arrest, and apoptosis of cancer cells.[24–26] In 2019, the FDA approved selinexor in combination with low dose dexamethasone for use in patients with relapsed/refractory (RR) multiple myeloma (MM),[27] and in 2020, selinexor was approved as a single agent to treat RR DLBCL, including transformation from follicular lymphoma.[28] Selinexor was also approved in 2020 for MM, after at least one line of therapy.[29]

In a phase 1 clinical trial for patients with RR DLBCL, single agent selinexor resulted in an overall response rate (ORR) of 32%, with complete response (CR) in 9.3% of patients.[30] In the phase 2 SADAL study, in 134 patients with RR DLBCL after 2-5 lines of therapy, single agent oral selinexor induced an ORR of 29.1%, a CR rate of 13.4%, a median duration of response (DOR) of 9.3 months, and a median OS of 9 months; the median OS of responders (≥PR) was not reached.[28] Given the novel mechanism of selinexor and its activity as a single agent, it is important to evaluate its effects based on number, type, and response to prior therapies. Here, we analyzed subpopulations from the SADAL study to determine if there is a patient group that might optimally benefit from selinexor based on number of lines of treatment, ASCT status, response to first and most recent therapies, as well as time to progressive disease.

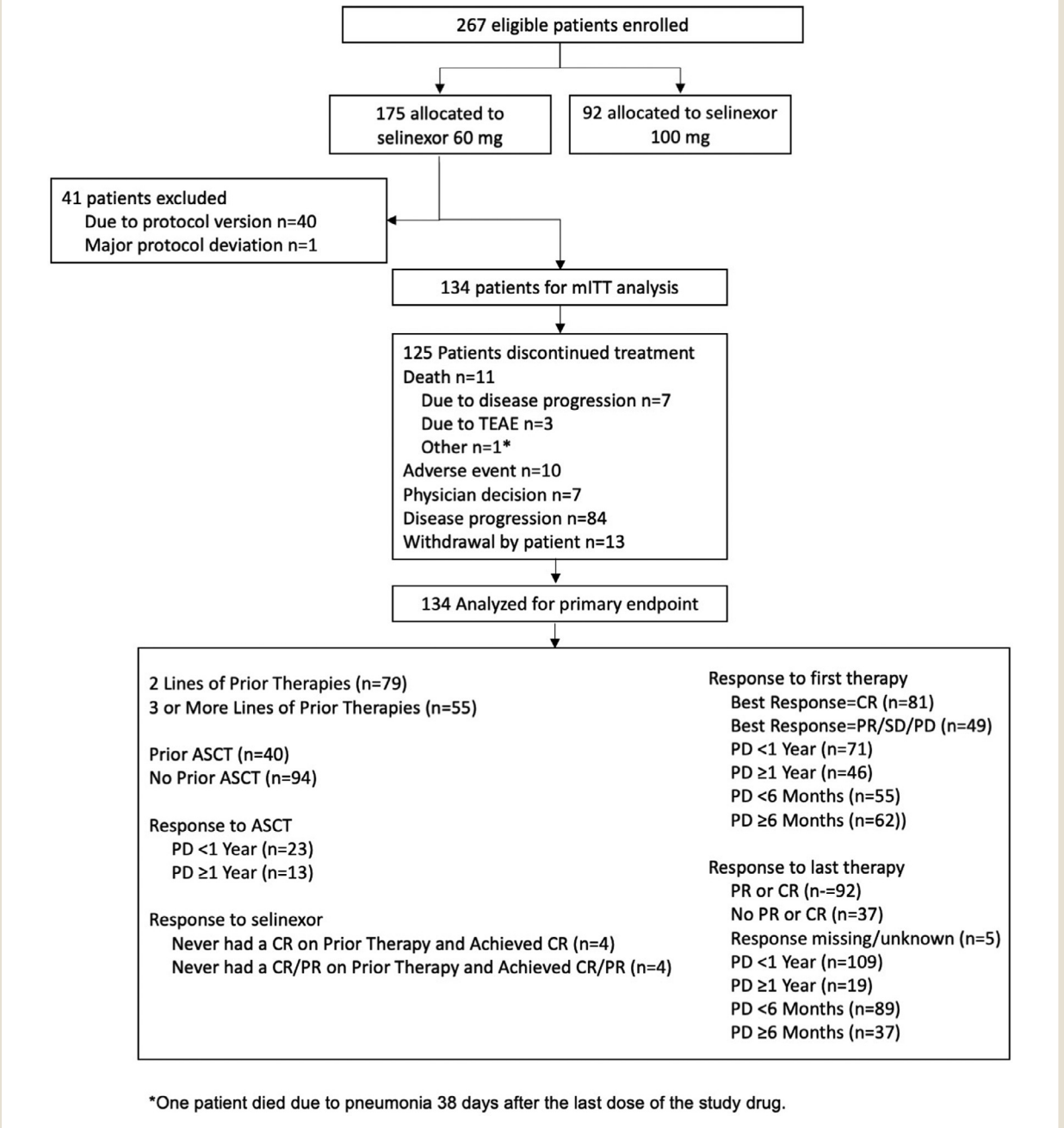
## Patients and Methods

### *Study Design and Patients*

The SADAL study has been previously described.[28] Briefly, patients were treated with the recommended monotherapy dose of 60mg selinexor orally on Days 1 and 3 each week. Patients eligible for the study were 18 years of age or older that had an Eastern Cooperative Oncology Group (ECOG) performance status between 0-2, with platelet counts over 75,000/$\mu$L, pathologically confirmed de novo or transformed RR DLBCL, and were not candidates for ASCT. Eligible patients must have received a minimum of two prior systemic therapies and no more than five in total, of which at least one included a course of anti-CD20 immunotherapy (eg, rituximab), and one course of anthracycline-based chemotherapy. Prior to enrollment, 60 days must have elapsed from the most recent systemic anti-DLBCL therapy for patients with therapy that induced CR or PR, and a minimum of 14 weeks must have elapsed for all other patients. Key outcomes included the overall response rate (ORR), duration of response (DOR), and safety assessments. ORR was defined as a PR or a CR according to the Lugano Classification; all responses were based on an independent radiological review. The data reported in the current analysis are based on a later cutoff date (August 1, 2019) than previously published.[28]

The study was approved and performed in accordance with the International Conference on Harmonization, the Guidelines for Good Clinical Practice, appropriate regulatory requirements, and with approval of institutional review boards at individual enrolling

**Figure 1** CONSORT Diagram. *One patient died due to pneumonia 38 days after the last dose of the study drug. Abbreviations: mg = milligram; TEAE = treatment-emergent adverse event; mITT = modified intention-to-treat; ASCT = autologous stem cell transplant; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.




institutions. All patients provided written informed consent before study start.

### *Statistical Analysis*

*Post hoc* statistical analyses were performed to compare patients from the following subgroups: number of prior therapies, the point at which patients responded to their: last therapy (< 1 year vs ≥ 1 year; <6 months vs ≥ 6 months), first therapy (primary refractory < 6 months vs ≥ 6 months), and to ASCT (< 1 year vs ≥1 year). Subgroups of patients who never achieved a CR or PR on prior therapy and achieved CR/PR on selinexor were also analyzed. Primary refractory disease was defined as progression within 6 months of frontline therapy, and refractory disease was defined as progression within 6 months of last therapy. For categori-

cal variables, summary tabulations of the number and percentage of patients within each category of the parameter is presented. Two-sided 95% exact confidence interval (CI) is presented for ORR. Chi-squared test with a two-sided *P* value was used to compare ORR between subgroups. A *P* value of $< .05$ was considered statistically significant. For time-to-event variables, the Kaplan–Meier method was used for descriptive summaries. Log-rank test was used to compare survival distributions between subgroups.

## Results

### *Patients*

A total of 134 patients were enrolled in the SADAL study (Figure 1). Amongst these, the number of patients with two prior lines of therapy was 79; 55 patients had ≥3 prior lines of therapy. Forty patients had undergone ASCT. There were 92 patients who had a PR or CR to their most recent systemic therapy. 37 patients had progressive disease (PD) > 6 months after their last line of treatment, including 19 patients with PD ≥1 year after their last line of treatment. In their first line of treatment, 81 patients achieved CR and 49 had a PR or did not respond. Sixty-two patients had PD after 6 months while 55 had PD within 6 months. In patients who received ASCT, 23 had PD within one year following treatment, 13 had PD ≥ 1 year, and 4 had unknown PD timing. In general, demographics between groups and their baseline characteristics were balanced among all subgroups (**Table 1** ).

### *Efficacy*

*Response According to Prior Therapy.* The ORRs with selinexor for patients who had 2 lines of treatment versus ≥ 3 lines were 27.8% and 30.9% ($P = .849$), respectively. In patients who had undergone ASCT, the ORR was 42.5%, significantly greater than those had not undergone ASCT at 23.4% ($P = .044$). Notably, of the 4 patients who never had a CR on any prior therapy, all achieved CR on selinexor. Four patients who never responded to any prior therapy achieved CR (n = 2) or PR (n = 2) on selinexor (Table 2).

*Response According to Last Prior Therapy.* Higher ORR was achieved in patients who had either PR or CR to their last line of therapy versus those who did not have a PR or CR in their last line of therapy: 35.9% versus 16.2% ($P = .047$). Similar, non-significant differences in ORR occurred in patients who had PD within 6 months of their last therapy (24.7%) compared to those patients who experienced PD in 6 months or more following last therapy (40.5%, $P = .119$, Table 2).

*Response in Patients with Primary Refractory Disease.* Patients who achieved a CR on their first line of therapy compared those who did not (PR/SD/PD) experienced similar ORR (28.4% vs. 30.6%, $P = .944$). Those patients who progressed within 6 months of their first line therapy (ie, had primary refractory disease) had a statistically similar ORR to those who progressed ≥ 6 months (21.8% vs. 37.1%, $P = .110$). Patients who experienced PD within 1 year of ASCT had an ORR of 52.5% compared to 30.8% in those with PD after one year or more ($P = .372$) (Table 2).

*Safety.* Similar to the overall population, the 4 most common treatment-emergent adverse events (TEAEs) across all of the subgroups were thrombocytopenia, nausea, fatigue, and anemia (**Table 3** ). These TEAEs were well-managed by dose reduction in conjunction with supportive care. No deaths due to TEAEs were reported to be related to selinexor.

*Safety According to Prior Therapies.* The tolerability of selinexor in the subgroups based on number of prior therapies was similar to those observed in the overall study population: Grade ≥ 3 TEAEs (mainly cytopenias) and SAEs occurring in 79.7% and 48.1% of patients with 2 prior lines and 81.8% and 45.5% of those with ≥ 3 prior lines, respectively. Patients who had prior ASCT had slightly higher grade 3 or greater TEAEs (87.5%) compared to those with no prior ASCT (77.7%), whereas the rate of SAEs were 47.5% and 46.8%. Dose modifications occurred more frequently in patients who had prior ASCT (85.0%) compared to those who did not (63.8%) while TEAEs leading to discontinuation was 20.0% and 16.0% in patients with and without prior ASCT, respectively. Deaths occurred in 2.5% of patients with prior ASCT and 4.3% of those without.

*Safety in Patients with Primary Refractory Disease.* With respect to timing of PD, grade 3 or greater TEAEs were similar in patients who had PD < 6 months (83.6%) or PD ≥ 6 months (85.5%) after the first line of therapy. SAEs also occurred at a similar frequency in patients with PD ≤ 6 months and those with PD > 6 months (45.5% and 53.2%, respectively). TEAEs leading to dose modification, reduction, interruption, and discontinuation for patients with PD ≤ 6 months occurred at a rate of 67.3%, 45.5%, 60.0%, and 16.4% patients, respectively, and at a rate of 75.8%, 50.0%, 67.7%, and 19.4% in patients that had PD after 6 months. Deaths due to TEAEs were 3.6% in those with PD < 6 months, and 4.8% in those with PD ≥ 6 months.

In patients who had a CR after their first line of treatment versus a PR/SD/PD, TEAEs of grade 3 or greater were experienced at rates of 87.7% and 79.6% respectively. In both subgroups, best response (CR) after the first line of therapy versus PR/SD/PD had TEAEs leading to dose modification (71.6% and 69.4%), dose reduction (49.4% vs. 44.9%), drug interruption (64.2% vs. 59.2%), and study treatment discontinuation (19.8% vs. 14.3%). Patients in the CR group had a higher rate of serious TEAEs (54.3%) than the PR/SD/PD group (36.7%), as well as TEAEs leading to death (4.9% vs 2.0%, respectively).

*Safety According to Timing of PD after ASCT.* Similar rates of grade 3 or higher TEAEs were observed in patients who had PD within a year of ASCT or PD > 1 year after ASCT (95.7% vs. 92.3%), with hematological disorders accounting for 82.6% and 76.9%, respectively. Serious TEAEs were notably higher in patients with PD ≥ 1 year after ASCT (61.5% vs. 43.5%), however patients who had PD within 1 year after ASCT had 1 TEAE leading to death, while none occurred in patients after 1 year or more. Dose modification from TEAEs (91.3% in the PD < 1 year group vs. 84.6% in the PD ≥ 1 year group) and dose reduction from TEAEs were 73.9% and 61.5%, respectively. These were also experienced

**Table 1** Baseline Characteristics.

| Characteristic | 2 Prior Lines | 3 or More Prior Lines | PR or CR to Last Prior Systemic Therapy | Failure to Reach PR or CR to Last Prior Systemic Therapy | Response Missing/Unknown to Last Prior Systemic Therapy | PD < 1 Year after the Last Line | PD ≥ 1 Year after the Last Line | PD < 6 Months after the Last Line | PD ≥ 6 Months after the Last Line |
|---|---|---|---|---|---|---|---|---|---|
| | n = 79 | n = 55 | n = 92 | n = 37 | n = 5 | n = 109 | n = 19 | n = 89 | n = 37 |
| Age (years), median (range) | 69.0 (45, 86) | 66.0 (35, 91) | 69.0 (41, 87) | 66.0 (35, 91) | 65.0 (46, 82) | 67.0 (41, 91) | 69.0 (44, 86) | 67.0 (46, 91) | 70.0 (41, 86) |
| ≥70 | 38 (48.1) | 22 (40.0) | 45 (48.9) | 13 (35.1) | 2 (40.0) | 48 (44.0) | 9 (47.4) | 38 (42.7) | 19 (51.4) |
| Male sex, n (%) | 46 (58.2) | 33 (60.0) | 52 (56.5) | 22 (59.5) | 5 (100.0) | 64 (58.7) | 11 (57.9) | 54 (60.7) | 20 (54.1) |
| DLBCL type | | | | | | | | | |
| *De novo* | 61 (77.2) | 42 (76.4) | 68 (73.9) | 31 (83.8) | 4 (80.0) | 86 (78.9) | 12 (63.2) | 71 (79.8) | 25 (67.6) |
| Transformed | 18 (22.8) | 13 (23.6) | 24 (26.1) | 6 (16.2) | 1 (20.0) | 23 (21.1) | 7 (36.8) | 18 (20.2) | 12 (32.4) |
| DLBCL Subtype | | | | | | | | | |
| GCB | 36 (45.6) | 27 (49.1) | 45 (48.9) | 15 (40.5) | 3 (60.0) | 52 (47.7) | 9 (47.4) | 41 (46.1) | 19 (51.4) |
| Non-GCB | 39 (49.4) | 27 (49.1) | 44 (47.8) | 20 (54.1) | 2 (40.0) | 53 (48.6) | 9 (47.4) | 45 (50.6) | 16 (43.2) |
| Non-Classified | 4 (5.1) | 1 (1.8) | 3 (3.3) | 2 (5.4) | 0 | 4 (3.7) | 1 (5.3) | 3 (3.4) | 2 (5.4) |
| Double Hit/Triple Hit | | | | | | | | | |
| Yes | 0 | 2 (3.6) | 1 (1.1) | 1 (2.7) | 0 | 1 (0.9) | 1 (5.3) | 1 (1.1) | 1 (2.7) |
| No | 45 (57.0) | 36 (65.5) | 56 (60.9) | 20 (54.1) | 5 (100.0) | 66 (60.6) | 11 (57.9) | 52 (58.4) | 23 (62.2) |
| Missing | 34 (43.0) | 17 (30.9) | 35 (38.0) | 16 (43.2) | 0 | 42 (38.5) | 7 (36.8) | 36 (40.4) | 13 (35.1) |
| Number of Prior Systemic Treatment Regimens, n (%) | | | | | | | | | |
| 2 | 79 (100.0) | 0 | 57 (62.0) | 19 (51.4) | 3 (60.0) | 67 (61.5) | 10 (52.6) | 57 (64.0) | 20 (54.1) |
| 3 | 0 | 33 (60.0) | 25 (27.2) | 7 (18.9) | 1 (20.0) | 24 (22.0) | 6 (31.6) | 18 (20.2) | 11 (29.7) |
| 4 | 0 | 16 (29.1) | 7 (7.6) | 8 (21.6) | 1 (20.0) | 12 (11.0) | 3 (15.8) | 10 (11.2) | 5 (13.5) |
| 5 | 0 | 6 (10.9) | 3 (3.3) | 3 (8.1) | 0 | 6 (5.5) | 0 | 4 (4.5) | 1 (2.7) |

(*continued on next page*)

**Table 1** (*continued*)

| Characteristic | 2 Prior Lines | 3 or More Prior Lines | PR or CR to Last Prior Systemic Therapy | Failure to Reach PR or CR to Last Prior Systemic Therapy | Response Missing/Unknown to Last Prior Systemic Therapy | PD < 1 Year after the Last Line | PD ≥ 1 Year after the Last Line | PD < 6 Months after the Last Line | PD ≥ 6 Months after the Last Line |
|---|---|---|---|---|---|---|---|---|---|
| Characteristic | Best Response = CR in the First Line | Best Response = PR/SD/PD in the First Line | Primary Refractory <6 Months | Primary Refractory ≥6 Months | PD < 1 Year after ASCT | PD ≥ 1 Year after ASCT | Never had a CR on Prior Therapy and Achieved CR on Selinexor | Never had a CR/PR on Prior Therapy and Achieved CR/PR on Selinexor | |
| | n = 81 | n = 49 | n = 55 | n = 62 | n = 23 | n = 13 | n = 4 | n = 4 | |
| Age (years), median (range) | 69.0 (41, 91) | 66.0 (35, 86) | 65.0 (35, 83) | 70.0 (41, 91) | 65.0 (41, 75) | 61.0 (44, 76) | 59.5 (51, 84) | 55.5 (51, 66) | |
| ≥70 | 40 (49.4) | 18 (36.7) | 20 (36.4) | 34 (54.8) | 7 (30.4) | 5 (38.5) | 1 (25.0) | 0 | |
| Male sex, n (%) | 44 (54.3) | 33 (67.3) | 37 (67.3) | 31 (50.0) | 15 (65.2) | 8 (61.5) | 3 (75.0) | 3 (75.0) | |
| DLBCL type | | | | | | | | | |
| De novo | 61 (75.3) | 39 (79.6) | 46 (83.6) | 44 (71.0) | 19 (82.6) | 9 (69.2) | 3 (75.0) | 2 (50.0) | |
| Transformed | 20 (24.7) | 10 (20.4) | 9 (16.4) | 18 (29.0) | 4 (17.4) | 4 (30.8) | 1 (25.0) | 2 (50.0) | |
| DLBCL Subtype | | | | | | | | | |
| GCB | 33 (40.7) | 27 (55.1) | 22 (40.0) | 29 (46.8) | 14 (60.9) | 8 (61.5) | 1 (25.0) | 1 (25.0) | |
| Non-GCB | 45 (55.6) | 20 (40.8) | 30 (54.5) | 31 (50.0) | 8 (34.8) | 4 (30.8) | 3 (75.0) | 2 (50.0) | |
| Non-Classified | 3 (3.7) | 2 (4.1) | 3 (5.5) | 2 (3.2) | 1 (4.3) | 1 (7.7) | 0 | 1 (25.0) | |
| Double Hit/Triple Hit | | | | | | | | | |
| Yes | 2 (2.5) | 0 | 0 | 1 (1.6) | 0 | 1 (7.7) | 0 | 0 | |
| No | 54 (66.7) | 25 (51.0) | 29 (52.7) | 42 (67.7) | 17 (73.9) | 8 (61.5) | 2 (50.0) | 3 (75.0) | |
| Missing | 25 (30.9) | 24 (49.0) | 26 (47.3) | 19 (30.6) | 6 (26.1) | 4 (30.8) | 2 (50.0) | 1 (25.0) | |
| Number of Prior Systemic Treatment Regimens, n (%) | | | | | | | | | |
| 2 | 46 (56.8) | 30 (61.2) | 34 (61.8) | 37 (59.7) | 11 (47.8) | 7 (53.8) | 3 (75.0) | 3 (75.0) | |
| 3 | 20 (24.7) | 12 (24.5) | 9 (16.4) | 15 (24.2) | 9 (39.1) | 4 (30.8) | 1 (25.0) | 1 (25.0) | |
| 4 | 10 (12.3) | 6 (12.2) | 10 (18.2) | 6 (9.7) | 1 (4.3) | 2 (15.4) | 0 | 0 | |
| 5 | 5 (6.2) | 1 (2.0) | 2 (3.6) | 4 (6.5) | 2 (8.7) | 0 | 0 | 0 | |

ASCT = autologous stem cell transplant; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

**Table 2** Response Rates According to Prior Treatment/Refractory Status

| Patients | ORR, % (95% CI) | *P value* |
|---|---|---|
| Prior treatments | | |
| 2 Lines of Prior Therapies (n = 79) | 27.8 (18.3, 39.1) | |
| 3 or More Lines of Prior Therapies (n = 55) | 30.9 (19.1, 44.8) | *.8490* |
| Prior ASCT (n = 40) | 42.5 (27.0, 59.1) | |
| No Prior ASCT (n = 94) | 23.4 (15.3, 33.3) | *.0435* |
| Response to Last Therapy | | |
| PR or CR (n = 92) | 35.9 (26.1, 46.5) | |
| No PR or CR (n = 37) | 16.2 (6.2, 32.0) | *.0470* |
| Response Missing/Unknown (n = 5) | 0 (NE) | |
| PD <1 Year (n = 109) | 27.5 (19.4, 36.9) | |
| PD ≥1 Year (n = 19) | 42.1 (20.3, 66.5) | *.3117* |
| PD <6 Months (n = 89) | 24.7 (16.2, 35.0) | |
| PD ≥6 Months (n = 37) | 40.5 (24.8, 57.9) | *.1185* |
| Response to First Therapy | | |
| Best Response=CR (n = 81) | 28.4 (18.9, 39.5) | |
| Best Response=PR/SD/PD (n = 49) | 30.6 (18.3, 45.4) | *.9439* |
| Primary Refractory <6 Months (n = 55) | 21.8 (11.8, 35.0) | |
| Primary Refractory ≥6 Months (n = 62) | 37.1 (25.2, 50.3) | *.1098* |
| Response to ASCT | | |
| PD <1 Year (n = 23) | 52.2 (30.6, 73.2) | |
| PD ≥1 Year (n = 13) | 30.8 (9.1, 61.4) | *.3722* |
| Response to Selinexor | | |
| Never had a CR on Prior Therapy and Achieved CR (n = 4) | 100.0 (NR) | |
| Never had a CR/PR on Prior Therapy and Achieved CR/PR (n=4) | 100.0 (NR) | *.0090* |

ASCT = autologous stem cell transplant; CI = confidence interval; CR = complete response; NR = not reached; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

earlier in the PD within a year after ASCT group compared to those with PD beyond 1 year. Patients with PD 1 year beyond ASCT treatment had a higher rate of TEAEs leading to drug interruption (78.3% < 1 year vs. 84.6% ≥ 1 year), and study treatment discontinuation (17.4 % < 1 year vs. 23.1% ≥ 1 year).

## Discussion

RR DLBCL following at least 2 lines of therapy is associated with poor prognosis, with a median OS of < 6 months.[31] Thus, there is a substantial unmet need in this patient population for novel treatments that can control the disease. Here, we examined subpopulations from the SADAL trial of single agent oral selinexor to determine whether a particular subgroup could be identified with a high response rate. These patients had a treatment-free interval of at least 60-days and a median treatment free interval of 5.4 months. We examined number of lines of treatment, ASCT status, response to initial and last therapy, and time before progressive disease both after last line and first line of therapy ( < 6 months, < 1 year, ≥ 6 months, ≥ 1 year).

The primary findings suggest that ORR with selinexor was comparable for patients who had 2 versus ≥ 3 lines of previous treatment; however, ORR was significantly greater for selinexor in patients who had received ASCT compared to those who had not. Similarly, higher ORR were achieved in patients who responded (PR or CR) to the last line of therapy as compared to those who did not. Interestingly, ORR was not significantly lower in patients with primary refractory as compared with non-refractory DLBCL, nor was number of prior lines of therapy (2 vs. ≥3) associated with ORR. Furthermore, those patients who never had either a CR or PR on any previous therapy all responded to selinexor (4 CR, 2 PR). All of these results are consistent with the novel mechanism of action of selinexor and lack of cross-reactivity with available therapies.

In the SCHOLAR-1 study, the largest patient-level pooled retrospective analysis in DLBCL patients, 73% of patients with refractory disease did not respond to salvage therapy or could not receive ASCT.[31] This highlights the need for novel and effective therapies to treat the RR DLBCL population, preferably with orally-available, non-cytotoxic regimens to minimize AEs, particularly neutropenia. The present subgroup analyses from the SADAL trial indicate that selinexor may provide benefit in patients with primary refractory DLBCL for whom the prognosis is particularly poor.

The safety profile of selinexor is supportive of use in patients with heavily pretreated DLBCL and is qualitatively consistent with the established and approved product label for selinexor (FDA

**Table 3** Overall Safety Profile of Selinexor According to Prior Treatment and Response.

| TEAE | 2 Prior Lines | 3 or More Prior Lines | ASCT | No ASCT | PR or CR to last prior systemic therapy | Failure to Reach PR or CR to Last Prior Systemic Therapy | Response Missing/Unknown to Last Prior Systemic Therapy | PD < 1 Year After the Last Line | PD ≥1 Year After the Last Line | PD < 6 Months After the Last Line | PD ≥ 6 Months After the Last Line |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n = 79 | n = 55 | n = 40 | n = 94 | n = 92 | n = 37 | n = 5 | n = 109 | n = 19 | n = 89 | n = 37 |
| Thrombocytopenia | 47 (59.5) | 35 (63.6) | 35 (87.5) | 47 (50.0) | 61 (66.3) | 20 (54.1) | 1 (20.0) | 64 (58.7) | 14 (73.7) | 53 (59.6) | 23 (62.2) |
| Nausea | 47 (59.5) | 29 (52.7) | 25 (62.5) | 51 (54.3) | 56 (60.9) | 20 (54.1) | 0 | 62 (56.9) | 10 (52.6) | 47 (52.8) | 24 (64.9) |
| Fatigue | 36 (45.6) | 27 (49.1) | 22 (55.0) | 41 (43.6) | 46 (50.0) | 15 (40.5) | 2 (40.0) | 50 (45.9) | 10 (52.6) | 43 (48.3) | 17 (45.9) |
| Anemia | 35 (44.3) | 22 (40.0) | 19 (47.5) | 38 (40.4) | 46 (50.0) | 11 (29.7) | 0 | 44 (40.4) | 11 (57.9) | 37 (41.6) | 16 (43.2) |
| Decreased appetite | 31 (39.2) | 18 (32.7) | 15 (37.5) | 34 (36.2) | 34 (37.0) | 14 (37.8) | 1 (20.0) | 41 (37.6) | 7 (36.8) | 37 (41.6) | 10 (27.0) |
| Diarrhea | 29 (36.7) | 17 (30.9) | 19 (47.5) | 27 (28.7) | 35 (38.0) | 10 (27.0) | 1 (20.0) | 35 (32.1) | 9 (47.4) | 29 (32.6) | 15 (40.5) |
| Neutropenia | 22 (27.8) | 20 (36.4) | 16 (40.0) | 26 (27.7) | 27 (29.3) | 14 (37.8) | 1 (20.0) | 35 (32.1) | 5 (26.3) | 29 (32.6) | 9 (24.3) |
| Constipation | 23 (29.1) | 17 (30.9) | 16 (40.0) | 24 (25.5) | 31 (33.7) | 9 (24.3) | 0 | 32 (29.4) | 7 (36.8) | 27 (30.3) | 12 (32.4) |
| Weight decreased | 23 (29.1) | 17 (30.9) | 12 (30.0) | 28 (29.8) | 28 (30.4) | 11 (29.7) | 1 (20.0) | 32 (29.4) | 7 (36.8) | 26 (29.2) | 13 (35.1) |
| Vomiting | 22 (27.8) | 16 (29.1) | 11 (27.5) | 27 (28.7) | 30 (32.6) | 8 (21.6) | 0 | 30 (27.5) | 7 (36.8) | 22 (24.7) | 14 (37.8) |
| Pyrexia | 18 (22.8) | 11 (20.0) | 9 (22.5) | 20 (21.3) | 22 (23.9) | 6 (16.2) | 1 (20.0) | 22 (20.2) | 5 (26.3) | 18 (20.2) | 9 (24.3) |
| Asthenia | 18 (22.8) | 10 (18.2) | 8 (20.0) | 20 (21.3) | 22 (23.9) | 6 (16.2) | 0 | 23 (21.1) | 4 (21.1) | 17 (19.1) | 9 (24.3) |
| Cough | 13 (16.5) | 11 (20.0) | 8 (20.0) | 16 (17.0) | 17 (18.5) | 7 (18.9) | 0 | 18 (16.5) | 3 (15.8) | 15 (16.9) | 6 (16.2) |
| Dizziness | 11 (13.9) | 8 (14.5) | 5 (12.5) | 14 (14.9) | 14 (15.2) | 5 (13.5) | 0 | 18 (16.5) | 1 (5.3) | 14 (15.7) | 4 (10.8) |

(*continued on next page*)

**Table 3** (*continued*)

| TEAE | 2 Prior Lines | 3 or More Prior Lines | ASCT | No ASCT | PR or CR to last prior systemic therapy | Failure to Reach PR or CR to Last Prior Systemic Therapy | Response Missing/Unknown to Last Prior Systemic Therapy | PD < 1 Year After the Last Line | PD ≥1 Year After the Last Line | PD < 6 Months After the Last Line | PD ≥ 6 Months After the Last Line |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TEAE | Best Response = CR in the First Line | Best Response = PR/SD/PD in the First Line | Primary Refractory < 6 Months | Primary Refractory ≥ 6 Months | PD <1 Year After ASCT | PD ≥ 1 Year After ASCT | Never had a CR on Prior Therapy and Achieved CR on Selinexor | Never had a CR/PR on Prior Therapy and Achieved CR/PR on Selinexor | | | |
| | n = 81 | n = 49 | n = 55 | n = 62 | n = 23 | n = 13 | n = 4 | n = 4 | | | |
| Thrombocytopenia | 47 (58.0) | 32 (65.3) | 34 (61.8) | 36 (58.1) | 21 (91.3) | 11 (84.6) | 2 (50.0) | 3 (75.0) | | | |
| Nausea | 48 (59.3) | 27 (55.1) | 32 (58.2) | 38 (61.3) | 16 (69.6) | 7 (53.8) | 3 (75.0) | 4 (100.0) | | | |
| Fatigue | 39 (48.1) | 23 (46.9) | 27 (49.1) | 29 (46.8) | 13 (56.5) | 8 (61.5) | 4 (100.0) | 3 (75.0) | | | |
| Anemia | 36 (44.4) | 18 (36.7) | 26 (47.3) | 25 (40.3) | 12 (52.2) | 5 (38.5) | 2 (50.0) | 3 (75.0) | | | |
| Decreased appetite | 29 (35.8) | 19 (38.8) | 24 (43.6) | 19 (30.6) | 12 (52.2) | 3 (23.1) | 2 (50.0) | 1 (25.0) | | | |
| Diarrhea | 32 (39.5) | 12 (24.5) | 12 (21.8) | 28 (45.2) | 12 (52.2) | 6 (46.2) | 1 (25.0) | 2 (50.0) | | | |
| Neutropenia | 25 (30.9) | 15 (30.6) | 16 (29.1) | 19 (30.6) | 10 (43.5) | 4 (30.8) | 3 (75.0) | 4 (100.0) | | | |
| Constipation | 22 (27.2) | 18 (36.7) | 18 (32.7) | 17 (27.4) | 11 (47.8) | 4 (30.8) | 2 (50.0) | 2 (50.0) | | | |
| Weight decreased | 25 (30.9) | 13 (26.5) | 17 (30.9) | 18 (29.0) | 7 (30.4) | 5 (38.5) | 3 (75.0) | 2 (50.0) | | | |
| Vomiting | 24 (29.6) | 13 (26.5) | 14 (25.5) | 19 (30.6) | 7 (30.4) | 3 (23.1) | 2 (50.0) | 1 (25.0) | | | |
| Pyrexia | 15 (18.5) | 14 (28.6) | 12 (21.8) | 14 (22.6) | 7 (30.4) | 2 (15.4) | 1 (25.0) | 2 (50.0) | | | |
| Asthenia | 16 (19.8) | 11 (22.4) | 11 (20.0) | 14 (22.6) | 7 (30.4) | 1 (7.7) | 0 | 1 (25.0) | | | |
| Cough | 14 (17.3) | 9 (18.4) | 9 (16.4) | 9 (14.5) | 6 (26.1) | 2 (15.4) | 3 (75.0) | 3 (75.0) | | | |
| Dizziness | 9 (11.1) | 10 (20.4) | 9 (16.4) | 6 (9.7) | 4 (17.4) | 1 (7.7) | 2 (50.0) | 3 (75.0) | | | |

ASCT = autologous stem cell transplant; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; TEAE = treatment-emergent adverse event

approved in June 2020 for DLBCL). The majority of AEs associated with selinexor are reversible, manageable, and/or preventable with standard supportive or prophylactic care and/or dose modifications. Thrombocytopenia is a frequently occurring TEAE, exacerbated by underlying bone marrow dysfunction following multiple lines of cytotoxic chemotherapy. However, there was no report of any serious concurrent bleeding complications, even in patients with high grade thrombocytopenia. Thrombocytopenia is reversible and is managed through dose interruption of selinexor, when necessary, and supportive care to boost platelet counts, including platelet transfusions and/or thrombopoietin receptor agonists.[32] Patients who had undergone ASCT had more frequent and severe thrombocytopenia; however 20%-40% of patients who undergo ASCT commonly experience late-onset thrombocytopenia.[33] In comparison to a study by Sehn and colleagues,[34] single-agent selinexor demonstrates similar rates of thrombocytopenia as polatuzumab vedotin plus bendamustine and rituximab (PBR), with grade 3/4 thrombocytopenia occurring in 45.7% with PBR versus 41.0% with selinexor. In addition, the oral administration of selinexor substantially reduces the burden on patients, as PBR requires parenteral delivery.

Key limitations of the SADAL study include the single-arm design and that the patients enrolled in this trial had recurrent disease after at least 2 lines of therapy, which may have included ASCT. Therefore, aside from the rituximab-containing, multi-agent salvage regimens indicated earlier and/or those comprising ibrutinib or lenalidomide, there is a paucity of comparator treatment options available, and none of the more recently approved agents such as polatuzumab vedotin,[34] or tafasitamab,[35] were available at the time of the study. A similar treatment-free interval was reported for tafasitamab plus lenalidomide,[35] and for CAR-T therapies.[36] In addition, the requirement of a 60-day interval without treatment excludes rapidly progressive patients. The results from this study suggest that heavily pre-treated patients could be considered for a non-cytotoxic therapy with oral selinexor, rather than be subjected to parenteral chemotherapeutic agents.

In conclusion, single-agent selinexor elicited durable responses regardless of number of prior lines of therapy, primary refractory disease, or prior treatment with high-dose chemotherapy and ASCT. The National Comprehensive Cancer Network recommends ibrutinib or lenalidomide (with or without rituximab), for which the ORR is 30%-40% in the activated B-cell subtype, but less than 10% in patients with germinal center disease; the DOR for these therapies is limited. Tafasitamab and polatuzumab are also recommended for non-germinal center DLBCL, with an ORR of ~55%.[34,35] In the SADAL trial, the ORR was 34% in RR germinal center DLBCL and 21% in the non-germinal center subtype. Furthermore, safety and tolerability do not seem to be significantly different across analyzed subgroups presented herein, and grade 3 or more toxicities and dose modifications occur in the majority of patients regardless of subgroup, compared to the overall SADAL trial population, indicating that the subpopulations are not at risk for selinexor-associated toxicity. Collectively, these data suggest that selinexor could be a safe, oral, single-agent option for patients with either germinal or non-germinal disease, and particularly for those with refractory DLBCL.

### *Clinical Practice Points*

- Patients with relapsed/refractory diffuse large B-cell lymphoma (RR DLBCL) who are refractory after autologous stem cell transplant (ASCT) or have inadequate response to salvage chemotherapy have poor outcomes especially when coupled with high risk factors, leaving the majority without curative treatment options.
- Given the high rate of relapse/refractory status of patients who receive multiple lines of therapy for DLBCL and difference in reported clinical outcomes based on therapeutic regimen, it is important to evaluate the effect of selinexor based on number, type, and response to prior therapies.
- Results demonstrated that patients were able to tolerate selinexor treatment, and there were no new safety signals identified. The majority of adverse events (AEs) experienced with selinexor were well-managed with standard supportive or prophylactic care, and/or dose modifications.
- Patients in the SADAL study benefited from selinexor treatment by having deep durable responses and improved outcomes, regardless of number of prior lines of therapy, primary refractory disease, or prior treatment with high-dose chemotherapy and ASCT.
- Selinexor could be a safe, orally available, single agent option for patients with RR DLBCL who have been heavily pretreated.

### *Author Contributions*

MS, JMZ, ROC, JSPV, NK, AG, SC, EVDN, BH, CT, FC, FDLC, JK, NH, UL, PC, RG, KW, SB, JMS, GF, ME, FO, TV, PS, MK, JS, SS, MGK, MC, MM collected the data. MS, JS, SS, and MGK contributed to the study design. XM analyzed the data. All authors interpreted the data. All authors edited, and reviewed manuscript drafts, and approved the final version.

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XM, KC, JS, SS, and MK are employees of Karyopharm.

MK and SS are stockholders of Karyopharm.

SS holds patents (8999996, 9079865, 9714226, PCT/US12/048319, and I574957) on hydrazide containing nuclear transport modulators and uses, and pending patents (PCT/US12/048319, 499/2012, PI20102724, and 2012000928) on hydrazide-containing nuclear transport modulators and uses.

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