Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

Selinexor in patients with relapsed refractory diffuse large B-cell lymphoma (SADAL): a single-arm international phase 2 trial

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Research in Context

Evidence before this study

Diffuse large B cell lymphoma (DLBCL) is typically treated with multi-agent chemotherapy plus an anti-CD20 monoclonal antibody leading to cure in ~50% of patients. High dose chemotherapy with autologous stem cell transplantation (ASCT) may cure another 10-15% of patients, but only a minority of patients are candidates for this intensive therapy. Patients whose disease is refractory to, or has relapsed after, two prior therapies and who are not candidates for chimeric antigen receptor modified anti-CD19 T cell (CAR-T) therapies are highly likely to die from their disease (studies identified in PubMed, searching for “diffuse large B cell lymphoma”, “DLBCL”, “relapse”, and “refractory”, between January 1, 2000 to January 1, 2020, with no language restrictions). Agents with novel mechanisms, including signaling through exportin 1 (XPO1), that can induce durable remissions are needed in this patient population, particularly given that most of these patients are older and have multiple comorbid conditions (studies identified in PubMed, searching for “exportin 1”, “XPO1”, “selinexor”, between September 19, 1997 to January 1, 2020, with no language restrictions).

Added value of this study

To our knowledge, SADAL is the one of the largest studies (N=127) evaluating a novel therapy in patients with relapsed/refractory (RR) DLBCL who are not candidates for ASCT or CAR-T therapy. SADAL evaluated the novel oral selective inhibitor of XPO1-mediated nuclear export (SINE) selinexor in patients with RR DLBCL after at least two prior therapies. The results showed that selinexor can induce objective radiographic responses in 28% of patients with a median duration of response (DOR) of 9.3 months. Approximately 11% of patients had a complete response (CR) with a median of duration of CR of 23 months. Responses were

observed in both the germinal center B cell (GCB) and non-GCB subtypes of DLBCL In contrast to chemotherapy, there is no maximum duration of therapy. Oral selinexor may represent an active treatment option for patients with RR DLBCL, particularly those who do not wish to receive parenteral agents and/or have significant major organ dysfunction and other comorbidities.

Implications of all the available evidence

Inhibition of XPO1-mediated nuclear export with selinexor leads to the forced nuclear retention and functional reactivation of tumor suppressor proteins, reductions in levels of several oncoproteins, and inhibition of DNA repair - including that associated with chemotherapy resistance. These results provide the scientific basis for the use of selinexor in a large variety of malignancies, both alone and in combination with other anti-cancer agents. Ongoing studies with selinexor in combination with other agents active in DLBCL, including both chemotherapy and non-cytotoxic drugs, may expand the utility of selinexor in lymphoma and in other malignant conditions.

Summary

Background Relapsed or refractory diffuse large B-cell lymphoma (RR DLBCL) is an aggressive cancer with a median survival of less than 6 months. The SADAL trial aims to assess the response to the oral selective inhibitor of nuclear export (SINE) selinexor in patients with RR DLBCL who have no therapeutic options of demonstrated clinical benefit

Methods SADAL was a multicenter, open-label Phase 2b study conducted at 59 sites globally. Patients ≥18 years with previously treated, pathologically confirmed de novo DLBCL, or DLBCL transformed from previously diagnosed indolent lymphoma, and having received at least two prior therapies were enrolled. Histological and molecular analyses were utilized to determine germinal center B-cell [GCB] or non-GCB tumor subtype as well as to assess the double and triple hit/expressor DLBCL status. Patients received 60 mg selinexor orally on days 1 and 3 weekly until disease progression or unacceptable toxicity. The primary outcome was overall response rate by central radiologic review. A modified intent-to-treat population was used for all efficacy endpoints. This trial is registered at ClinicalTrials.gov, NCT02227251.

Findings 127 patients were enrolled from October 21, 2015 through November 2, 2019. The overall response rate was 28.3% (95% CI: 20.7%, 37.0%), including complete response in 15 (11.8%) and partial response in 21 (16.5%) patients. Median overall survival (OS) was 9.1 months (95% CI: 6.6, 15.1) with longer OS observed in responding patients. Responses were observed across different subgroups regardless of age, gender, prior therapy, DLBCL subtype, refractory status or prior ASCT therapy. Adverse events were generally reversible and managed with dose modifications and/or standard supportive care.

Interpretation In both GCB- and non-GCB DLBCL subtypes, single agent oral selinexor induced durable responses which were associated with longer survival. Selinexor may be a new oral, non-cytotoxic treatment option for patients with RR DLBCL after two lines of chemo-immunotherapy.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the commonest form of non-Hodgkin's lymphoma (NHL).[1] DLBCL is a heterogeneous disease with clinically and molecularly distinct subtypes. At initial diagnosis, treatment includes combination chemoimmunotherapy[2] (e.g., R-CHOP, EPOCH-R) which can be curative in approximately 40-65% of patients. Outcomes for patients with primary refractory or relapsed disease remain poor. At first relapse, non–cross-resistant chemo-immunotherapy, followed by autologous stem cell transplantation (ASCT) in eligible patients, can lead to long term survival for some patients. However, the long term outlook for patients who relapse post-salvage regimens (with or without ASCT) remains dismal.[3–6] Emergent treatment options for this patient population with RR DLBCL include chimeric antigen receptor (CAR) T cell therapy and the parenteral combination of polatuzumab vedotin, a CD79b-directed antibody-drug conjugate with bendamustine and rituximab, as well as lenalidomide (plus rituximab) and BTK inhibitors. Despite these options, few patients achieve long term remission and most patients require additional treatment options. Thus, there is an unmet medical need in patients with RR DLBCL.

Exportin 1 (XPO1), a nucleo-cytoplasmic shuttling protein involved in the export of proteins from the nucleus to the cytoplasm, is overexpressed in DLBCL and correlates with poor prognosis. XPO1 mediates the functional inactivation of multiple tumor suppressors (e.g., p53, p73, IκB, FOXO) and facilitates the increased expression of oncoproteins that are relevant to B-cell biology and DLBCL.[7] XPO1 blockade in DLBCL re-establishes the tumor-suppressing and growth-regulating effects of multiple tumor suppressors by forcing their nuclear retention, and potentially reverses chemotherapy resistance.[8] Several oncoprotein mRNAs such as c-Myc, Bcl-X_L, Bcl2, Bcl6, survivin and Cyclin D1 bind to the eukaryotic translation initiation factor 4E (eIF4e), which is overexpressed in most B cell lymphomas.[9] The oncoprotein mRNA-eIF4e complexes are exported out of the nucleus by XPO1, facilitating the cytoplasmic translation and increasing the levels of these oncoproteins.

Preclinical studies show that XPO1 inhibitors induce transient cell cycle arrest, suppress tumor growth, and induce significant apoptosis independent of tumor cell genotype, with minimal effects on normal lymphocytes.[7,10,11]

Selinexor, an oral selective inhibitor of XPO1-mediated nuclear export (SINE), induces the expected nuclear accumulation and activation of tumor suppressor proteins and reductions in Bcl2, Bcl-X_L and c-Myc oncoprotein levels. Recently, the combination of selinexor and low-dose dexamethasone (Sel-dex) was approved by the FDA for patients with triple-class refractory multiple myeloma based on safety and efficacy data from the single-arm Phase 2b Selinexor Treatment of Refractory Myeloma (STORM) study.[12] In heavily pretreated DLBCL, single agent selinexor has previously demonstrated an investigator-assessed overall response rate (ORR) of 32% with complete response in 9·3%, in a Phase 1 study supporting the broad activity of selinexor in multiple hematologic malignancies including myeloma and DLBCL.[13] The objective of the SADAL (Selinexor Against Diffuse Aggressive Lymphoma) study was to evaluate the efficacy and safety of single-agent selinexor in patients with RR DLBCL (*de novo* or transformed) who have received at least two prior lines of systemic therapy, including those who progressed after ASCT, or those not eligible for ASCT or CAR-T therapy.

Methods

Study design and participants

The SADAL study was a phase 2b, open-label, multicenter study in patients with RR DLBCL with two to five lines of prior therapy, who may have progressed post-ASCT or who were not candidates for ASCT. Patients were enrolled from October 21, 2015 through November 2, 2019 at 59 sites in the United States, Canada, Europe, Israel, Australia, New Zealand, and India. The institutional review board or independent ethics committee at each study center approved the protocol (complete study protocol is available in the appendix, page 14), and the study was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was designed by the sponsor (Karyopharm Therapeutics Inc.). Efficacy was assessed according to the revised 2014 Cheson criteria for response assessment of lymphoma[14] by independent central review and separately based on investigator assessments.

Eligible patients had pathologically confirmed *de novo* DLBCL, or DLBCL transformed from previously diagnosed indolent lymphoma and have measurable disease (2014 Lugano Criteria[15]). Patients received at least 2, but no more than 5, previous systemic regimens including at least 1 course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active agents such as etoposide, bendamustine, or gemcitabine were given) and at least 1 course of anti-CD20 immunotherapy such as rituximab. Patients were deemed not eligible for high-dose chemotherapy with ASCT at the time of study entry. An Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2 and platelet count >75,000/mm^3 were required. Exclusion criteria included known central nervous system lymphoma, meningeal involvement, or creatinine clearance <30 mL/min. A full list of inclusion and exclusion criteria is provided in the appendix (pages 2-4). Written informed consent was obtained from all patients before enrollment. Tumor biopsy samples were analyzed histologically[16] to determine DLBCL subtype (germinal center

B-cell [GCB] or non-GCB [activated B-cell (ABC) or primary mediastinal B-cell lymphoma]). In addition, fluorescent in situ hybridization (FISH) was performed to detect the translocation/rearrangement status of c-Myc, Bcl-2, and Bcl-6 genes and immunohistochemistry (IHC) was performed to detect the expression levels of c-Myc, Bcl-2 and Bcl-6 proteins. These parameters were utilized to define "double hit/triple hit" DLBCL (DH/TH-DLBCL) and "double expressor/triple expressor" (DE/TE-DLBCL) status in all patients.

Procedures

Oral selinexor (60 mg) was administered as a single agent on days 1 and 3 of each week (BIW) until disease progression, death or unacceptable toxicities. Although the study was initially designed to evaluate both 60 mg and 100 mg BIW dose of oral selinexor, an improved therapeutic window (similar ORR and lower adverse event [AE] rates) was observed at the lower 60 mg dose, resulting in discontinuation of the 100 mg arm. All patients were required to receive 8 mg of ondansetron (or equivalent) before the first dose of study drug and continued 2 to 3 times daily, as needed. Supportive care was provided at the discretion of the investigator per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology.

Outcomes

The primary endpoint was the overall response rate (ORR) defined as the proportion of patients who achieved either complete response (CR) or partial response (PR) according to the 2014 Lugano criteria for assessment of lymphoma.[14] Analyses were conducted using these criteria[14] based on independent central radiographic review. Secondary endpoints included: duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Definitions of endpoints are provided in the appendix, page 5. An independent oncologist reviewed the clinical data and confirmed the responses and duration until progression. Cell origin subtype

(GCB versus non-GCB) was determined by IHC-based Hans algorithm. Safety and AEs were assessed through history taking, ECOG PS, physical examination, laboratory assessments, and 12-lead electrocardiography. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

The sample size was based on assumptions to evaluate the clinical effect of selinexor by reference to a minimal threshold level for ORR, set to 0·15 (15%). For the primary analysis, a sample size of 127 patients allowed for a one-sided test at an alpha level of 0·025 to detect a minimum of 25% of patients with a PR or better against a value of 15% under the null hypothesis with 80% power. The modified intention-to-treat population (mITT) was used for the primary efficacy analysis; this comprised all enrolled patients who met all eligibility criteria and received at least one dose of 60 mg selinexor. This population included patients who discontinued study treatment due to toxicity or disease progression and patients who died from any cause. The safety population consisted of all patients who received at least one dose of study treatment.

The ORR primary endpoint was assessed using a 97·5% lower one-sided binomial confidence interval (CI) using exact methods, calculated for the percentage of patients with a PR or better in the mITT population, with statistical significance declared if the lower boundary of this interval was more than 15%. Summary statistics were computed and displayed for each of the defined analysis populations and according to each assessment time point. Summary statistics for continuous variables minimally included number, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, percentages, and 2-sided 95% CIs are presented. For time-to-event variables, the Kaplan–Meier method was used for descriptive summaries.

Role of the funding source

Karyopharm Therapeutics was the sponsor of this study and was responsible for study design (in the collection, analysis, and interpretation of data), writing of the report, and the decision to submit the paper for publication. The corresponding authors (NK and MM) 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.

Results

A total of 127 patients were included in the mITT and safety populations (figure S1). The median age was 67 years (44·9% of patients were ≥70 years of age), and the median interval from initial DLBCL diagnosis to selinexor treatment was 2·6 years (range: 0·1 – 26·2). Overall, 94 patients (74%) had *de novo* DLBCL and 31 patients (24·4%) had transformed DLBCL; 2 patients (1·6%) had unknown etiology. Regarding subtypes, 59 patients (46·5%) had GCB and 63 patients (49·6%) had non-GCB DLBCL (Han algorithm), with 5 patients unclassified. The median number of prior regimens for DLBCL was 2 (range: 2-5); 52 patients (40·9%) received ≥3 prior regimens. Fifty-five patients (43.3%) had disease refractory to initial therapy (i.e. progression within one year of initial therapy). Thirty-eight patients (29·9%) had prior ASCT for DLBCL. Of these, 21 patients (16.5%) had refractory DLBCL or relapse < 1 year of last ASCT therapy (table 1).

Of the 127 patients who received selinexor, 118 patients (92·9%) discontinued treatment; disease progression (67·8%) and withdrawal by patient (11·0%) being the most common reasons (figure S1). The target dose of selinexor was 120 mg per week (60 mg twice weekly) and the median selinexor average dose received per week was 100 mg (range: 48 –180). The median total dose received was 960 mg (range: 60–15,960) and the median duration of treatment was 9 weeks (range: 1–193).

The study met its primary objective with an ORR of 28·3% (exact 95% CI: 20·7%, 37·0%) [as assessed by the central imaging laboratory] including CR in 15 patients (11·8%) and PR in 21 patients (16·5%) [table 2]. The clinical benefit rate (CBR), defined as CR+PR+SD, was 37·0%. Time to PR or better occurred at first radiographic assessment (median 8 weeks, range: 7–16). For patients with a GCB subtype, the ORR was 33·9%, including CR in 8 patients (13·6%) and PR in 12 patients (20·3%). Nine patients had ongoing responses at the last disease assessment (median DOR follow-up of 11·1 months) before the data cutoff, including 7 patients with ongoing CRs and 2 with ongoing PRs. The median DOR in the mITT population was 9·3 months (95% CI: 4·8, 23·0). The median

DOR was 23·0 months (95% CI: 10·4, 23·0) for patients with CR, and 4·4 months (95% CI: 2·0, NE) for patients with PR.

Responses were consistent across many different subgroups regardless of age, gender, prior therapy, DLBCL subtype, refractory status or prior ASCT therapy (figure 1). The ORR in patients <70 years of age was 31·4% (n=22) as compared with 24·6% (n=14) in patients >70 years of age (figure 1). Overall, a total of 54 patients (66·3%) with a baseline target lesion and at least one post-baseline assessment had a reduction in tumor burden, which was observed regardless of cell of origin (figure 3). Among 38 patients with prior ASCT, 16 patients (42·1%) achieved ≥PR versus 20 patients (22·5%) out of 89 without prior transplantation. Among those with *de novo* DLBCL, 23 patients (24·5%) achieved a response versus 12 patients (38·7%) with transformed DLBCL. Among patients with DLBCL refractory to their most recent treatment regimen, 25 patients (27·5%) achieved ≥PR, whereas 11 patients (36·7%) with DLBCL not refractory to the most recent treatment achieved ≥PR. Of selinexor responders or non-responders, the median time between progressive disease from last prior therapy to the start of selinexor was 56 and 51 days respectively, indicating that outcomes were not influenced by time since last therapy.

In the mITT population, the median PFS was 3·5 months (95% CI: 2·0, 4·0) (figure S2), and the median OS was 9·1 months (95% CI: 6·6, 15·1) (figure 2). In patients with a response (≥PR), the median OS was not reached, and in patients who had SD, the median OS was 18.3 months. In patients who had progressive disease, the median OS was 4·3 months (95% CI: 3·0, 5·4).

Regarding predictive/prognostic biomarker analysis, DLBCL with high levels of c-Myc (based on a cutoff of 40% positive cells as determined by IHC) had a 12·8% ORR, while those with low levels had a 42·3% ORR (P=0·002). Similar results were observed with double or triple over-expressors (DE/TE) [P=0·006], but these differences were largely a reflection of c-Myc overexpression as neither expression levels of Bcl-2 or Bcl-6 nor GCB subtype affected the ORR (figure 4).

As selinexor represents a novel mechanism of action quite distinct from cytotoxic therapy, several patients' courses are highlighted here. One patient, a 76-year old female with transformed DLBCL with 3 lines of prior therapy, demonstrated an anatomic PR after 6 months of selinexor therapy, and a complete metabolic response after 9 months (figure S3). Another patient, a 55-year old male with primary refractory bulky GCB-DLBCL entered the study with a large abdominal mass. After 6 cycles of R-CHOP and 2 courses of gemcitabine-based salvage regimen, he achieved a PR after 4 months and CR after 8 months of selinexor therapy (figure S4). A third patient a, 70-year old female with double-hit DLBCL (GCB subtype) developed a CD20 negative relapse and entered the study. Following 4 cycles of selinexor, this patient achieved a mPR, then to mPD at 6 cycles and went on ASCT after the final visit.

Finally, selinexor treatment enabled two patients who previously progressed following ASCT to become eligible and undergo CAR-T cell therapy. A 45-year old male with GCB-DLBCL and previous ASCT treatment demonstrated a rapid reduction of tumor burden and metabolic PR within 59 days of initiation of selinexor; this patient then moved to CAR-T therapy A 70-year old female, also with GCB-DLBCL, had demonstrated progressive disease eight months following ASCT. An initial PR was observed within 47 days of initiation of selinexor. Selinexor was discontinued after more than one year as the patient was moved to CAR-T therapy. These results further support and highlight the activity and clinical benefit of selinexor in patients with high-risk disease who can achieve responses and can enable CAR-T therapy.

While the safety profile of selinexor was qualitatively similar to that of prior reports of selinexor in hematological malignancies, the AEs were less severe and less frequent than in prior reports in patients with refractory multiple myeloma. Overall, 98·4% of patients (n=125) experienced at least one treatment-emergent adverse event (TEAE). The most common TEAEs occurring in ≥20% of patients were thrombocytopenia (61·4%), nausea (58·3%), fatigue (47·2%), anemia (42·5%),

decreased appetite (37·0%), diarrhea (35·4%), constipation (30·7%), neutropenia (29·9%), weight loss (29·9%), vomiting (29·1%), pyrexia (22·0%), and asthenia (21·3%) (table 3). Most non-hematological TEAEs were limited in severity to grades 1 or 2. The most common grade 3 or 4 AEs were thrombocytopenia (45·7%), neutropenia (24·4%), anemia (22·1%), fatigue (11·0%), hyponatremia (7·9%), and nausea (6·3%); these were typically reversible with standard supportive care and/or dose modification. Thrombocytopenia was not typically associated with clinically significant bleeding, and febrile neutropenia (12·9%) usually recovered with standard growth factor and antibiotic treatment.

In all, 17·3% of patients discontinued study treatment due to a TEAE. TEAEs leading to dose modification (reduction or interruption) occurred in 68·5% of patients, with the majority of events occurring in the first two cycles. The most common TEAEs (≥5% of patients) that required dose modification (≥5% of patients) were thrombocytopenia (37·8%), neutropenia (15·0%), fatigue (12·6%), nausea (7·9%), diarrhea (7·1%), pyrexia (7·1%), and anemia (6·3%). For thrombocytopenia, neutropenia, nausea, vomiting, decreased appetite and hyponatremia; the median number of events per patient was 1, and most occurring during cycle 1 or 2. Supportive care included moderate to high doses of thrombopoietin-receptor agonists, granulocyte colony stimulating factors, additional anti-nausea agents (e.g., oral olanzapine 2·5 mg to 5 mg daily), appropriate fluid and caloric intake, appetite stimulants, and psychostimulants; these usually reduced the intensity and/or duration of AEs.

Serious adverse events (SAEs) occurred in 61 patients (48·0%). the most common SAEs (≥3%) were pyrexia (7·1%), pneumonia (4·7%), fatigue (3·9%), anemia (3·1%), cardiac failure (3·1%), febrile neutropenia (3·1%), and sepsis (4·7%) (Appendix, page 9). Twenty-five patients (19·7%) died within 30 days of the last dose of selinexor. Of these, 20 patients (15.7%) died due to disease progression and 5 patients (3.9%) died due to a TEAE. The TEAEs leading to a fatal outcome

included acute respiratory distress syndrome (n=1), cerebrovascular accident (n=1), and sepsis (n=3). None of these TEAEs were considered by the investigator to be selinexor-related. Three of the 5 deaths due to TEAEs occurred in patients ≥70 years old. Deaths due to TEAEs were higher (4.4%) in patients with best overall response of SD, PD or NE compared to fatal TEAEs (2.8%) in patients with best overall response of CR or PR.

Discussion

The outcomes for patients with heavily pretreated RR DLBCL who are not candidates for transplantation (ASCT or CAR-T therapy), or those who relapse after ASCT, are typically very poor. In this population, single-agent oral selinexor demonstrated an ORR of 28·3% (11% CR), meeting the primary endpoint. The median DOR was 9·3 months (23 months for patients in CR) and the median overall survival of 9·1 months (not reached for patients in CR). The side effects associated with selinexor use were generally reversible and manageable with dose modifications and appropriate supportive care; there is no maximal duration of therapy with this agent.[17] Three responding patients experienced reduced disease burdens and became eligible for ASCT (N=1) and CAR-T (N=2) therapies; where these treatment interventions were not an option prior to entering the study.

Patients who entered the SADAL trial had heavily pretreated DLBCL with objective disease progression at study entry. Patients had to have at least 2 prior therapeutic regimens, and 40·9% of patients received at least 3 prior therapies over the course of 2·6 years since diagnosis, indicative of aggressive disease. In addition, this trial represents one of the largest clinical datasets of elderly patients with RR DLBCL: 45% of patients were ≥70 years old, and efficacy observed in this subgroup was comparable to that observed in the overall study population. Furthermore, the SADAL trial enrolled patients with particularly poor prognostic factors including 43·3% with disease progression within one year of diagnosis, 49·6% with the non-GCB subtype (46·5% with GCB subtype), 71·7% with DLBCL refractory to the most recent systemic treatment, and 16·5% with disease refractory to or relapsed <1 year from ASCT therapy. Moreover, there were relatively few exclusions for significant organ dysfunction and none for concomitant non-oncologic medications in the SADAL study (Appendix pages 2-4).

Several contemporary studies document that the survival for patients with RR DLBCL after at least 2 regimens is <6 months. First, the median survival was 5·6 months for patients with RR DLBCL who were not eligible for ASCT and received single agent nivolumab; this population was

similar to that in SADAL.[18] Second, the parenteral triplet polatuzumab-vedotin plus bendamustine and rituximab (pola-BR), which approved for third line use, showed a median OS was 12.4 months compared to 4·7 months for patients receiving a current standard of care bendamustine and ritixumab.[19] Third, patients with RR DLBCL in the SCHOLAR retrospective study who did not undergo ASCT, with 1-2 prior therapies, had a median OS of 5·1 months.[6] Finally, the median OS for patients on SADAL who had no benefit from therapy (i.e. those whose best response was PD or whose disease was not evaluable) had a median OS of 4·1 months. For this subpopulation of SADAL patients with PD/NE, (1) there were no or few available active agents for these patients once they progressed on selinexor, (2) the median OS was similar to that reported in the literature for ineffective therapies and (3) patients enrolled in SADAL were similar to typical patients in the community. In contrast, the median OS for all patients in SADAL was 9·1 months, and responses correlated with longer OS: In patients with ≥PR, the median OS was not reached and was 18.3 months in patients with SD. The apparently longer median OS in patients with SD on SADAL is consistent with the ability to continue selinexor indefinitely while there is adequate disease control – which contrasts with chemotherapeutic agents where cumulative toxicities preclude continuous dosing.

Adverse events (AEs) were similar to those reported in previous selinexor trials including from the STORM multiple myeloma trial but generally occurred somewhat less frequently and with reduced severity, consistent with the 25% lower dose used in SADAL as compared to that in the myeloma STORM trial.[12] The most common AEs such as nausea, vomiting, decreased appetite, fatigue, hyponatremia, neutropenia and thrombocytopenia, were generally reversible and improved with dose modification and/or standard supportive care. Prophylactic 5-HT3 antagonists for days 1-4 of dosing, along with optional use of a second anti-nausea agent (eg, NK1 antagonist or olanzapine) and/or appetite stimulant (eg, olanzapine 2·5-5·0 mg nightly) is associated with reduced rates and

severity of the common side effects.[20] Similarly, G-CSF for neutropenia is quite effective[21] and moderate to high doses of thrombopoietin receptor agonists can mitigate thrombocytopenia, reducing selinexor dose interruptions.[22–24] Monitoring for common side effects with weekly visits including blood counts, simple chemistry and body weight during the first 6-8 weeks of therapy allow for early identification and use of appropriate support in patients with RR DLBCL. Selinexor causes AEs that are well characterized, predictable, reversible, and manageable with standard supportive care and dose modifications in patients with RR DLBCL. This characteristic of the AE profile is critical as this allows physicians to anticipate, prevent and manage side effects. There is no evidence of cumulative toxicity or major organ toxicity, which allows selinexor to be used in patients with multiple comorbidities taking a variety of non-oncologic medications. There is no maximum duration of treatment and the longest duration of treatment with selinexor has been > 3.5 years.

Although there are no approved oral non-chemotherapeutic therapies for patients with RR DLBCL, current NCCN guidelines recommend ibrutinib or lenalidomide (± rituximab) for patients with non-GCB DLBCL.[25] These agents have shown ORR of 30-40% and DOR 4-5 months in patients with the ABC subtype DLBCL but <10 % ORR in patients with GCB DLBCL. Selinexor resulted in an ORR of 34% (CR 14%) in RR GCB DLBCL compared to 21% (CR 10%) in non-GCB disease (table 2). These results suggest that selinexor is a viable single agent oral option for patients with *either* GCB or non-GCB DLBCL. These observations are consistent with the broad mechanism of action of XPO1 inhibition in the treatment of malignancies, and similar to the lack of disease subtype specificity in myeloma[12] and other hematologic[13,26] and solid tumor[27–29] neoplasms.

Novel treatments for RR DLBCL need to be placed in the context of other therapeutic options. CAR-T cell trials and the use of these therapies are currently restricted to fit patients with good performance status, most of whom are candidates for other transplantation regimens, and have shown ORR ranging from 50%-72% and median DOR ~9.4 months for patients with RR DLBCL.

Patient selection is extremely important given the substantial toxicities and the potential for prolonged hospitalization,[30,31] limited availability (authorized centers of excellence only), ~7% reported manufacturing failure rate and the relatively young patient population included in these trials (median age 56 years old). Overall, these have limited the utility of these cell-based therapies in the generally older, frail population of patients with RR DLBCL. The recent approval of pola-BR for the treatment of adult patients with RR DLBCL after at least 2 prior therapies was based on ORR in a Phase 2, open-label clinical study comparing pola-BR (n=40) versus the doublet combination of BR (n=40) in patients with RR DLBCL not eligible for ASCT.[19] In this trial, ~29% of patients had received a *single* prior systemic therapy and few patients were >70 years of age. The study reported ORR of 45% vs 18%, and a median DOR of 12·6 vs 7·7 months for P-BR vs BR respectively.[19] The rates of AEs and serious AEs with the pola-BR triplet were comparable or higher than those reported in the SADAL population, and the required parenteral administration was an additional burden on the patients.

Many patients with DLBCL are older and/or have a large number of comorbid conditions, which preclude aggressive and complicated therapies. In contrast, there were relatively few restrictions on comorbid conditions and none on non-oncologic concomitant medications for patients on the SADAL study taking oral selinexor. Given the poor prognosis of patients with RR DLBCL following at least 2 prior regimens, the limitations of available therapeutic interventions, and the aging population, single agent oral selinexor administered in the out-patient setting showed clear durable anti-DLBCL activity. Responses were associated with substantially longer survival, underscoring the potential of oral XPO1 inhibition as an oral, non-chemotherapeutic option for patients with RR-DLBCL.

Contributors

Karyopharm Therapeutics designed the study, enrolled/treated patients, gathered data, and analyzed and interpreted data. All authors participated in writing the article, provided feedback throughout the development process, and approved the final submitted version.

Declaration of interests

XX reports… All other authors declare no competing interests.

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Tables and Figures

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	(N=127)
Age, years	
Median (range)	67·0 (35-87)
≥70 years (%)	57 (44.9)
Sex, n (%)	
Female	52 (40·9)
Male	75 (59·1)
ECOG performance-status score, n (%)	
0	55 (43·3)
1	58 (45·7)
2	13 (10·2)
3	1 (0·8)
Time since DLBCL diagnosis, years	
Median (range)	2.6 (0·01-26·2)
DLBCL type, n (%)	
De novo DLBCL	94 (74·0)
Transformed DLBCL	31 (24·4)
DLBCL subtype, n (%)	
GCB	59 (46·5)
Non-GCB	63 (49·6)
Unclassified	5 (3·9)
Double Hit/Triple Hit DLBCL, n (%)	
Yes	2 (1.6)
No	75 (59.1)
Missing	50 (39.4)
Creatinine Clearance, n (%), mL per minute	
<30	2 (1·6)
30 - <60	32 (25·2)
≥60	93 (73·2)
Lactic Acid Dehydrogenase (LDH) > 2xULN at Baseline, n (%)	
Yes	16 (12.6)
No	108 (85.0)
Missing	3 (2.4)
Number of prior systemic treatment regimens for DLBCL	
Median (range)	2·0 (2·0-5·0)
Number of prior systemic regimens for DLBCL, n (%)	
2	75 (59·1)
>3	52 (40·9)
Time since most recent progression from prior regimen to start of selinexor, weeks	

Characteristic	(N=127)
Median (range)	8·1 (1·9-406·3)
Prior ASCT therapy for DLBCL, n (%)	
Yes	38 (29·9)
Refractory to the most recent systemic treatment regimen for DLBCL, n (%)	
Yes	91 (71·7)
No	29 (22·8)
Unknown	7 (5·5)
Relapse status to the last ASCT therapy for DLBCL, n (%)	
Refractory or relapse <1 year	21 (16·5)
Relapses within 1 year of DLBCL diagnosis, n (%)	
Yes	42 (33·1)
No	49 (38·6)
Unknown	36 (28·3)

ASCT= autologous stem cell transplantation, ECOG=Eastern Cooperative Oncology Group, DLBCL=diffuse large B-cell lymphoma,

Table 2. Responses* in evaluable patients

Category	N	ORR (%)	CR (%)	PR (%)	SD (%)	PD/NR (%)
All Patients	127	36 (28·3)	15 (11·8)	21 (16·5)	11 (8·7)	80 (63·0)
GCB Subtype	59	20 (33·9)	8 (13·6)	12 (20·3)	7 (11·9)	32 (54·2)
Non-GCB Subtype	63	13 (20·6)	6 (9·5)	7 (11·1)	3 (4·8)	47 (74·6)
Unclassified	5	3 (60·0)	1 (20·0)	2 (40·0)	1 (20·0)	1 (20·0)

*Responses were adjudicated according to central imaging assessment. ORR=overall response rate (CR + PR). CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NR=No response recorded.

Table 3. Treatment-emergent adverse events (TEAE) in ≥10% of patients (mITT population)

Adverse Event	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at Least One TEAE	125 (98·4)	7 (5·5)	11 (8·7)	61 (48·0)	41 (32·3)
Thrombocytopenia	78 (61·4)	6 (4·7)	14 (11·0)	39 (30·7)	19 (15·0)
Nausea	74 (58·3)	36 (28·3)	30 (23·6)	8 (6·3)	0
Fatigue	60 (47·2)	26 (20·5)	20 (15·7)	14 (11·0)	0
Anaemia	54 (42·5)	3 (2·4)	23 (18·1)	27 (21·3)	1 (0·8)
Decreased appetite	47 (37·0)	21 (16·5)	21 (16·5)	5 (3·9)	0
Diarrhoea	45 (35·4)	26 (20·5)	15 (11·8)	4 (3·1)	0
Constipation	39 (30·7)	25 (19·7)	14 (11·0)	0	0
Neutropenia	38 (29·9)	1 (0·8)	6 (4·7)	20 (15·7)	11 (8·7)
Weight decreased	38 (29·9)	6 (4·7)	32 (25·2)	0	0
Vomiting	37 (29·1)	27 (21·3)	8 (6·3)	2 (1·6)	0
Pyrexia	28 (22·0)	16 (12·6)	7 (5·5)	5 (3·9)	0
Asthenia	27 (21·3)	8 (6·3)	13 (10·2)	6 (4·7)	0
Cough	23 (18·1)	14 (11·0)	9 (7·1)	0	0
Upper respiratory tract infection	19 (15·0)	1 (0·8)	17 (13·4)	1 (0·8)	0
Dizziness	18 (14·2)	13 (10·2)	5 (3·9)	0	0
Hypotension	17 (13·4)	9 (7·1)	4 (3·1)	4 (3·1)	0
Oedema peripheral	16 (12·6)	10 (7·9)	4 (3·1)	1 (0·8)	0
Dyspnoea	14 (11·0)	9 (7·1)	3 (2·4)	1 (0·8)	1 (0·8)
Hyponatraemia	14 (11·0)	4 (3·1)	0	10 (7·9)	0

*Shown are events that occurred in at least 10% of the patients. MedDRA Preferred Term used. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Figure 1. Overall response rate

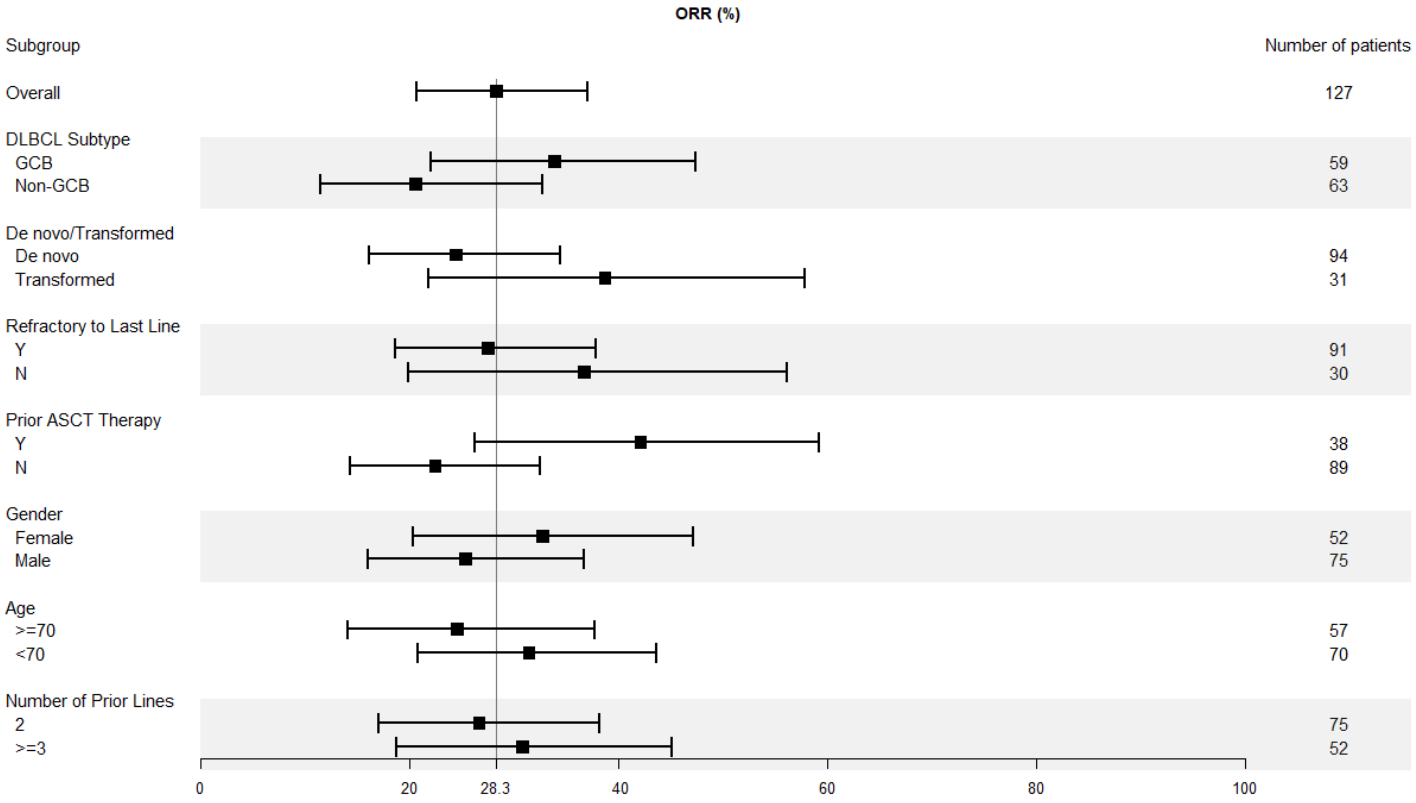
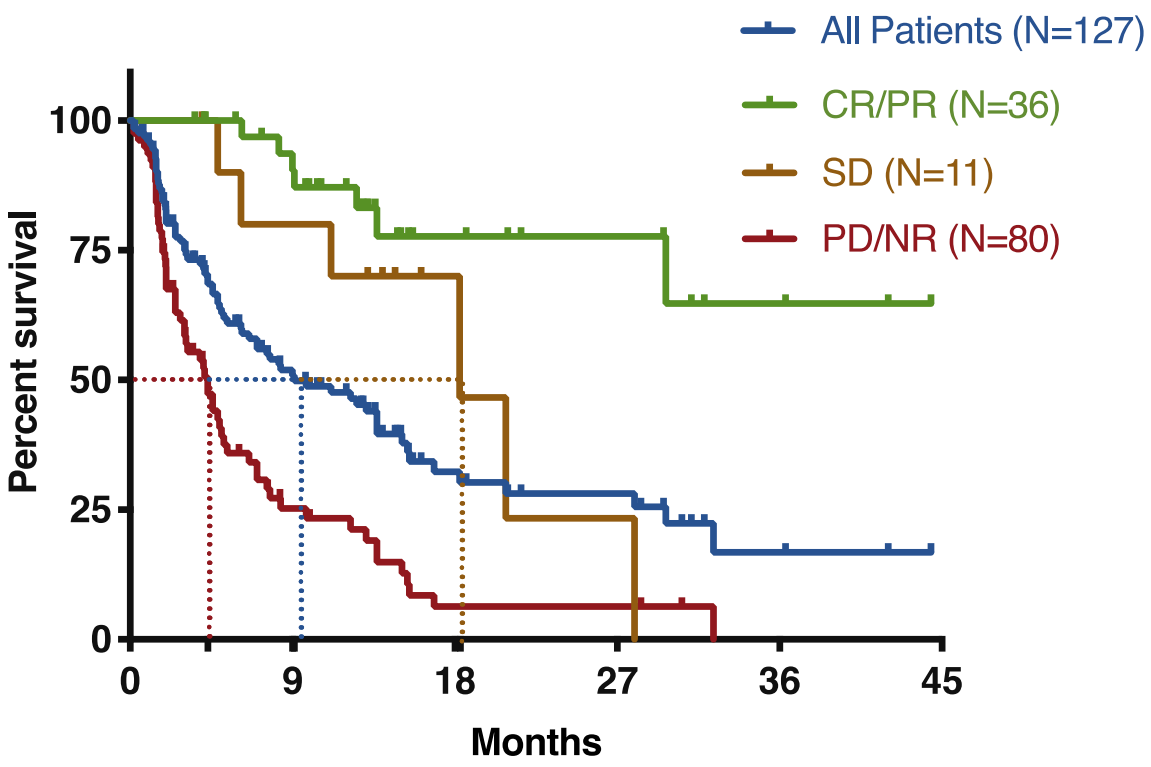


Figure 2. Kaplan-Meier analysis of overall survival in all patients in the modified intent to treat population



	Selinexor	
	Overall Survival, months	
	Median	(95% CI)
All patients	9·1	(6·6, 15·1)
CR/PR patients	NE	(29·7, NE)
SD Patients	18·3	(11·1, 28·0)
PD/NR Patients	4·3	(3·0, 5·4)

CI=confidence interval, CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=Not evaluated, NR=No response recorded

Figure 3. Changes in anatomical tumor burden for all patients

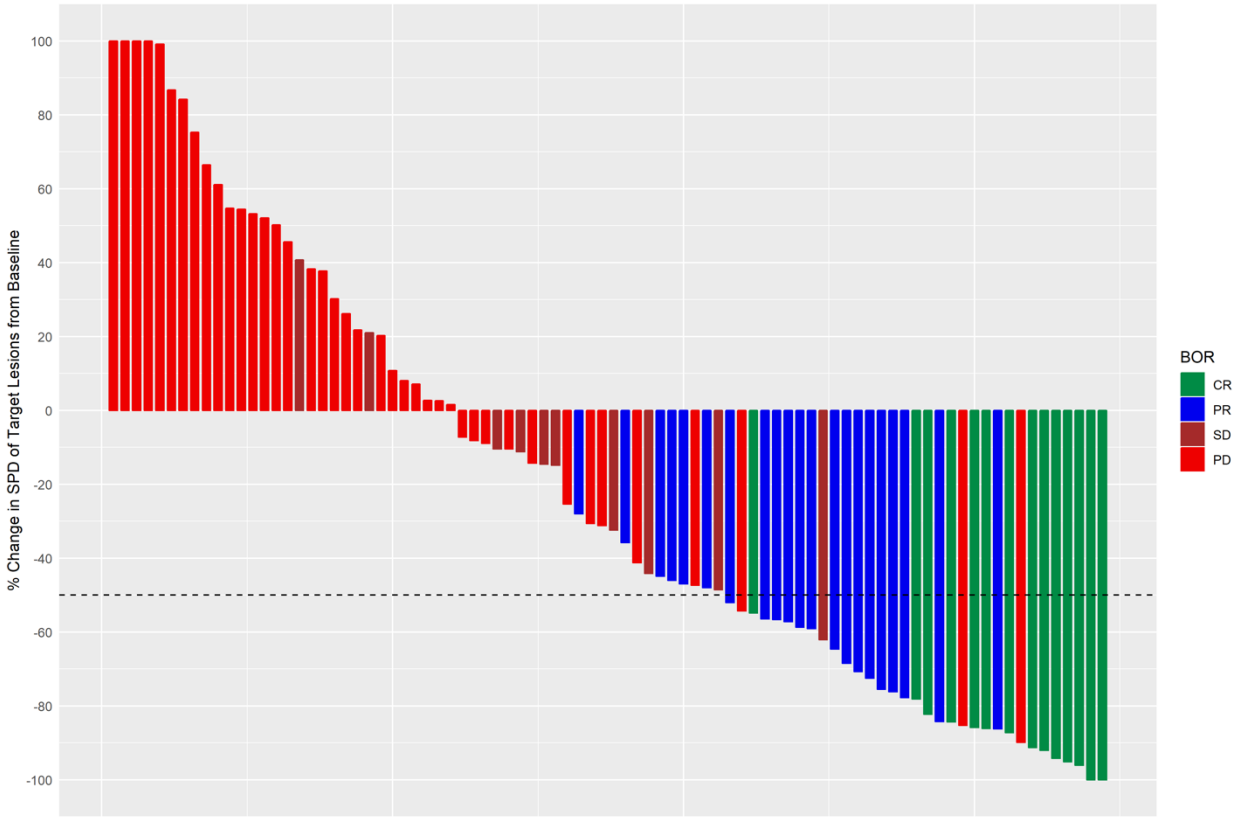
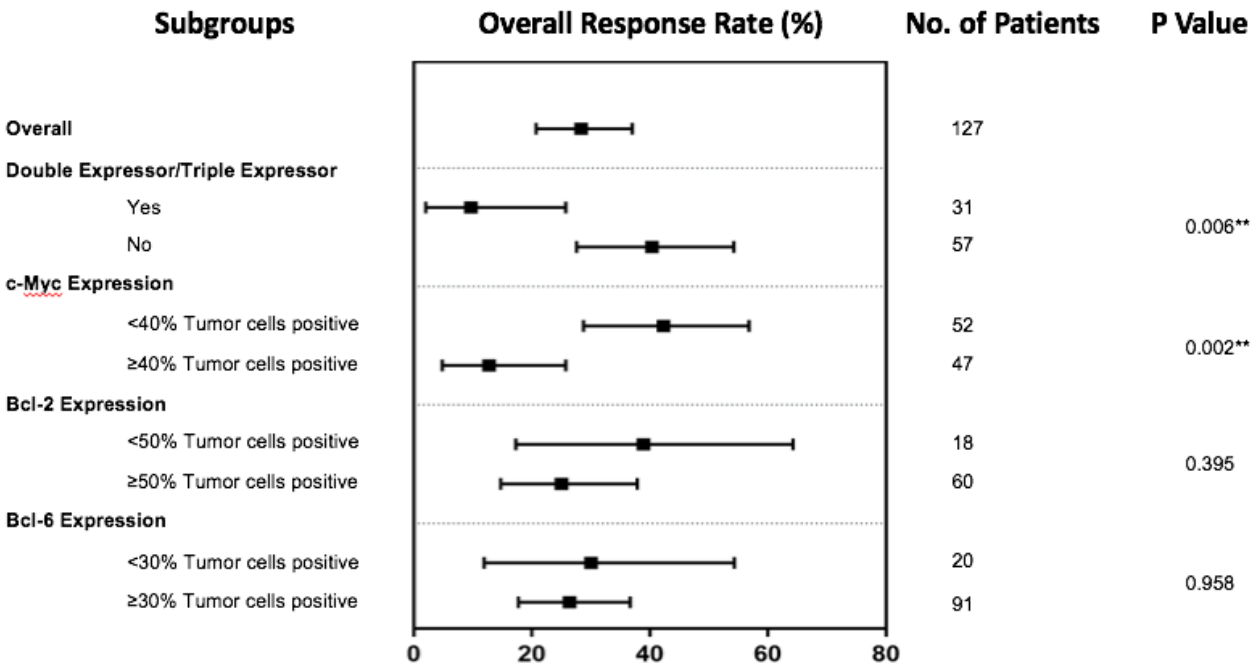


Figure 2. Predicative/prognostic biomarker analysis



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