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

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Summary

Background Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is an aggressive cancer with a median overall survival of less than 6 months. We aimed to assess the response to single-agent selinexor, an oral selective inhibitor of nuclear export, in patients with relapsed or refractory DLBCL who had no therapeutic options of potential clinical benefit.

Methods SADAL was a multicentre, multinational, open-label, phase 2b study done in 59 sites in 19 countries. Patients aged 18 years or older with pathologically confirmed diffuse large B-cell lymphoma, an Eastern Cooperative Oncology Group performance status of 2 or less, who had received two to five lines of previous therapies, and progressed after or were not candidates for autologous stem-cell transplantation were enrolled. Germinal centre B-cell or non-germinal centre B-cell tumour subtype and double or triple expressor status were determined by immunohistochemistry and double or triple hit status was determined by cytogenetics. Patients received 60 mg selinexor orally on days 1 and 3 weekly until disease progression or unacceptable toxicity. The study was initially designed to evaluate both 60 mg and 100 mg twice-weekly doses of selinexor; however, the 100 mg dose was discontinued in the protocol (version 7.0) on March 29, 2017, when an improved therapeutic window was observed at 60 mg. Primary outcome was overall response rate. The primary outcome and safety were assessed in all patients who received 60 mg selinexor under protocol version 6.0, or enrolled under protocol versions 7.0 or higher and received at least one dose of selinexor. This trial is registered at ClinicalTrials.gov, NCT02227251 (active but not enrolling).

Findings Between Oct 21, 2015, and Nov 2, 2019, 267 patients were randomly assigned, with 175 allocated to the 60 mg group and 92 to the discontinued 100 mg group. 48 patients assigned to the 60 mg group were excluded due to enrolment before version 6.0 of the protocol; the remaining 127 patients received selinexor 60 mg and were included in analyses of primary outcome and safety. The overall response rate was 28% (36/127; 95% CI 20·7–37·0); 15 (12%) achieved a complete response and 21 (17%) a partial response. The most common grade 3–4 adverse events were thrombocytopenia (n=58), neutropenia (n=31), anaemia (n=28), fatigue (n=14), hyponatraemia (n=10), and nausea (n=8). The most common serious adverse events were pyrexia (n=9), pneumonia (n=6), and sepsis (n=6). There were no deaths judged as related to treatment with selinexor.

Interpretation Single-drug oral selinexor induced durable responses and had a manageable adverse events profile in patients with relapsed or refractory DLBCL who received at least two lines of previous chemoimmunotherapy. Selinexor could be considered a new oral, non-cytotoxic treatment option in this setting.

Funding Karyopharm Therapeutics Inc.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma.[1] DLBCL is a heterogeneous disease with clinically and molecularly distinct subtypes. At initial diagnosis, treatment includes combination chemoimmunotherapy[2] (eg, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; and etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), 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 chemoimmunotherapy, followed by autologous stem-cell transplantation in eligible patients, can lead to long-term survival for some patients. However, the outlook for patients who relapse after salvage regimens (with or without autologous stem-cell transplantation) remains poor.[3–6] Emergent treatment options for this patient population with refractory or relapsed DLBCL include chimeric antigen receptor T-cell therapy or the parenteral

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Research in context

Evidence before this study

We searched PubMed between Jan 1, 2000, to Jan 1, 2020, with no language restrictions for studies investigating the treatment of patients with diffuse large B-cell lymphoma. We used the search terms "diffuse large B cell lymphoma", "DLBCL", "relapse", and "refractory". Our search showed that DLBCL is typically treated with multi-agent chemotherapy plus an anti-CD20 monoclonal antibody leading to responses in approximately 50% of patients. High-dose chemotherapy with autologous stem-cell transplantation could induce lasting remission another 20–40% of patients with relapsed or refractory disease, but only a minority of patients are candidates for this intensive therapy. Patients whose disease is refractory to, or has relapsed after, two previous therapies and who are not candidates for anti-CD19 chimeric antigen receptor T-cell therapies are highly likely to die from their disease. Drugs with novel mechanisms, including those that target XPO1 (exportin 1), that can induce durable remissions are needed in this patient population, particularly in this population, especially patients who are elderly or harbour co-morbidities. We also searched PubMed between Sept 19, 1997, to Jan 1, 2020, with no language restrictions for the search terms "exportin 1", "XPO1", and "selinexor". The reviewed literature showed that inhibition of XPO1 in DLBCL can restore the function of tumour suppressor proteins (which require nuclear localisation for activity) and could contribute to the reversal of chemotherapy resistance. Data from a phase 1 study also exist that support treatment of DLBCL with selinexor, as single drug, based on an overall response rate in 13 (32%) of 41 patients, and a complete response achieved in 4 (10%) patients.

Added value of this study

To our knowledge, SADAL is the one of the largest studies evaluating a novel therapy in patients with relapsed or refractory DLBCL who are not candidates for autologous stem-cell transplantation therapy. SADAL evaluated single-drug selinexor, an oral selective inhibitor of XPO1-mediated nuclear export, in patients with relapsed or refractory DLBCL after at least two previous therapies. The results suggest that selinexor can induce durable objective radiographic responses and improve overall survival in this setting. Responses were observed in both the germinal centre B cell and non-germinal centre B-cell subtypes of DLBCL. By contrast to chemotherapy, there is no maximum duration of therapy. Oral selinexor could be a treatment option for patients with relapsed or refractory DLBCL, particularly those who do not wish to receive parenteral drugs or have substantial major organ dysfunction and other comorbidities.

Implications of all the available evidence

Emergent treatment options for patients with relapse or refractory DLBCL include chimeric antigen receptor 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 bruton tyrosine-kinase inhibitors. Despite these options, few patients achieve long-term remission and most patients require additional treatment options. Inhibition of XPO1-mediated nuclear export with oral selinexor leads to the forced nuclear retention and functional reactivation of tumour suppressor proteins, reductions in levels of several oncoproteins, and inhibition of DNA repair, including that associated with chemotherapy resistance. Our results provide the rationale for the use of selinexor, both as a single drug and in combination with other anticancer drugs, in patients with relapsed or refractory diffuse large B-cell lymphoma. Ongoing studies with selinexor in combination with other drugs active in DLBCL, including both chemotherapy and non-cytotoxic drugs, could expand the utility of selinexor in lymphoma and in other malignant conditions.

combination of polatuzumab vedotin, a CD79b-directed antibody–drug conjugate with bendamustine, and rituximab, as well as lenalidomide (plus rituximab) and bruton tyrosine-kinase inhibitors. Despite these options, few patients achieve long-term remission and most patients require additional treatment options. Therefore, there is an unmet medical need in patients with refractory or relapsed DLBCL.

XPO1 (exportin 1), one of eight nucleo-cytoplasmic shuttling proteins involved in the export of proteins from the nucleus to the cytoplasm, is overexpressed in DLBCL and correlates with poor prognosis.[7] XPO1 mediates the functional inactivation of multiple tumour suppressor proteins (eg, p53, p73, IkBκ, FOXO) and facilitates the increased translation of oncoproteins that are relevant to B-cell biology and DLBCL.[8,9] XPO1 blockade in DLBCL re-establishes the tumour-suppressing and growth-regulating effects of multiple tumour suppressor proteins by forcing their nuclear retention, and potentially reverses chemotherapy resistance.[10] 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.[11] These oncogene mRNA-eIF4E complexes are exported out of the nucleus by XPO1, facilitating the cytoplasmic translation and increasing the levels of oncoproteins. Blockade of XPO1 prevents mRNA-eIF4E complexes from exiting the nucleus, thus preventing translation of oncoproteins. Preclinical studies show that XPO1 inhibitors induce transient cell-cycle arrest, suppress tumour growth, and induce substantial apoptosis independent of tumour cell genotype, with minimal effects on normal lymphocytes.[12–14]

Selinexor, an oral selective inhibitor of XPO1-mediated nuclear export, induces the expected nuclear accumulation and activation of tumour suppressor proteins and reduces Bcl2, Bcl-X_L, and c-Myc oncoprotein concentrations. The combination of selinexor (80 mg twice

weekly) and low-dose dexamethasone was approved by the US Food and Drug Administration for patients with advanced refractory multiple myeloma based on safety and efficacy data from the STORM study.[15] In heavily pretreated DLBCL, single-drug selinexor has previously shown an investigator-assessed overall response rate (ORR) in 13 (32%) of 41 patients, and a complete response in 4 (10%), in a phase 1 study supporting the preliminary activity of selinexor in multiple haematologic malignancies, including myeloma and DLBCL; the recommended dose from that study was 35 mg/m² (~60 mg) twice weekly.[9,16] The objective of this selinexor study (SADAL) in DLBCL was to evaluate the activity and safety of single drug selinexor in patients with relapsed or refractory DLBCL.

Methods

Study design and participants

The SADAL study was a phase 2b, open-label, multicentre study done in 59 sites in 19 countries (appendix pp 12–14). The study was initially designed to evaluate both 60 mg and 100 mg twice weekly dose of selinexor; however, an improved therapeutic window (similar overall response rate and lower adverse events) was observed at 60 mg in a prespecified interim analysis done on Nov 1, 2016, resulting in discontinuation of the 100 mg group in the protocol (version 7.0) on March 29, 2017.

Eligible patients were aged 18 years or older, and had pathologically confirmed de novo DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma; an Eastern Cooperative Oncology Group performance score of 0–2; received two to five lines of previous therapy and progressed after, or were not candidates for autologous stem-cell transplantation; and had measurable disease (2014 Lugano criteria).[18] Patients could not have primary mediastinal B-cell lymphoma. Patients whose most recent systemic anti-DLBCL therapy induced a partial response or complete response had to have at 60 days or more elapsed since the end of that therapy. All other patients, had to have at least 14 weeks (98 days) elapsed since the end of their most recent systemic anti-DLBCL therapy. These treatment intervals helped ensure that patients had an estimated life expectancy of more than 3 months, as required by the study. Previous systemic regimens permitted included at least one course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active drugs such as etoposide, bendamustine, or gemcitabine were given) and at least one course of anti-CD20 immunotherapy such as rituximab. Low dose dexamethasone (4 mg) was permitted as it does not show anti-lymphoma activity. Refractory disease was defined as progressive disease less than 6 months (if no previous autologous stem-cell transplantation) or less than 12 months (if previous autologous stem-cell transplantation) from end of treatment. Patients were deemed not eligible for high-dose chemotherapy with autologous stem-cell transplantation at the time of study entry. Platelet counts more than 75 000/µL were required at study entry. Exclusion criteria included known CNS lymphoma, meningeal involvement, or creatinine clearance less than 30 mL/min. A full list of inclusion and exclusion criteria is provided in the appendix (pp 2–4).

The institutional review board or independent ethics committee at each study centre approved the protocol (appendix p 15), and the study was done in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before enrolment.

Procedures

Oral selinexor (60 mg) tablet form was administered on days 1 and 3 of each week until disease progression, death, or unacceptable toxicities (appendix p 5).[18] 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. Supportive care was provided at the discretion of the investigator per institutional guidelines or the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.

See Online for appendix

Activity was assessed according to the revised 2014 Lugano criteria for response assessment of lymphoma[19] by independent central review and separately based on investigator assessments. An independent oncologist reviewed the clinical data and confirmed the best responses and their duration, and confirmed disease progression. DLBCL status was assessed by PET and CT (or PET and MRI) every 8 weeks plus or minus 1 week. Patients with durable responses (eg, >1 year) were permitted to have every other radiological evaluation without PET. Patients removed from study based on progressive disease confirmed by the central imaging laboratory were followed up for survival.

Complete blood count differential, complete serum chemistry, and coagulation tests were assessed each treatment cycle. Both fresh and archival tumour biopsy samples were analysed histologically[20] to determine DLBCL subtype (germinal centre B cells or non-germinal centre B cells). Cell of origin subtype was determined by immunohistochemistry-based Hans algorithm. Biopsies were requested and collected from 111 (87%) of 127 patients before selinexor dosing. Of the samples, 54% (60) were collected less than 6 months before the initiation of selinexor treatment, 17% (19) were collected between 6 months and 1 year before the initiation of selinexor treatment, and 29% (32) were collected more than 1 year before the initiation of selinexor treatment. Fluorescent in-situ hybridisation was done to detect the translocation or rearrangement status of c-Myc, Bcl-2, and Bcl-6 genes and immunohistochemistry was done to detect the expression levels of c-Myc, Bcl-2, and Bcl-6 proteins. These parameters

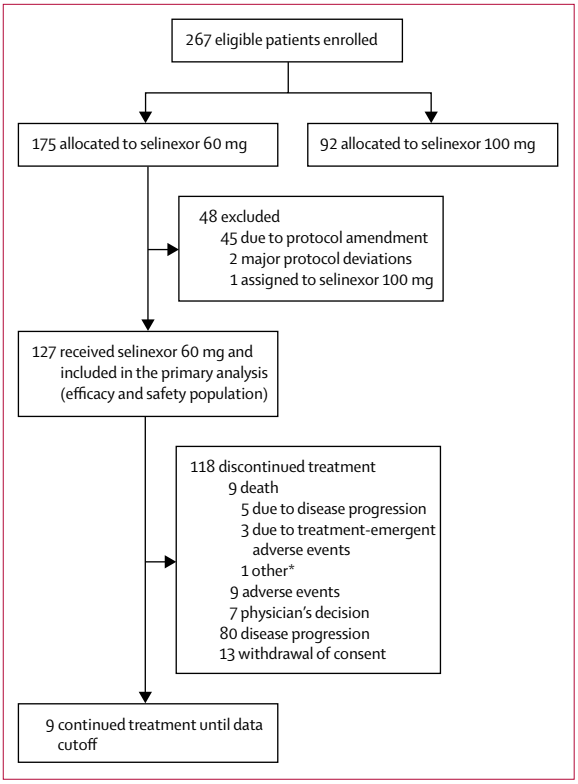

Figure 1: **Trial profile**
Modified intention-to-treat (mITT) analysis included all patients who received 60 mg selinexor under protocol version 6.0, or enrolled under protocol versions 7.0 or higher and received at least one dose of selinexor. *One patient died due to pneumonia 38 days after the last dose of the study drug.

were utilised to define double hit or triple hit DLBCL and double expressor or triple expressor status in all patients.

Safety was monitored by assessing adverse events, concomitant medications, laboratory parameters, physical examinations, vital signs, weight, Eastern Cooperative Oncology Group 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. A serious adverse event was defined as any occurrence of death, life-threatening event, in-patient hospitalisation, or congenital anomaly or birth defect.

Outcomes

The primary endpoint was overall response, defined as the proportion of patients who achieved either a complete response or partial response according to the 2014 Lugano criteria.[19]

Secondary endpoints were duration of response, defined as the duration of time from first occurrence of complete response or partial response until the first date that disease progression was objectively documented; and disease control rate, defined as the proportion of patients who achieved complete response, partial response, or stable disease after enrolment (ie, overall response rate plus stable disease).

Exploratory endpoints included progression-free survival, defined as the duration of time from enrolment until progression or death due to any cause; overall survival, defined as the duration of time from enrolment until death due to any cause; quality of life; time to progression; pharmacokinetic and pharmacodynamic endpoints; and subgroup analyses of overall response, duration of response, disease control rate, overall survival, progression-free survival, and quality-of-life in patients with and without the germinal B-cell subtype; double-hit DLBCL versus non-double-hit disease; response to last previous therapy; and the revised International Prognostic Index categories.

Statistical Analysis

The sample size was based on assumptions to evaluate the clinical effect of selinexor by reference to a minimal threshold level for overall response rate, set to 0·15 (15%). A pre-planned interim analysis included a total of 63 patients enrolled on protocol (version 6.0) before Nov 1, 2016, who were eligible for response evaluation. For the primary analysis, a sample size of 127 patients allowed for a one-sided test at an α level of 0·025 to detect a minimum of 25% of patients with a partial response or better against a value of 15% under the null hypothesis with 80% power. The modified intention-to-treat population was used for the primary efficacy and consisted of all patients who received 60 mg selinexor under protocol version 6.0, or enrolled under protocol versions 7.0 or higher and received at least one dose of selinexor. The primary safety population consisted of all patients in the modified intention-to-treat population. Our protocol stated that the primary efficacy analyses will be done in both the modified intention-to-treat population and the per-protocol populations; however, because these populations are the same, we report only one analysis.

At data cutoff (Aug 1, 2019), the primary analysis of overall response rate was done using the two-sided 95% CI and one-sided 97·5% CI, calculated for the overall response rate among the intention-to-treat population. The exact method was used to calculate the CIs for overall response rate. A prespecified subgroup analysis was done to assess the primary outcome between patients with and without the germinal B-cell subtype. Summary statistics were computed and displayed for each of the defined analysis populations and according to each assessment timepoint. Summary statistics for continuous variables minimally included number, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, percentages, and two-sided 95% CIs are presented. For time-to-event variables, the Kaplan–Meier method was used for descriptive summaries. Two-proportion z-test was used to test two group proportions. SAS (version 9.4) was used for statistical analyses. The trial is registered with ClinicalTrials.gov, NCT02227251.

	Total (N=127)
Age, years	
Median (range)	67·0 (35–87)
≥70 year	57 (45%)
Sex	
Female	52 (41%)
Male	75 (59%)
ECOG performance-status score	
0	55 (43%)
1	58 (46%)
2	13 (10%)
3	1 (1%)
Time since DLBCL diagnosis, years	2·7 (1.38–4.92)
DLBCL type	
De novo DLBCL	94 (74%)
Transformed DLBCL	31 (24%)
DLBCL subtype	
GCB	59 (47%)
Non-GCB	63 (50%)
Unclassified	5 (4%)
Double hit or triple hit DLBCL	
Yes	5 (4%)
No	84 (66%)
Missing	38 (30%)
Creatinine Clearance, mL per min	
<30	2 (2%)
30–<60	32 (25%)
≥60	93 (73%)
Lactic acid dehydrogenase more than two times ULN at baseline	
Yes	16 (13%)
No	108 (85%)
Missing	3 (2%)
Number of previous systemic treatment regimens for DLBCL	2·0 (2·0–3·0)
(Table 1 continues in next column)	

	Total (N=127)
(Continued from previous column)	
Number of previous systemic regimens for DLBCL	
2	75 (59%)
>3	52 (41%)
Time since most recent progression from previous regimen to start of selinexor, weeks	8·1 (4·57–15·14)
Previous ASCT therapy for DLBCL	
Yes	38 (30%)
No	89 (70%)
Refractory to the most recent systemic treatment regimen for DLBCL	
Yes	91 (72%)
No	29 (23%)
Unknown	7 (6%)
Refractory or relapse DLBCL less than 1 year after last ASCT therapy	21 (17%)
Relapses within 1 year of DLBCL diagnosis	
Yes	42 (33%)
No	49 (39%)
Unknown	36 (28%)

Data are n (%) or median (IQR). ASCT=autologous stem-cell transplantation. ECOG=Eastern Cooperative Oncology Group. DLBCL=diffuse large B-cell lymphoma. ULN=upper limit of normal. There was a protocol deviation because patient with ECOG status 3 recruited.

Table 1: **Baseline characteristics**

Role of the funding source

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.

Results

Between Oct 21, 2015, and Nov 2, 2019, 267 patients were randomly assigned and 175 allocated to the 60 mg selinexor group and 92 to the 100 mg selinexor group. 48 patients were excluded mainly due to enrolment before version 6.0 of the protocol, resulting in the inclusion of 127 patients in the modified intention-to-treat and safety populations (figure 1). Median age was 67 years (45% of patients were aged ≥70 years), and the median interval from initial DLBCL diagnosis to selinexor treatment was 2·7 years (range 0·1–26·2, IQR 1·38–4·92; table 1).

Of the 127 patients who received selinexor, 118 (93%) discontinued treatment due to disease progression (n=80), death (n=9), physician decision (n=7), adverse events (n=9), and withdrawal by patient (n=13; figure 1).

The target dose of selinexor was 120 mg per week (60 mg twice weekly) and the median average dose received per week was 100 mg (range 48–180; IQR 78·3–120·0). The median total dose received was 960 mg (range 60–15 960; IQR 570–1890) and the median duration of treatment was 9 weeks (range 1–193; IQR 6–24).

The primary endpoint of overall response rate was 28% (36/127; 95% CI 20·7–37·0; one-sided 97·5% CI 20·7 to 100·0), including 15 (12%; 95% CI 6·8–18·7) complete responses and 21 (17%; 10·5–24·2) partial responses (table 2). The disease control rate was 37% (95% CI 28·6–46·0). At a median follow-up of 11·1 months (IQR 1·87–10·27, the median duration of response was 9·3 months (95% CI 4·8–23·0). The median duration of response was 23·0 months (95% CI 10·4–23·0) for patients with complete response, and 4·4 months (95% CI 2·0–not evaluable) for patients with partial response. Time to partial response or better occurred at first radiographic assessment (median 8 weeks, range 7–16 [IQR 7·86–8·43]).

Subgroup analyses showed that the overall response rate in patients with a germinal centre B-cell subtype was

	Overall response rate	Complete response	Partial response	Stable disease	Progressive disease or no response recorded
All patients	36/127 (28%) (20·7–37·0)	15 (12%) (6·8–18·7)	21 (17%) (10·5–24·2)	11 (9%) (4·4–15·0)	80 (63%) (54·0–71·4)
GCB subtype	20/59 (34%) (22·1–47·4)	8 (14%) (6·0–25·0)	12 (20%) (11·0–32·8)	7 (12%) (4·9–22·9)	32 (54%) (40·8–67·3)
Non-GCB subtype	13/63 (21%) (11·5–32·7)	6 (10%) (3·6–19·6)	7 (11%) (4·6–21·6)	3 (5%) (1·0–13·3)	47 (75%) (62·1–84·7)
Unclassified	3/5 (60%) (14·7–94·7)	1 (20%) (0·5–71·6)	2 (40%) (5·3–85·3)	1 (20%) (0·5–71·6)	1 (20%) (0·5–71·6)

Data are n/N (%; 95% CI). Responses were adjudicated according to central imaging assessment. GCB=germinal centre B cell. See results section in main text for one-sided 97·5% CI.

***Table 2*: Responses in evaluable patients**

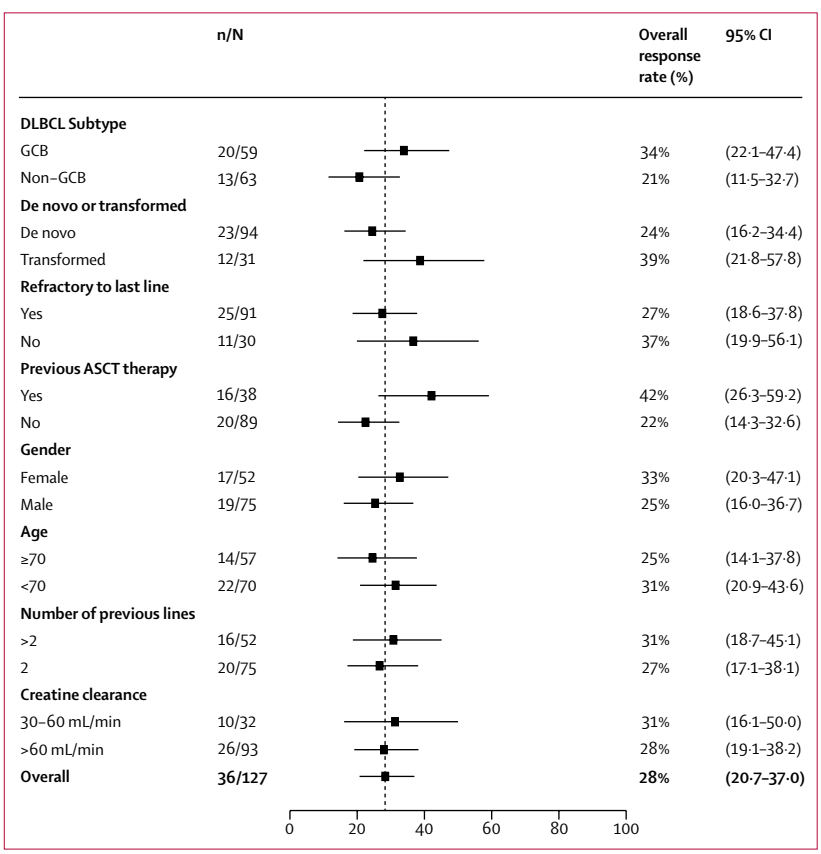

***Figure 2*: Overall response rate**

Bars represent 95% CI. Germinal centre B cell versus non-germinal centre B cell, double hit DLBCL versus non-double hit DLBCL, response to last previous DLBCL therapy, and the revised International Prognostic Index were prespecified analyses. Dotted line represents the overall response rate of 28% among the 127 patients. Bars represent two-sided exact 95% CI (lower and upper bounds of the CI are shown in the last column on the figure)

34% (20/59; 95% CI 22·1–47·4), including eight (14%; 6·0–25·0) complete responses and 12 (20%; 11·0–32·8) partial responses. Nine (7%) patients had ongoing responses at the last disease assessment before the data cutoff (seven patients with ongoing complete responses and two with ongoing partial responses).

Responses were consistent across many different subgroups regardless of age, gender, previous therapy, DLBCL subtype, and refractory status or previous ASCT therapy (figure 2). The median time between progressive disease from last previous therapy to the start of selinexor was 59 days in selinexor responders and 52 days in non-responders, indicating that outcomes were not influenced by time since last therapy, defined as the date of progressive disease to the date of signed consent.

At a median follow-up time of 14·7 months (IQR 2·0–13·2), median progression-free survival was 2·6 months (95% CI 1·9–4·0; appendix p 9) and median overall survival was 9·1 months (95% CI 6·6–15·1; appendix, p 10). In patients with a response (≥partial response), the median overall survival was not reached, and in patients who had stable disease, the median overall survival was 18·3 months (95% CI 11·1–28·0). In patients who had progressive disease or not evaluable response, the median overall survival was 4·3 months (3·0–5·4). A total of 56 (65%) patients with a baseline target lesion and at least one after baseline assessment had a reduction in tumour burden (figure 3).

Regarding predictive or prognostic biomarker analysis, patients with high levels of c-Myc (based on a cutoff of 40% positive cells as determined by immunohistochemistry) had a 13% overall response rate (6/47; 95% CI 4·8–25·7), whereas those with low levels had a 42% (22/52; 28·7–56·8) overall response rate (p=0·0024). Similar results were observed with overall response rate for DLBCL with double or triple expressor status (3/31; 9·7%, 95% CI 2·0–25·8), and for DLBCL without double or triple expressor status (23/57; 40·3%, 27·6–54·2; p=0·0056), but these differences were largely a reflection of c-Myc overexpression because expression levels of neither Bcl-2 nor Bcl-6 affected the overall response rate (appendix p 11).

Because 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 three lines of previous therapy, showed an anatomic partial response after 6 months of selinexor therapy, and a complete metabolic response (complete response) after 9 months. Another patient, a 55-year-old male with primary refractory disease and bulky abdominal mass of germinal centre B-cell subtype after six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and two courses of gemcitabine-based salvage regimen, entered the study and achieved a partial response after 4 months and complete response after 8 months of selinexor therapy.

Last, selinexor treatment enabled three patients who previously progressed following ASCT to become eligible and undergo chimeric antigen receptor T-cell therapies. A 70-year old female with double-hit DLBCL (germinal B-cell subtype), developed a CD20 negative relapse and entered the study. After four cycles of selinexor, this patient

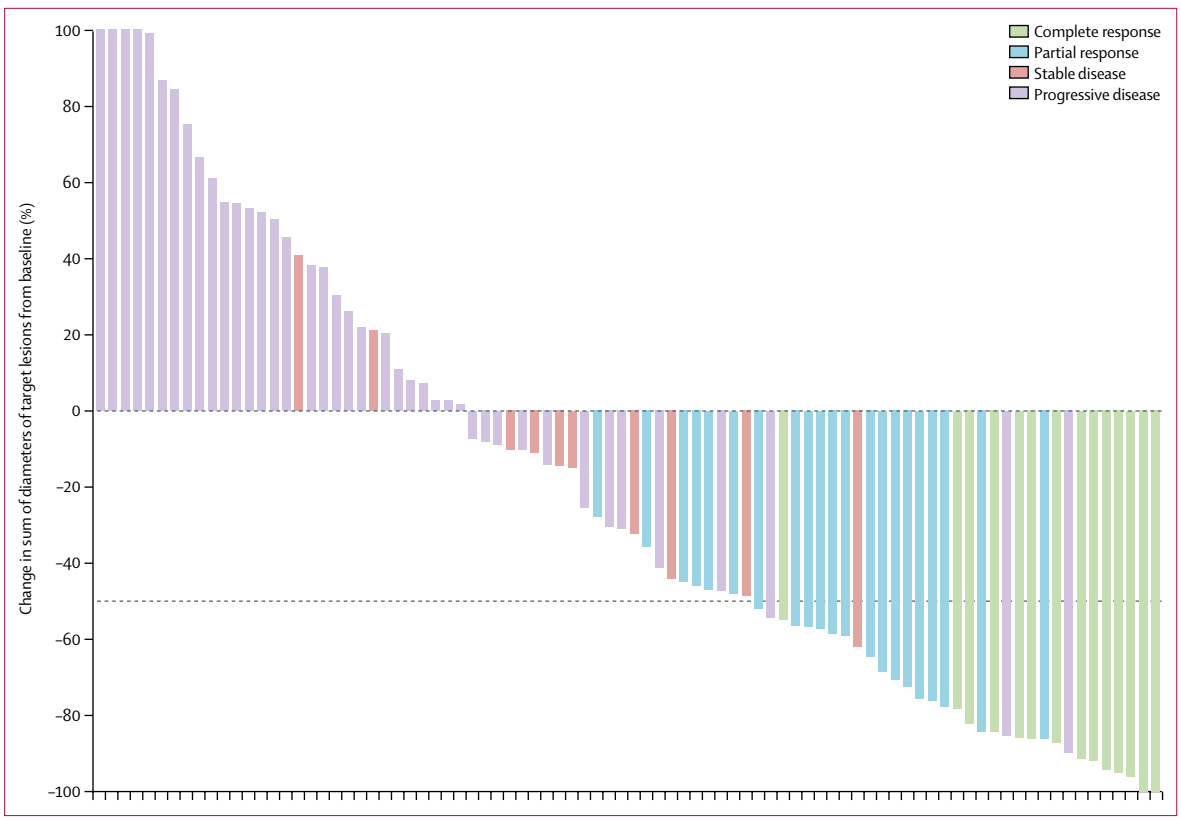

Figure 3: **Changes in tumour burden for all patients**
Response based on metabolic response or anatomic response if PET missing.

achieved a metabolic partial response, then despite a metabolic progressive disease at six cycles went on to have chimeric antigen receptor T-cell therapy after the final visit. A 45-year-old male with germinal centre B-cell DLBCL and previous ASCT treatment demonstrated a rapid reduction of tumor burden and metabolic partial response within 59 days of initiation of selinexor; this patient received chimeric antigen receptor T-cell therapy. A 70-year old female, also with germinal centre B-cell DLBCL, showed progressive disease 8 months following ASCT. An initial partial response was observed within 47 days of initiation of selinexor. Selinexor was discontinued after more than 1 year as the patient was changed to chimeric antigen receptor T-cell 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 chimeric antigen receptor T-cell therapy.

Regarding safety, 125 (98%) patients had at least one treatment-emergent adverse event (table 3). The most common treatment-emergent adverse events occurring in 20% or more of patients were thrombocytopenia (n=78, 61%), nausea (n=74, 58%), fatigue (n=60, 47%), anaemia (n=54, 43%), decreased appetite (n=47, 37%), diarrhoea (n=45, 35%), constipation (n=39, 31%), neutropenia (n=38, 30%), weight loss (n=38, 30%), vomiting (n=37, 29%), pyrexia (n=28, 22%), and asthenia (n=27, 21%; table 3). Most treatment-emergent adverse events that were nonhaematological were limited in severity to grades 1 or 2. The most common grade 3 or 4 adverse events were thrombocytopenia (n=58, 46%), neutropenia (n=31, 24%), anaemia (n=28, 22%), fatigue (n=14, 11%), hyponatraemia (n=10, 8%), and nausea (n=8, 6%); these were typically reversible with standard supportive care or dose modification. There were no grade 3 or higher bleeding events reported in patients with thrombocytopenia and febrile neutropenia (n=4, 3%) usually resolved (neutrophil counts returning to normal with resolution of fever) after standard growth factor and antibiotic treatment. There were no fatal outcomes due to febrile neutropenia.

22 (17%) patients discontinued treatment due to a treatment-emergent adverse events. Treatment-emergent adverse events leading to dose modification (reduction or interruption) occurred in 89 (70%) patients, with the majority (73 [57%]) of patients having modifications in the first two cycles (appendix p 7). No significant differences in adverse events leading to discontinuation were observed across various subgroups (data not shown). The most common treatment-emergent adverse events (>5% of patients) that required dose modification were thrombocytopenia 49 (39%), neutropenia 20 (16%), fatigue 17 (13%), nausea 13 (10%), diarrhea 7 (6%), pyrexia 10 (8%), and anaemia 11 (9%). For thrombocytopenia,

	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (16%)	39 (31%)	19 (15%)
Nausea	66 (52%)	8 (6%)	0
Fatigue	46 (36%)	14 (11%)	0
Anaemia	26 (21%)	27 (21%)	1 (1%)
Decreased appetite	42 (33%)	5 (4%)	0
Diarrhoea	41 (32%)	4 (3%)	0
Constipation	39 (31%)	0	0
Neutropenia	7 (6%)	20 (16%)	11 (9%)
Weight loss	38 (30%)	0	0
Vomiting	35 (28%)	2 (2%)	0
Pyrexia	23 (18%)	5 (4%)	0
Asthenia	21 (17%)	6 (5%)	0
Cough	23 (18%)	0	0
Upper respiratory tract infection	18 (14%)	1 (1%)	0
Dizziness	18 (14%)	0	0
Hypotension	13 (10%)	4 (3%)	0
Oedema peripheral	14 (11%)	1 (1%)	0
Dyspnoea	12 (10%)	1 (1%)	1 (1%)
Hyponatraemia	4 (3%)	10 (8%)	0

Data are n (%). Data are for events that occurred in at least 10% of the patients, for serious adverse events in ≥2% patients see appendix p 8. The Medical Dictionary for Regulatory Activities preferred terms were used. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). No Grade 5 events were reported in 10% or more of the patients.

Table 3: **Treatment-emergent adverse events in 10% or more of patients**

neutropenia, nausea, vomiting, decreased appetite and hyponatraemia, the median number of events per patient was 1, and most occurred during cycles one or two. The majority of patients who required a dose reduction due to adverse events received selinexor 40 mg twice weekly, which, with appropriate supportive care, was shown to be effective for resolution of the events. Supportive care included additional anti-nausea drugs (eg, oral olanzapine 2·5 mg to 5 mg once daily), appropriate fluid and caloric intake, appetite stimulants, psychostimulants, moderate to high doses of thrombopoietin-receptor agonists (n=21), and granulocyte colony stimulating factors (n=31). These drugs usually reduced the intensity or duration of adverse events, or both.

Serious adverse events occurred in 61 (48%) patients (appendix p 8). The most common serious adverse events (≥3%) were pyrexia (n=9, 7%), pneumonia (n=6, 5%), fatigue (n=5, 4%), anaemia (n=4, 3%), cardiac failure (n=4, 3%), febrile neutropenia (n=4, 3%), and sepsis (n=6, 5%; appendix p 8). A total of 73 (58%) patients died during the study, 25 of these patients died within 30 days of the last dose of selinexor (20 due to disease progression and five due to a treatment-emergent adverse events). The treatment-emergent adverse events leading to a fatal outcome included acute respiratory distress syndrome (n=1), cerebrovascular accident (n=1), and sepsis (n=3). Three of the five deaths due to treatment-emergent adverse events occurred in patients aged 70 years or older. Deaths due to treatment-emergent adverse events were higher (n=4, 4%) in patients with best overall response of stable disease, progressive disease, or not evaluable disease than were deaths due to fatal treatment-emergent adverse events (n=1, 3%) in patients with best overall response of complete response or partial response. 48 (38%) patients died after 30 days of the last dose of selinexor, of these, 41 deaths were due to disease progression, four deaths were due to influenza B infection (n=1), respiratory insufficiency (n=1), pneumonia (n=1), and pleural effusion (n=1) and cause of death was unknown in three patients. None of the deaths in the study were considered related to selinexor by the investigator.

Discussion

The outcomes for patients with heavily pretreated relapsed or refractory DLBCL who are not candidates for autologous stem-cell transplantation or chimeric antigen receptor therapy, or for those who relapse after autologous stem-cell transplantation, are generally very poor. In this population, single-drug oral selinexor showed an overall response rate of 28% (97·5% CI 20·7 to 100·0; 12% complete response), meeting the primary endpoint of the study. The median duration of response was 9·3 months (95% CI 4·8 to 23·0) (23 months [10·4 to 23·0] for patients in complete response) and the median overall survival of 9·1 months (95% CI 6·6 to 15·1; not reached [29·7 to not reached] for patients in complete response). The side-effects associated with selinexor were generally reversible and manageable with dose modifications and appropriate supportive care; there is no specific organ toxicity and no maximal duration of therapy with this drug.[21] Three responding patients experienced reduced disease burdens and proceeded to chimeric antigen receptor therapy (n=3); this intervention was not considered to be an option.

Patients in the SADAL trial had heavily pretreated DLBCL with objective disease progression at study entry. Patients had to have at least two previous therapeutic regimens, and 41% of patients received at least three previous therapies over the course of 2·7 years (IQR 1·38–4·92) since diagnosis, indicative of aggressive disease. In addition, this trial represents one of the largest clinical datasets of elderly patients with relapsed or refractory DLBCL: 57 (45%) of patients were aged 70 years or older, and activity 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 (table 1). Moreover, there were relatively few exclusions for significant organ dysfunction and none for concomitant non-oncologic medications in the SADAL study (appendix pp 2–4).

Although selinexor was dosed in the early phase of the study on the basis of body surface area to minimise inter-individual variation in the pharmacokinetic exposure of

selinexor in patients, results from a different study[22] comparing flat dosing to body surface area-adjusted dosing indicated that body surface area-adjusted dosing of selinexor did not reduce interpatient variability as anticipated for a non-cytotoxic oral drug. Moreover, oral dosing is associated with a 20–30% variation in drug levels, which exceeds any differences that would be incorporated by adjusted dosing. As a flat dosing approach can reduce dosing error, improve patient adherence, and prevent delays in dosing due to time-consuming dose calculations,[18] selinexor dosing was changed to fixed-dose administration in the study.

Although cross-trial comparisons might be done with caution, several studies have shown that the median overall survival for patients with relapsed or refractory DLBCL after at least 2 regimens was less than 6 months.[23,24] The median survival was 5·8 months (95% CI 3·09–9·17) for patients with relapsed or refractory DLBCL who were not eligible for autologous stem-cell transplantation and received nivolumab monotherapy; this population was similar to that in SADAL.[23] Second, the parenteral triplet polatuzumab-vedotin plus bendamustine and rituximab, approved for third-line therapy use, showed a median overall survival of 12·4 months (95% CI 9 to not evaluable) compared with 4·7 months (3·7 to 8·3) for patients receiving a current standard of care bendamustine and ritixumab (hazard ratio 0·42, 0·24 to 0·75).[24] Third, patients with relapsed or refractory DLBCL in the SCHOLAR retrospective study[6] who did not undergo autologous stem-cell transplantation, with one to two previous therapies, had a median overall survival of 5·1 months (95% CI not reported). Last, the median overall survival for patients in SADAL who had no benefit from therapy (ie, those whose best response was progressive disease or whose disease was not evaluable) was 4·3 months (3·0 to 5·4). For this subpopulation with progressive disease on selinexor, there were no or few available active drugs once they progressed with selinexor, the median overall survival was similar to that reported for ineffective therapies, and patients enrolled in SADAL were similar to typical patients in the community.

By contrast, the median overall survival for all patients in SADAL was 9·1 months (95% CI 6·6–15·1), and responses correlated with longer overall survival: in patients with partial response or better, the median overall survival was not reached and was 18·3 months (11·1–28·0) in patients with stable disease. The apparently longer median overall survival in patients with stable disease in SADAL is consistent with the ability to continue selinexor indefinitely while there is adequate disease control, which contrasts with chemotherapeutic drugs and some antibody-toxin conjugates with which cumulative toxicities preclude continuous dosing.

Adverse events were similar to those reported in previous selinexor trials, including the STORM multiple myeloma trial,[15] but generally occurred somewhat less frequently and with reduced severity, consistent with the 25% lower dose used in SADAL as compared with that in STORM.[15] In a report by Gavriatopoulou and colleagues,[25] the most common adverse events such as nausea, vomiting, decreased appetite, fatigue, hyponatraemia, neutropenia, and thrombocytopenia mainly occured within the first 8 weeks, were generally reversible, and improved with dose modification or standard supportive care. In the study by Gilmore and colleagues,[26] prophylactic 5-HT3 antagonists for days 1–4 of dosing, along with optional use of a second anti-nausea drug (eg, neurokinin 1 antagonist or olanzapine) or appetite stimulant (eg, olanzapine 2·5–5·0 mg once nightly) was associated with reduced rates and severity of the common side-effects. Similarly, G-CSF for neutropenia was quite effective in a study by Mehta and colleagues.[27] Previous reports have also shown that moderate to high doses of thrombopoietin receptor agonists can mitigate thrombocytopenia, reducing selinexor dose interruptions.[25,28,29] Monitoring for common side-effects with weekly visits including blood counts, simple chemistry, and bodyweight during the first 6–8 weeks of therapy allow for early identification and use of appropriate support in patients with relapsed and refractory DLBCL.[25] In our study, selinexor caused adverse events that are well characterised, predictable, reversible, and manageable with standard supportive care and dose modifications in patients with relapsed or refractory DLBCL. This characterisation of the adverse events profile is essential as this allows physicians to anticipate, prevent, and manage side-effects. There is no maximum duration of treatment and the longest duration of treatment in our study with selinexor has been for more than 3·5 years.

In comparison to a study of polatuzumab vedotin plus bendamustine and rituximab (n=39) by Sehn and colleagues,[24] single agent selinexor showed an improved overall adverse event profile. The occurrence of grade 3 or 4 thrombocytopenia was similar: 41·0% (16/39) with polatuzumab-vedotin plus bendamustine-rituximab and 45·7% (58/127) with selinexor.

Although there are no approved oral non-chemotherapeutic drugs for relapsed or refractory DLBCL, current National Comprehensive Cancer Network guidelines recommend ibrutinib or lenalidomide (with or without rituximab) for patients with non-germinal centre B-cell DLBCL.[30] These drugs have been shown to have an overall objective response rate of 30–40% and duration of response of 4–5 months in patients with the activated B-cell subtype, but a less than 10% objective response rate in patients with germinal centre B-cell DLBCL.[25] In this study, selinexor resulted in an objective response rate of 34% (complete response 14%) in relapsed or refractory germinal centre B-cell DLBCL compared with 21% (complete response 10%) in non-germinal centre B-cell disease (table 2), and responses were durable. These results suggest that selinexor is a viable single-drug option for patients with either germinal centre B-cell or non-germinal centre B-cell DLBCL. These observations

are consistent with the broad mechanism of action of XPO1 inhibition in the treatment of malignancies, and similar to the absence of disease subtype specificity in myeloma[12] and other haematological[9,31] and solid tumour[22,32,33] neoplasms.

Although it is true that most patients with DLBCL that overexpressed c-Myc showed poor responses to selinexor, a subset of these tumours did respond. C-Myc translation is dependent on the XPO1 cargo eIF4E, that carries its mRNA to be translated in the cell cytoplasm. Selinexor treatment blocks the eIF4E-mRNA transport, retaining c-Myc mRNA in the cell nucleus. It is possible that combinations of drugs will be necessary to induce responses in most cases of c-Myc overexpressing DLBCL.

Novel treatments for relapsed or refractory DLBCL need to be placed in the context of other therapeutic options. Chimeric antigen receptor T-cell trials were restricted to fit patients with good performance status, most of whom are candidates for other transplantation regimens, and most trials have shown overall survival rates ranging from 50% to 72% and median duration of response approximately 9·4 months in patients with relapsed or refractory DLBCL. Patient selection is extremely important given the substantial toxicities and the potential for prolonged hospitalisation,[34,35] limited availability (authorised centres of excellence only), approximately 7% reported manufacturing failure rate and the young patient population included in these trials (median age 56 years). The long-term outcomes of these cell-based therapies in the generally older, frail population of patients with relapsed and refractory DLBCL is yet to be determined. The approval of the parenteral triplet polatuzumab-vedotin plus bendamustine-rituximab for the treatment of adult patients with relapsed or refractory DLBCL after at least two previous therapies was based on the overall response rate in a phase 2, open-label clinical study[24] comparing six cycles of the parenteral triplet combination (n=40) versus the doublet combination of bendamustine-rituximab (n=40) in patients with relapsed or refractory DLBCL not eligible for autologous stem-cell therapy.[24] In the trial, approximately 29% of patients had received a single systemic therapy previously and few patients were older than 70 years. The study reported overall response rate of 45% and a median duration of response of 12·6 months (95% CI 4·0 to not evaluable) in the parenteral triplet combination group versus an overall response rate of 18% and a median duration of response of 7·7 months (4·0 to 18·9) in the doublet combination group.[24] The proportion of adverse events and serious adverse events with the triplet combination were similar or higher than those reported in SADAL, and the required parenteral administration was an additional burden on the patients. In addition, therapy duration was limited to six cycles due to cumulative toxicities, which might be suboptimal for prolonged disease control.

An important limitation of the SADAL study is the single-arm design. However, because patients enrolled in the study had received at least two previous lines of therapy and whose disease had progressed after autologous stem-cell transplant therapy or were ineligible for the therapy, appropriate comparator treatment options are scarce. Many patients with DLBCL are older or have a substantial number of comorbid conditions, which preclude aggressive and complicated therapies. By contrast, there were relatively few restrictions on comorbid conditions and none on non-oncological concomitant medications for patients in SADAL.

Another limitation of the study was the requirement for at least 60 days (and as much as 98 days) to have elapsed since the most recent previous therapy. This requirement was consistent with the protocol inclusion criterion for an expected lifespan of at least 3 months, which is standard in advanced haematologic malignancies. In earlier protocol versions, it was noted that patients with heavily pretreated DLBCL actively progressing while receiving salvage combination chemoimmunotherapy had a high rate of disease-associated mortality. On the basis of the results from this study, patients with heavily pretreated disease could be considered for treatment with a non-chemotherapy regimen such as selinexor, which could provide disease control and tumour reduction through a novel mechanism, rather than immediate retreatment with standard cytotoxic drugs to which their tumours are often resistant and with which cumulative toxicities could be exacerbated.

Because of the poor prognosis of patients with relapsed or refractory DLBCL after at least two previous regimens, the limitations of available therapeutic interventions, and the ageing population, single-drug selinexor administered in the out-patient setting showed meaningful durable anti-DLBCL activity. Responses were associated with substantially improved survival, underscoring the potential of oral XPO1 inhibition as an oral, non-chemotherapeutic option for patients with relapsed or refractory DLBCL.

Contributors

MK and SS contributed to the study design. JMS, CT, SC, ME, GF, BH, NK, and EVDN enrolled patients. SB, RB, OC, FC, MC, HC, ME, GF, AG, NH, UJ, NK, MM, JRSM, FO, JS, MS, JSPV, TPV, HW, KW, and JZ were involved in the acquisition of the study data. XM did the statistical analyses. SB, RB, FC, MC, HC, BH, UJ, XM, JRSM, MS, JSPV, EVDN, TPV, and HW analysed the study data. SB, OC, FC, MC, HC, GF, AG, NH, BH, AJ, MK, XM, JRSM, FO, SS, JS, MS, CT, JSPV, EVDN, TPV, HW, and JZ interpreted the study data. KC and DM centrally managed the trial and trial data. AJ, MK, and NK participated in drafting the manuscript. All authors provided critical review of the manuscript and approved the final submitted version.

Declaration of interests

NK reports research support from Verastem, Gilead, Celgene, and Roche, as well as honoraria from Gilead, Janssen, and Karyopharm. FC reports personal fees from Takeda, Gilead, and Janssen, outside the submitted work. MC reports personal fees from Celgene, Gilead, Janssen, Karyopharm, Novartis, Roche, Sandoz, and Servier outside the submitted work. GF reports personal fees from Karyopharm and Roche, outside the submitted work. AG reports personal fees and honoraria from AstraZeneca, personal fees and board membership from Cota and Kite/Gilead, personal fees from Janssen, Celgene, Acerta, and research funding from Constellation, Bayer, CALBG, Genentech, Hoffman-La Roche, MD Anderson, Morphosys, Pharmacyclics, and the University of

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Data sharing

Karyopharm Therapeutics agrees to share individual participant data that underlie the results reported in this article (after deidentification), including the study protocol and statistical analysis plan. Data availability will begin 9 months after publication and will be available 36 months after publication. To gain access, data requestors should submit a proposal to medicalinformation@karyopharm.com. Proposals will be reviewed by an independent review committee identified for this purpose.

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References

1 Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ, Go RS. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am J Hematol* 2015; **90:** 790–95.

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 Ardeshna KM, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol* 2005; **130:** 363–72.

4 Hitz F, Connors JM, Gascoyne RD, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. *Ann Hematol* 2015; **94:** 1839–43.

5 Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *Am J Hematol* 2013; **88:** 890–94.

6 Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017; **130:** 1800–08.

7 Luo B, Huang L, Gu Y, et al. Expression of exportin-1 in diffuse large B-cell lymphoma: immunohistochemistry and TCGA analyses. *Int J Clin Exp Pathol* 2018; **11:** 5547–60.

8 Culjkovic-Kraljacic B, Fernando TM, Marullo R, et al. Combinatorial targeting of nuclear export and translation of RNA inhibits aggressive B-cell lymphomas. *Blood* 2016; **127:** 858–68.

9 Kuruvilla J, Savona M, Baz R, et al. Selective inhibition of nuclear export with selinexor in patients with non-Hodgkin lymphoma. *Blood* 2017; **129:** 3175–83.

10 Laín S, Xirodimas D, Lane DP. Accumulating active p53 in the nucleus by inhibition of nuclear export: a novel strategy to promote the p53 tumor suppressor function. *Exp Cell Res* 1999; **253:** 315–24.

11 Kodali D, Rawal A, Ninan MJ, et al. Expression and phosphorylation of eukaryotic translation initiation factor 4E binding protein 1 in B-cell lymphomas and reactive lymphoid tissues. *Arch Pathol Lab Med* 2011; **135:** 365–71.

12 Van Der Watt PJ, Maske CP, Hendricks DT, et al. The karyopherin proteins, Crm1 and Karyopherin β1, are overexpressed in cervical cancer and are critical for cancer cell survival and proliferation. *Int J Cancer* 2009; **124:** 1829–40.

13 Gray LJ, Bjelogrlic P, Appleyard VCL, et al. Selective induction of apoptosis by leptomycin B in keratinocytes expressing HPV oncogenes. *Int J Cancer* 2007; **120:** 2317–24.

14 Zhang K, Wang M, Tamayo AT, et al. Novel selective inhibitors of nuclear export CRM1 antagonists for therapy in mantle cell lymphoma. *Exp Hematol* 2013; **41:** 67–78.e4

15 Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med* 2019; **381:** 727–38.

16 Ben-Barouch S, Kuruvilla J. Selinexor (KTP-330) - a selective inhibitor of nuclear export (SINE): anti-tumor activity in diffuse large B-cell lymphoma (DLBCL). *Expert Opin Investig Drugs* 2019; **29:** 15–21.

17 Van Heertum, RL, Scarimbolo R, Wolodzko J, et al. Lugano 2014 criteria for assessing FDG-PET/CT in lymphoma: an operational approach for clinical trials. *Drug Des Devel Ther* 2017; **11:** 1719–28.

18 Mathijssen RHJ, de Jong FA, Loos WJ, van der Bol JM, Verweij J, Sparreboom A. Flat-fixed dosing versus body surface area–based dosing of anticancer drugs in adults: does it make a difference? *Oncologist* 2007; **12:** 913–23.

19 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:** 3059–67.

20 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:** 200–7.

21 XPOVIO [package insert]. Karyopharm Therapeutics Inc. Newton, MA. 2019. https://www.karyopharm.com/wp-content/uploads/2019/07/NDA-212306-SN-0071-Prescribing-Information-01July2019.pdf (accessed Dec 18, 2019).

22 Abdul Razak AR, Mau-Soerensen M, Gabrail NY, et al. First-in-class, first-in-human phase i study of selinexor, a selective inhibitor of nuclear export, in patients with advanced solid tumors. *J Clin Oncol* 2016; **34:** 4142–50.

23 Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: A single-arm, phase II study. *J Clin Oncol* 2019; **37:** 481–89.

24 Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2020; **38:** 155–65.

25 Gavriatopoulou M, Chari A, Chen C, et al. Integrated safety profile of selinexor in multiple myeloma: Experience from 437 patients enrolled in clinical trials. *Leukemia* 2020; published Feb 24. DOI:10.1038/s41375-020-0756-6.

26 Gilmore J, D'amato S, Griffith N, Schwartzberg L. Recent advances in antiemetics: new formulations of 5HT 3 -receptor antagonists. *Cancer Manag Res* 2018; **10:** 1827–57.

27 Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia. *J Immunol* 2015; **195:** 1341–49.

28 Machlus KR, Wu SK, Vijey P, et al. Selinexor-induced thrombocytopenia results from inhibition of thrombopoietin signaling in early megakaryopoiesis. *Blood* 2017; **130:** 1132–43.

29 Soff GA, Miao Y, Bendheim G, et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. *J Clin Oncol* 2019; **37:** 2892–98.

30 The National Comprehensive Cancer Network. Diffuse large B-cell lymphoma. 2017. https://www.nccn.org/patients/guidelines/content/PDF/nhl-diffuse-patient.pdf (accessed Dec 18, 2019).

31 Garzon R, Savona M, Baz R, et al. A phase 1 clinical trial of single-agent selinexor in acute myeloid leukemia. *Blood* 2017; **129:** 3165–74.

32 Gounder MM, Zer A, Tap WD, et al. Phase IB study of selinexor, a first-in-class inhibitor of nuclear export, in patients with advanced refractory bone or soft tissue sarcoma. *J Clin Oncol* 2016; **34:** 3166–74.

33 Vergote IB, Lund B, Peen U, et al. Phase 2 study of the exportin 1 inhibitor selinexor in patients with recurrent gynecological malignancies. *Gynecol Oncol* 2019; **156:** 308–14.

34 Chen R, Song X-T, Chen B. CD19 chimeric antigen receptor T cell therapy for the treatment of B cell lineage acute lymphoblastic leukemia. *Discov Med* 2015; **20:** 185–90.

35 Schuster SJ, Bartlett NL, Assouline S, et al. Mosunetuzumab induces complete remissions in poor prognosis non-hodgkin lymphoma patients, including those who are resistant to or relapsing after chimeric antigen receptor t-cell (CAR-T) therapies, and is active in treatment through multiple lines. *Blood* 2019; **134** (suppl)**:** 6 (abstr).