A Phase 2b , Open-Label Study of Selinexor (KPT-330) in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

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Primary Objective:To evaluate the efficacy of selinexor 60 mg in comparison to a minimally effective lower threshold level of ORR of 15% in patients with R/R DLBCL Secondary Objectives:* To determine DOR* To determine the disease control rate (DCR...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas NEC
Study type	Interventional

Summary

ID

NL-OMON46935

Source
ToetsingOnline

Brief title
SADAL: Selinexor Against Diffuse Aggressive Lymphoma

Condition

- Lymphomas NEC

Synonym
Lymphoma, relapse/refractory Diffuse large B-cell lyphoma

Research involving
Human

Sponsors and support

Primary sponsor: Karyopharm Therapeutics, Inc.

Source(s) of monetary or material Support: industry

Intervention

Keyword: Diffuse Aggressive Lymphoma, DLBCL, Relapsed/Refractory DLBCL, Selinexor (KPT-330)

Outcome measures

Primary outcome

Efficacy:

Objective disease response assessment will be made according to the revised criteria for response assessment of lymphoma (Cheson, 2014). The data used for primary statistical analysis will be provided by the central imaging laboratory.

The primary endpoint of ORR will be assessed as the ORR of selinexor 60 mg compared to a minimally effective lower threshold level of ORR of 15%.

* The ORR is defined as the proportion of patients who achieve either CR or PR.

* Progression is defined as the first occurrence of PD per the revised response criteria. Clinical disease progression in the absence of formal criteria for PD should be radiographically confirmed whenever possible and must be comprehensively documented by the treating physician. Patients who have clinical disease progression in the absence of formal criteria for PD or radiographical confirmation will be censored at the time of last non-PD adequate response assessment.

* DOR is defined as the duration of time from first occurrence of CR or PR until the first date that disease progression is objectively documented

* DCR is defined as the proportion of patients who achieve CR, PR, or SD for a minimum of 4 weeks, following randomization/enrollment (i.e., ORR + SD)
* PFS is defined as the duration of time from randomization/enrollment until progression or death due to any cause. A sensitivity analysis will also be performed for PFS where death will be included if it may be reasonably attributed to the patient*s underlying DLBCL.

* OS is defined as the duration of time from randomization/enrollment until death due to any cause. A sensitivity analysis will also be performed for OS where death will be included if it may be reasonably attributed to the patient*s underlying DLBCL.
* Each patient*s TTP on selinexor compared with the TTP of his/her most recent prior therapy. TTP is defined as the duration of time from the date of randomization/enrollment until the date of progression.

Safety:

The safety and tolerability of selinexor will be evaluated by means of adverse event (AE) reports, Eastern Cooperative Oncology Group (ECOG) performance status, physical examinations, electrocardiograms (ECGs), ophthalmic examinations, concomitant medications, vital signs, and laboratory safety evaluations.

PK and PDn Assessments:

PK and PDn will be determined at various times following administration of

selinexor.

PK endpoints to be evaluated will include maximum plasma concentration (Cmax)

and time-to-peak plasma concentration.

The PDn endpoints will include:

* Each patient*s DLBCL molecular subtype (GCB or non-GCB) using gene expression

and/or protein profiling, DNA sequencing, and FISH

* Changes in transcripts, or levels, or activation of relevant oncogenes,

phenotype-related proteins, and XPO1 targets

Secondary outcome

See above

Study description

Background summary

DLBCL is an aggressive cancer with a median survival of less than 6 months without treatment. With current immunochemotherapy, 60 to 65% of patients are progression-free at 2 years, and ~30% of patients with DLBCL are disease-free at 10 years following initial diagnosis. The remaining patients have a poor prognosis with disease resistant to available agents, including high-dose chemotherapy with stem cell transplantation. A very clear unmet medical need persists for patients with R/R DLBCL.
Selinexor is an orally bioavailable SINE compound that specifically blocks exportin 1 (XPO1). In Phase 1 studies including patients with heavily pretreated DLBCL, single agent oral selinexor showed an overall response rate (ORR) of 32% (41 evaluable patients). Activity was observed in both the GCB and non GCB subtypes of DLBCL. Patients with response had an improved overall survival (OS) versus those who had stable disease (SD) or PD (Karyopharm Oral Lymphoma Presentation, 2015 International Conference on Malignant Lymphoma).
The current study is designed to confirm selinexor activity with R/R DLBCL in patients who have had at least 2 but no more than 5 previous systemic regimens and are not eligible for high dose chemotherapy with stem cell rescue at the time of study entry.
A pre-planned interim futility analysis (that included a total of 63 patients enrolled on protocol Version 6.0 prior to 01 November 2016 who were eligible

for response evaluation) found the 60 mg dose to have a significantly lower AE burden with reduced discontinuations due to toxicities, while providing a central review adjudicated ORR (~28%) equivalent to the higher dose, but with a longer duration of response (DOR) and longer OS. Based on these results, the 100 mg Arm will be discontinued as of protocol Version 7.0 and the study will be completed with a single 60 mg Arm based on Food and Drug Administration feedback provided in March 2017.

Study objective

Primary Objective:
To evaluate the efficacy of selinexor 60 mg in comparison to a minimally effective lower threshold level of ORR of 15% in patients with R/R DLBCL

Secondary Objectives:
* To determine DOR
* To determine the disease control rate (DCR)
* To assess the safety profile of selinexor

Exploratory Efficacy Objectives:
* To determine the median progression-free survival (PFS) and median OS
* To make a preliminary comparison of PFS, ORR, DOR, DCR, quality of life (QoL), and OS in patients with GCB and non-GCB DLBCL
* To assess QoL using 1) the Functional Assessment of Cancer Therapy * Lymphoma (FACT-Lym) questionnaire and 2) the EuroQol 5 dimensions 5 levels (EQ 5D 5L) Health Questionnaire
* To make a preliminary comparison of PFS, ORR, DOR, DCR, QoL, and OS in patients with DH-DLBCL, including translocations identified by cytogenetic analysis during study screening or overexpression of both MYC and BCL2 or BCL6, and with non-DH- DLBCL
* To make a preliminary comparison of PFS, ORR, DOR, DCR, QoL, and OS in patients with *very good*, *good*, and *poor* Revised International Prognostic Index (R-IPI)
* To make a preliminary comparison of PFS, ORR, DOR, DCR, QoL, and OS based on the response to last prior DLBCL therapy (complete response [CR] or partial response [PR] versus all others)
* To compare each patient*s time to progression (TTP) on selinexor with the TTP of the patient*s most recent prior therapy

Exploratory Pharmacokinetic (PK) and Pharmacodynamic (PDn) Objectives:
PK studies:
* To further describe PK properties of selinexor in patients with R/R DLBCL
PDn studies in peripheral blood and/or tumor biopsies:
* To define each patient*s DLBCL molecular subtype, including GCB or non GCB, using gene-expression profiling, immunophenotyping, deoxyribonucleic acid (DNA) sequencing, and fluorescence in situ hybridization (FISH) analysis
* To evaluate messenger ribonucleic acid (mRNA), protein levels, and cellular

localization of tumor suppressor and oncogene proteins as well as microribonucleic acid (miRNA) following treatment with selinexor, in general, and as related to response

Study design

This is a multicenter, open-label Phase 2b study of the selective inhibitor of nuclear export (SINE) selinexor (60 mg) given orally to patients with relapsed and/or refractory (R/R) diffuse large B cell lymphoma (DLBCL) who have no therapeutic options of demonstrated clinical benefit.

The primary analysis population will include all patients who meet eligibility criteria and who were assigned to the 60-mg Arm under protocol Version *6.0 (for those enrolled under protocol Version 7.0 or higher, patients must also receive at least 1 dose of selinexor). This population consists of ~130 patients with R/R DLBCL.
DLBCL histology, DLBCL subtype (germinal center B-cell [GCB] or non-GCB), and *double hit* DLBCL (DH-DLBCL) status will be confirmed/determined in all patients.
It is planned that at least 50% of the ~130 patients will have the GCB subtype of DLBCL. The remaining patients may have DLBCL of either the GCB or the non-GCB subtype.
Patients will be treated with a fixed milligram dose of 60 mg selinexor orally twice weekly (BIW).
Study site personnel will provide all scans performed for disease assessment during the study to the central imaging laboratory and all radiology reports to Karyopharm Therapeutics Inc. (Karyopharm).
The central imaging laboratory will review all scans performed for disease assessment during the study, to independently assess disease response and time of progressive disease (PD).
Patients should remain on study treatment until the assessment of PD from the central imaging laboratory has been obtained (unless medically contraindicated).
* Patients who have PD confirmed by the central imaging laboratory will discontinue study treatment and be followed for survival.
For patients with progression of disease on imaging assessment, if disease progression is not clearly unequivocal and/or the patient is clearly deriving clinical benefit, after discussion with the Karyopharm Medical Monitor, the Investigator may elect to continue the patient on study and repeat imaging within 4 to 8 weeks for confirmation or negation of PD.
* Patients who have PD assessed by the treating physician that is not confirmed by the central imaging laboratory should remain on study treatment (unless medically contraindicated). If the treating physician decides to discontinue these patients from study treatment, they will discontinue study treatment and be followed for survival.
Previous Protocol Versions
Protocol Versions *3.0 required administration of selinexor in conjunction with

lowdose dexamethasone (12 mg with each dose of selinexor). As of Version 4.0, dexamethasone is no longer required to be given in conjunction with selinexor. In addition, the inclusion criteria were updated in protocol Version 6.0. In protocol
Versions 7.0 and higher, the inclusion criteria were further updated and the high (100 mg) dose Arm was removed. Details for the statistical analysis of the various protocol populations are provided in the Statistical Methods subsection.

Intervention

Selinexor will be given at an oral fixed milligram (mg) dose of 60 mg on Days 1 and 3 (e.g., Monday and Wednesday or Tuesday and Thursday, etc.) of Weeks 1 to 4 of each 4 week cycle (total of 8 doses per cycle).

Patients who achieve a partial remission or better will transition to maintenance dosing. The maintenance dose of selinexor will be 60 mg orally QW. Patients whose dose has been reduced such that the total weekly dose is <60 mg will continue on that tolerated dose. If a patient experiences a subsequent increase in disease burden, or per the discretion of the PI, the dose of selinexor can be increased to 60 mg orally BIW, after discussion with the Medical Monitor.

Patients treated under Versions 2.0 to 6.0 of the protocol may have been randomized to the 100 mg Arm in which selinexor may have been given at an oral fixed milligram (mg) dose of 100 mg on Days 1 and 3 (e.g., Monday and Wednesday or Tuesday and Thursday, etc.) of Weeks 1 to 3 (Versions 2.0 to 4.0) or Weeks 1 to 4 (Versions 5.0 and 6.0) of each 4-week cycle (total of 8 doses per cycle).
The 100 mg Arm has been removed in Version 7.0.
Patients randomized to the 100 mg Arm on earlier versions of the protocol and still on treatment at doses >60 mg BIW (i.e., 120 mg selinexor per week) will have their dosing regimen immediately decreased to a maximum dose of 120 mg per week. If, in the opinion of the Investigator, the patient*s dose should not be immediately reduced, continuation of a dose > 60 mg BIW (> 120 mg per week) will only be allowed after approval by the Karyopharm Medical Monitor.

Study burden and risks

Very common side effects (*10%): In 100 people receiving selinexor more than 10 people may have:
Nausea
Vomiting
Diarrhea
Decreased appetite
Hyponatremia * low sodium
Dehydration

Vision Blurred
Thrombocytopenia * decrease in platelets, which help your blood clot
Anemia * decrease in red blood cells
Neutropenia * decrease in neutrophils * a specific type of white blood cell that helps fight infections
Leukopenia * decrease in white blood cells
Fatigue
Weight decrease
Dysgeusia * change in taste
Dizziness
Constipation
Dyspnea * shortness of breath
Asthenia * loss of energy; weakness

Common side effects (*1-10%): In 100 people receiving selinexor about 1 to 10 people may have:
Dry mouth
Blood Creatinine Increased * increase of creatinine in the blood due to a reduction in kidney function, often related to dehydration
Worsening of pre-existing cataracts
Febrile neutropenia * Fever in the absence of a normal white blood cell response that may mean you have an infection
Syncope * fainting
Confusion
Pneumonia
Sepsis * potentially life-threatening complication of an infection
Cognitive disorder

Uncommon side effects (>0.1-1%): In 1,000 people receiving selinexor about 1 to 10 people may have:
Altered behavior
Tumor lysis syndrome * potentially a life-threatening side effect caused by the rapid breakdown of tumor cells and may cause irregular heartbeat, kidney failure or abnormal blood test results which included elevated uric acid level, elevated serum potassium and phosphorus levels, and a decreased calcium level

Rare side effects (>0.01-0.1%):In 10,000 people receiving selinexor about 1 to 10 people may have:
Acute cerebellar syndrome * symptoms can include a sudden loss of coordination, balance, or slurred speech

Serious adverse effects: *3 cases reported as related by the principal investigator:
Acute kidney injury
Aspartate aminotransferase increased * elevated liver enzyme level
Bacteremia * bacterial infection in the blood
Delirium * state of acute confusion

Encephalopathy * brain disease, damage, or malfunction, which can present different symptoms that range from mild, such as some memory loss or subtle personality changes, to severe, such as dementia, seizures, or coma.
General physical health deterioration
Hyperglycemia * elevated blood sugar level
Hypotension * low blood pressure
Pulmonary embolism * pulmonary embolism occurs when a clump of material, most often a blood clot, gets wedged into an artery in your lungs.
Pyrexia * fever
Septic shock
Upper respiratory tract infection

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients, age *18 years, with pathologically confirmed or transformed DLBCL whose disease is R/R, with documented evidence of disease progression (according to the revised criteria for response assessment of lymphoma (Cheson, 2014) and who in the opinion of the Investigator are not candidates for high-dose chemotherapy with autologous stem cell rescue, may be considered for enrollment. If the patient*s most recent systemic anti DLBCL therapy induced a PR or CR, at least 60 days must have elapsed since the end of that therapy; otherwise at least 14 weeks (98 days) must have elapsed since the end of their most recent systemic anti-DLBCL therapy. Patients must have received at least 2 but no more than 5 previous systemic regimens for the treatment of their DLBCL including at least 1 course of anthracycline-based chemotherapy (unless absolutely contraindicated due to cardiac dysfunction, in which case other active agents such as etoposide, bendamustine, or gemcitabine must have been given) and at least 1 course of anti-CD20 immunotherapy (e.g., rituximab), unless contraindicated due to severe toxicity. Patients who were considered ineligible for standard multi-agent immunochemotherapy must have received at least 2 (but no more than 5) previous systemic regimens including at least 1 course of anti CD20 antibodies and must be approved by the Medical Monitor. Prior stem cell transplantation is allowed; induction, consolidation, stem cell collection, preparative regimen, and transplantation ± maintenance are considered a single line of therapy. Patients should have an estimated life expectancy of more than 3 months at study entry.

Exclusion criteria

Patients with DLBCL with mucosa-associated lymphoid tissue [MALT] lymphoma, composite lymphoma (Hodgkin*s lymphoma [HL]+ non-Hodgkin*s lymphoma [NHL]), or DLBCL transformed from diseases other than indolent NHL are excluded from this study. Primary mediastinal (thymic) large B-cell lymphoma (PMBL) and central nervous system lymphoma are excluded. Patients must not be eligible for high-dose chemotherapy with autologous stem cell transplantation and documentation for ineligibility must be provided. Patients with hemoglobin <10.0 g/dL, a circulating lymphocyte count >50,000/*L, or who have had a red blood cell transfusion within 14 days prior to and including Cycle 1 Day 1 are excluded.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-07-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Selinexor
Generic name:	(Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide

Ethics review

Approved WMO Date:	02-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	12-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	09-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-001977-15-NL
ClinicalTrials.gov	NCT02227251
CCMO	NL56132.029.16