A Randomized, Double-blind, Placebo-Controlled, Active Comparator, Multicenter, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination With Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

Published: 05-11-2020
Last updated: 08-04-2024

This study will evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab among subjects with relapsed or refractory CD30-positive (CD30 expression >=1%) or CD30

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON52039

Source
ToetsingOnline

Brief title
SGN35-031 - ECHELON-3

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
DLBCL, Non Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Seagen Inc.
Source(s) of monetary or material Support: Seattle Genetics

Intervention

Keyword: large B-cell lymphoma, relapsed

Outcome measures

Primary outcome

Evaluate and compare PFS between the 2 treatment arms in the intent-to-treat

(ITT) population

Evaluate and compare PFS between the 2 treatment arms in the CD30-positive

population

Secondary outcome

Evaluate and compare OS between the 2 treatment arms in the ITT population

* Evaluate and compare OS between the 2 treatment arms CD30-positive population

* OS in the ITT population

* OS in the CD30-positive population

* Evaluate and compare objective response rate (ORR) between the 2 treatment

arms in the ITT population

Study description

Background summary

Both brentuximab vedotin and lenalidomide have single-agent activity in R/R DLBCL and unique mechanisms of action. Potential mechanisms for lenalidomide*s activity include augmentation of innate and adaptive immune function, alterations of the cytokine profile of the tumor microenvironment, and effects on angiogenesis. Combinations of lenalidomide with agents that have minimal effect on these components of the immune system, such as brentuximab vedotin, are less likely to have antagonistic effects. Although brentuximab vedotin is thought to act primarily through delivery of MMAE to the malignant cells, it is possible that lenalidomide may enhance the activity of the anti-CD30 antibody through immune-mediated mechanisms. Rituximab, lenalidomide and brentuximab vedotin all have manageable safety profiles, making this an attractive combination in multiply relapsed and heavily pretreated subjects.

Study objective

This study will evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab among subjects with relapsed or refractory CD30-positive (CD30 expression >=1%) or CD30 <1% (CD30 expression <1%) DLBCL.

Study design

This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab versus placebo in combination with lenalidomide and rituximab for the treatment of subjects with relapsed or refractory DLBCL.

Intervention

NVT

Study burden and risks

Subjects should come to the study center every 21 days for infusion administration and blood draw controls. every 6 weeks a CT scan should be made to monitor tumor development. The administered medication also has a chance of side effects as described in detail in the test subject information. In view of the prognosis for this group of subjects and the group that has already been extensively treated, the burden in relation to the expected outcome is acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Participants with relapsed or refractory diffuse and transformed large B-cell lymphoma (R/R DLBCL). DLBCL and cell of origin (GCB versus non- GCB) will be histologically determined by the most recent local pathology assessment for the purposes of study eligibility and stratification.
- Participants must have R/R disease following 2 or more lines of prior systemic therapy. For subjects with transformed DLBCL (subtype k), at least the last systemic therapy used must have been for DLBCL.
- Participants must be HSCT or CAR-T ineligible according to the investigator and must meet at least one of the following criteria:
o One or more co-morbidities, including cardiac, pulmonary, renal or hepatic dysfunction that in the opinion of the Investigator make the subject medically unfit to received HSCT or CAR-T therapy
o Active disease following induction and salvage chemotherapy
o Inadequate stem cell mobilization (for HSCT)
o Relapse following prior HSCT or CAR-T
o Unable to receive CAR-T therapy due to financial, geographic, insurance or manufacturing issues

- Participants must have tumor tissue submitted to the central pathology lab for the determination of CD30 expression.
- An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2
- Participants must have fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and bidimensional measurable disease of >1.5 cm by computed tomography (CT), as assessed by the site radiologist within 28 days of Day 1.

Other protocol defined inclusion criteria may apply.

Exclusion criteria

- History of another malignancy within 2 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy.
- History of progressive multifocal leukoencephalopathy (PML).
- Active cerebral/meningeal disease related to the underlying malignancy. Subjects with a history of cerebral/meningeal disease related to the underlying malignancy are allowed if prior CNS disease has been effectively treated and without progression for at least 3 months.
- Any uncontrolled Grade 3 or higher (per NCI CTCAE version 5.0) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted
- Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 3 weeks prior to first dose of study drug, unless underlying disease has progressed on treatment
- Participants who are breastfeeding
- Known hypersensitivity to any study drug or excipient contained in the drug formulation of the study drugs
- Any contraindication to associated study treatments.
- Known to be positive for hepatitis B by surface antigen expression.
- Subjects who are hepatitis B surface antigen (HBsAg) negative but hepatitis B core antibody (HBcAb) positive are eligible, but should start hepatitis B prophylaxis therapy prior to receiving the first dose of rituximab. Known to be positive for hepatitis C (HCV) infection (either confirmed positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
- Participants with previous allogeneic HSCT if they meet either of the following criteria:
1. <100 days from HSCT
2. Active acute or chronic graft-versus-host disease (GVHD) or receiving immunosuppressive therapy as treatment for or prophylaxis against GVHD
- Previous treatment with brentuximab vedotin or lenalidomide. Previous

treatment with other vedotin-based ADCs is permitted if the last dose is at least 6 months prior to Day 1. Current therapy with immunosuppressive medications (including steroids), other systemic anti-neoplastic, or investigational agents.
a) Prednisone (or equivalent) <=10 mg/day may be used for nonlymphomatous purposes
- Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, pulmonary embolism, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose
of study drugs
- Congestive heart failure, Class III or IV, by the NYHA criteria
- Grade 2 or higher peripheral sensory or motor neuropathy at baseline

Other protocol defined exclusion criteria may apply.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Adcetris

Generic name:	Brentuximab Vendotin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mabthera
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	Lenalidomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-11-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-05-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	27-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2020-002686-33-NL
CCMO	NL75158.058.20