An Open-Label, Single-arm, Phase I study of AEB071 (a Protein Kinase C Inhibitor) in Patients with CD79-mutant Diffuse Large B-Cell Lymphoma

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Estimate the maximum tolerated dose (MTD) of AEB071 (dose escalation) and characterize the safety and tolerability of the MTD or recommended Phase 2 dose of AEB071 in patients with DLBCL (dose expansion).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON38217

Source
ToetsingOnline

Brief title
COEB071X2101

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Diffuse Large B Cell Lymphoma, non-hodgkin lympohma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

Source(s) of monetary or material Support: bedrijf

Intervention

Keyword: AEB071, CD79 mutated, Diffuse Large B Cell Lymphoma DLBCL, Protein Kinase C Inhibitor

Outcome measures

Primary outcome

Occurrence of dose limiting toxicities (dose escalation) and occurrence of AEs,

SAEs, assessments of clinical laboratory values, and vital sign measurements

(dose expansion).

Secondary outcome

Overall response rate, AEB071 pharmacokinetics

Study description

Background summary

Patients with diffuse Large B-Cell Lymphoma (DLBCL) of the ABC subtype have significantly inferior overall survival and response compared with GCB subtype despite optimal chemotherapy. The NF-kappaB pathway is constitutively activated in most ABC-DLBCL cases, which has been ascribed to the activity of a signaling cascade from the B cell receptor (BCR). Mutations have been identified in many of the signaling molecules that lie downstream of the B cell receptor and that result in NF-kappaB activation. In the clinic, agents such as bortezomib, improved clinical response to combination chemotherapy in patients with ABC-DLBCL. These and other observations of kinase inhibitors that impair BCR signaling cited above suggest that targeting this pathway is a strategy for improving treatment of DLBCL.

Study objective

Estimate the maximum tolerated dose (MTD) of AEB071 (dose escalation) and characterize the safety and tolerability of the MTD or recommended Phase 2 dose of AEB071 in patients with DLBCL (dose expansion).

Study design

An open-label, multicenter, single-arm, phase I dose escalation (Bayesian) and expansion study.

Intervention

treatment with AEB071

Study burden and risks

Toxicity of AEB071 therapy.
Radiation exposure, CT scan / MRI.
Frequent visits and blood sampling.

An overview of all procedures during the visits are given in Appendix B of the patient information
The side effects can be found in Appendix C of the patient information
It is not certain that participation in the research is of direct benefit, the data gathered can be useful for the future.
The burden on the patients is as expected for a phase I trial.

Contacts

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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

-Diffuse large B-cell lymphoma with activating mutations in CD79 (A or B subunits). DLBCL that arose from transformed indolent lymphoma is allowed.
-Prior treatment and relapse following anthracycline-based chemotherapy and autologous bone marrow or stem cell transplant. Patients who are not transplant eligible or those with refractory disease may be considered for the study following a single regimen of chemotherapy such as R-CHOP or R-EPOCH. There is no limit to number of prior therapy allowed.
* Patients may be treated with localized radiation to as many as two sites of disease, so long as measurable or evaluable disease remains at untreated sites
* Patients may be treated with corticosteriods immediately prior to enrollment and during the course of study treatment as long as steroid treatment is tapered to a total daily dosage of 10mg or less of prednisone (or it*s equivalent) prior to AEB071 administration

Exclusion criteria

1. Patients at screening who are treated with strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4) that can not be discontinued
2. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
* History or presence of ventricular tachyarrhythmia
* Presence of unstable atrial fibrillation (ventricular response > 100 bpm); Patients with stable atrial fibrillation are eligible, provided they do not meet any of the other cardiac exclusion criteria.
* Angina pectoris or acute myocardial infarction * 3 months prior to starting study drug
* Other clinically significant heart disease (e.g. symptomatic congestive heart failure; uncontrolled arrhythmia or hypertension; history of labile hypertension or poor compliance with an antihypertensive regimen)
3. Patients with another malignancy that was treated within the last three years with the exceptions of localized basal cell carcinoma and cervical carcinoma
4. Patients with impairment of GI function or GI disease that could interfere with the absorption of AEB071
5. Patients with severe systemic infections, current or within the two weeks prior to initiation of AEB071
6. Patients with a known history of Human Immunodeficiency Virus (HIV) .
* HIV testing is not required as part of this study.

7. Time since the last prior therapy for treatment of underlying malignancy**:
* Cytotoxic chemotherapy: * than the duration of the most recent cycle of the previous regimen (with a minimum of 2 weeks for all)
* Biologic therapy (e.g. antibodies): * 4 weeks
* * 5 x PK half-life of a small molecule therapeutic, not otherwise defined above
**Patients must have recovered or stabilized from all toxicities related to their previous treatment except for alopecia
8. Patients with any history of significant coagulopathy or a medical condition requiring long term systemic anticoagulation that would interfere with biopsies. Low-dose aspirin treatment (up to 200 mg/day) or anticoagulation therapy that can be interrupted to allow biopsies are allowed. (This exclusion criterion applies only to study subjects who consent to the optional pre- and post-dose tumor biopsies)
9. Patients with abnormal laboratory values, defined as one of the following:
a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times upper limit of normal (ULN) combined with total bilirubin > 2 ULN
b. AST or ALT > 5 times ULN
c. Total bilirubin >2 ULN
d. Absolute neutrophil count (ANC) * 1.0 x 109/L (1000/mm3)
e. Platelets * 75 x 109/L (75,000/mm3)
f. Hemoglobin (Hgb) * 90 g/L (9 g/dL)
g. Abnormal coagulation profile including Prothombin (PT), activated Partial thromboplastin Time (PTT) and fibrinogen
10. Patients having undergone major surgery less than 4 weeks prior to enrollment or that have not fully recovered from prior surgery
13. Patients with a known history of active hepatitis B or C infection unless they are on antiviral therapy.
* The determination of active hepatitis status should be as per standard of care at each site.
* Hepatitis B and C testing is not required as part of this study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-11-2011
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	sotrastuarin

Ethics review

Approved WMO Date:	20-06-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	06-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-024367-41-NL
CCMO	NL36883.078.11