A Phase 3, Randomized, Open-Label, Controlled, Multicenter Study of Zandelisib (ME-401) in Combination with Rituximab Versus Standard Immunochemotherapy in Patients with Relapsed Indolent Non-Hodgkin*s Lymphoma (iNHL) - The COASTAL Study

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This study aims to test the hypothesis that zandelisib in combination with rituximab has better clinical activity and risk/benefit profile compared to standard 2nd line immunochemotherapy (R-CHOP/R-B) in subjects with relapsed FL or MZL. Primary…

Ethical review	Approved WMO
Status	Completed
Health condition type	Lymphomas non-Hodgkin's unspecified histology
Study type	Interventional

Summary

ID

NL-OMON51210

Source
ToetsingOnline

Brief title
The COASTAL Study

Condition

- Lymphomas non-Hodgkin's unspecified histology

Synonym
cancer from white blood cells, Lymph node cancer. Recurring, slow growing

Research involving
Human

Sponsors and support

Primary sponsor: MEI Pharma Inc.
Source(s) of monetary or material Support: Farmaceutische Industrie: MEI Pharma;Inc.

Intervention

Keyword: Open Label, Phase 3, Relapsed Indolent Non-Hodgkin□s Lymphoma (iNHL), Zandelisib

Outcome measures

Primary outcome

PFS as determined by the IRRC

Secondary outcome

• Efficacy: ORR and CRR as determined by the IRRC

• OS

• PRO - time to deterioration in the 9-item DRS-P subset of FlymSI-18

• PRO-change from baseline in EQ-5D total score at specified study visits

• Treatment-emergent AEs, serious AEs, and laboratory abnormalities

Study description

Background summary

Indolent B-cell lymphomas (NHLs), which include follicular lymphoma (FL) and marginal zona lymphoma (MZL), generally have a good prognosis and median survival rates longer than 10 years, but are not curable with current available therapeutic options, especially for those with advanced stages at diagnosis. While FL and MZL respond initially to therapy, their natural history is characterized by remissions and relapses. Although most relapses can be generally treated with success, the quality and duration of remissions decreases over time. Finally, these lymphomas evolve into refractory disease or undergo transformation into an aggressive histologic type with poor prognosis.

Therapeutic options for previously untreated FL and MZL include single agent anti-CD20 immunotherapy (most commonly with rituximab (Rituxan®, MabThera®, or biosimilar, [R]); in this protocol, henceforth, R refers to rituximab, i.e., Rituxan, MabThera, or biosimilar); to anti-CD20-based immunochemotherapy (most commonly the combination of R with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone (CHOP) designated as R-CHOP or the alkylating agent bendamustine (B) designated as R-B. Other chemotherapy regimens are also acceptable in combination with an anti-CD20 antibody as well as the combination of R and lenalidomide (Revlimid® [L]) (R-L).
For patients with relapsed disease, a similar immunochemotherapy approach, utilizing a chemotherapy regimen not previously administered, can be used. The combinations of R-B showed high rates of objective response of >=90%, and median progression-free survival (PFS) of 23-24 months. Combination of R and chemotherapy for relapsed disease is associated with a PFS of about 18 months. Response outcome varies based on duration of prior response, disease-and patient related factors. However, the disease will inevitably relapse.
Therefore, active agents with different mechanisms of action than cytotoxic chemotherapy are needed for patients with relapsed disease. Furthermore, since the median age of patients with FL and MZL at relapse is >60 years, new treatment options must be well-tolerated and avoid the toxicities typically reported with chemotherapy.
Phosphoinositide 3 kinase (PI3K) inhibitors, a novel class of drugs for B-cell malignancies, have proven to be active in patients with FL and MZL, but the benefit of therapy is often limited by class-associated toxicities potentially related to immune dysfunction, including effects on regulatory T-cells. These toxicities are often delayed and cumulative in nature, and include diarrhea and colitis, stomatitis, hepatitis (elevation of transaminases), infectious and non-infectious pneumonitis.
Zandelisib (code name ME-401), is an orally bioavailable PI3Kδ inhibitor with optimal pharmacologic properties and high potency, with a plasma half-life (t*) of approximately 28 hours supporting once-daily dosing. In an ongoing Phase 1b study (ME-401-002), zandelisib has been evaluated in a continuous daily dosing schedule (CS) and an intermittent schedule (IS), with zandelisib given daily for 2 initial cycles followed by 1 week on, 3 weeks off therapy in every subsequent 28-day cycle. Preliminary data indicate that both treatment schedules were associated with a high and comparable response rate in subjects with indolent B-cell malignancies, while the IS led to a significant reduction in Grade (Gr) 3 class-related adverse events (AE) compared to CS. The incidence of these AEs with the IS and the CS, respectively, were: colitis/diarrhea (5% and 23%), rash/skin reaction (0% and 8%), stomatitis (0% and 3%), AST/ALT elevation (2% and 8%), pneumonia/infectious pneumonitis (2% and 10.0%). With IS dosing, these Gr 3 AEs were not reported beyond Cycle 3, when zandelisib is administered for 1 week per cycle, whereas there is a continued increase in the cumulative risk of Gr 3 AEs in the CS group.
In 36 subjects with FL in the IS group, the overall response rate (ORR) was 83% (76% in monotherapy group, 89% in zandelisib in combination with rituximab), and the median duration of response was not reached with a median follow-up of

13.2 months (15.4 months for monotherapy and 12.8 months in combination with rituximab). The ORR in 9 subjects with CLL/SLL was 89% (100% monotherapy and 83% combination therapy with rituximab) and 100% in 4 subjects with MZL (all enrolled in the rituximab combination group). Therapy on IS proved to be well tolerated, with few subjects experiencing Gr 3 class-related AEs. Those who had treatment interruptions were successfully re-challenged with zandelisib therapy.
To date, over 150 subjects have been treated with zandelisib as a single agent or in combination with other agents. Zandelisib monotherapy is being evaluated in a global Phase 2 study in subjects with FL who have received 2 prior lines of therapy. IS dosing is being evaluated in all clinical studies with zandelisib.

Study objective

This study aims to test the hypothesis that zandelisib in combination with rituximab has better clinical activity and risk/benefit profile compared to standard 2nd line immunochemotherapy (R-CHOP/R-B) in subjects with relapsed FL or MZL.

Primary Objective
• To demonstrate that zandelisib in combination with R is superior to standard immunochemotherapy in prolonging PFS as determined by the Independent Response Review Committee (IRRC) in previously treated subjects with follicular and marginal zone lymphoma

Secondary objectives
• Time to next anti-lymphoma treatment (TTNT)
• PFS on next anti-lymphoma treatment (PFS2)
• To compare zandelisib + R to standard immunochemotherapy by ORR and complete response rate (CRR) as determined by the IRRC
• To compare zandelisib + R to standard immunochemotherapy by overall survival (OS)
• To evaluate Patient Reported Outcome (PRO) assessment with:
o FlymSI-18
o PRO with EuroQol 5 Dimension 3 Level (EQ-5D-3L)
• To evaluate the safety and tolerability of zandelisib in combination with R

Exploratory objectives
To evaluate
• Efficacy:
o PFS, CRR and ORR, as determined by the Investigator
o ORR at week 24 by the Investigator and by the IRRC
o DOR by the Investigator and by the IRRC
o Time to progression (TTP) by the Investigator and by the IRRC
• To characterize the relationship between zandelisib exposure in plasma with

efficacy and safety

Study design

This is an open label, randomized, two-arm Phase 3 study in subjects with relapsed or refractory FL and MZL to evaluate efficacy and safety of zandelisib in combination with rituximab in comparison to standard immunochemotherapy (R-B or R-CHOP). Subjects must have relapsed after at least one previous line of systemic immunochemotherapy. Previous treatments must have included an anti-CD20 monoclonal antibody (mAb) with chemotherapy such as B, CHOP, CVP, FND, or similar regimens, or an anti-CD20 mAb with L.

Subjects who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the treatment arms:
• Arm 1: R plus zandelisib
• Arm 2: R plus chemotherapy (CHOP or B)

Subjects will be stratified based on following criteria:
• Prior treatment regimen: anti-CD20 mAb in combination with non bendamustine chemotherapy regimen or R-L vs. anti-CD20 mAb in combination with B
• Number of prior therapies: 1 vs. >1
• NHL histology: FL vs. MZL
• Duration of treatment-free interval from the last lymphoma-directed therapy: <=24 months vs. >24 months

Study treatments will be administered as detailed above. Treatment will be discontinued at any time in case of disease progression or unacceptable toxicity. Before treatment discontinuation due to any reason, including disease progression, the Investigator must review the reasons with the Sponsor*s medical monitor or designee.

Primary analysis will be based on assessment of efficacy by an IRRC. Subject management will be based on disease response assessment according to investigators.
During the study, continuing review of safety data by the sponsor and an independent Data Monitoring Committee (DMC) will be performed. An independent DMC will regularly review safety and efficacy data from all subjects to assess benefit/risk profile of zandelisib-rituximab therapy. The DMC will meet at least once every 3 months, with the first data review meeting occurring when approximately 60 subjects (~30 in each arm) have completed at least 1 cycle of treatment or 6 months after the first subject is dosed, whichever occurs first. Details of this review will be outlined in a separate DMC charter document.
The study is composed of the following periods:
• Screening
• Treatment
• Follow-up (efficacy follow-up until disease progression, safety follow-up,

and survival follow-up)

Intervention

Study Treatments

Zandelisib:
Administered in a 28-day cycle.
Zandelisib capsule should be taken once a day on dosing days at approximately the same time in the morning on an empty stomach on the following schedule:
60 mg daily for the first two cycles of therapy (56 days) followed by:
60 mg for the first 7 days followed by 21 days off treatment in every subsequent 28 day cycle, defined as the IS.

Rituximab:
R is administered by intravenous infusion according to institutional standards
• R 375 mg/m2 body surface on Day (D)1, D8, D15, and D22 of Cycle (C)1 and then on D1 of C3, C4, C5, and C6 for a total of 8 doses in 6 cycles

Dosing of immunochemotherapy (C1-C6):
R-B will be administered in a 28-day cycle as follows:
• R intravenously (IV) 375 mg/m2 body surface on D1
• B IV 90 mg/m2 body surface on D1 and D2

R-CHOP will be administered in a 21-day cycle as follows:
• R IV 375 mg/m2 body surface on D1
• Cyclophosphamide IV 750 mg/m2 body surface on D1
• Doxorubicin IV 50 mg/m2 body surface on D1
• Vincristine IV 1.4 mg/m2 body surface (maximum dose 2 mg) on D1
• Prednisone 100 mg daily orally (PO) from D1 to D5

The chemotherapy regimen administered in the study must be different from the one used as prior line of therapy.
• Subjects who received B with anti-CD20 antibody (R or obinutuzumab [O]) as a prior line of therapy will be allocated to R CHOP if randomized to the R chemotherapy treatment group
• Subjects who received CHOP or another chemotherapy regimen, (e.g., cyclophosphamide, vincristine, prednisone (CVP), fludarabine, + mitoxantrone + dexamethasone, [FND]), with anti-CD 20 antibody (R or O) or R-L previously, will be allocated to R-B if randomized to the R-chemotherapy group.

Study burden and risks

Participants may experience the side effects and discomforts as described below and in Appendix. D of the Patient Information Form
- There may be some discomfort from the measurements during the study.

- Taking part in the study will cost the participant extra time.
- The participant will need to come to the hospital more often
- The participant will have to comply with the study agreements.
- The participant will have to follow strict rules about taking medicines.
- The questionnaires can be confrontational
- The participant will be exposed to 83-133 mSv of radiation in the first year, 33-63 mSv in the second year and 22-42 mSv for each year onwards. If MUGA scan will be used, the participant will be exposed to an additional 7-8 mSv radiation dose

The following side effects of the study drug are common (in 10% or more): (Applicable for participants in Group 1 only)
• Diarrhea (loose stools) and colitis (inflammation of the colon).
• Abdominal pain (stomach pain) and constipation.
• Decreased appetite.
• Gastroesophageal reflux disease (heartburn, acid reflux).
• Nasal congestion, wet cough, upper respiratory tract infection.
• Rash and skin reactions.
• Nausea.
• Fatigue (tiredness).
• Cough.
• Oedema peripheral (swelling of legs).
• Stomatitis (inflammation of the mouth and lips).
• Hepatitis (iInflammation of the liver) as reflected by increased liver enzymes in laboratory measurements.
• Pneumonitis (iInflammation of the lungs) and pneumonia (inflammation of the lungs caused by an infection).
• Neutropenia (a rReduction of certain white blood cells circulating around the body).
• Blood creatinine increased (dDecreased kidney function).
• Thrombocytopenia (a reduction of bloodplatelets/thrombocytes [components of blood that react to bleeding from blood vessel injury by clumping together and forming a blood clot] circulating around the body).
• Pyrexia (raised Raised temperature, fever).

For participants in group 1, treatment may include a more effective, safer and less toxic option compared to standard treatment but also participants in group 1 may not get any direct benefit at all

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or female subjects >=18 years of age, >=19 years in Korea, or >=20 years for subjects in Japan and Taiwan, at time of signing informed consent
2. Histologically confirmed diagnosis of CD20 positive iNHL with histological subtype limited to:
a. FL Gr 1, Gr 2, or Gr 3a
b. MZL (splenic, nodal, or extra-nodal)
[Histopathological report confirming diagnosis must be available during screening procedures]
3. Subjects with relapsed or refractory disease who received >=1 prior lines of therapy that must have included an anti-CD20 antibody in combination with cytotoxic chemotherapy or L, with or without subsequent maintenance therapy. [A line of therapy is defined as following: a minimum of 2 consecutive cycles of immunochemotherapy or R-L, at least 4 doses of anti-CD20 mAb (R) single agent therapy a minimum of 2 consecutive cycles of therapy with an investigational agent. Maintenance therapy given after an induction treatment (e.g., R maintenance) is considered as the same line of therapy]. [Please seeExclusion Criteria #2 for further clarification]. Relapsed or refractory disease defined as:
• Relapsed disease: disease progression after a response (complete response

[CR] or partial response [PR]) lasting >=6 months
• Refractory disease: no response to therapy (no CR or PR) or response lasting <6 months
4. Subjects must have at least one bi-dimensionally measurable nodal lesion with the longest diameter > 1.5 cm and/or an extranodal lesion >1.0 cm in the longest diameter (that has not been previously irradiated) according to the Lugano Classification
5. Adequate hematologic parameters at screening unless abnormal values are due to disease per Investigator assessment:
• Absolute neutrophil count (ANC) >=1.0 × 109/L (>=1,000/mm3)
• Platelet count >=75.0 × 109/L (>=75,000/mm3)
• Hemoglobin >=9 g/dL
6. Adequate renal and hepatic function per local laboratory reference range at screening as follows:
• Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <=1.5 × upper limit of normal (ULN)
• Total bilirubin <=2.0 × ULN or <=3 × ULN for subjects with Gilbert-Meulengracht syndrome
• Estimated glomerular filtration rate (eGFR) >50 mL/min using the Cockcroft-Gault equation (Appendix 2)
7. QT-interval corrected according to Fridericia*s formula (QTcF) <=450 msec; subjects with QTc >450 msec but <480 msec may be enrolled provided the QTc prolongation is due to a right bundle branch block (RBBB), left bundle branch block (LBBB), or pacemaker and is confirmed stable by a cardiologist.
8. Left ventricular ejection fraction (LVEF) >=45% as measured by echocardiogram (ECHO) or multi-gated acquisition scan. [If LVEF <45% by ECHO, a repeat measurement can be conducted within the screening period.]
9. Subjects must have completed any prior systemic anti-cancer treatment >=4 weeks (or >=5 times the half-life [t*] of used therapeutics [including investigational therapy], whichever is longer) or radiation therapy >=2 weeks before study D1, and >=3 months before study D1 for high dose therapy with stem cell transplantation, radioimmunotherapy, and CAR T-cell therapy.
10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
11. Life expectancy of at least 3 months
12. All AEs and laboratory toxicities related to prior therapy must resolve to Gr <=1 prior to the start of the study therapy (unless otherwise specified in eligibility criteria)
13. For females of childbearing potential, a negative serum human chorionic gonadotropin pregnancy test within 28 days of study D1 and negative result (urine or serum) on study D1
14. Subjects must agree to use appropriate contraception methods during the clinical study (Appendix 3)
15. Subject is willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures

Exclusion criteria

1. Histologically confirmed diagnosis of FL Gr 3b or transformed disease
• For subjects with clinical signs of rapid disease progression (e.g., marked B-symptoms), and laboratory or radiographic indication (e.g., high lactate dehydrogenase level or standardized uptake value by PET), a fresh biopsy is recommended to rule out transformed disease
2. Subjects who received both R/O-B and R/O-CHOP (or other anthracycline-containing regimen) as previous lines of therapy, and those who received only single agent anti-CD20 mAb therapy as prior line of treatment
3. Prior therapy with PI3K inhibitors
4. Ongoing or history of drug-induced pneumonitis
5. Known lymphomatous involvement of the central nervous system
6. Seropositive for or active viral infection with hepatitis B virus:
• HBsAg positive
• HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA by PCR
[Note: Subjects who are HBsAg negative and viral DNA PCR negative are eligible. These subjects should receive prophylactic therapy for hepatitis as per institutional standards.]
7. Known seropositive for, or active infection with hepatitis C virus.
• Subjects with positive hepatitis C virus (HCV) antibodies are eligible with negative PCR test for HCV
8. Known seropositive for, or active and uncontrolled infection with human immunodeficiency virus (HIV), or with acquired immunodeficiency syndrome (AIDS), or currently taking medications for HIV that are contraindicated for concomitant use in this study
9. Known seropositive for, or active infection with human T-cell leukemia virus type 1
10. Any uncontrolled clinically significant illness including, but not limited to, active infections requiring systemic antimicrobial therapy, hypertension, angina, arrhythmias or other uncontrolled cardiovascular condition, pulmonary disease, autoimmune dysfunction and urinary infection or flow obstruction.
11. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients or other therapy used in the study
12. Major surgical procedure within 4 weeks prior to study D1 (minor surgical procedures, e.g., lymph node biopsy, performed within 1 day or with an overnight stay are allowed)
13. Previous or concurrent cancer that is distinct in primary site or histology from indolent B cell NHL within 3 years before start of study treatment except for curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]), and asymptomatic localized prostate cancer with no requirement for systemic therapy or requiring only hormonal therapy and with normal prostate-specific antigen values within >=12 months prior to randomization

14. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association (NYHA) classification >= II [NYHA 1994]), myocardial infarction within 6 months of study entry.
15. History of clinically significant gastrointestinal (GI) conditions, particularly:
• Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
• Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption
16. Females who are pregnant; females who plan to breastfeed during study treatment through 90 days after ending treatment
17. Substance abuse, medical, psychological or social conditions that may interfere with the subject*s participation in the study or evaluation of the study results.
18. Any illness or medical conditions that are unstable or could jeopardize the safety of the subjects and their compliance in the study. Inability to understand and sign informed consent form.
19. Received a live virus vaccination within 28 days of first dose of study drug, (e.g., yellow fever vaccination)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-01-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bendamustin Hikma
Generic name:	Bendamustin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednison HEXAL
Generic name:	Prednisone
Product type:	Medicine
Brand name:	Truxima
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Yet unknown
Generic name:	Zandelisib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-04-2021
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	01-06-2021
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	04-01-2022
Application type:	Amendment

Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2020-004199-16-NL
ClinicalTrials.gov	NCT04745832
CCMO	NL76898.075.21

Study results

Date completed:	20-03-2023
Results posted:	12-05-2023
Actual enrolment:	1

Summary results
Trial ended prematurely

First publication

28-04-2023