A Phase 3 Randomized, Open-Label, Multicenter Study Comparing Zanubrutinib (BGB-3111) plus Rituximab Versus Bendamustine plus Rituximab in Patients with Previously Untreated Mantle Cell Lymphoma Who Are Ineligible for Stem Cell Transplantation

Published: 13-01-2021
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2023-509908-15-00 check the CTIS register for the current data. All primary and secondary objectives will compare zanubrutinib (also known as BGB-3111) plus rituximab followed by zanubrutinib...

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

Summary

ID

NL-OMON54364

Source
ToetsingOnline

Brief title
Mangrove study

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
non-Hodgkin, white blood cells cancer

Research involving
Human

Sponsors and support

Primary sponsor: BeiGene Ltd.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Mantle Cell Lymphoma, Previoulsy untreated, Randomized

Outcome measures

Primary outcome

The primary efficacy analysis of PFS will be conducted as assessed by independent central review, per the 2014 Lugano Classification for NHL. Progression-free survival will be compared between the 2 arms using a log-rank test stratified by MIPI score (low vs. intermediate or high), age (>= 70 years vs. < 70 years), and geographic region (North America/Europe and Asia-Pacific region.

The primary hypothesis testing for PFS by independent central review is for non-inferiority. The non inferiority of zanubrutinib plus rituximab (R) followed by zanubrutinib monotherapy to bendamustine plus rituximab (BR) followed by observation will be tested for the Intent-to-Treat analysis set under the prespecified margin of 1.17 (hazard ratio of zanubrutinib + R to BR). The primary objective of the study is met if the non inferiority is demonstrated. The null and alternative hypotheses for testing PFS non inferiority of Arm A to Arm B are as follows:

H0N1: Hazard ratio (HR) (Arm A/Arm B) >= 1.17

HaN1: HR (Arm A/Arm B) < 1.17

The HR and its 2-sided 95% confidence interval will be estimated from a stratified Cox regression model. The p-value to test H0N1 will be based on Wald test for the treatment effect from the Cox regression. The distribution of PFS, including median PFS and PFS rate at selected timepoints such as 12 and 24 months, will be estimated using the Kaplan-Meier method for each arm.

There will be 2 interim analyses of PFS determined by independent central review, and performed when approximately 157 and 210 events (60% and 80% of the target number of events at final analysis) from the Arms A and B are observed. It is estimated that it will take approximately 46 and 61 months from the study start to observe 157 and 210 events, respectively, from 500 patients. The final analysis of PFS will take place after 262 events are observed, which is estimated to be approximately 81 months from study start.

If non-inferiority is demonstrated at either an interim or final analysis, superiority of zanubrutinib + R followed by zanubrutinib monotherapy to BR followed by observation will be tested next. The monitoring boundary for the superiority test is based on the O*Brien-Fleming type alpha spending function. The monitoring boundary for the non-inferiority test at the interim analyses is simply the monitoring boundary for the superiority test as described by the hazard ratio. These boundaries are depicted in Table 7 and Table 8. The p-value will be used for the primary inference.

Justification of Non-Inferiority Margin

The non-inferiority margin was conservatively derived using the 95%-95% fixed margin method based on the Food and Drug Administration (FDA) Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness (FDA,

2016). The PFS HR of bendamustine plus rituximab compared to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in STIL frontline study (Rummel et al, 2013) in the MCL subgroup was 0.49 (95% CI 0.28-0.79). The PFS HR of bendamustine plus R-CHOP/rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) in BRIGHT study (Flinn et al, 2014) in the MCL subgroup was 0.4 (95% CI 0.21-0.75). Both studies are well controlled with disease status measured by radiology assessment and conducted in first-line patients, same as this study. The MCL subgroups were stratified for randomization in both studies with sample size of 94 (for BRIGHT study) and 74 (for STIL study). The PFS status in MCL subgroups were followed enough to estimate the median PFS for both arms with enough precision. The efficacy of bendamustine plus rituximab (M1) in PFS hazard ratio scale was estimated as 0.676 from the results of these 2 studies by a fixed effects meta-analysis. Requiring 60% of M1 to be retained in zanubrutinib plus rituximab, a non-inferiority margin of 1.17 is generated. The margin is also clinically relevant.

Secondary outcome

Secondary efficacy endpoints will be analyzed and compared between the 2 treatment groups if the non inferiority test of the primary endpoint is significant either at the interim or final analyses. PFS, ORR, DOR, rate of CR or complete metabolic response, and time to response based on the assessment by independent central review as well as investigator assessment will be analyzed.

• PFS by investigator assessment will be calculated based on investigator-assessed tumor responses. PFS by investigator assessment will be

analyzed using the same analysis methods as the primary endpoint of PFS by independent central review.

• ORR will be estimated as the crude proportion of patients in each treatment group who achieve partial response (PR) or higher. Associated 95% Clopper-Pearson confidence intervals will be calculated by treatment group. The odds ratio (and 95% confidence intervals), which will be provided as a measure of the relative treatment effect, will be estimated using the stratified Cochran-Mantel-Haenszel method.

• Duration of response: The distribution of DOR, including median and other quartiles, will be estimated using the Kaplan-Meier method for each treatment group. Hypothesis testing comparing DOR between the 2 treatment groups will not be performed.

• Overall survival: OS between the treatment groups will be compared using the same methods employed for the PFS comparison.

• Rate of complete response or complete metabolic response will be analyzed using the same methods employed for ORR analysis.

• Time to response will be summarized for each treatment group using sample statistics, such as sample mean, median, and standard deviation.

• Patient-reported outcomes: The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be utilized. The scores and their changes from baseline will be summarized and compared between the 2 treatment groups.

Study description

Background summary

Mantle cell lymphoma (MCL) is diagnosed in 0.51-0.55/100,000 persons per year in the United States of America, making up 6% of all non-Hodgkin lymphoma (NHL), with a similar incidence rate worldwide (Smedby and Hjalgrim, 2011; Wang et al, 2015). MCL is a cancer of older persons with a median age at diagnosis of approximately 70 years (Sharman et al, 2017, Dreyling et al, 2017) and a male preponderance of roughly 2.5:1 (Barista et al, 2001; Smedby and Hjalgrim, 2011). Patients usually present with advanced disease; 70% are diagnosed in stage IV. Most commonly, there is generalized lymphadenopathy and organomegaly. Approximately 10-20% of patients present with bone marrow involvement, and B symptoms (fever, night sweats, and weight loss) are present in approximately 40% of patients. Extranodal involvement of the gastrointestinal tract, particularly the colon, is common, but central nervous system involvement is uncommon (Skarbnik and Goy, 2015).The diagnosis is based on pathological assessment with typical immunophenotype of CD5+, CD20+, CD43+, CD23-/+,cyclin D1+, and CD10-/+ (NCCN Guideline, 2018).
In addition to the classic MCL immunophenotype of CD20+, the pathognomonic feature of MCL is overexpression of cyclin D1, which is a consequence of juxtaposition of the proto-oncogene CCND1 on chromosome 11q13 to the immunoglobulin (Ig) heavy chain gene at chromosome 14q32. Cyclin D1 can be confirmed by immunohistochemistry in almost 100% of specimens. The molecular consequence of cyclin D1 overexpression is deregulation of cell cycle control by overcoming the suppressor effect of the retinoblastoma 1 (RB1) and the cell cycle inhibitor p27. Frequent companion anomalies include secondary chromosomal and molecular alterations targeting proteins that regulate the cell cycle and senescence (B lymphoma Mo-MLV insertion region 1 homolog [BMI1], inhibitor of kinase 4a [INK4a], alternate reading frame [ARF], cyclin D-dependent kinase [CDK]4, and RB1), and interfere with the cellular response to deoxyribonucleic acid (DNA) damage (ataxia telangiectasia mutated [ATM]), checkpoint kinase 2 [CHK2] and p53) (Rickert, 2013). Concomitantly, β2 microglobulin and lactate dehydrogenase (LDH) are increased in 56% and 45% of patients, respectively; these markers should be monitored for disease activity and are also prognostic. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is composed of the parameters of the Eastern Cooperative Oncology Group (ECOG) performance status, age, leukocyte count, and LDH, and classifies patients into low, intermediate, and high-risk groups, with corresponding median overall survival (OS) time of 72 months, 51 months, and 29 months, respectively (Vose, 2013). The histological pattern of MCL is also prognostic, with complete response (CR) rates of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for mantle-zone/nodular/diffuse patterns of 73%, 25%, and 19%, respectively, and 3 year survival rates of 100%, 50%, and 55%, respectively (Barista, 2001). Another prognostic factor is the expression of the proliferation-associated antigen Ki-67; 60% of patients have over 10% of their tumors staining positive for Ki-67, with highly proliferative cases showing a much poorer outcome than tumors with low proliferation.

Management of MCL has been with chemo-immunotherapeutic combinations, most commonly rituximab-CHOP (R-CHOP) or bendamustine plus rituximab (BR) combinations that result in high response rates; however, patients invariably relapse (Rummel et al, 2013; Kluin-Nelemans et al, 2012). Younger, fit patients have the option of high intensity chemotherapy, such as hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper- CVAD), or induction chemotherapy followed by stem cell transplantation, with many patients achieving prolonged remissions (Dreyling et al, 2005; Romaguera et al, 2005). Among the available therapies, the BR combination has demonstrated better tolerability with lower rates of hematological toxicities, infections, peripheral neuropathy, alopecia, and stomatitis when compared with R-CHOP. Furthermore, the BR combination also showed better efficacy in that median progression-free survival of BR is significantly longer than R-CHOP (69.5 months versus 31.2 months; $p < 0.0001$) in treatment-naive MCL patients (Rummel et al, 2013; Flinn et al, 2014). Combination therapy with bendamustine and rituximab has become one of the most used first-line regimens for MCL, given the recent evidence showing longer progression-free survival with this combination than with R-CHOP (35.4 versus. 22.1 months); and a better safety profile (Martin et al, 2021). However, elderly patients and those with comorbidities that preclude treatment with standard chemoimmunotherapy regimens and stem cell transplantation have few options, and treatment is largely palliative. No standard approach to treatment has been defined for these patients (Dreyling et al, 2017).
Additionally, there is as yet no conclusive evidence that rituximab maintenance therapy following a combination of rituximab and bendamustine treatment provides a benefit in MCL. In an ongoing study of 120 patients with previously untreated stage II (with bulky disease > 7 cm), III or IV MCL treated with up to 6 cycles of rituximab and bendamustine followed by 1:1 randomization to either rituximab maintenance (375 mg/m2 every 2 months for a total of 2 years) or observation only arms, after a median time of observation of 4.5 years, no significant difference in progression-free survival (PFS) could be observed between the 2 arms (p=0.130, 47 events, hazard ratio [HR] 0.64, 95% CI: 0.73-1.14). The median for rituximab maintenance was not yet reached, whereas for the observation arm the median was 54.7 months (95% CI: 40.1. - not yet reached). There was no difference in OS between arms (p = 0.271, 27 events, HR 1.53, 95% CI 0.73 - 3.32) with a median of 69.6 months for rituximab maintenance versus a median not yet reached in the observation arm (Rummel et al, 2016). National Comprehensive Cancer Network (NCCN) guidelines currently recommend against rituximab maintenance following bendamustine-based therapy for mantle cell lymphoma (NCCN v5.2018).

Study objective

This study has been transitioned to CTIS with ID 2023-509908-15-00 check the CTIS register for the current data.

All primary and secondary objectives will compare zanubrutinib (also known as

BGB-3111) plus rituximab followed by zanubrutinib monotherapy versus bendamustine plus rituximab followed by observation only.
Primary:
• To compare efficacy, as measured by progression-free survival (PFS) determined by independent central review

Secondary:
• To evaluate efficacy, as measured by the following:
- Progression-free survival determined by investigator assessment
- Overall response rate (ORR), as determined by independent central review and by investigator assessment
- Duration of response (DOR), as determined by independent central review and by investigator assessment
- Overall survival (OS)
- Rate of complete response (CR) or complete metabolic response determined by independent central review and by investigator assessment
- Time to response, as determined by independent central review and by investigator assessment
- Patient reported outcomes
- To evaluate safety and tolerability

Exploratory:
- To evaluate the pharmacokinetics (PK) of zanubrutinib (zanubrutinib plus rituximab arm only) when co administered with rituximab
- To evaluate the correlation of certain pathologic features (eg, Ki-67) and molecular characteristics (including but not limited to mutations in genes and pathways of the cell cycle and senescence, DNA damage response, and cell survival) with rate of CR or complete metabolic response, ORR, DOR, and PFS
- To evaluate the mechanisms of resistance to zanubrutinib

Study design

This is an international, multicenter, Phase 3, open-label, randomized, active-controlled study of zanubrutinib plus rituximab followed by zanubrutinib monotherapy versus bendamustine plus rituximab followed by observation in approximately 500 patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for stem cell transplantation due to age or comorbidities.
The primary efficacy endpoint is PFS as determined by independent central review. Disease response will be assessed per the Lugano Classification for Non-Hodgkin Lymphoma (NHL) (Cheson et al, 2014), hereafter referred to as Lugano Classification for NHL.
Central randomization (1:1) will be used to assign patients to one of the following study drug treatments:
• Arm A: zanubrutinib plus rituximab for 6 cycles, followed by zanubrutinib monotherapy
• Arm B: bendamustine plus rituximab for 6 cycles, followed by observation
Randomization will be stratified by MCL International Prognostic Index (MIPI)

score (low vs. intermediate or high), age (>= 70 years vs. < 70 years), and geographic region (North America/Europe and Asia-Pacific region).

Study treatment must commence within 5*days after randomization. Each cycle of zanubrutinib and rituximab or bendamustine and rituximab consists of 28 days. Study drug treatments will be administered as follows, depending on treatment assignment:
In Arm A, zanubrutinib will be administered as two 80-mg capsules orally twice a day (160 mg twice a day) with or without food. Rituximab will be administered intravenously at a dose of 375 mg/m2 on Day 1 of Cycles 1 to 6 only. Zanubrutinib will be administered prior to the start of rituximab infusion. For patients considered by the investigator to be at high risk for infusion reaction, rituximab may be administered by split dosing over more than one day for the first and/or subsequent cycles as per institutional guidelines. (NOTE: Rituximab split dosing is not available in Japan based on local labeling). Following completion of Cycle 6, patients in Arm A will continue on zanubrutinib monotherapy until disease progression, withdrawal of consent, death, lost to follow-up, or end of study, whichever occurs first. Following disease progression, subjects will be followed further for survival and subsequent MCL therapies.

In Arm B, bendamustine will be administered intravenously at a dose of 90 mg/m2/day on Days 1 and 2 of Cycles 1 to 6, and rituximab will be administered intravenously at a dose of 375 mg/m2 on Day 1 of Cycles 1 to 6. Following completion of Cycle 6, patients in Arm B will receive no further treatment but will continue to be observed (including assessments for safety and efficacy) until disease progression, withdrawal of consent, death, lost to follow up, or end of study, whichever occurs first. Following disease progression, subjects will be followed further for survival and subsequent MCL therapies.

Intervention

• Arm A: zanubrutinib plus rituximab for 6 cycles, followed by zanubrutinib monotherapy
• Arm B: bendamustine plus rituximab for 6 cycles, followed by observation

Rituximab is given by intravenous (IV) infusion

Study burden and risks

Zanubrutinib is an experimental agent and therefore it is not known if zanubrutinib will have any direct benefit to the patient. Taking part in this medical scientific research may or may not improve the patient's health. Even if there is no direct benefit others may benefit from what is learned from this study.

Disadvantages of participation in the study may be:
- possible side effects/complications of the intervention;
- possible adverse effects/discomforts of the measurements in the study.

Participation in the study also means:
- additional time;
- an additional or an extended hospitalization;
- additional testing;
- that the patient has appointments to attend;

Contacts

Public
BeiGene Ltd.

Gateway Drive, 3rd Floor 1840
San Mateo CA 94404
US
Scientific
BeiGene Ltd.

Gateway Drive, 3rd Floor 1840
San Mateo CA 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- >=*70 years of age at the time of informed consent, OR

>= 60 and < 70 years of age with comorbidities precluding autologous stem cell transplantation
- Histologically confirmed diagnosis of MCL based on the World Health Organization 2016 classification
- No prior systemic treatments for MCL
- Presence of measurable disease
- Availability of archival tissue confirming diagnosis of MCL, or willing to undergo fresh tumor biopsy
- ECOG performance status of 0, 1, or 2
- Life expectancy of >=*3 months
- Adequate organ function (refer to Protocol Synopsis for more details)
- Female patients of childbearing potential must practice highly effective methods of contraception
- Male patients are eligible if abstinent, vasectomized or if they agree to the use of barrier contraception in combination with other methods
- Ability to provide written informed consent and ability to understand and comply with the requirements of the study
- For all patients irrespective of their age, Creatinine clearance of >= 30 mL/min

Exclusion criteria

- Known central nervous system involvement by lymphoma
- Prior hematopoietic stem cell transplantation
- Prior exposure to a BTK inhibitor, rituximab, or bendamustine
- Patients for whom the goal of therapy is tumor debulking prior to stem cell transplant
- Prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer
- Clinically significant cardiovascular disease (for more details refer to the Protocol)
- History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
- History of stroke or intracranial hemorrhage within 6 months before first dose of study drug
- Unable to swallow capsules or disease significantly affecting gastrointestinal function
- Active fungal, bacterial and/or viral infection requiring systemic therapy
- Underlying medical conditions that, in the investigator*s opinion, will render the administration of study drug hazardous or obscure the interpretation of safety or efficacy results
- Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or C infection (Refer to the Protocol for more

details)
- Major surgery within 4 weeks of the first dose of study drug
- Pregnant or lactating women
- Vaccination with a live vaccine within 35 days prior to the first dose of study drug
- Ongoing alcohol or drug addiction
- Hypersensitivity to zanubrutinib, bendamustine, or rituximab or any of the other ingredients of the study drugs
- Requires ongoing treatment with a strong CYP3A inhibitor or inducer
- Concurrent participation in another therapeutic clinical trial.
- Patients enrolled in Germany only, who are severe immunocompromised

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:	Recruiting
Start date (anticipated):	29-10-2021
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	NA
Generic name:	Zanubrutinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	Bendamustine

Ethics review

Approved WMO Date:	13-01-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-06-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	25-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	02-11-2023
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
EU-CTR	CTIS2023-509908-15-00
EudraCT	EUCTR2019-000413-36-NL
ClinicalTrials.gov	NCT04002297
CCMO	NL75419.078.20