KARTA BADANIA
NAZWA BADANIA: A Phase 3 Randomized, Open-Label Multicenter Study of Zanubrutinib (BGB-3111) Plus Anti-CD20 Antibodies Versus Lenalidomide Plus Rituximab in Patients With Relapsed/Refractory Follicular or Marginal Zone Lymphoma
NUMER PROTOKOŁU: **BGB-3111-308**
WSKAZANIE- C82 - Chłoniak nieziarniczy guzkowy [grudkowy]

Criteria

Inclusion Criteria:

Each patient who is eligible to participate in this study must meet all the following criteria:

1. Age of ≥ 18 years at the time of informed consent.

2. Histologically confirmed grade 1-3a FL or MZL according to World Health Organization 2016 classification. All three subtypes of MZL (extranodal, nodal, and splenic) are eligible. NOTE: a formalin-fixed, paraffin-embedded specimen must be available for central review. If an archival specimen is not available, or if suspicion of transformation, a re-biopsy is required before randomization.

3. Previously treated with at least one line of systemic therapy including anti-CD20 monoclonal antibody (≥ 4 doses as consecutive monotherapy or ≥ 2 doses as consecutive combination therapy). Must have a documented failure to achieve at least PR during the most recent systemic therapy or documented progressive disease after the most recent systemic therapy. Systemic therapy does not include Helicobacter pylori eradication or local involved field radiotherapy.

4. Need for systemic therapy for FL or MZL if, based on the investigators' assessment, the patient has ≥ 1 of the following symptoms:

a. Local symptoms from progressive or bulky nodal disease.

b. Compromise of normal organ function from progressive or bulky disease.

c. B-symptoms including fevers, weight loss, and night sweats.

d. Symptomatic extranodal disease such as effusions.

e. Severe cytopenias from bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia, or hypersplenism.

f. An increase in disease tempo as defined per British National Lymphoma Investigation (BNLI) criteria (rapid, generalized disease progression in the preceding 3 months) as assessed by the investigator (Ardeshna et al 2003).

g. Gastrointestinal bleeding.

5. Measurable disease by CT or magnetic resonance imaging (MRI). Measurable disease as defined by ≥ 1 nodal lesion that is > 1.5 cm in longest diameter and/or ≥ 1 extranodal lesion that is > 1.0 cm in longest diameter, and lesion(s) measurable in 2 perpendicular diameters, as defined by the Lugano classification (Cheson et al 2014). Site of measurable disease cannot be previously irradiated.

6. ECOG performance status of 0 to 2.

7. Life expectancy ≥ 6 months
8. Adequate BM function, defined as:
a. Absolute neutrophil count (ANC) ≥ 1000 cells/mm3 (1.0 x 109 /L), except for the patients with BM involvement or hypersplenism by FL or MZL, in which case ANC must be ≥ 750 cells/mm3
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NOTE: The screening hematology values confirming the patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim (or other pegylated myeloid growth factors) and at least 7 days following the most recent administration of filgrastim or other myeloid growth factors.
b. Platelet count ≥ 75,000 cells/mm3 (75 x 109 /L) (without growth factor support or platelet transfusion within 7 days) except for patients with BM involvement or hypersplenism by FL or MZL, in which case platelet count must be ≥ 50,000 cells/mm3 (50 x 109 /L) (without growth factor support or platelet transfusion within 7 days).
9. Adequate organ function, defined as:
a. CrCL of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation, MDRD or

CKD-epi equations, see Appendix 6).
b. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase and alanine aminotransferase/serum glutamic pyruvic transaminase ≤ 2.5x upper limit of normal unless documented liver involvement by FL or MZL.
c. Serum total bilirubin ≤ 2.0x upper limit of normal unless due to Gilbert's syndrome or documented liver or pancreatic involvement by FL or MZL.
10. Able to provide written informed consent and understand and comply with study requirements.
11. Women of childbearing potential (WOCBP1
; Section 6.3) must:
a. Either commit to true abstinence2
from heterosexual contact (which must be reviewed
on a monthly basis and source documented) or agree to use highly effective methods of contraception (2 forms of contraception for WOCBP in Arms A and C if using hormonal contraceptives such as birth control pills or devices) initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, and according to the approved obinutuzumab and rituximab product/prescribing information, whichever is longer.
b. Have 2 negative pregnancy tests (minimum sensitivity 25 mIU/mL) as verified by the Investigator prior to starting study treatment (between Days -14 and -10 before the first dose of study treatment, and the other test is performed ≤ 24 hours before the start of lenalidomide). She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the patient practices true abstinence2
from heterosexual contact.
c. Either commit to true abstinence2
from heterosexual contact (which must be reviewed
on a monthly basis and source documented) or agree to use, and be able to comply with two forms of contraception: one highly effective, and one additional effective (barrier) measure of contraception without interruption during screening for all WOCBP, and during the study treatment for WOCBP in Arm B and Arm D (including dose interruptions), and for at least 28 days after the last dose of lenalidomide.
12. Male patients are eligible if:
a. Abstinent, vasectomized, or if they agree to use barrier contraception (condom) with other methods (Section 6.4; even if vasectomized male patients receiving lenalidomide must practice true abstinence2
) during the study treatment period and for
≥ 90 days after the last dose of zanubrutinib, for ≥ 28 days after the last dose of lenalidomide, and according to the approved obinutuzumab and rituximab product/prescribing information, whichever is longer.
b. Agree to not donate semen during study treatment therapy and for ≥ 90 days after the last dose of zanubrutinib, for ≥ 28 days after the last dose of lenalidomide, and according to the approved obinutuzumab and rituximab product/prescribing information, whichever is longer.
13. All patients must:
a. Have an understanding that the study treatment could have a potential teratogenic risk.
b. Agree to abstain from donating blood while taking study treatment therapy and for 4 weeks after discontinuation of study treatment therapy.

c. Agree not to share study medication with another person.
d. Agree to be counseled about pregnancy precautions and risk of fetal exposure.
e. Female patients must agree to abstain from breastfeeding during study participation and for ≥ 14 days after the last dose of zanubrutinib, for ≥ 28 days after the last dose of lenalidomide, and according to the approved obinutuzumab and rituximab product/prescribing information, whichever is longer.

4.2. Exclusion Criteria

Each patient who is eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. History of transformation to aggressive lymphoma, such as diffuse large B-cell lymphoma or grade 3b FL. If transformation is suspected, a biopsy of the suspected area is required to exclude transformation.
2. Requiring ongoing need for corticosteroid treatment, except for adrenal replacement.
NOTE: Systemic corticosteroids must be fully tapered off/stopped ≥ 5 days before the first dose of study treatment
3. Clinically significant cardiovascular disease including the following:
a. Myocardial infarction ≤ 6 months before screening.
b. Unstable angina ≤ 3 months before screening.
c. New York Heart Association class 3 or 4 congestive heart failure (see Appendix 3).
d. History of clinically significant arrhythmia (eg, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes).
e. QTcF (Fridericia's correction) > 480 msec.
f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place.
g. Uncontrolled hypertension as indicated by ≥ 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening.
4. Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized prostate cancer (Gleason score of ≤ 6).
5. 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.
6. History of stroke or intracranial hemorrhage ≤ 180 days before the first dose of study treatment.
7. Severe or debilitating pulmonary disease.
8. Inability to swallow capsules or gastrointestinal disfunction such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery, inflammatory bowel disease, or bowel obstruction.
9. Active fungal, bacterial, and/or viral infection that requires systemic therapy.
Note: Patients with infections that are managed by oral antibiotics and who are otherwise clinically stable are not excluded from study participation
10. Confirmed central nervous system involvement by FL or MZL.
11. Underlying medical conditions that, in the investigator's opinion, will render the administration of study treatment hazardous or obscure the interpretation of safety.
12. Severely immunocompromised state.
13. History or active infection with human immunodeficiency virus (seropositive patients with sustained undetectable viral load may be enrolled).
14. Serologic status reflecting active viral HBV or HCV infection as follows:
a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody

(HBcAb). Patients with presence of HBcAb, but without HBsAg, are eligible if HBV DNA is undetectable (NOTE: the limit of detection for HBV DNA must have a sensitivity of < 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (NOTE: the limit of detection for HCV RNA must have a sensitivity of < 15 IU/mL) and if they are willing to undergo monthly monitoring for HCV reactivation.
15. Major surgery ≤ 4 weeks before the first dose of study treatment or planned during study.
16. Prior treatment with a BTK inhibitor (including zanubrutinib)
17. Prior treatment with lenalidomide and without response (response is defined as best overall response that is PR or CR) or with short remission (short remission defined as: a response was achieved but the DOR was < 24 months).
18. Last dose of prior therapy for FL or MZL, including herbal medicine with anti-neoplastic intent ≤ 21 days before the first dose of study treatment with additional exclusion requirements:
a. Treatment with monoclonal antibody-based therapy (including bispecifics antibody) ≤ 28 days before the first dose of study treatment.
b. Chimeric antigen receptor T-cell therapy ≤ 180 days before the first dose of study treatment.
c. Allogeneic hematopoietic cell transplantation ≤ 1 year before the first dose of study treatment.
d. Autologous hematopoietic stem cell transplantation ≤ 3 months before the first dose of study treatment
19. Any chemotherapy or radiation treatment for non-FL or MZL indications ≤ 21 days before the first dose of study treatment.
20. Ongoing toxicity of Grade ≥ 2 from prior anticancer therapy (except for alopecia, ANC, and platelets. For ANC and platelets, please follow inclusion criterion #8).
21. Pregnant or lactating women.
22. Vaccination with a live vaccine ≤ 35 days before the first dose of study treatment.
23. Hypersensitivity to zanubrutinib, lenalidomide, obinutuzumab or rituximab, murine products, thalidomide, or any of the other ingredients/excipients of the study drugs.
24. Requiring ongoing therapy with strong or moderate cytochrome P450 3A (CYP3A) inducers.
Use of strong/moderate CYP3A inhibitors (see Appendix 4) within 7 days or 5 half-lives prior to the first dose of zanubrutinib; usage of strong/moderate CYP3A inducers (see Appendix 4) within 14 days prior to the first dose of zanubrutinib.
Patients who are at a risk for a thromboembolic event and are not willing to take venous thromboembolism (VTE) prophylaxis.
27. Neuropathy of Grade > 1.