KARTA BADANIA
NAZWA BADANIA: A Study of BGB-16673 Compared to Investigator's Choice (Idelalisib Plus Rituximab or Bendamustine Plus Rituximab or Venetoclax Plus Rituximab Retreatment) in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Previously Exposed to Both BTK and BCL2 Inhibitors.
NUMER PROTOKOŁU: **BGB-16673-302**
WSKAZANIE- C83.0 - Z małych komórek (rozlany)

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria:

1. Patients must sign the ICF and be capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Patients must be ≥ 18 years of age or the legal age of consent in the jurisdiction in which the study is taking place (whichever is older) at the time of signing the informed consent.
3. Confirmed diagnosis of CLL or SLL, requiring treatment, based on 2018 iwCLL criteria (Hallek et al 2018).
4. Previously received treatment for CLL/SLL with both a BTKi and a BCL2i.
   a. Patients should have disease relapsed after or refractory to at least 1 line of therapy including a BTKi or been intolerant to a therapy with BTKi.
   b. Patients should have disease relapsed after or refractory to at least 1 line of therapy including a BCL2i or been intolerant to a therapy with BCL2i.
   c. Patients who have received prior treatment with an ncBTKi can be enrolled. In regions where an ncBTKi is approved and available, patients should have disease relapsed after or refractory to at least 1 line of therapy including an ncBTKi or been intolerant to a therapy with ncBTKi.

   NOTE: A line of therapy is considered 2 or more consecutive cycles of a systemic anticancer regimen.
   NOTE: See Appendix 21 for guidance regarding the definition of intolerant to BTKi.
5. For patients to be considered for bendamustine + rituximab as the investigator's choice regimen, the disease should not have del(17p) or *TP53* mutation.
6. For patients to be considered for venetoclax + rituximab as the investigator's choice regimen: The best overall response of the last BCL2i-based regimen should be PR or better, the last dose of BCL2i should have been at least 1 year prior to the most recent disease progression, and the patient should have been able to tolerate previous BCL2i treatment.
7. Patients with SLL must have measurable disease by CT/MRI, defined as ≥ 1 lymph node > 1.5 cm in LDi and measurable in 2 perpendicular diameters.
8. ECOG Performance Status of 0 to 2.
9. Patients must have adequate organ function as indicated by the following laboratory values during screening:

a. Adequate bone marrow function as defined by:
   - ANC ≥ 1000/mm^3 (or ≥ 750/mm^3 for patients with bone marrow involvement) without growth factor support within 7 days.
   - Platelets ≥ 75,000/mm^3 (or ≥ 50,000/mm^3 for patients with bone marrow involvement), without growth factor support or transfusion within 7 days.
   - Hemoglobin ≥ 7.5 g/dL (may be post-transfusion); patients may have hemoglobin < 7.5 g/dL if the reduced hemoglobin is secondary to bone marrow infiltration by CLL.

b. Estimated glomerular filtration rate ≥ 30 mL/min as determined by the Chronic Kidney Disease Epidemiology Collaboration equation 2021 (Appendix 11).
c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN with conjugated bilirubin ≤ 1.5 x ULN for patients with Gilbert syndrome).
d. Amylase ≤ 1.5 x ULN, and lipase ≤ 1.5 x ULN
e. Adequate liver function as indicated by AST and ALT ≤ 3.0 x ULN.
f. Adequate blood clotting function as defined by international normalized ratio ≤ 1.5 x ULN and aPTT ≤ 1.5 x ULN.

10. Female patients of childbearing potential must be willing to use a highly effective method of birth control and refrain from egg donation for the duration of the study and ≥ 30 days after the last dose of BGB-16673 in Arm A, and 1 month after the last dose of idelalisib or venetoclax, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is later, in Arm B. In both Arm A and Arm B, all women of childbearing potential must undergo a highly sensitive serum pregnancy test within 14 days before the first dose of study treatment, which should be repeated within 24 hours prior to administration of the first dose of study treatment. See Section 8.3.5. Note: A woman is considered of childbearing potential (ie, fertile, following menarche and until becoming postmenopausal) unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy (see Appendix 2).
11. Nonsterile male patients must be willing to use a highly effective method of birth control and refrain from sperm donation for the duration of the study and for ≥ 30 days after the last dose of BGB-16673 in Arm A, and 1 month after the last dose of idelalisib or venetoclax, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is later, in Arm B. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Men with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study (see Appendix 2).
12. For patients to be considered for idelalisib + rituximab as the investigator's choice regimen, the disease must be CLL, not SLL.

5.2. Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria:

1. Known prolymphocytic leukemia or history of, or currently suspected, Richter's transformation.
2. Prior autologous stem cell transplant or chimeric antigen receptor-T cell therapy in the last 3 months.
3. Patients who have a history of severe allergic reactions or hypersensitivity to the active ingredient and excipients of study treatment (BGB-16673, bendamustine, idelalisib, rituximab, or venetoclax).
4. Patients who are unable to comply with the requirements of the protocol.
5. Current or history of central nervous system involvement including the brain, spinal cord, leptomeninges, and cerebrospinal fluid (as documented by imaging, cytology, or biopsy) by CLL/SLL.
6. Patients with any malignancy ≤ 3 years before randomization except for CLL/SLL and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast). The exceptions include:
   a. Malignancies surgically treated with curative intent and with no known active disease present for ≥ 3 years before randomization.
   b. Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease.
   c. Adequately treated cervical carcinoma in situ without evidence of disease.
   d. Localized prostate cancer with Gleason score ≤ 6.
7. History of ischemic stroke or intracranial hemorrhage within 6 months before first dose of study drug
8. Active fungal, bacterial and/or viral infection requiring parenteral systemic therapy
9. Positive HIV serology (HIV antibody) status or serologic status reflecting active hepatitis B or C infection as follows:
   a. Presence of HBsAg.
   b. Patients with presence of HBcAb, in the absence of HBsAg, with detectable HBV DNA.
      – NOTE: The limit of detection for HBV DNA must have a sensitivity of < 20 IU/mL; see Section 8.1.3. Patients with presence of HBcAb but undetectable HBV DNA and who are willing to undergo HBV DNA monitoring every 4 weeks for HBV reactivation are eligible.
   c. Patients with presence of HCV antibody and detectable HCV RNA.
      – NOTE: The limit of detection for HCV RNA must have a sensitivity of < 15 IU/mL; see Section 8.1.3. Patients with presence of HCV antibody and undetectable HCV RNA and who are willing to undergo HCV RNA monitoring every 4 weeks for HCV reactivation are eligible.
10. Prior exposure to any BTK protein degraders.

11. Patients with any major surgical procedure ≤ 28 days before first dose of study treatment. Patients must have recovered adequately from the procedure and/or complications from the procedure before first dose of study treatment.
12. Patients with clinically significant cardiovascular disease such as the following:
    a. Myocardial infarction within 3 months of the first dose of study treatment.
    b. NYHA Classification III or IV congestive heart failure (Appendix 12).
    c. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes).
    d. QTcF > 480 milliseconds based on Fridericia's formula. Patients with prolonged QTcF due to bundle branch block can be allowed after consultation with the cardiologists.
    e. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place.
    f. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg at screening.
13. Patients who have received any biologic and/or immunologic-based anticancer therapy(ies) including experimental therapy(ies) (including, but not limited to, monoclonal antibody therapy such as rituximab and/or cancer vaccine therapy) ≤ 28 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study treatment, or, who have received systemic chemotherapy or radiation therapy ≤ 14 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study treatment.
14. Patients who have received corticosteroid given with antineoplastic intent (symptom control will not be considered as antineoplastic intent) ≤ 7 days before the first dose of study treatment. Note: A short course (≤ 7 days) of systemic steroid use is allowed if needed to control lymphoma-related symptoms and it is tapered off within 5 days after initiation of study treatment. Ongoing systemic corticosteroid treatment (defined as ≥ 10 mg/day of prednisone or equivalent) is not allowed.
15. Requires treatment with warfarin or other vitamin K antagonists.
16. Patients who have received BTKi, tyrosine kinase inhibitor, or other targeted small molecules given with antineoplastic intent ≤ 7 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study treatment.
17. Patients with toxicities (because of prior anticancer therapy) that have not recovered to baseline or stabilized, except for adverse events not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities).
18. Patients who were administered a live vaccine ≤ 28 days before the first dose of study treatment. Vaccines for COVID-19 are allowed except for any live vaccine that may become available. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
19. Any Chinese patent medicine with anticancer activity approved by the China National Medical Products Administration (regardless of the type of cancer) used ≤ 14 days before the first dose of study treatment.

20. Patients with underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study treatment, will affect the explanation of drug toxicity or adverse events, or will result in insufficient or impaired compliance with study conduct.
21. Female patients who are pregnant or are breastfeeding.
22. Patients with concurrent participation in another therapeutic clinical study. Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.
23. Patients who are unable to swallow tablets or with disease/procedure significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or gastrointestinal perforation or fistulae. Note: Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed (assuming no drug interaction potential). Refer to Section 6.9.
24. Receiving treatment with a strong CYP3A inhibitor or strong CYP3A inducer ≤ 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment(s) OR requiring long-term use of strong CYP3A inhibitors or inducers. For a list of selected strong CYP3A inhibitors or inducers, see Appendix 8.