KARTA BADANIA
NAZWA BADANIA: Study of Tazemetostat Versus Placebo When Given in Combination With Lenalidomide and Rituximab in Participants With Relapsed/Refractory Follicular Lymphoma (SYMPHONY-1)
NUMER PROTOKOŁU: **EZH-302**
WSKAZANIE- C82 - Chłoniak nieziarniczy guzkowy [grudkowy]

Criteria

Inclusion Criteria:

1. Have voluntarily agreed to provide written informed consent and demonstrated willingness and ability to comply with all aspects of the protocol.
2. Males or females are ≥18 years of age (≥20 years for Taiwan) at the time of providing voluntary written informed consent.
3. Life expectancy ≥3 months before enrollment.
4. Subjects with a history of hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion #15 but with normal ALT and are hepatitis B surface antigen negative with undetectable HBV DNA and/or have undetectable hepatitis C virus (HCV) RNA if HCV antibody positive.
5. Have histologically confirmed FL, Grades 1 to 3A.
6. Must have been previously treated with at least 1 prior systemic chemotherapy, immunotherapy, or chemoimmunotherapy:

   a. Systemic therapy includes treatments such as:

   i. Rituximab monotherapy

   ii. Chemotherapy given with or without rituximab

   iii. Radioimmunoconjugates such as 90Y-ibritumomab tiuxetan and 131I-tositumomab.

   b. Systemic therapy does not include, for example:

   i. Local involved field radiotherapy for limited-stage disease

   ii. Helicobacter pylori eradication

   c. Prior investigational therapies will be allowed provided the subject has received at least 1 prior systemic therapy as discussed in Inclusion Criterion #6a.

   d. Prior autologous/allogeneic hematopoietic stem cell transplant (HSCT) will be allowed.

   e. Prior chimeric antigen receptor T-cell therapy (CAR T) will be allowed.

7. Must have documented relapsed, refractory, or PD after treatment with systemic therapy (refractory defined as less than PR or disease progression <6 months after last dose).
8. Have measurable disease as defined by the Lugano Classification (Cheson, 2014; Appendix 5).
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
10. For subjects who have experienced any clinically significant toxicity related to a prior anticancer treatment (ie, chemotherapy, immunotherapy, and/or radiotherapy):

    a. At the time the subject provides voluntary written informed consent, all toxicities have either resolved to Grade 1 per National Cancer Institute CTCAE Version 5.0 OR are clinically stable and no longer clinically significant.

11. Have provided sufficient tumor tissue for EZH2 mutation testing in all subjects to allow for stratification and for CNG determination in a subset of WT EZH2 subjects from the Phase 3 portion of the study.

    a. If EZH2 mutation status is known from site-specific testing, subjects can be enrolled, but additional tumor tissue will be required for confirmatory testing of EZH2 status at study-specific laboratories. If the archival tumor sample was collected more than 15 months prior to administration of the first dose (cycle 1 day 1), then a fresh biopsy must be provided. Fresh tumor biopsy is appropriate except for procedures deemed to result in unacceptable risk because of the anatomical location including brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel. Archival tumor biopsy sections mounted on slides are also acceptable.

    NOTE: Confirmatory testing will also be performed for Stage 1, if local EZH2 testing is conducted, unless there is insufficient tumor tissue to perform testing after discussion with the Sponsor's or Designee Medical Monitor.

12. Time between prior anticancer therapy and first dose of tazemetostat as follows:
    1. Cytotoxic chemotherapy - At least 21 days.
    2. Noncytotoxic chemotherapy (eg, small molecule inhibitor) - At least 14 days.
    3. Nitrosoureas - At least 6 weeks.
    4. Monoclonal and/or bispecific antibodies or CAR T - At least 28 days.
    5. Radiotherapy - At least 6 weeks from prior radioisotope therapy; at least 12 weeks from 50% pelvic or total body irradiation.
13. Adequate renal function defined as calculated creatinine clearance ≥30 mL/minute per the Cockcroft and Gault formula.
14. Adequate bone marrow function:

    a. Absolute neutrophil count (ANC) ≥1000/mm3 (≥1.0 × 10^9/L) if no lymphoma infiltration of bone marrow OR ANC ≥750/mm3 (≥75 × 10^9/L) with bone marrow infiltration

    - Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days.

b. Platelets ≥75,000/mm3 (≥75 × 10^9/L)

- Evaluated at least 7 days after last platelet transfusion.

c. Hemoglobin ≥9.0 g/dL

- May receive transfusion

15. Adequate liver function:
    1. Total bilirubin ≤1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
    2. Alkaline phosphatase (ALP) (in the absence of bone disease), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (≤5 × ULN if subject has liver metastases).
16. International normalized ratio (INR) ≤1.5 × ULN and activated partial thromboplastin time (aPTT) ≤1.5 × ULN (unless on warfarin, then INR ≤3.0). In subjects with thromboembolism risk, prophylactic anticoagulation, or antiplatelet therapy at investigator discretion is recommended.
17. Females of childbearing potential (FCBP) must have two negative urine or serum pregnancy tests (beta-human chorionic gonadotropin [β-hCG] tests with a minimum sensitivity of 25 mIU/mL or equivalent units of β-hCG) at screening prior to dosing. The first pregnancy test must be performed within 10 to 14 days prior to first dose of study drug and the second pregnancy test must be performed within 24 hours prior to first dose of study drug. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 24 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (ie, total hysterectomy and/or bilateral oophorectomy, with surgery completed at least 1 month before dosing).
18. Females of childbearing potential (FCBP) enrolled must either practice complete abstinence or agree to use two reliable methods of contraception simultaneously. This includes ONE highly effective method of contraception and ONE additional effective contraceptive method. Contraception must begin at least 28 days prior to first dose of study drug, continue during study treatment (including during dose interruptions), and for 12 months after study drug discontinuation. Female subjects must also refrain from breastfeeding for 12 months following last dose of study drug. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. The following are examples of highly effective and additional effective methods of contraception:

    Examples of highly effective methods:

    - Intrauterine device (IUD)
    - Hormonal (ovulation inhibitory combined [estrogen and progesterone] birth control pills or intravaginal/transdermal system, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone

acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel]) NOTE: There is a potential for tazemetostat interference with hormonal contraception methods due to enzymatic induction.

- Bilateral tubal ligation
- Partner's vasectomy (if medically confirmed [azoospermia] and sole sexual partner).

Examples of additional effective methods:

- Male latex or synthetic condom,
- Diaphragm,
- Cervical Cap

NOTE: Female subjects of childbearing potential exempt from these contraception requirements are subjects who practice complete abstinence from heterosexual sexual contact. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

19. All study participants enrolled must be registered into the mandatory Revlimid REMS™ program for the US or Revlimid Global PPP for ex-US and be willing and able to comply with the requirements of the Revlimid REMS™ or Revlimid Global PPP program as appropriate for the country in which the drug is being used.

    a. Female subjects of childbearing potential (FCBP) must adhere to the scheduled pregnancy testing as required in the Revlimid REMS™ program (for the US) or Revlimid Global PPP (for ex-US). During study treatment, FCBP must agree to have pregnancy testing weekly for the first 28 days of study participation and then every 28 days for FCBP with regular or no menstrual cycles OR every 14 days for FCBP with irregular menstrual cycles. FCBP must also have a pregnancy test at end of lenalidomide treatment, and at days 14 and 28 following the last dose of lenalidomide. Female subjects exempt from this requirement are subjects who have been naturally postmenopausal for at least 24 consecutive months OR have had a total hysterectomy and/or bilateral oophorectomy.

20. Male subjects must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), during sexual contact with a pregnant female or FCBP from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

NOTE: Male subjects must not donate semen or sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

Exclusion Criteria:

All Subjects

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. Prior exposure to lenalidomide.
3. Grade 3b, mixed histology, or FL that has histologically transformed to DLBCL (subjects transformed from DLBCL to FL may be enrolled).
4. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE Version 5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or myeloproliferative neoplasm (MPN).
5. Has a prior history of T-cell lymphoblastic lymphoma (T-LBL)/T-cell acute lymphoblastic leukemia (T-ALL).
6. Subjects with uncontrolled leptomeningeal metastases or brain metastases or history of previously treated brain metastases.
7. Subjects taking medications that are known strong CYP3A inhibitors and strong or moderate CYP3A inducers (including St. John's wort).
8. Are unwilling to exclude grapefruit juice, Seville oranges, and grapefruits from the diet and/or consumed within 1 week of the first dose of study drug and for the duration of the study.
9. Major surgery within 4 weeks before the first dose of study drug.

   a. Note: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.
10. Are unable to take oral medication OR have malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, vomiting) that might impair the bioavailability of tazemetostat.
11. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac ventricular arrhythmia (Appendix 3).
12. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to ≥480 msec at screening or history of long QT syndrome.
13. Venous thrombosis or pulmonary embolism within the last 3 months before starting tazemetostat.

    a. whereas subjects greater than 3 months since deep vein thrombosis/pulmonary embolism are eligible but recommended to receive prophylaxis.
14. Have an active infection requiring systemic therapy.
15. Known hypersensitivity to any component of tazemetostat or lenalidomide; known severe hypersensitivity to any component of rituximab requiring hospitalization or resuscitation.
16. Inability to be treated with a Pneumocystis prophylaxis medication.
17. Active viral infection with or seropositive for hepatitis B virus (HBV): HBV surface antigen (HBsAg) positive OR HBsAg negative, anti-HBs positive and/or anti-HBc positive with detectable HBV DNA.

NOTE: Subjects who are HBsAg negative, anti-HBs positive and/or anti-HBc positive, but with undetectable viral DNA and normal ALT are eligible. Subjects who are seropositive due to HBV vaccination (HBsAg negative, HBV surface antibody [anti-HBs] positive, and HBV core antibody [anti-HBc] negative) are eligible.

18. Active viral infection with hepatitis C virus (as measured by positive HCV antibody and detectable viral RNA), human immunodeficiency virus (HIV), AND/OR human T-cell lymphotropic virus 1 (as measured by positive HTLV-1 antibody) or known history of HIV positive status.

    NOTE: Subjects with a history of hepatitis C infection (HCV antibody reactive) who have normal ALT and undetectable HCV RNA are eligible.

19. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the subject's participation in this study OR interfere with their ability to receive study treatment or complete the study.
20. Female subjects who are pregnant or lactating/breastfeeding.
21. Subjects who have undergone a solid organ transplant.
22. Subjects with malignancies other than FL. a. Exception: Subjects with another malignancy who have been disease-free for 5 years, or subjects with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.