KARTA BADANIA
NAZWA BADANIA: A Multicenter, Open-label, Phase 2 Dose Escalation and Confirmation, and Efficacy Expansion Study of Zilovertamab Vedotin (MK-2140) in Combination With R-CHP in Participants With DLBCL (waveLINE) **(MK-2140-010)**
NUMER PROTOKOŁU: **MK-2140-010**
WSKAZANIE- C83.3 - Z dużych komórek (rozlany)

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Histologically-confirmed diagnosis of DLBCL, by prior biopsy, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Alaggio, R., et al 2022], which includes but is not limited to: DLBCL, NOS; DLBCL leg-type; EBV+ DLBCL; and T-cell histiocytic-rich DLBCL.
   NOTE: HGBL participants will be excluded from this study.
2. Has PET-positive disease at screening, defined as 4 to 5 on the Lugano 5-point scale.
3. Has received no prior treatment for their DLBCL.

Demographics

4. Is an individual of any sex/gender, ≥18 years of age at the time of providing documented informed consent.

Assigned Male Sex at Birth

5. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is:
   - Zilovertamab vedotin: 110 days
   - Cyclophosphamide: 90 days
   - Doxorubicin: 90 days
   - Rituximab (or biosimilar): no contraception needed
   - Vincristine: 110 days
- Refrains from donating sperm

PLUS either:

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method (refer to Section 10.5.3), as a condom may break or leak
- Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Note: If the participant is azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), no contraception is required.

Assigned Female Sex at Birth

6. A POCBP is eligible to participate if not pregnant and a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention has been obtained. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
7. A POCBP is eligible to participate if not breastfeeding during the study intervention period and for at least 180 days or 210 days after study intervention in Arm 1 and Arm 2, respectively.
8. A POCBP is eligible to participate if a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency is used, or penile-vaginal intercourse abstinence, as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), is adhered to as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. In addition, the participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for each study intervention is:
   - Zilovertamab vedotin: 50 days
   - Cyclophosphamide: 180 days
   - Doxorubicin: 180 days
   - Rituximab (or biosimilar): 365 days
   - Vincristine: 50 days

Note: The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed. Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

9. The participant has provided documented informed consent for the study.

Note: Participants who are legally blind, unable to read, or have a mild developmental or intellectual disability and can indicate a wish to participate in this study may enroll if the eligibility criteria are met, a legally acceptable representative provides consent on their behalf, and an impartial witness participates in the consent process. If eligible, these participants may be enrolled in this study to allow the possibility of benefit from the planned treatment(s).

Note: References to a participant's "legally acceptable representative" for consenting purposes are not applicable for participants in the EEA. Participants in the EEA who are unable to provide documented informed consent because they are confirmed by the investigator to be unable to read or write, legally blind, and/or unable to sign due to a physical disability, but are able to indicate a willingness to participate, will be allowed to enroll in the study. Such participants will have an impartial witness appointed.

Additional Categories

10. Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Procedures Manual. See Appendix 7 for country-specific requirements.
    Note: Fresh or newly obtained tissue biopsy (obtained ≤60 days) or archival tumor biopsy tissue (obtained >60 days) prior to screening.

    Note: If no tumor tissue is available, participants may be eligible for enrollment after consultation with the Sponsor.
11. Has an ECOG performance status of 0 to 2 assessed within 7 days before randomization.
    Note: Participants with ECOG performance status of 2 will be capped at 20% per arm.
12. Has an IPI score of 2 to 5 assessed within 7 days before randomization.
    Note: enrollment of participants with an IPI score of 2 will be capped at 30% per arm.
13. Has an ejection fraction ≥45% as determined by either ECHO or MUGA.

14. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening
    b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening
    c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months
    d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
    e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

    See Appendix 7 for country-specific requirements.

15. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy and have undetectable HBV viral load prior to randomization.
    Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    Hepatitis B screening tests should include HBsAg and HBcAb.

    See Appendix 7 for country-specific requirements.

16. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.
    Note: Participants must have completed curative antiviral therapy at least 4 weeks prior to randomization.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority

    See Appendix 7 for country-specific requirements.

17. Adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days before the start of study intervention.
    Note: Participants with asymptomatic elevation in unconjugated bilirubin related to Gilbert syndrome can be included.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1000/μL [a, b]
Platelets	≥50 000/μL [a, b]
Hemoglobin	≥8 g/dL [a, b]
Renal	
Measured or calculated creatinine clearance [c]	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed.

[b] No lower limit if cytopenia is related to bone marrow involvement.

[c] CrCl calculated using the Cockcroft-Gault CrCl formula =

$$\frac{[(140 - \text{age [years]}) \times \text{weight (kg)}]}{\text{Serum creatinine } \left(\frac{\text{mg}}{\text{dL}}\right) \times 72} \times \text{F}$$

where F = 0.85 for participants assigned female sex at birth and F=1 for participants assigned male sex at birth. As an alternative, CrCl can be determined from a 24-hour urine collection.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has a history of transformation of indolent disease to DLBCL.
2. Has received a diagnosis of PMBCL or Grey zone lymphoma.
3. Has Ann Arbor Stage I DLBCL.
4. Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥II), or serious cardiac arrhythmia requiring medication.
5. Has QTc prolongation of >480 msec.
6. Has clinically significant pericardial or pleural effusion.
7. Has ongoing Grade >1 peripheral neuropathy.
8. Has a demyelinating form of Charcot-Marie-Tooth disease.

9. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

Prior/Concomitant Therapy

10. Has ongoing corticosteroid therapy (exceeding 30 mg daily of prednisone equivalent). Prednisone equivalent dosing must have been stable for at least 28 days prior to randomization.
    Note: If corticosteroid treatment is required for lymphoma symptom control prior to C1D1, up to 100 mg per day of prednisone equivalent can be given for up to 5 days. All tumor assessments must have been completed prior to the start of corticosteroid treatment.
11. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.
12. Known intolerance to any of the study interventions and/or their excipients.
13. Received a strong inhibitor or inducer of CYP3A4 within 14 days prior to randomization or is expected to require chronic use of a strong CYP3A4 inhibitor during treatment study intervention until 30 days after the last dose (see Section 6.5.2).
    Note: For participants requiring antifungal prophylaxis/therapy, oral fluconazole or isavuconazonium can be considered. Echinocandins (eg, caspofungin, anidulafungin, or micafungin) are also acceptable, realizing the disadvantage of the requirement for IV administration.

    Note: For examples of CYP3A4 induces and inhibitors, refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
14. Received a strong modulator of CYP2D6 or P-gp within 14 days prior to randomization or is expected to require chronic use of a modulator of CYP2D6 or P-gp during treatment study intervention until 30 days after the last dose (see Section 6.5.2).
    Note: For examples of modulators of CYP2D6 and P-gp, refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Prior/Concurrent Clinical Study Experience

15. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

16. Known additional malignancy that is progressing or has required active treatment within the past 2 years.
    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the

skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.

17. Known active CNS lymphoma.
18. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
19. Active infection requiring systemic therapy.
20. Concurrent active HBV (defined as HBsAg positive and detectable HBV DNA) and HCV (defined as anti-HCV antibody positive and detectable HCV RNA) infection.
21. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's ability to cooperate with the requirements of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

Other Exclusions

22. History of allogeneic tissue/solid organ transplant.
23. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should avoid ingestion of grapefruit, grapefruit juice, Seville oranges, or starfruit (all of which contain CYP3A4 inhibitors) and should not use St. John's wort (which is a potent CYP3A4 inducer). Otherwise, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

See Appendix 7 for country-specific requirements.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Alcohol consumption is discouraged while receiving study intervention.