Karta badania
Numer protokołu: 64007957MMY3005
NAZWA BADANIA: A Phase 3 Randomized Study Comparing Teclistamab in Combination with Daratumumab SC and Lenalidomide (Tec-DR) and Talquetamab in Combination with Daratumumab SC and Lenalidomide (Tal-DR) versus Daratumumab SC, Lenalidomide, and Dexamethasone (DRd) in Participants with Newly Diagnosed Multiple Myeloma Who are Either Ineligible or not Intended for Autologous Stem Cell Transplant as Initial Therapy **(MMY3005)**
WSKAZANIE: Szpiczak mnogi

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Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified as per Amendment 3.

1.1. Plasma cell leukemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), or primary amyloid light chain amyloidosis. Any treated plasma cell dyscrasia (eg, monoclonal gammopathy of undefined significance).

2. Criterion modified as per Amendment 3.

2.1. Received any prior therapy for multiple myeloma or smoldering myeloma other than a short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent). In addition, received a cumulative dose of systemic corticosteroids equivalent to ≥20 mg of dexamethasone during the Screening Phase (see

Appendix 12).

3. Criterion modified as per Amendment 3.

3.1. Received focal radiation therapy within 14 days of randomization. However, if the radiation is given for palliative purposes and the radiation portal covered ≤5% of the bone marrow reserve, the participant is eligible irrespective of the end date of radiotherapy (see Appendix 23). Radiotherapy within 14 days on measurable softtissue plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management.

4. Criterion modified as per Amendment 3.

4.1. Had plasmapheresis within 28 days of randomization

5. Criterion modified as per Amendment 3.

5.1. Had a stroke, transient ischemic attack, or seizure within 6 months prior to randomization.

6. Criterion modified as per Amendment 3.

6.1. CNS or meningeal involvement of multiple myeloma. If either is suspected, negative brain and total spine MRI (with and without contrast) and cerebral spinal fluid cytology are required.

7. Has COPD with an FEV1 <50% of predicted. (FEV1 testing is required for participants suspected of having COPD).

8. Has moderate or severe persistent asthma within the past 2 years (see Appendix 13) or uncontrolled asthma of any classification (Participants who have controlled intermittent asthma or control mild persistent asthma are allowed in the study).

9. Seropositive for hepatitis B: defined by a positive test HBsAg. Participants with resolved

infection (ie, participants who are HBsAg negative with antibodies to total anti-HBc with or without the presence of anti-HBs) must be screened using RT-PCR measurement of HBV-DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV-DNA by RT-PCR (see Section 8.3.5 and Appendix 21).

10. Has active hepatitis C infection as measured by positive HCV-RNA testing. Participants with a history of HCV antibody positivity must undergo HCV-RNA testing. If a participant with history of chronic hepatitis C infection (defined as both HCV antibody and HCV-RNA positive) completed antiviral therapy and has undetectable HCV-RNA 12 weeks following the completion of therapy, the participant is eligible for the study.

NOTE: Participants who completed treatment for HCV will be required to undergo regular assessments for HCV reactivation during the study and are to be withdrawn from the study if he/she test positive at any time during the study.

11. Criterion modified as per Amendment 3.

11.1. Participants who are HIV-positive with 1 or more of the following:

a. History of AIDS-defining conditions

b. CD4 count <350 cells/mm3

c. Detectable viral load (ie, >50 copies/mL) during screening or within 6 months prior to randomization

d. Not receiving highly active antiretroviral therapy

e. Had a change in antiretroviral therapy within 6 months prior to randomization

f. Receiving antiretroviral therapy that may interfere with study treatment as assessed after discussion with the Medical Monitor

12. Criterion modified as per Amendment 3.

12.1. Participants will be excluded if they have any of the following:

a. Any ongoing myelodysplastic syndrome or B cell malignancy (other than multiple myeloma)

b. Any history of malignancy, other than multiple myeloma, which is considered at high risk of recurrence requiring systemic therapy

c. Any active malignancy (ie, progressing or requiring treatment change in the last 24 months prior to randomization) other than multiple myeloma. The only allowed exceptions are malignancies treated within the last 24 months that are considered cured:

1) Non-muscle invasive bladder cancer (solitary Ta-papillary urothelial neoplasm of low malignancy or low grade, <3 cm, no carcinoma in situ)

2) Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone

3) Noninvasive cervical cancer

4) Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ or history of localized breast cancer (anti-hormonal therapy is permitted)

5) Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (radical prostatectomy/radiation therapy/focal treatment)

6) Other malignancy that is considered cured with minimal risk of recurrence

in consultation with the sponsor's medical monitor.
NOTE: In the event of any questions, consult with the sponsor's medical monitor prior to enrolling a participant.

13. Participant has concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:

- Acute diffuse infiltrative pulmonary disease
- Evidence of active systemic viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy
- Active autoimmune disease or a documented history of autoimmune disease with the exception of vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing
- Disabling psychiatric conditions (eg, alcohol or drug abuse), severe dementia, or altered mental status
- Any other issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
- History of noncompliance with recommended medical treatments.

14. Criterion modified as per Amendment 3.

14.1. Presence of the following cardiac conditions:

- New York Heart Association stage III or IV congestive heart failure
- Myocardial infarction or coronary artery bypass graft ≤6 months prior to

randomization

 History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration

 Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities.

15. Participant had significant traumatic injury or major surgery within 2 weeks prior to the start of administration of study treatment, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to be treated in the study.

NOTE: Participants with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question whether a procedure is considered a major surgery, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study.

16. Known allergies, hypersensitivity, or intolerance to teclistamab or talquetamab excipients (refer to the IB).

17. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information.

18. Taken any disallowed therapies as noted in Section 6.12.3 before the planned first dose of study treatment.

19. Criterion modified as per Amendment 3.

19.1. Received a live, attenuated vaccine within 4 weeks before randomization. Nonlive or non-replicating vaccines authorized for emergency use (eg, COVID-19; see Appendix 20) are allowed.

20. Any condition for which, in the opinion of the investigator, participation would not be

in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

21. Criterion added as per Amendment 3.

Myeloma Frailty Index of ≥2 with the exception of participants who have a score of 2 based on age alone (Appendix 22).

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3.

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Each potential participant must satisfy all of the following criteria before randomization in the study:

1. Be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent.

2. Have a diagnosis of multiple myeloma according to the IMWG diagnostic criteria (Appendix 5)

3. Be newly diagnosed and not considered a candidate for high-dose chemotherapy with ASCT due to

□ Ineligible due to advanced age OR

□ Ineligible due to the presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT OR

□ Deferral of high-dose chemotherapy with ASCT as initial treatment.

4. Criterion modified as per Amendment 3.

4.1. Measurable disease at Screening as defined by any of the following:

□ Serum monoclonal paraprotein (M-protein) level □1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or

□ Light chain multiple myeloma in whom only measurable disease is by sFLC levels: Serum Ig free light chain □10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio.

NOTE: All attempts should be made to determine eligibility of the participant based on the central laboratory results of screening blood, urine M-protein measurements, and sFLC. In exceptional circumstances and after discussion with and approval by the sponsor, the local laboratory results of blood, urine M-protein measurements, and sFLC may be used to determine initial eligibility, but only if the results are ≥25% above the thresholds for measurability. In such cases, central laboratory results should still be obtained prior to the start of administration of study treatment in order to establish baseline central laboratory values and confirm the results from the local laboratory.

5. Have an ECOG performance status score of 0 to 2 (Section 8.3.8, Appendix 7).

6. Have clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥7.5 g/dL (≥4.65 mmol/L; without prior RBC transfusion or recombinant human erythropoietin use within 7 days before the laboratory test)
Platelets	≥70×10^9/L in participants in whom <50% of bone marrow nucleated cells are plasma cells and ≥50×10^9/L in participants in whom ≥50% of bone marrow nucleated cells are plasma cells (without transfusion support or thrombopoietin receptor agonist within 7 days before the laboratory test)
Absolute neutrophil count	≥1.0×10^9/L (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated-G-CSF)
Chemistry	
AST and ALT	≤2.5×ULN
Creatinine clearance	≥30 mL/min based on Cockcroft-Gault (see Appendix 8)

Total bilirubin	≤2.0 × ULN; except in participants with congenital hyperbilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required)
Serum calcium corrected for albumin	≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L; see Appendix 10)

7. A participant of childbearing potential must have a negative highly sensitive serum pregnancy test at screening and a serum or urine pregnancy test within 24 hours of the start of study treatment and must agree to further serum or urine pregnancy tests during the study as described in Section 8.3.6 and in agreement with the global PPP or local PPP/REMS program for lenalidomide.

8. Criterion modified as per Amendment 3.

8.1. A participant must be either of the following (as defined in Appendix 11)

a. Not of childbearing potential, or

b. Of childbearing potential and practicing at least 2 methods of reliable contraception including 1 highly effective method of contraception (details in Appendix 11) from the time of signing the ICF until 6 months after the last dose of study treatment. Contraception must begin 4 weeks prior to dosing of lenalidomide. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy (Appendix 11). See Section 6.12.3.2 for details regarding concomitant use of estrogen-containing products and lenalidomide.

NOTE: If a participant becomes of childbearing potential after the start of the study, the participant must comply with (b.)

9. A participant must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 6 months after receiving the last dose of study treatment. Participants should consider preservation of eggs prior to study treatment as anticancer treatments may impair fertility.

10. A participant must wear a condom (with or without spermicidal foam/gel/film/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person during the study and for 3 months after receiving the last dose of study treatment. If the participant's partner is of childbearing potential, the participant must use condoms (with or without spermicide) and the partner of the participant must also be practicing a highly effective method of contraception (see Appendix 11). A participant who is vasectomized must still use a condom (with or without spermicide), but the partner is not required to use contraception.

11. A participant must agree not to donate sperm for the purposes of reproduction during the study and for 3 months after receiving the last dose of study treatment. Participants should consider preservation of sperm prior to study treatment as anticancer treatments may impair fertility.

12. A participant must agree not to be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.

13. A participant must agree not to plan to father a child while enrolled in this study or within 3 months after the last dose of study treatment.

14. Must sign an ICF (or their legally acceptable representative must sign in accordance with local legislation) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

15. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.