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

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This study has been transitioned to CTIS with ID 2023-503442-30-00 check the CTIS register for the current data. The purpose of this study is to compare the efficacy of teclistamab and talquetamab both in combination with daratumumab and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON56272

Source
ToetsingOnline

Brief title
Study to Compare Tec-DR & Tal-DR with DRd in TI NDMM / MajesTEC-7

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: door de opdrachtgever

Intervention

Keyword: DRd, Multiple Myeloma, Talquetamab, Teclistamab

Outcome measures

Primary outcome

Primary Outcome Measure:

1. Progression Free Survival (PFS) from randomization to the date of disease progression or death (Up to 9 years). PFS is defined as the duration from the date of randomization to either progressive disease or death, whichever comes first. Disease progression will be determined according to the International Myeloma Working Group (IMWG) response criteria.

2. Complete Response (CR) or Better. From randomization up to 9 years. CR or better is defined as the percentage of participants achieving CR or stringent

complete response (sCR) prior to subsequent antimyeloma therapy in accordance with the IMWG criteria during or after the study treatment.

Secondary outcome

1. Very Good Partial Response (VGPR) or Better. Timeframe: From randomization up to 9 years. VGPR or better is defined as the percentage of participants achieving VGPR and CR (including stringent complete response [sCR]) prior to subsequent antimyeloma therapy in accordance with the International Myeloma Working Group (IMWG) criteria during or after the study treatment.
2. Sustained Minimal Residual disease (MRD)-negative Complete Response (CR). From randomization up to 9 years. Sustained MRD-negative CR is defined as participants with CR or better who sustain MRD-negative status, as determined by next-generation sequencing (NGS) with sensitivity of 10^-5, for at least 12 months
without any examination showing MRD positive status or progressive disease in between.
3. MRD-negative CR. Timeframe: From randomization up to 9 years. MRD-negative CR is defined as the percentage of participants who achieve MRD-negative status, as determined by NGS with sensitivity of 10^-5, at any time after randomization and prior to progressive disease or subsequent antimyeloma therapy and who achieve CR or better.
4. Progression Free Survival on Next-line Therapy (PFS2). Timeframe: From randomization up to 9 years. PFS2 is defined as the time interval between the date of randomization and date of event, which is defined as progressive disease as assessed by investigator that starts after the next line of

subsequent therapy, or death from any cause, whichever occurs first.

5. Overall Survival (OS). Timeframe: From randomization to the date of death (up to 9 years). OS is defined as the time from the date of randomization to the date of death due to any cause.

6. Number of Participants with Adverse Events (AEs) by Severity. Timeframe: From randomization up to 9 years. An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: life-threatening, and Grade 5: death related to adverse event.

7. Number of Participants with Abnormalities in Laboratory Parameters. Timeframe: From randomization up to 9 years. Number of participants with abnormalities in laboratory parameters (serum chemistry and hematology) will be reported.

8. Number of Participants with Abnormalities in Vital Signs. Timeframe: From randomization up to 9 years. Number of participants with abnormalities in vital signs (temperature, pulse/heart rate, respiratory rate, blood pressure) will be reported.

9. Number of Participants with Abnormalities in Physical Examination. Timeframe: From randomization up to 9 years. Number of participants with abnormalities in physical examination will be reported.

10.. Number of Participants with Abnormalities in Electrocardiogram (ECG). Timeframe: From randomization up to 9 years. Number of participants with abnormalities in ECG will be reported.

11. Serum Concentrations of Teclistamab and Talquetamab. Timeframe: From randomization up to 9 years. Serum samples will be analyzed to determine concentrations of teclistamab using validated, specific, and sensitive methods.

12. Number of Participants with Anti-drug Antibodies (ADAs) to Teclistamab and Talquetamab: Timeframe: From randomization up to 9 years. Number of participants with ADAs to teclistamab will be reported.

13. Change from Baseline in Symptoms, Functioning, and Health-related Quality of Life (HRQoL) as Assessed by European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC-QLQ-C30). Timeframe: From baseline up to 9 years. The EORTC-QLQ-C30 Version 3 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea/vomiting), and 5 single symptom items (dyspnea, insomnia, appetite loss, constipation, and diarrhea) and a single impact item (financial difficulties). The recall period is 7 days (*past week*), and responses are reported using a verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning and a high score for the global health status represents high HRQoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

14. Change from Baseline in Treatment-related Symptoms as Assessed by Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Timeframe: Baseline through Cycle 6 (each cycle of28 days) (up to 196 days). The National Cancer Institute's (NCI's) PRO-CTCAE is an item library of common AEs experienced by people with cancer that are appropriate for self-reporting of treatment tolerability. Each symptom selected for inclusion can be rated by up to 3 attributes characterizing the presence/frequency, severity, and/or interference of the AEs. It ranges from 0 to 4 with higher scores indicating higher frequency or greater severity/impact.
15. Change from Baseline in Symptoms, Functioning, and Overall HRQoL as Assessed by EuroQol Five Dimension Questionnaire 5-Level (EQ-5D-5L). Timeframe: From baseline up to 9 years. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analog scale rating *health today* with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).
16. Time to Sustained Worsening in Symptoms, Functioning, and HRQoL: Timeframe: From randomization up to 9 years. Time to sustained worsening in symptoms, functioning and HRQoL is defined as the interval from the date of randomization to the start date of meaningful change.

Study description

Background summary

A Phase 3 Randomized Study Comparing Teclistamab and Talquetamab both in Combination with Daratumumab SC and Lenalidomide (Tec-DR and 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.
Teclistamab and talquetamab are IgG4-PAA bispecific antibodies targeting the CD3 receptor expressed on the surface of T cells. Teclistamab additionally targets BCMA, which is expressed on the surface of multiple myeloma B cell lineage cells, as well as late-stage B cells and plasma cells. Talquetamab additionally targets GPRC5D, which is expressed on multiple myeloma cells. Both bispecific antibodies draw T cells in close proximity to target expressing cells, leading to activation of T cells and subsequent lysis of target cells.

Study objective

This study has been transitioned to CTIS with ID 2023-503442-30-00 check the CTIS register for the current data.

The purpose of this study is to compare the efficacy of teclistamab and talquetamab both in combination with daratumumab and lenalidomide (Tec-DR and Tal-DR) versus daratumumab, lenalidomide, dexamethasone (DRd).

Study design

Teclistamab is a full-size, immunoglobin G4 proline, alanine, alanine (IgG4-PAA) bispecific antibody that targets the cluster of differentiation 3 (CD3) receptor expressed on the surface of T cells and B cell maturation antigen (BCMA). Talquetamab is a full-size, humanized IgG4-PAA bispecific antibody designed to target the CD3 receptor complex on T cells and G protein-coupled receptor class C group 5 member D (GPRC5D), which is a 7-transmembrane receptor protein that is classified as a type C G protein-coupled receptor. DRd is an approved regimen for the treatment of participants with newly diagnosed, transplant-ineligible multiple myeloma. The primary hypothesis is that Tec-DR and Tal-DR will significantly improve PFS or the rate of CR or better compared with DRd in participants with newly diagnosed multiple myeloma who are ineligible or not intended for ASCT as initial therapy.. The study will be conducted in 3 phases: Screening, Treatment, and Follow-up. Safety Assessment includes adverse events (AEs), laboratory test results, vital sign measurements, physical examination findings, assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade, and immune effector cell associated encephalopathy (ICE) score (Tec-DR and Tal-DR).

Intervention

Arm A: Teclistamab, Daratumumab SC, Lenalidomide (Tec-DR): Participants will receive teclistamab as subcutaneous (SC) injection in combination with

daratumumab lenalidomide.
Arm B: Talquetamab, Daratumumab SC, Lenalidomide (Tal-DR): Participants will receive talquetamab as subcutaneous (SC) injection in combination with daratumumab lenalidomide.
Arm C: Daratumumab SC, Lenalidomide, and Dexamethasone (DRd): Participants will receive daratumumab as SC injection with lenalidomide and dexamethasone.

Study burden and risks

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified for combination therapy of Tec-DR or Tal-DR are justified by the anticipated benefits. The addition of teclistamab or talquetamab to daratumumab SC and lenalidomide offers a unique mechanism of action of T-cell redirection that could lead to synergistic antimyeloma effects. A short course of lower dose steroids mitigates the risk for sARR and CRS while reducing the risk of long-term steroid-induced toxicities.

There is potential risk for overlapping toxicities with the planned study drugs, specifically the unknown effect of daratumumab SC on CRS (which is the main toxicity of concern with teclistamab) and sARRs. The risk mitigation measures planned for the Tec-DR arm include:
* Implementation of step-up doses of teclistamab to reduce risk or severity of CRS
* Subsequent to the urgent safety measure and consistent with data (as of December 2023) from more than 400 participants showing that administration of an IMiD starting after step-up dosing of teclistamab or talquetamab results in a CRS profile similar to monotherapy of the bispecific antibody, dosing of lenalidomide will start in Cycle 2.
* Implementation of pretreatment medications to reduce risk or severity of sARRs and CRS
* SC administration of daratumumab reduces the risk of high-grade sARRs
* Specification of recommended therapies, including antimicrobial prophylaxis and immunoglobulin replacement to reduce risk of infection.
* Robust management strategies for potential toxicities (Section 6.5).

In addition, to further characterize the safety profile of Tec-DR and Tal-DR and mitigate potential risk of this new combination to study participants, safety data from all participants in the Safety Run-in Cohorts , as well as other relevant data from the clinical development program will be evaluated by the sponsor*s Safety Review Committee prior to initiating the Randomized Part of MajesTEC-7.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria:
- Have a diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria
- Be newly diagnosed and not considered a candidate for high-dose chemotherapy with autologous stem cell transplant (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
- Have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2
- 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
- A participant must agree not to plan to father a child while enrolled in this study or within 100 days after the last dose of study treatment

Exclusion criteria

Exclusion Criteria:
- Received any prior therapy for multiple myeloma or smoldering myeloma other than a short course of corticosteroids (not to exceed 40 milligrams [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 greater than or equals to (>=)20 mg of dexamethasone during the Screening Phase
- Had plasmapheresis within 28 days of randomization
- Had a stroke, transient ischemic attack, or seizure within 6 months prior to randomization
- Known allergies, hypersensitivity, or intolerance to teclistamab excipients
- Known contraindications to the use of daratumumab or lenalidomide per local prescribing information
- Myeloma Frailty Index of >=2 with the exception of participants who have a score of 2 based on age alone

For a full list of exclusion criteria, please refer to section 5.2 of the study protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-10-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Daratumumab
Generic name:	DARZALEX
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	dexamethason
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lenalidomide
Generic name:	Lenalidomide Accord
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Talquetamab
Generic name:	NAP
Product type:	Medicine
Brand name:	Teclistamab
Generic name:	TECVAYLI

Ethics review

Approved WMO Date:	23-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	13-09-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

(Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-503442-30-00
EudraCT	EUCTR2022-000909-28-NL
CCMO	NL81954.056.22