A Phase 3 Randomized Study Comparing Bortezomib, Lenalidomide and Dexamethasone (VRd) followed by Ciltacabtagene Autoleucel, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA versus Bortezomib, Lenalidomide, and Dexamethasone (VRd) followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants with Newly Diagnosed Multiple Myeloma for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy

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This study has been transitioned to CTIS with ID 2023-505850-16-00 check the CTIS register for the current data. To compare the efficacy of VRd followed by cilta-cel therapy versus VRd followed by Rd therapy in terms of progression free survival (...

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

Summary

ID

NL-OMON56056

Source
ToetsingOnline

Brief title
CARTITUDE-5

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Multiple Myeloma / symptomatic plasma cell disorder

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BCMA CAR-T, CAR-T Therapy, cellular therpay, newly diagnosed multiple myeloma

Outcome measures

Primary outcome

Primairy objective: To compare the efficacy of VRd followed by cilta-cel

therapy versus VRd followed by Rd therapy in terms of progression free survival

(PFS)

primary endpoint: PFS, defined as the duration from the date of randomization

to either progressive disease according to the IMWG criteria, or death,

whichever occurred first.

Secondary outcome

Most important secondary objectives:

#To further characterize minimal residual disease (MRD) negativity

outcomes:

Sustained MRD negative complete response (CR) rate, as determined by next generation sequencing (NGS) with sensitivity of 10-5 and defined by MRD negative CR plus at least 12 months durability of the MRD negative CR status.

• MRD negative CR rate at 9 months is defined as the proportion of participants who achieve MRD negative CR status at 9±3 months after the randomization date

• Sustained MRD negative CR using different MRD cutoffs (eg, 10-4 and 10-6)

• Sustained MRD negative CR requiring a longer durability (eg, 18 months, 24 months)

• Overall MRD negative CR rate

#To further compare the efficacy of VRd followed by cilta-cel therapy versus VRd followed by Rd therapy

outcomes:

Rate of CR or better

• PFS on next-line therapy (PFS2)

• Overall survival (OS)

Study description

Background summary

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by the production of monoclonal immunoglobulin (Ig) proteins or protein fragments (M proteins) that have lost their function. JNJ-68284528 (ciltacabtagene autoleucel [cilta-cel]) is an autologous chimeric antigen receptor T cell (CAR-T) therapy that targets B-cell maturation antigen (BCMA), a molecule expressed on the surface of mature B lymphocytes and malignant plasma cells.

The primary hypothesis of this study is that in participants with newly diagnosed MM, treatment with VRd induction followed by a single administration of cilta-cel will significantly improve progression free survival compared to Bortezomib, Lenalidomide and Dexamethasone (VRd) induction followed by Rd maintenance.

Study objective

This study has been transitioned to CTIS with ID 2023-505850-16-00 check the CTIS register for the current data.

To compare the efficacy of VRd followed by cilta-cel therapy versus VRd followed by Rd therapy in terms of progression free survival (PFS)

Study design

The study will screen participants with newly diagnosed MM who are not planned to receive autologous stem cell transplant (ASCT) as initial therapy. This study will be conducted in 4 phases: Screening (up to 28 days), Pre-randomization Treatment, Treatment, and Follow-up. Assessments like patient-reported outcome(s) (PROs), electrocardiogram (ECG), vital signs and pharmacokinetics will be performed during the study. Safety evaluations will include review of adverse events, laboratory test results, vital sign measurements, physical examination findings, assessment of cardiac function, Immune-Effector Cell-Associated Encephalopathy (ICE) and handwriting assessments (only for Arm B) and Eastern Cooperative Oncology Group (ECOG) performance status. Safety data will be periodically reviewed by an Independent Data Monitoring Committee (IDMC). The duration of the study is approximately 12 years 5 months.

Intervention

Arm A: VRd+Rd (Standard Therapy)
Participants will receive bortezomib, lenalidomide, and dexamethasone (VRd) regimen for 6 cycles before randomization. Following randomization, participants in Arm A will receive 2 more cycles of VRd. In VRd treatment, participants will receive bortezomib 1.3 milligram per meter square (mg/m^2) subcutaneously (SC) on Days 1, 4, 8 and 11 of each cycle (Cycles 1 to 8), oral lenalidomide 25 mg on Days 1 to 14 of each cycle (Cycles 1 to 8) and oral dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle (Cycles 1 to 8). Each cycle will consist of 21 days. After 8 cycles of VRd, treatment will continue with lenalidomide and dexamethasone (Rd) maintenance therapy. In Rd treatment, participants will receive oral lenalidomide 25 mg on Days 1 to 21 of each cycle and oral dexamethasone 40 mg on Days 1, 8, 15, and 22 of each cycle. Each cycle will consist of 28 days. Participants will continue to receive Rd until confirmed progressive disease or unacceptable toxicity.

Arm B: VRd+Ciltacabtagene Autoleucel (Cilta-cel)
Participants will receive VRd regimen for 6 cycles before randomization. Following randomization, participants in Arm B will undergo apheresis and receive two more cycles of VRd as bridging therapy. In VRd treatment, participants will receive bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8 and 11 of each cycle for Cycles 1 to 8; oral lenalidomide 25 mg on days 1 to 14 of each cycle for Cycles 1 to 8 and oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 of each cycle for Cycles 1 to 8. Each cycle will consist of 21 days. After 8 cycles of VRd, participants will receive a conditioning regimen (cyclophosphamide 300 mg/m^2 intravenous [IV] and fludarabine 30 mg/m^2 IV daily for 3 days) and Cilta-cel infusion 0.75*10^6 chimeric antigen receptor (CAR)-positive viable T cells/kilogram (kg).

Study burden and risks

Preliminary results of cilta-cel show good efficacy results in study MMY2001 and for the LEGEND 2 study. In this phase 3 study standard therapies are being compared for efficacy to cilta-cel. The primary hypothesis is that cilta-cel will significantly improve PFS compared with standard therapy (PVd or DPd). The potential risks of cilta-cel are identified from the following:
1) results of nonclinical studies;
2) mechanism of action; and
3) previous clinical experience with cilta-cel and LCAR-B38M CAR-T cells.
Clinical experience with cilta-cel and LCAR-B38M CAR-T cells is limited. Therefore, the treatment of additional subjects and prolonged follow-up may reveal additional risks. By stimulating an inflammatory cascade, there is potential for toxicity in other tissues or organs by nonspecific immune cell activation. Therefore, special attention will be given to both immunological and immunogenicityrelated toxicities. The patient information sheet of the informed consent form describes in detail the potential risks for the patient. This includes side effects such as cytokine release syndrome, tumor lysis syndrome, neurologic adverse events, effects on blood cells, etc. Due to the risks for side effects like CRS patient will be admitted in the hospital at the day of the cilta-cel infusion until day 14, for the follow up of side effects with potential discharge on day 10 (when the patients has no side effects). Until day 21 the patient needs to staty in a short distance (1hour max) from the hospital. When there are side effects, f.e. fever, the patient needs to come directly to the hospital.

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

- Documented diagnosis of multiple myeloma (MM) according to International Myeloma Working Group (IMWG) diagnostic criteria
- Measurable disease at screening as defined by any of the following: Serum monoclonal paraprotein (M-protein) level greater than or equal to (>=)1.0 gram per deciliter (g/dL) or urine M-protein level >=200 milligram (mg)/24 hours; or Light chain MM in whom only measurable disease is by serum free light chain (FLC) levels: Serum immunoglobin (Ig) free light chain >=10 milligrams per deciliter (mg/dL) and abnormal serum Ig kappa/lambda FLC ratio. For participants that have received 1 cycle of VRd therapy prior to enrollment (as allowed by Exclusion Criterion 17) measurable disease must be assessed by local laboratory on the most recent evaluation prior to the start of the VRd therapy.
- Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0 or 1
- Not considered for high-dose chemotherapy with Autologous Stem Cell Transplant (ASCT) due to: Ineligible due to advanced age; or Ineligible due to 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
- A woman of childbearing potential (WOCBP) must have 2 negative highly

sensitive serum or urine pregnancy (beta-human chorionic gonadotropin) tests prior to starting Bortezomib, Lenalidomide and Dexamethasone (VRd) and must agree to further testing during the study.
- Clinical laboratory values meeting the following criteria during the screening phase: hemoglobin greater than (>)8.0 g/dL (>=5 millimoles per liter [mmol/L]), recombinant human erythropoietin use is permitted; platelets >=75 *10^9/L; absolute lymphocyte count >=0.3 *10^9/L; absolute neutrophil count (ANC) >=1.0 ×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to (<=) 3.0 * upper limit of normal (ULN); estimated glomerular filtration rate >=40 milliliter per minute/1.73 meter square (mL/min/1.73 m^2) based upon modified diet in renal disease formula (MDRD-4) calculation or a 24-hour urine collection; 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)

Exclusion criteria

- Frailty index of >=2 according to Myeloma Geriatric Assessment score
- Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5
- Known active, or prior history of central nervous system (CNS) involvement or clinical signs of meningeal involvement of MM
- Stroke or seizure within 6 months of signing Informed Consent Form (ICF)
- Seropositive for human immunodeficiency virus (HIV)
- Vaccinated with live, attenuated vaccine within 4 weeks prior to first dose of VRd
- Participant must not require continuous supplemental oxygen
- Hepatitis B infection
- Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or detectable HCV- ribonucleic acid [RNA]) or known to have a history of hepatitis C
- Prior treatment with chimeric antigen receptor T (CAR-T) therapy directed at any target
- Any therapy that is targeted to B-cell maturation antigen (BCMA)

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:	Pending
Start date (anticipated):	30-12-2021
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	JENAPHARM
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lenalidomide Mylan
Generic name:	Lenalidomide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Velcade
Generic name:	bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-08-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	09-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	CTIS2023-505850-16-00
EudraCT	EUCTR2021-001242-35-NL
CCMO	NL77822.000.21