A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma

Published: 18-12-2019
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This study has been transitioned to CTIS with ID 2023-506588-32-00 check the CTIS register for the current data. Primary objective: To compare the efficacy of JNJ-68284528 with standard therapy, either pomalidomide, bortezomib and dexamethasone (PVd...

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

Summary

ID

NL-OMON54594

Source
ToetsingOnline

Brief title
68284528MMY3002/ CARTITUDE-4

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: B-cell maturation antigen, Chimeric Antigen Receptor T cell, Relapsed and Lenalidomide-Refractory Multiple Myeloma

Outcome measures

Primary outcome

Primary endpoint:

- progression free survival

Secondary outcome

- define further responses per IMWG:

* Rate of CR/sCR

* Overall MRD negative rate

* Rate of MRD negativity in subjects with CR/sCR at 12 months ±3 months*

* Rate of sustained MRD negative status

* OS

* ORR

* PFS on next line of therapy

- Incidence and severity of adverse events

- PK and PD markers

- Presence of anti-JNJ-68284528 antibodies

- Change from baseline in health-related quality of life

Study description

Background summary

Multiple myeloma is characterized by the production of monoclonal immunoglobulin (Ig) proteins or protein fragments
(M proteins) that have lost their function. The proliferation of multiple myeloma cells leads to subsequent displacement of normal bone marrow hematopoietic precursors and overproduction of M-proteins. Hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurologic complications. Treatment options for multiple myeloma have substantially improved over time and vary depending on the aggressiveness of the disease, underlying prognostic factors, physical condition of the patient, and existing co-morbidities. Therapeutic options include agents such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies, and stem cell transplantation. Despite these therapeutic achievements, the disease recurs and remains incurable. Thus, there is a need for novel therapeutic approaches.

Chimeric antigen receptor T (CAR-T) cell therapy is a new therapy that uses the patient's modified specific immune cells / T cells to target and destroy cancer cells in the body in a targeted manner. CAR-T cell therapy is a form of immunotherapy.
Comparative studies show a lack of a certain protein, BCMA, in most normal tissues and absence of expression in certain stem cells. However, BCMA is frequently seen on multiple myeloma cells. This makes BCMA a promising target for CAR-T based immunotherapy, such as JNJ-68284528. Analysis of the data from 74 subjects from previous research showed good results. These results support further research into this approach, such as in this study.

Study objective

This study has been transitioned to CTIS with ID 2023-506588-32-00 check the CTIS register for the current data.

Primary objective: To compare the efficacy of JNJ-68284528 with standard therapy, either pomalidomide, bortezomib and dexamethasone (PVd) or daratumumab, pomalidomide and dexamethasone (DPd).

Study design

This is a Phase 3, randomized, open-label, multicenter study to determine whether treatment with JNJ-68284528 will provide efficacy benefit compared to standard therapy (PVd or DPd) in subjects with relapsed and lenalidomide-refractory MM.
The study will be conducted in 3 phases: Screening, Treatment, and Follow-Up. Approximately 400 subjects will be randomized 1:1 to receive either standard therapy with PVd or DPd (Arm A) or to receive JNJ-68284528 (Arm B). Decision PVd or DPd treatment is by investigator's choice.

Intervention

For this study, study treatment refers to PVd or DPd in Arm A and to the PVd or DPd given as bridging therapy, cyclophosphamide/fludarabine conditioning regimen, and JNJ-68284528 infusion in Arm B.

Study burden and risks

Preliminary results of JNJ-68284528 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 JNJ-68284528. The primary hypothesis is that JNJ-68284528 will significantly improve PFS compared with standard therapy (PVd or DPd). The potential risks of JNJ-68284528 are identified from the following: 1) results of nonclinical studies; 2) mechanism of action; and 3) previous clinical experience with JNJ-68284528 and LCAR-B38M CAR-T cells. . 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 non-specific immune cell activation. Therefore, special attention will be given to both immunological and immunogenicity-related 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 JNJ-68284528 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 stay in a short distance (1 hour 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

- Have documented diagnosis of Multiple myeloma diagnosis according to the IMWG diagnostic criteria
- Measurable disease at screening as defined by any of the following:
* Serum monoclonal paraprotein (M-protein) level >=0.5 g/dL or urine M-protein level >=200 mg/24 hours; or
* Light chain MM without measurable M-protein in the serum or the urine: Serum free light chain >=10 mg/dL and abnormal serum free light chain ratio.
- Have received 1 to 3 prior lines of therapy including a PI and IMiD. Subject must have undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy
- PD per IMWG criteria <=6 months of last.
- Subjects with only 1 prior line of therapy must have progressed within 36

months of a stem cell transplant or if not transplanted, then within 42 months of starting initial therapy.
- Be refractory to lenalidomide per IMWG consensus guidelines ((failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy). Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For subjects with more than 1 prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy. However, participants must be refractory to lenalidomide in at least one prior line.
- Have an ECOG Performance Status score of 0 or 1
- Have clinical laboratory values as specified in the protocol.
- Women of childbearing potential must have 2 negative pregnancy tests before start treatment
- When a woman is of childbearing potential, the subject must commit either to abstaining
continuously from heterosexual intercourse or agree to use 2 methods of reliable birth
control simultaneously.
- A man who is sexually active with a woman of childbearing potential or a pregnant
woman must agree to use a barrier method of contraception (condom)
- Women and men must agree not to donate eggs or sperm, respectively, during the study and for at least 3 months after receiving the last dose of daratumumab or bortezomib, or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B)
For additional information see section 5.1 of the protocol

Exclusion criteria

- Prior treatment with CAR-T therapy directed at any target.
- Any previous therapy that is targeted to BCMA.
- Ongoing toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade 1 or less; except for alopecia.
- Subjects with Grade 1 peripheral neuropathy with pain or Grade 2 or higher peripheral neuropathy will not be permitted to receive PVd as standard therapy or bridging therapy; however, subject may receive DPd as standard therapy or bridging therapy.
- Was vaccinated with live attenuated vaccines within 4 weeks prior to randomization
- Subject received any antitumor therapy as specified in the protocol, prior to randomization
- Active malignancies (ie, progressing or requiring treatment change in the last

24 months) other than the disease being treated under study. Refer to the protocol for allowed exceptions.
- Plasma cell leukemia at the time of screening, Waldenström*s macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.
- Contraindications or life-threatening allergies, hypersensitivity, or intolerance to JNJ 68284528 or its excipients, including dimethylsulfoxide, or to fludarabine, cyclophosphamide, tocilizumab, pomalidomide, dexamethasone.
* Subjects with contraindications or life-threatening allergies, hypersensitivity, or
intolerance to daratumumab will not be permitted to receive DPd as standard therapy or bridging therapy; however, subjects may receive PVd as standard therapy or bridging therapy. Likewise, subjects with contraindications or life-threatening allergies, hypersensitivity, or intolerance to bortezomib will not be permitted to receive PVd as standard therapy or bridging therapy; but may receive DPd as standard therapy or bridging therapy.

- Stroke or seizure within 6 months of signing ICF.
- Received either of the following:
* An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must have stopped all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease. Subjects with active graft-versus-host disease are excluded.
* An autologous stem cell transplantation <= 12 weeks before apheresis.
- Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of MM.

For additional information, see section 5.2 of the 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):	28-10-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	DARZALEX
Generic name:	daratumumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	IMNOVID
Generic name:	Pomalidomide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	JENAPHARM
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	VELCADE
Generic name:	bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	18-12-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-05-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-11-2020
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2020
Application type:	Amendment
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-07-2021
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Approved WMO Date:	24-03-2022
Application type:	Amendment
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Approved WMO	

Date:	31-03-2022
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
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	Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-11-2023
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	CTIS2023-506588-32-00
EudraCT	EUCTR2019-001413-16-NL
CCMO	NL71982.000.19