A Phase 1b Study of Subcutaneous Daratumumab Regimens in Combination with Bispecific T Cell Redirection Antibodies for the Treatment of Subjects with Multiple Myeloma

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This study has been transitioned to CTIS with ID 2023-503468-17-00 check the CTIS register for the current data. Primary- Part 1: To identify recommended Phase 2 doses and schedules (RP2Ds) for each combination.- Part 2: To characterize the safety…

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

Summary

ID

NL-OMON54604

Source
ToetsingOnline

Brief title
TRIMM-2

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Multiple Myeloma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bispecific T Cell Redirection Antibodies, Dose Escalation, Dose Expansion, Multiple Myeloma

Outcome measures

Primary outcome

- Frequency and severity of dose-limiting toxicities

- Frequency and severity of adverse events and serious adverse events

Secondary outcome

- Serum concentrations and pharmacodynamic markers

- Presence of anti-drug antibodies

- Overall response rate

- Clinical benefit rate (minimal response or better)

- Duration of and time to response

Study description

Background summary

Multiple myeloma is a malignant plasma cell dis order characterized by osteolytic lesions, increased susceptibility to infections, and renal failure, and is the third most common hematological malignancy. 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. Despite these therapeutic achievements, the disease recurs and is associated with additional risk factors such as comorbidities or increasing age. Thus, multiple myeloma remains an incurable malignancy and an unmet medical need with significant morbidity and mortality warranting

the need for novel therapeutic approaches.

The combination of daratumumab with talquetamab or teclistamab is based on the following rationale. Daratumumab, in addition to its direct cytotoxicity to myeloma cells, has been shown to increase helper and cytotoxic T cells and deplete CD38+ immunoregulatory cells.2 In preclinical testing, the benefits of such immune modulation were observed from in vivo pretreatment of multiple myeloma patients with daratumumab, which increased the in vitro cell lysis of multiple myeloma cells to a bispecific antibody targeting BCMA and CD3.16 Therefore, daratumumab in combination with talquetamab or teclistamab may lead to enhanced
clinical responses in the treatment of relapsed or refractory multiple myeloma through multiple mechanisms of action. By targeting CD38, daratumumab exhibits conventional anti-tumor effects of CDC, ADCC, ADCP and apoptosis, as well as immunomodulatory effects. By targeting either GPRC5D or BCMA with a bispecific antibody, enhanced T cell-mediated cytotoxicity is expected through recruitment of CD3-expressing T cells to the GPRC5D- or BCMA-expressing cells. By jointly targeting different epitopes on multiple myeloma cells, effector T cells and NK cells, as well as the bone marrow microenvironment through discrete and complementary mechanisms of action, this combination may be an effective therapeutic
approach in treating relapsed or refractory multiple myeloma.

Study objective

This study has been transitioned to CTIS with ID 2023-503468-17-00 check the CTIS register for the current data.

Primary
- Part 1: To identify recommended Phase 2 doses and schedules (RP2Ds) for each combination.
- Part 2: To characterize the safety of each RP2D for each combination

Secondary
- To characterize the pharmacokinetics and pharmacodynamics of each study treatment
- To assess the immunogenicity of each study treatment
- To evaluate the antitumor activity of each combination

Study design

This is an open-label, multicenter, multi-cohort study of daratumumab in combination with bispecific T cell redirecting antibodies in subjects with multiple myeloma who have received prior therapy that included at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who have disease that is double refractory to a PI and an IMiD.

These combinations will be tested concurrently, and enrollment will be independent. The sponsor will allocate patients to each combination. The following combinations will be studied:

• Combination 1 (SC-1): daratumumab (SC) & talquetamab (SC)
• Combination 2 (SC-2): daratumumab (SC) & teclistamab (SC)
• Combination 3 (SC-3): daratumumab (SC) & talquetamab(SC) en pomalidomide
• Combination 4 (SC-4): daratumumab (SC) & teclistamab(SC) en pomalidomide
The study of each combination will be conducted in 2 parts:
- Part 1: dose escalation to establish the RP2D(s) of each combination
- Part 2: dose expansion at the RP2D(s) for each combination
The aim of the study is to evaluate the safety of daratumumab in combination with T cell redirectingantibodies, and to evaluate the antitumor activity of each combination.

Intervention

Daratumumab dosing: All subjects will receive daratumumab, administered subcutaneously at a dose of 1800 mg in 28-day cycles as follows: weekly in Cycles 1-2, biweekly in Cycles 3-6, and every 4 weeks thereafter.
Bispecific antibody dosing: talquetamab or teclistamab will be administered subcutaneous in 28-day cycles.
Pomalidomide dosing: daily dosis of 4mg.

Study burden and risks

Please see document K6. Risk Benefit Analyse_20JUN2019:

Efficacy has been observed for IV daratumumab in combination with chemoimmunotherapy in subjects with multiple myeloma. The efficacy and adverse event profiles of SC daratumumab are consistent with those of IV daratumumab, with a lower rate of IRRs. Nonclinical pharmacology
studies of talquetamab and teclistamab showed effective killing of target malignant lymphocytes and suggest that these agents may result in decreased tumor burden for subjects with multiple myeloma, which is supported by preliminary efficacy data in the ongoing FIH Studies 64407564MMY1001 and 64007957MMY1001, respectively. Preliminary safety data in subjects with multiple myeloma from
Studies 64407564MMY1001 and 64007957MMY1001 for talquetamab monotherapy and teclistamab monotherapy demonstrate favorable safety profiles for each.

Contacts

Public

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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 initial diagnosis of multiple myeloma according to International Myeloma Working Group (IMWG) diagnostic criteria
- Must have either of the following: a) received at least 3 prior lines of therapy including a proteasome inhibitor (PI) (greater than or equal to [>=] 2 cycles or 2 months of
treatment) and an immunomodulatory drug (IMiD) (>=2 cycles or 2 months of treatment) in any order during the treatment or b) disease that is double refractory to a PI
and an IMiD
- Measurable disease at screening as defined by any of the following: Serum monoclonal protein (M-protein) level >=1.0 grams per deciliter (g/dL) (in non-immunoglobulin
G (IgG) myeloma, an M-protein level >=0.5 g/dL); or Urine M-protein level >=200 milligrams (mg)/24 hours; or Light chain multiple myeloma: Serum immunoglobulin (Ig)
free light chain (FLC) >=10 milligrams per deciliter (mg/dL) and abnormal serum

Ig kappa lambda FLC ratio
- Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1 at screening and at Cycle 1, Day 1 predose
- Female participants of childbearing potential must have a negative highly-sensitive serum beta*human chorionic gonadotropin (beta-hCG) pregnancy test (less than [<] 5
international units per milliliter [IU/mL]) at screening and a negative urine or serum pregnancy test within 1 day before the first dose of study drug

Exclusion criteria

- Treatment in the prior 3 months with an anti- cluster of differentiation 38 (CD38) therapy (example, daratumumab), or discontinuation of a prior anti-CD38 therapy at any time due to an adverse event related to the anti-CD38 therapy - Live, attenuated vaccine within 4 weeks prior to the first
dose of study drug unless approved by sponsor
- Active Central nervous system involvement or exhibits clinical signs of meningeal involvement of multiple myeloma. If either is suspected, brain magnetic
resonance imaging (MRI) and lumbar cytology are required
- Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Participants with resolved infection must be screened using real-time
polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels. Those who are PCR positive will be excluded
- Active hepatitis C infection as measured by positive hepatitis C virus-ribonucleotide (HCV)-RNA testing. Participants with a history of Hepatitis C virus antibody
positivity must undergo HCV-RNA testing

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NAP
Generic name:	talquetamab
Product type:	Medicine
Brand name:	NAP
Generic name:	teclistamab

Ethics review

Approved WMO Date:	13-08-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	CTIS2023-503468-17-00
EudraCT	EUCTR2019-000330-19-NL
ClinicalTrials.gov	NCT04108195
CCMO	NL70702.029.19