# A phase 1 and phase 2 study of daratumumab in combination with all-trans retinoic acid in relapsed/refractory multiple myeloma

Published: 19-01-2016
Last updated: 19-04-2024

Evaluation of the effect of daratumumab in combination with ATRA in patients with relapsed/refractory multiple myeloma

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Plasma cell neoplasms |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46225

**Source**
ToetsingOnline

**Brief title**
Daratumumab in combination with ATRA

### Condition

- Plasma cell neoplasms
- Haematopoietic neoplasms (excl leukaemias and lymphomas)

**Synonym**
multiple myeloma; Kahler's disease

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum

**Source(s) of monetary or material Support:** farmaceutische industrie,Janssen-Cilag

## Intervention

**Keyword:** Atra, Daratumumab, Refractory MM, Relapsed MM

## Outcome measures

### Primary outcome

Primary objective for phase I part:

- To determine the maximum tolerated dose (MTD) and recommended phase 2 dose level (RDL) of daratumumab combined with ATRA. See paragraph 13 for definitions of MTD and RDL.

Primary objective for phase II part:

- To investigate the efficacy of daratumumab combined with ATRA at the RDL, as determined by the (s)CR+VGPR+PR rate.

### Secondary outcome

For phase I part:

- To evaluate toxicity.

For phase II part:

Secondary objectives

- To evaluate toxicity.

- To evaluate progression-free survival

- To evaluate overall survival

- To evaluate prognostic factors for response and survival

- To evaluate the effects of daratumumab and daratumumab plus ATRA on CD38

expression levels, complement-inhibitory

proteins, and immune cells by using flow cytometric

analysis and CYTOF

- To analyze the prognostic value of myeloma gene expression profiles

- To assess the prognostic value of mutations as determined by sequencing

# Study description

**Background summary**

Myeloma patients that develop bortezomib and lenalidomide-resistant disease have a very poor survival of only a median of 9 months, indicating that new agents are urgently needed.
Recent studies have shown that daratumumab as a single agent is effective and well tolerated in these heavily pretreated MM patients.
Daratumumab is a humanized anti-CD38 monoclonal antibody. CD38 is highly and uniformly expressed on all MM cells.
Daratumumab has potent antimyeloma activity. Approximately 40% of patients achieve a partial response or better.
However, approximately 60% of patients do not achieve a partial response, and ultimately all patients will develop progressive disease during daratumumab therapy.
It has been demonstrated that all-trans retinoic acid (ATRA) upregulates CD38 levels and downregulates CD55/CD59 levels on MM cells, both in daratumumab naïve cells and in cells that are resistant to daratumumab because of previous exposure to this drug. These alterations in expression explain the strong syngergy between ATRA and daratumumab, both in MM cells derived from daratumumab naïve patients and from patients with daratumumab-refractory disease.

**Study objective**

Evaluation of the effect of daratumumab in combination with ATRA in patients

with relapsed/refractory multiple myeloma

**Study design**

Prospective, multicenter, non-randomized, phase 1/2 study.

During the phase 1 part of the study, the MTD and RDL of daratumumab in combination with ATRA, will be determined according to a slightly modified *3+3* dose-escalation scheme. A maximum of 3 dose levels will be evaluated. Enrollment at each dose-level will consist of a minimum of 3 patients and a maximum of 6 patients.

When the phase 1 part has established the RDL of daratumumab combined with ATRA for the phase 2 study, all further included patients will be treated with daratumumab plus ATRA at the RDL in the phase 2 part.

**Intervention**

In part A of the study patients will be treated with daratumumab as a single agent.
In case patients have PD after cycle 1, or or in case patients achieve less than minimal response after cycle 2, or patients achieve less than PR after cycle 3, or in case patients experience progression during daratumumab therapy after having obtained a response,
then ATRA will be added to daratumumab.

**Study burden and risks**

The burden will be that daratumumab has to administered as intravenous infusion. They may also suffer from side effects, although they are generally mild with daratumumab. Side effects of ATRA are also expected to be limited especially since it is given only during three days around the daratumumab infusion.
See for a complete overview the patient information document.

# 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

1. Age 18 years and older
2. Subject must have documented multiple myeloma as defined by the criteria below:
• Monoclonal plasma cells in the bone marrow >=10% at some point in their disease history or presence of a biopsy proven plasmacytoma.
• Measurable disease as defined by any of the following:
o Serum monoclonal paraprotein (M-protein) level >=5 g/L (0.5 g/dL); or urine M-protein level >=200 mg/24 hours; or serum immunoglobulin free light chain >=100 mg/L (10 mg/dL) and abnormal serum immunoglobulin kappa lambda free light chain ratio (See Appendix A)
3. Relapsed from or refractory to 2 or more different prior therapies, including IMiDs (eg, thalidomide, lenalidomide) and proteasome inhibitors, chemotherapy-based regimens, or ASCT and without further established treatment options.
--Relapse is defined as progression of disease after an initial response (MR or better) to previous treatment, more than 60 days after cessation of treatment
--Refractory disease is defined as < 25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment
4. WHO performance 0, 1, or 2
5. Life expectancy at least 3 months
6. Written informed consent

## Exclusion criteria

1. Subject has received daratumumab or other anti-CD38 therapies previously.
2. Non-secretory myeloma
3. Systemic AL amyloidosis or plasma cell leukemia (>2.0x109/L circulating plasma cells by standard differential) or Waldenstrom*s macroglobulinemia
4. subject has known meningeal involvement of multiple myeloma
5. Subject has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before start of treatment. This included subjects who have received a cumulative dose of corticosteroid greater than or equal to the equivalence of 140 mg prednisone or a single dose of corticosteroid greater than or equal to the equivalence of 40 mg/day dexamethasone within the 2-week period before start of treatment.
6. previously an allogeneic stem cell transplantation within 1 year before the date of registration and has not used immunesuppressive drugs within one months before the date of registration.
7. Inadequate marrow reserve as defined by a platelet count <50 x 109/L or an absolute neutrophil count <1.0 x 109/L
8. a) known chronic obstructive pulmonary disease (COPD) with an Forced Expiratory Volume in 1 second (FEV1) < 50% of predicted normal. Note that FEV1 testing is required for patients suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.
b) known moderate or severe persistent asthma within the past 2 years (see Attachment 5), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).
9. presence of clinically significant cardiac disease, including:
• Myocardial infarction within 6 months before Cycle 1, Day 1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)
• Cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] Version 4 Grade 2 or higher) or clinically significant ECG abnormalities.
• Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia*s formula (QTcF) >470 msec.
10. Significant hepatic dysfunction (total bilirubin >= 3 times normal value or transaminases >= 3 times normal value), unless related to myeloma
11. Creatinine clearance <30 ml/min.
12. Known hypersensitivity to components of the investigational product or severe allergic or anaphylactic reactions to humanized products.
13. Subject has any concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, etc.) 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.
14. Subject is known to be seropositive for human immunodefiency virus (HIV) or have active hepatitis B or hepatitis C.
15. History of active malignancy during the past 5 years, except squamous cell and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion

of the local investigator, with concurrence with the principal investigator, is considered cured with minimal risk of recurrence within 5 years.
16. Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.
17. Pregnant or lactating females
18. Women of childbearing potential not willing to use adequate contraception, defined as hormonal birth control or intrauterine device, during the trial and for 1 year after the last dose of daratumumab. For patients in the US, the use of a double-barrier method is also considered adequate.
19. Sensory or motor neuropathy of >=grade 3.

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 06-07-2016 |
| Enrollment: | 52 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Daratumumab |
| Generic name: | Daratumumab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |

| | |
|---|---|
| Brand name: | Vesanoid |
| Generic name: | Tretinoin - all trans retinoic acid |
| Registration: | Yes - NL outside intended use |

## Ethics review

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| Approved WMO Date: | 19-01-2016 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 01-04-2016 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 01-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 03-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-05-2017 |
| 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 |
|---|---|
| EudraCT | EUCTR2015-003862-10-NL |
| ClinicalTrials.gov | NCT02751255 |
| CCMO | NL54913.029.15 |

# Study results

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| Date completed: | 18-10-2022 |
| Actual enrolment: | 63 |