A phase 2 study of nivolumab combined with daratumumab with or without low-dose cyclophosphamide in relapsed/refractory multiple myeloma

Published: 25-04-2017
Last updated: 13-04-2024

Evaluation of the effect of nivolumab and daratumumab with or without low dose cyclophosphamide in patients with relapsed/refractory multiple myeloma

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

Summary

ID

NL-OMON47546

Source
ToetsingOnline

Brief title
NIVO/DARA study

Condition

- Plasma cell neoplasms
- Plasma cell neoplasms

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: Bristol-Myers Squibb,farmaceutische industrie,Janssen-Cilag

Intervention

Keyword: daratumumab, nivolumab, refractory MM, relapsed MM

Outcome measures

Primary outcome

Part A:

Primary objective

- To determine which regimen of nivolumab with daratumumab (either with or without low dose cyclophosphamide) merits further evaluation in MM patients with previous exposure to proteasome inhibitor and lenalidomide-resistant disease, based on safety and efficacy data

Part B

Primary objective

- To investigate the efficacy of nivolumab combined with daratumumab with or without low dose cyclophosphamide, as determined by the (s)CR+VGPR+PR rate.

Secondary outcome

Part A:

Secondary objective

- Evaluate the safety of nivolumab-daratumumab with or without low dose cyclophosphamide in MM patients with previous exposure to proteasome inhibitor and lenalidomide-refractory disease

- Evaluate the preliminary efficacy of nivolumab-daratumumab with or without

low dose cyclophosphamide in MM patients with previous exposure to proteasome inhibitor and lenalidomide-resistant disease

- To evaluate the immunomodulatory effects of nivolumab combined with daratumumab with or without low dose cyclophosphamide in blood and bone marrow by using flow cytometric analysis

Part B:

Secondary objectives

- To evaluate toxicity.

- To evaluate progression-free survival

- To evaluate overall survival

- To evaluate prognostic factors for response and survival, which includes cytogenetic abnormalities by FISH, *2-microgloublin, LDH, and MRD-negativity, as well as analysis of CD38, CIPs (CD46, CD55, and CD59), PD-L1 and PD1 expression

- To evaluate the effects of daratumumab plus nivolumab with or without low dose cyclophosphamide on CD38 expression levels, CIPs (CD46, CD55, and CD59), and immune cells (e.g. T cells, NK cells, Tregs, and MDSCs) 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 who 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. However, approximately 60% of patients do not achieve a partial response, and ultimately all patients will develop progressive disease during daratumumab therapy. In less pretreated patients daratumumab-based combinations (daratumumab plus lenalidomide-dexamethasone or daratumumab plus bortezomib-dexamethasone) were very effective and well tolerated. Therefore, in this study, we will combine daratumumab with other agents to improve survival of heavily pretreated MM patients.

The PD1 blocker nivolumab, as single agent, does not induce objective responses but induces stable disease in approximately 67% of relapsed/refractory MM patients. We have recently shown that daratumumab treatment results in increased T cell frequencies by eliminating CD38-positive immune suppressor cells, which probably contributes to the durable responses observed with daratumumab.
Importantly, low dose cyclophosphamide markedly improves the activity of monoclonal antibodies such as CD38-targeting antibodies and PD-1 blocking antibodies.
In this study, we will combine two or three immune modulating agents with different mechanisms of action in order to improve the outcome of relapsed/refractory MM patients.
We will evaluate in Part A, nivolumab combined with daratumumab with or without low dose cyclophosphamide (total 40 patients). Based on efficacy and tolerability, we will treat in Part B 20 additional patients with nivolumab combined with daratumumab either with or without low dose cyclophosphamide based on tolerability and efficacy data obtained in Part A.

Study objective

Evaluation of the effect of nivolumab and daratumumab with or without low dose cyclophosphamide in patients with relapsed/refractory multiple myeloma

Study design

Prospective, multicenter, phase 2 study

Intervention

daratumumab plus nivolumab of daratumumab plus nivolumab plus low dose cyclophosphamide

Study burden and risks

The burden will be that daratuumab and nivolumab will be administered as intravenous infusion. Patients may suffer form side effects, although they are generally mild for daratumumab. The side effects for nivolumab are also well described. A small part of the patients (<5%) can experience a immuno mediated reaction, eg. colitis or hypophysitis or hypothyroidism.
Also for cyclophosphamide the side effects are well known.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age ><=18 years

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:
- 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 or refractory disease. Relapse is defined as progression of disease after an initial response 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. Subject had at least 2 prior anti-myeloma regimens.
(Note: Induction, bone marrow transplant with or without maintenance therapy is considered one regimen.)
5. Subject has developed lenalidomide-refractory disease during prior treatment with a lenalidomide-containing regimen.
Refractory disease is defined as <25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment.
6. Subject received prior treatment with a proteasome inhibitor-containing regimen for at least 2 consecutive cycles.
7. WHO performance 0, 1, or 2
8. Life expectancy at least 3 months
9. Written informed consent

Exclusion criteria

1. Prior therapy with daratumumab or other anti-CD38 therapies
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. Prior treatment with an anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody
7. Subject has previously received an allogeneic stem cell transplantation (at any time)
8. Inadequate marrow reserve as defined by a platelet count <75 x 10^9/L (<50 x 10^9/L if *50% of bone marrow mononucleated cells are plasma cells) or an absolute neutrophil count <1.0 x 10^9/L
9. a) Subject has 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) Subject has known moderate or severe persistent asthma within the past 2 years, 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).
10. Subject has clinically significant cardiac disease
11. Significant hepatic dysfunction (total bilirubin *>= 1.5 times normal value (except subjects with Gilbert syndrome, who can have total bilirubin <3.0 mg/dL) or transaminases >= 3 times normal value), unless related to myeloma
12. Creatinine clearance <30 ml/min.
13. Known hypersensitivity to components of the investigational products or severe allergic or anaphylactic reactions to humanized products.
14. Subject has any concurrent severe and/or uncontrolled medical condition 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.
15. Subject is known to be seropositive for HIV or known to have AIDS, or any positive test for hepatitis B or hepatitis C indicating acute or chronic infection.
16. History of active malignancy during the past 3 years, except squamous cell and basal cell carcinomas of the skin and carcinoma in situ of the cervix or breast and incidental histologic finding of prostate cancer or prostate cancer that is cured, 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 3 years.
17. Subjects with active interstitial pneumonitis
18. Subjects with active, known or suspected autoimmune disease or inflammatory disorder. Subjects with vitiligo,type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions
not expected to recur in the absence of an external trigger are permitted to enroll.
19. Subjects with a condition (other than MM) requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
20. 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 or that could prevent, limit, or confound the protocol-specified assessments.
21. Pregnant or lactating females
22. 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 or nivolumab or low dose cyclophosphamide. Men who are sexually active with women of childbearing potential who are not willing to use adequate contraception for the duration of treatment with the study drugs and for 1 year after the last dose of daratumumab or nivolumab or low dose cyclophosphamide
23. Peripheral neuropathy of *grade 2.

24. History of allergy to study drug components

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-02-2018
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Darzalex
Generic name:	daratumumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Opdivo
Generic name:	nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2021

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	EUCTR2017-000169-60-NL
CCMO	NL60544.029.17