Revlimid, Endoxan, Prednisone Evaluation After prior revlimid Treatment (REPEAT):;A phase 1 and phase 2 study of lenalidomide (Revlimid) in combination with cyclophosphamide (endoxan) and prednisone (REP) in relapsed/refractory multiple myeloma

Published: 25-02-2011
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Phase 1Primary objective- To determine the maximum tolerated dose (MTD) and recommended phase 2 dose level (RDL) of lenalidomide administered during 21 days of a 4 week cycle, combined with continuous cyclophosphamide and prednisone. See paragraph...

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

Summary

ID

NL-OMON41710

Source
ToetsingOnline

Brief title
REPEAT

Condition

- Plasma cell neoplasms

Synonym
morbus Kahler, multiple myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: celgene,Celgene Corporation

Intervention

Keyword: cyclophosphamide, lenalidomide, myeloma, prednisone

Outcome measures

Primary outcome

Phase 1

Primary endpoint

- Dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended

phase 2 dose (RDL) of lenalidomide, cyclophosphamide, combined with prednisone

(REP).

Phase 2

Primary endpoint

- Overall response rate. In this analysis we will consider the best response

obtained during treatment

Secondary outcome

Phase 1

Secondary endpoints

- Toxicity, especially myelosuppression, polyneuropathy and thrombosis

Phase 2

Secondary endpoints

- Toxicity, especially myelosuppression, polyneuropathy and thrombosis

- Progression free survival (PFS; i.e. time from registration to progression or

death from any

cause, whichever comes first

- Overall survival measured from registration. Patients still alive or lost to

follow up are

censored at the date they were last known to be alive

- Prognostic factors for response and survival

- Immunomodulatory effects of lenalidomide by evaluation of T cell subsets and

cytokine analysis

Study description

Background summary

Rationale
We have shown that the combination of lenalidomide, cyclophosphamide, and prednisone was feasible and effective in heavily pre-treated myeloma patients (19). However, the optimal dose of lenalidomide with continuous cyclophosphamide and prednisone has not yet been defined. The aims of this study were to develop a safe cyclophosphamide, lenalidomide and prednisone combination suitable for clinical use and evaluation in subsequent randomized clinical trials. To this end, the maximum tolerated dose (MTD) and toxicity profile of lenalidomide, cyclophosphamide, and prednisone (REP) was determined for patients with relapsed refractory disease, who were already exposed to lenalidomide.

Study objective

Phase 1
Primary objective

- To determine the maximum tolerated dose (MTD) and recommended phase 2 dose level (RDL) of lenalidomide administered during 21 days of a 4 week cycle, combined with continuous cyclophosphamide and prednisone. See paragraph 10 for definitions of MTD and RDL.

Secondary objective
- To evaluate toxicity.

Phase 2
Primary objective
- To investigate the efficacy of lenalidomide administered during 21 days of a 4 week cycle, combined with continuous cyclophosphamide and prednisone at the RDL, as determined by the (s)CR+VGPR+PR rate.

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 immunomodulatory effects of lenalidomide by using flow cytometric and cytokine analysis

Study design

This is a prospective, non-randomized, open label, phase 1/2 study.
Details of all treatments (dose and schedule) are given in section 5 of the protocol. All eligible patients will be registered (see section 11) and treated with REP chemotherapy at different dose-levels (phase 1 part) or at the recommended dose level (RDL) in the phase 2 part of the study.

Intervention

Treatment with lenalidomide, endoxan and prednisone.

Study burden and risks

Until now the number of different treatment modalities for multiple myeloma is limited, which indicates the need for new treatment regimens. The REP regimen is active in patients with heavily pretreated myeloma including those with lenalidomide-refractory disease (van de Donk, BJH 2010). The most optimal dosing schedule of REP is currently unknown, and therfore this study is initiated.

Besides potential beneficial effects such as response and therefore increased survival, it is possible that REP chemotherapy (lenaliomide, endoxan and prednisone) induces cytopenias with associated risk of infections and bleeding. Other side effects of these drugs are described on the protocol and patient information letter.

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

• Multiple myeloma/Salmon & Durie stage II/III A or B
• Previous lenaliomide- refractory disease (refractory to prior treatment indicates progressive disease on last prior therapy, best response of stable disease (not CR, VGPR, PR or PD) to last prior therapy, or progressive disease within 3 months (International Uniform Response Criteria for Multiple Myeloma)) is required in both the phase 1 and 2 part of the study1

• * 1 previous line of treatment
• Age * 18 years
• WHO performance 0, 1, 2, or 3
• Measurable disease i.e. serum M-protein (>10 g/l), or urinary light-chain excretion (>200 mg/24 h), or proven plasmacytoma by biopsy
• Life expectancy at least 3 months
• Written informed consent
• Patient commits to pregnancy prevention program (for detailed information see section 10.1)
•Negative pregnancy tests before inclusion if female of child baring potential;
Sexually active women of child bearing potential must agree to use 2 reliable forms of adequate contraception while on study drug (and 4 weeks before and after study drug) (for detailed information see section 10.1)
Men must agree not to father a child and to use a condom if his partner is of childbearing potential
1) A therapy-free interval or other lines of therapy between prior lenalidomide therapy and REP is allowed

Exclusion criteria

• Non-secretory myeloma
• Known hypersensitivity to lenalidomide
• Inadequate marrow reserve as defined by a platelet count <100 x 109/L or an absolute neutrophil count <1.5 x 109/L
• Systemic AL amyloidosis
• Uncontrolled or severe cardiovascular disease (NYHA class III or IV heart failure; myocardial infarction within the last 6 months of study entry); unstable angina; unstable cardiac arrythmias; clinically significant pericardial disease)
• Significant hepatic dysfunction (total bilirubin * 3 times normal value or transaminases * 3 times normal value), unless related to myeloma
• Creatinine clearance <30 mL/min
• Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, etc.)
• Patients known to be HIV-positive
• History of active malignancy during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma
• Unable or unwillingness to comply with the pregnancy prevention program (for detailed information see section 10.1)
• Not able and/or willing to use adequate contraception
• Pregnant or lactating females

Study design

Design

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):	08-08-2011
Enrollment:	90
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	prednisone
Generic name:	prednisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	Lenalidomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	25-02-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	24-06-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	28-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2010-023577-20-NL
ClinicalTrials.gov	NCT01352338

Register	ID
CCMO	NL34649.041.11

Study results

Date completed:	01-05-2016
Actual enrolment:	82