OPEN-LABEL, MULTI-CENTER, SINGLE-ARM STUDY FOR THE SAFETY AND EFFICACY OF POMALIDOMIDE (CC-4047) MONOTHERAPY FOR SUBJECTS WITH REFRACTORY OR RELAPSED AND REFRACTORY MULTIPLE MYELOMA. A COMPANION STUDY FOR CLINICAL TRIALCC-4047-MM-003.

Published: 19-05-2011
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The primary objective is:To evaluate the efficacy of pomalidomide (CC-4047) monotherapy in subjects with refractory orrelapsed and refractory multiple myeloma who discontinued treatment after being treated withdexamethasone alone (Treatment Arm B)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skeletal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON39077

Source
ToetsingOnline

Brief title
CC-4047-MM-003/C

Condition

- Skeletal neoplasms malignant and unspecified

Synonym
multiple myeloma, type of bone marrow cancer

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: multiple myeloma, pomalidomide

Outcome measures

Primary outcome

The primary endpoint is overall response rate (ORR) using the new International

Myeloma

Working Group Uniform (IMWG) response criteria. An analysis comparing the

results of

response assessments judged by the EMBT criteria (Blade, 1998) to those of the

IMWG criteria

will also be performed.

Secondary outcome

- Safety (type, frequency, and severity of adverse events [AEs], and

relationship of

AEs to study drug)

- Progression-free survival (PFS)

- Time to progression (TTP)

- Duration of response

- Overall survival (OS)

Study description

Background summary

The phase 1 segment of the Celgene sponsored Study CC-4047-MM-002 determined the maximum tolerated dose (MTD) of pomalidomide in this subject population to be 4 mg/day. In
Study CC-4047-MM-002, responses were seen in both the 2 and 4-mg dose levels; however, the
best response rate and duration of response was associated with a dose of 4 mg/day of
pomalidomide (the starting dose in the present trial) in a cyclic 21 out of 28-day dosing schedule.
This regimen will allow a one-week rest period per every 28-day cycle for bone marrow
recovery to minimize the occurrence of neutropenia, which were the
DLTs during the phase 1 segment of the study. The Phase 2 segment of the study CC-4047-
MM-002 was started in November 2009 and as of September 22, 2010 enrolment has been
completed and 221 subjects have been enrolled.

The results of a number of investigator-initiated studies conducted thus far indicate that
pomalidomide produces responses in subjects who are refractory to lenalidomide, another
IMiDs® compound, aligning with the non-clinical results observed in lenalidomide-resistant cells
(Adams, 2009). The phase 2 study using pomalidomide plus low-dose dexamethasone for
relapsed multiple myeloma (Lacy, 2009; 2010) showed a response rate of 40% in lenalidomiderefractory
patients. These results imply a non-cross resistance for pomalidomide and suggesting
a special role for this drug in the treatment of refractor/relapsed patients. Pomalidomide, to date,
has an acceptable safety profile, and the most common hematological toxicity experienced by

subjects is neutropenia (non-febrile), which can be managed by dose reductions or interruptions and growth factors.
The most common non-hematological toxicities are fatigue and pneumonia.

Based on these published data, pomalidomide would be expected to provide clinical benefit to
such subjects with high unmet medical need who have very limited available treatment options.
This companion study will provide more information about the safety and efficacy of singleagent
pomalidomide in patients who are refractory or relapse after multiple lines of therapy

Study objective

The primary objective is:
To evaluate the efficacy of pomalidomide (CC-4047) monotherapy in subjects with refractory or
relapsed and refractory multiple myeloma who discontinued treatment after being treated with
dexamethasone alone (Treatment Arm B) in Study CC-4047-MM-003 due to the development of
documented disease progression during treatment.

The secondary objective is:
To evaluate the safety of pomalidomide monotherapy in subjects with refractory or relapsed and
refractory multiple myeloma who discontinued treatment after being treated with dexamethasone
alone (Treatment Arm B) in Study CC-4047-MM-003 due to the development of documented
disease progression during treatment.

Study design

Study CC-4047-MM003/C is the companion study for clinical trial CC-4047-MM-003. This is a
multi-center, open-label, single-arm study to evaluate the safety and efficacy of pomalidomide
monotherapy in subjects with refractory or relapsed and refractory multiple myeloma. This
companion study will enroll subjects who have discontinued study treatment with dexamethasone alone (Treatment Arm B) in the CC-4047-MM-003 trial due to disease progression. Subjects who have discontinued study treatment with pomalidomide plus
dexamethasone (Treatment Arm A) will not be eligible to participate in the

companion study.
The key inclusion criteria in the CC-4047-MM-003/C trial limits the enrollment to all evaluable
subjects in the CC-4047-MM-003 study who discontinue therapy after at least starting the second cycle of
dexamethasone alone (Treatment Arm B) due to development of documented disease progression according to the IMWG criteria and as decided by an IRAC. Subjects who
discontinue therapy with dexamethasone alone (Treatment Arm B) due to toxicity or intolerance
to dexamethasone and not due to development of confirmed progressive disease will not be
eligible to enroll in the companion trial.

It is estimated that 30% to 60% of subjects in the control arm of Study CC-4047-MM-003
(dexamethasone alone; n = 142) could be enrolled in the companion study. Thus the estimated
number of subjects in Study CC-4047-MM-003/C will be in the range of 42-85. Enrollment of
subjects will be opened to all investigator sites that participated in Study CC-4047-MM-003 (EU,
Switzerland, Russia, Australia and Canada.

Figure 1 summarizes the flow and the transition between both CC-4047-MM-003 and CC-4047-
MM-003/C. For subjects with treatment discontinuation visit assessments for Study CC-4047-MM-003 performed within <= 28 days of screening for Study CC-4047-MM-003/C, any overlapping assessments do not have to be repeated for screening in this study if approved by the Study Team. If the assessments were done > 28 days from screening, these assessments need to be repeated at the screening phase.
Subjects will not be eligible to enroll in the companion study if 120 days or more have passed
since their discontinuation from CC-4047-MM-003 study. No other anti-myeloma therapies are
allowed from the time of disease progression on CC-4047-MM-003 to the time of treatment
initiation in the companion study.

The oral pomalidomide starting dose is 4 mg daily on Days 1-21 every 28 days. Dosing
interruptions and reductions are permitted throughout the study. All subjects participating in the
trial will continue treatment until they stop taking the study medication because of disease progression or another reason. For all subjects who enroll into this study, study visits and serial measurements of safety and

efficacy will be performed as outlined in Table 1 Table of Events.

Intervention

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Study burden and risks

The patient needs to visit the hospital as described in E2. The folloWing study procedures will be done as described in the
schedule on page 31 of the protocol:
- bone marrow biopsy or aspirate
- ECG
- Physical examination
- Pregnancy test
- Blood drawing
- Completion of questionnaires

Risks of the study are described in the appendix of the informed consent.

Contacts

Public
Celgene Corporation

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Summit NJ 07901
US
Scientific
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Morris Avenue 86
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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. Subjects with refractory or relapsed and refractory multiple myeloma who were enrolled in Study CC-4047-MM-003 and discontinued study therapy with dexamethasone alone (Treatment Arm B) after at least starting the second cycle of dexamethasone treatment and due to
development of documented disease progression according to the IMWG criteria and as decided by an IRAC.
2. Must be >= 18 years at the time of signing the informed consent form.
3. The subject must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted. The only exception is if a skeletal survey was performed within 90 days prior to the start of Cycle 1, then a new survey will not be required.
4. Must be able to adhere to the study visit schedule and other protocol requirements.
5. Subjects must have documented diagnosis of multiple myeloma and have measurable disease (serum M-protein >= 0.5 g/dL or urine M-protein >= 200 mg/24 hours).
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
7. Females of childbearing potential (FCBP*) must agree to utilize two reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 28 days before starting study drug, while participating in the study (including dose interruptions), and for at least 28 days after study treatment discontinuation and must agree to regular pregnancy testing during this timeframe.
8. Females must agree to abstain from breastfeeding during study participation and 28 days after study discontinuation.
9. Males must agree to use a latex condom during any sexual contact with FCBP while participating in the study and for 28 days following discontinuation from this study, even if he has undergone a successful vasectomy.
10. Males must also agree to refrain from donating semen or sperm while on pomalidomide and for 28 days after discontinuation from this study treatment.
11. All subjects must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment.
12. All subjects must agree not to share study medication.

Exclusion criteria

1. Subjects with multiple myeloma who were not treated as a part of Study CC-4047-MM-003 (Arm B).

2. Subjects who received any anti-myeloma or anti-cancer therapies within the last 14 days of wash-out period before initiation of study treatment.
3. Subjects who discontinued CC-4047-MM-003 study >=120 days.
4. Subjects who initiate another anti-myeloma therapy from the time of disease progression on study CC-4047-MM-003 to the time of treatment initiation in the companion study.
5. Any of the following laboratory abnormalities:
- Absolute neutrophil count (ANC) < 1,000/µL.
- Platelet count < 75,000/µL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 30,000/µL for subjects in whom >= 50% of bone marrow nucleated cells are plasma cells
- Creatinine Clearance < 45 mL/min according to Cockcroft-Gault formula (If creatinine clearance calculated from the 24-hour urine sample is >=45 ml/min, patient will qualify for the trial)
- Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L)
- Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted)
- Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN)
- Serum total bilirubin > 2.0 mg/dL (34.2 µmol/L); or > 3.0 x ULN for subjects with hereditary benign hyperbilirubineamia
6. Prior history of malignancies, other than MM, unless the subject has been free of the disease for >= 5 years. Exceptions include the following:
- Basal or Squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix or breast
- Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)
7. Hypersensitivity to thalidomide or lenalidomide. (This includes >= Grade 3 rash during prior thalidomide or lenalidomide therapy).
8. Peripheral neuropathy >= Grade 2.
9. Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment and who have not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment and are currently dependent on such treatment.
10. Subjects who are planning for or who are eligible for stem cell transplant.
11. Subjects with any one of the following:
- Congestive heart failure (NY Heart Association Class III or IV)
- Myocardial infarction within 12 months prior to starting study treatment
- Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
12. Subjects who received any of the following within the last 14 days of initiation of study treatment:
- Plasmapheresis
- Major surgery (kyphoplasty is not considered major surgery)
- Radiation therapy
13. Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of treatment.
14. Subjects with chronic conditions such as rheumatoid arthritis, multiple sclerosis and lupus, which likely need additional steroid or immunosuppressive treatments in addition to the study treatment.

15. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
16. Incidence of gastrointestinal disease that may significantly alter the absorption of pomalidomide.
17. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.
18. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
19. Pregnant or breastfeeding females.
20. Known HIV positivity or active infectious hepatitis A, B or C.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-11-2012
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	Pomalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-05-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	13-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	08-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	02-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	06-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	01-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-023343-16-NL
ClinicalTrials.gov	NCT01324947
CCMO	NL36039.078.11