A PHASE 2 MULTICENTER, OPEN-LABEL STUDY TO DETERMINE THE EFFICACY AND SAFETY OF POMALIDOMIDE (CC-4047) IN COMBINATION WITH LOW-DOSE DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA AND MODERATE OR SEVERE RENAL IMPAIRMENT INCLUDING SUBJECTS UNDERGOING HEMODIALYSIS

Published: 06-09-2013
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Primary Objective:- Evaluate efficacy of the combination of pomalidomide and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma and impaired renal function.Secondary Objectives:- Evaluate renal efficacy of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50306

Source
ToetsingOnline

Brief title
CC-4047-MM-013 ; 0451/0116 ; POM013

Condition

- Other condition

Synonym
a type of bone marrow cancer, multiple myeloma

Health condition

Multiple myeloma and moderate or severe renal impairment

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Dexamethasone, Multiple myeloma, Pomalidomide, Renal impairment

Outcome measures

Primary outcome

Primary Endpoints:

- Overall response rate (ORR) according to the International Myeloma Working

Group (IMWG) uniform response criteria with additional clarifications according

to the IMWG Consensus panel (Rajkumar, 2011).

Secondary outcome

Secondary Endpoints:

- Assessment of renal response according to the criteria defined by Dimopoulos

and Ludwig (Dimopoulos, 2009; Dimopoulos, 2010 b,c; Ludwig, 2010).

- Time to Myeloma response, time to renal response, duration of response (DOR),

progression-free survival (PFS), time to progression (TTP), overall survival

(OS).

- Adverse events (AEs) assessment (type, frequency, seriousness, severity, relationship to pomalidomide and/or dexamethasone and outcomes) including second primary malignancy (SPM).

- Pharmacokinetics (PK) of pomalidomide in subjects with relapsed or refractory multiple myeloma and impaired renal function (moderate to severe renal impairment).

Study description

Background summary

Multiple myeloma (MM) is an incurable disease that is characterized by the accumulation of clonal plasma cells in the bone marrow (Alexanian, 1994) and accounts for 10% of all hematological malignancies. In 2011, it was estimated that 20,520 new cases of MM and 10,610 deaths from the disease would occur in the United States (US) (Siegel, 2011). In Europe, there are approximately 27,800 new cases each year (Boyle, 2005). The disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. While MM patients with relapsed and/or refractory disease may achieve responses to subsequent antimyeloma therapies, the duration of response typically decreases with successive relapses (Kumar, 2004) until resistant disease develops reflecting changes in disease biology, with more tumor cells expressing a more aggressive phenotype, higher proliferative thrust, and lower apoptotic rates (Anderson, 2008).

Pomalidomide in combination with low-dose dexamethasone has shown activity in several Phase 1, Phase 2, and recently in a Phase 3 trial. The dose of 4 mg was established in a Phase 1 trial (CC-4047-MM-002; NCT00833833) which also achieved 42% minimal response or better, 21% partial response or better and 3% complete response in a heavily pretreated population (Richardson, 2012). In a Phase 2 trial following this Phase 1, response rates of a partial response (PR) of at least 31.3% could be achieved as well as a median progression-free survival of 3.8 months (Richardson, 2011). A Phase 2 trial conducted by the Intergroupe Francophone du Myelome (IFM) confirmed high efficacy of the combination of pomalidomide and dexamethasone in subjects refractory to bortezomib and lenalidomide with response rates of 35% (Leleu, 2013). Recently, results of a Phase 3 trial comparing pomalidomide plus low-dose dexamethasone

to high dose dexamethasone in heavily pretreated patients have shown significant improvement in progression free survival as well as overall survival (Dimopoulos, 2012).
However, only few subjects with renal insufficiency were evaluated so far, as inclusion criteria of most trials did not allow inclusion of subjects suffering from renal insufficiency having a creatinine clearance < 45 mL/min. Very preliminary data suggest that subjects with renal insufficiency will benefit from treatment with pomalidomide and low-dose dexamethasone. A Phase 1 trial is currently ongoing to define the maximum tolerated dose of pomalidomide in combination with low-dose dexamethasone in subjects with RRMM and impaired renal function.
However, as pomalidomide is highly metabolized and as only 5% of doses are unchanged in urine, it is hypothesized that renal impairment will not affect exposure to pomalidomide in a clinically relevant manner. This trial will further investigate the activity of the combination of pomalidomide and low-dose dexamethasone in subjects with renal insufficiency. In order to be able to better distinguish between different grades of renal insufficiency three different cohorts were chosen dependent on the grade of renal impairment. Very preliminary data suggest that adverse events occurring in subjects with renal impairment might not be different from adverse events occurring in subjects with normal renal function when being treated with pomalidomide and low dose dexamethasone (Siegel, 2012). Looking at three different cohorts will give specific information about response rates as well as renal response rates dependent on the eGFR at the time of inclusion into this trial.
Cohort A will include subjects with an estimated Glomerular Filtration Rate of 30 < eGFR < 45 mL/min/1.73 m2. It was chosen to limit the upper level to 45 mL/min/m2 according to the available data from other trials, as subjects having an eGFR of more than 45 mL/min/1.73 m2 were already included into other trials. Subjects who show renal insufficiency with an eGFR of < 30 mL/min/1.73 m2 will be included into Cohort B, as long as they do not need to undergo dialysis; cohort C will include subjects on dialysis.
Subjects may be enrolled either if developing acute renal insufficiency or showing chronic renal insufficiency over a longer period. For subjects who develop acute renal insufficiency the deterioration over time will be evaluated and recorded. Treatment Duration Treatment will be given until disease progression, as other studies investigating pomalidomide in combination with low-dose dexamethasone have proven to show benefit for subjects if they are on continuous treatment.
All three cohorts will enroll in parallel; subjects will remain in their assigned cohorts even when renal function might improve or deteriorate during the study. Subjects will be discontinued at time of disease progression or in the case of intolerable toxicity. All subjects will be followed for survival, subsequent antimyeloma therapies, and second primary malignancies.

Study objective

Primary Objective:

- Evaluate efficacy of the combination of pomalidomide and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma and impaired renal function.

Secondary Objectives:
- Evaluate renal efficacy of the combination of pomalidomide and low-dose dexamethasone in subjects with various degrees of renal impairment.
- Evaluate safety and tolerability of the combination of pomalidomide and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma and impaired renal function.
- Evaluate the pharmacokinetics of pomalidomide in subjects with various degrees of renal impairment.

Study design

This is an international Phase 2 multicenter open-label study of pomalidomide in combination with low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma and impaired renal function requiring or not requiring hemodialysis.
This study will include three cohorts (Cohorts A, B, and C)
- Cohort A will be relapsed or refractory multiple myeloma subjects with moderate renal impairment (30 < estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m2)
- Cohort B will be relapsed or refractory multiple myeloma subjects with severe renal impairment not requiring hemodialysis (eGFR < 30 mL/min/1.73 m2)
- Cohort C will be relapsed or refractory multiple myeloma subjects with severe renal impairment requiring hemodialysis

This study consists of the following consecutive phases: Screening, Treatment, and Follow-up.:

Screening Phase
Potential study subjects will sign an informed consent document (ICD) prior to undergoing any study-related procedure. Subjects will undergo screening for protocol eligibility within 28 days prior to Cycle 1 Day 1.
Subjects in Cohorts A and B may participate in an exploratory biomarker substudy conducted at selected clinical sites able to perform the required collection and processing of samples.

Treatment Phase
Study treatment administration should start within 72 hours after enrollment of the subject into the study, provided that the inclusion/exclusion criteria are still met. Each subject will receive the following study treatment until progressive disease (PD) or study discontinuation due to other reasons:
- Pomalidomide administered orally at the starting dose of 4 mg on Days 1to 21 of a 28-day cycle

- Low-dose dexamethasone administered orally at the starting dose of 40 mg/day (* 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle
All three cohorts will enroll in parallel; all cohorts will receive the same study treatment, subjects who are included in Cohort C should receive IP after hemodialysis on non-PK dialysis days. Subjects may not be enrolled in more than 1 cohort. The study will be conducted in Europe.

Follow-up Phase
All study subjects will enter the follow-up phase within 28 days of last study treatment administration. During long-term follow-up the following information will be collected from all subjects every 3 months for up to 5 years after last subject enrollment or longer if clinically indicated: SPM, survival and all subsequent antimyeloma treatment (type of treatment, start and stop dates, best response) as well as date of progression based on the updated IMWG uniform response criteria at each change of treatment line.

Intervention

All subjects will receive oral doses of pomalidomide, at a starting dose of 4 mg on Days 1to 21 of a 28-day cycle and low-dose dexamethasone administered orally at a starting dose of 40 mg/day in subjects * 75 years and 20 mg in subjects aged over 75 years on Days 1, 8, 15, and 22 of the 28-day cycle. All subjects will continue study treatment until disease progression or unacceptable toxicity leading to treatment discontinuation. All subjects will be followed up for survival, serious adverse events (specifically including second primary malignancy) and subsequent antimyeloma therapies within 28 days of the last study treatment. Thereafter, every 3 months for a period of 5 years after last subject enrollment (or longer if clinically warranted), survival, subsequent anti-myeloma therapies and SPM will be collected during Follow-up-phase.

Study burden and risks

See section E9.

Contacts

Public
Celgene Corporation

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Summit, NJ 07901
US

Scientific
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Summit, NJ 07901
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must satisfy the following criteria to be enrolled in the study., 1. Must be * 18 years at the time of signing the informed consent form., 2. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted., 3. Able to adhere to the study visit schedule and other protocol requirements., 4. 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)., 5. Subjects must have had at least 1 prior antimyeloma regimen including lenalidomide and documented progression as per the IMWG uniform response criteria (Durie, 2006) during or after the last antimyeloma regimen. Induction therapy followed by ASCT and consolidation/ maintenance will be considered as one regimen., 6. Subjects must have an impaired renal function with an estimated GFR of, < 45 mL/min/1.73 m2 according to the MDRD equation., a. Impaired renal function must be due to multiple myeloma which needs to be, confirmed by kidney biopsy., b. Subjects may have acute myeloma related renal failure or chronic myeloma related renal failure; they may also have been treated with dialysis before, including dialysis with high cut off membranes., 7. ECOG performance status score of 0, 1, or 2, 8. Females of childbearing potential must:, a. Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject

practices true abstinence from heterosexual contact., b. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy., 9. Male subjects must:, a. Must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following IP discontinuation, even if he has undergone a successful vasectomy.

Exclusion criteria

The presence of any of the following will exclude a subject from enrollment, 1. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study., 2. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study., 3. Renal insufficiency due to other reasons than multiple myeloma or due to hypercalcaemia only., 4. Any of the following laboratory abnormalities:, a. Absolute neutrophil count (ANC) < 1,000/*L, b. Subject with platelet count < 50,000/*L are not eligible regardless of the percentage of plasma cells in the bone marrow, c. Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L), d. Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted), e. Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN), f. Serum total bilirubin > 2.0 mg/dL (34.2 *mol/L); or > 3.0 x ULN for subjects with hereditary benign hyperbilirubinemia, 5. Prior history of malignancies, other than MM, unless the subject has been free of the disease for * 5 years; exceptions include the following:, a. Basal or squamous cell carcinoma of the skin, b. Carcinoma in situ of the cervix or breast, c. Incidental histological finding of prostate cancer (TNM stage of T1a or T1b), 6. Previous therapy with pomalidomide., 7. Hypersensitivity to thalidomide, lenalidomide, or dexamethasone (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.

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):	18-12-2013
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	na
Generic name:	Pomalidomide

Ethics review

Approved WMO Date:	06-09-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-12-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-10-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2015
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	04-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2013-001903-36-NL
CCMO	NL45799.056.13

Study results

First publication
28-07-2022