A phase 2 study of CC220 (iberdomide) combined with low-dose cyclophosphamide and dexamethasone in relapsed/refractory multiple myeloma (IberCd): ICON STUDY

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This study has been transitioned to CTIS with ID 2023-508902-66-00 check the CTIS register for the current data. Primary objective: To evaluate progression-free survival

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

Summary

ID

NL-OMON54066

Source
ToetsingOnline

Brief title
ICON Study

Condition

- Plasma cell neoplasms

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Iberdomide, Relapsed/Refractory Multiple myeloma

Outcome measures

Primary outcome

- Progression free survival (PFS; i.e. time from the first dose of

iberdomide-cyclophosphamide-dexamethasone to progression or death from any

cause, whichever comes first)

Secondary outcome

- To investigate the efficacy of IberCd, as determined by the (s)CR+VGPR+PR

rate according to the international myeloma working group (IMWG) criteria.

- To evaluate toxicity

- To evaluate overall survival

- To evaluate time to response

- To evaluate duration of response

- To evaluate Time to Second Objective Disease

- Progression (PFS2)

- To evaluate time to next treatment (TTNT)

Exploratory endpoints:

- To evaluate prognostic factors (including ISS stage, LDH, cytogenetic

abnormalities, number of prior lines of therapy) for response and survival

- To evaluate the immunomodulatory effects of IberCd by using flow cytometric

analysis

Study description

Background summary

Novel drugs such as lenalidomide (an immunomodulatory drug; IMiD) have markedly improved the prognosis of multiple myeloma patients. Over the recent years, lenalidomide is increasingly used as part of first line therapy, typically until the development of progressive disease. These lenalidomide-refractory patients can be treated with several regimens. However, these regimens frequently contain proteasome inhibitors which are associated with neuropathy (bortezomib) or heart disease (carfilzomib). These proteasome inhibitors also need to be administered subcutaneously or intravenously in the hospital, once or twice per week. Also these regimens have limited efficacy in lenalidomide-refractory patients. This indicates that there is still an unmet medical need for new treatment options for patients who develop lenalidomide-refractory disease. These new treatment regimens should be active and safe without induction of neuropathy or cardiovascular disease. Moreover, an all oral regimen is frequently preferred by patients.

Available data indicates that the Cereblon E3 ligase modifying drug (CELMoD) iberdomide (CC220) is pharmacologically distinct from lenalidomide and pomalidomide with a higher potency against Cereblon, leading to differentiated antitumor and immunostimulating effects. Since iberdomide plus dexamethasone is active and well-tolerated in heavily pretreated patients including those with lenalidomide/pomalidomide-refractory disease, this two-drug regimen forms a new platform to which other agents can be added.

We and others have shown that low-dose cyclophosphamide can be effectively combined with the IMiDs lenalidomide and pomalidomide. These combinations are effective and are well-tolerated.

To address the unmet medical need for new treatment options for lenalidomide-refractory MM patients, we aim at further improving the efficacy of IMiD/CELMoD plus low-dose cyclophosphamide combination therapy in terms of response and progression-free survival, by adding cyclophosphamide to the iberdomide-dexamethasone backbone (IberCd). We will test this all-oral regimen in a lenalidomide-refractory patient population with 2-4 prior lines of therapy. The goal of this trial is to investigate the efficacy and safety of the IberCd combination in multiple myeloma patients who have refractory disease

or a relapse after prior treatment with lenalidomide.

Study objective

This study has been transitioned to CTIS with ID 2023-508902-66-00 check the CTIS register for the current data.

Primary objective: To evaluate progression-free survival

Study design

Prospective, multicenter, phase 2 study

Intervention

Patients will be treated with iberdomide plus low-dose cyclophosphamide and dexamethasone (IberCd)

Study burden and risks

The benefit will be that patients with lenalidomide- refractory disease, who have a poor outcome, will be treated with iberdomide plus low-dose cyclophosphamide and dexamethasone. Treatment options for these patients are limited, and frequently associated with marked toxicity and the need for frequent hospital visits for the administration of subcutaneously administered bortezomib and intravenously administered carfilzomib or daratumumab. Iberdomide is active in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab-refractory disease (overall response rate of approximately 30%). Importantly, iberdomide can be given orally and is associated with remarkably low toxicity.

Based on high efficacy and good tolerability profile of the combination of lenalidomide or pomalidomide with low-dose cyclophosphamide/corticosteroid, in this study we will treat lenalidomide-refractory patients with iberdomide plus low-dose cyclophosphamide and dexamethasone. We expect that the response rate and outcome will markedly improve with this combination, while tolerability profile of the combination will be good. The burden will be that patients may still suffer from side effects, such as cytopenias and infections, although these can be well managed by dose-reductions, temporarily stopping the drug(s), or by institution of adequate supportive care.

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.

2. Subject must have documented diagnosis of multiple myeloma and have 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 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 <50% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment.

4. Subject had 2-4 prior anti-myeloma regimens.

(Note: Induction, bone marrow transplant with or without maintenance therapy is considered one regimen; Prior pomalidomide is allowed)

5. Subject has developed lenalidomide-refractory disease (any dose) during prior treatment with lenalidomide or a lenalidomide-containing regimen Lenalidomide-refractory MM is defined as progressive disease during therapy, no response (< PR) to prior lenalidomide-containing therapy, or progression within 60 days of discontinuation from lenalidomide-containing regimens, according to the International Myeloma Working Group criteria.

6. WHO performance 0, 1, or 2

7. Life expectancy at least 3 months

8. Written informed consent

9. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not
been naturally postmenopausal (amenorrhea following cancer therapy does not rule out
childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time
in the preceding 24 consecutive months) and must:
a. Have two negative pregnancy tests as verified by the Investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. 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 and source documented) or agree to use, and be able to comply with two forms of contraception: one highly effective, and one additional effective (barrier) measure of contraception without interruption 28 days prior to starting investigational product, during the study treatment
(including dose interruptions), and for at least 28 days after the last dose of CC-220, 90 days after the last dose of cyclophosphamide, whichever is longer. Contraception requirements are detailed in Appendix H.

10. Male subjects must:
a. Practice true abstinence* (which must be reviewed on a monthly basis and source documented) 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 90 days following the last dose of study treatment, even if he has undergone a successful vasectomy.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation,

symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.]

11. Males must agree to refrain from donating sperm while on study treatment, during dose
interruptions and for at least 90 days following last dose of study treatment.

12. All subjects must agree to refrain from donating blood while on study treatment, during
dose interruptions and for at least 28 days following the last dose of study treatment.

13. All male and female subjects must follow all requirements defined in the Pregnancy
Prevention Program (v5.1). See Appendix H for CC-220 Pregnancy Prevention Plan for
Subjects in Clinical Trials.

Exclusion criteria

1. Subjects who previously received continuous low-dose cyclophosphamide alone or in combination with other anti-MM agents are excluded (cyclophosphamide once weekly such as in bortezomib-cyclophospahmide-dexametahsone regimen (VCD) is allowed).

2. Treatment with prior iberdomide

3. Non-secretory MM

4. Systemic AL amyloidosis or plasma cell leukemia (>2.0x109/L circulating plasma cells by standard differential) or Waldenstrom*s macroglobulinemia

5. Subject has known meningeal involvement of multiple myeloma

6. Inadequate marrow reserve as defined by a platelet count <75 x 109/L or an absolute neutrophil count <1.0 x 109/L

7. Corrected serum calcium >13.5 mg/dL (>3.4 mmol/L)

8. Subject has a history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide,
pomalidomide, dexamethasone, or cyclophosphamide. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of iberdomide, dexamethasone, or cyclophosphamide.

9. Subject has received any of the following within the last 14 days of initiating IberCd:
- Plasmapheresis
- Major surgery (as defined by the Investigator)
- Radiation therapy other than local therapy for MM associated bone lesions
- Use of any systemic myeloma drug therapy

10. Subject has been treated with an investigational agent (ie, an agent not commercially
available) within 28 days or 5 half-lives (whichever is longer) of initiating IberCd treatment
11. Subject has current or prior use of immunosuppressive medication within 14 days prior to the first dose of IP. The following are exceptions to this criterion:
- Intranasal, inhaled, topical or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids at physiologic doses that do not exceed 10 mg/day of prednisone or equivalent
- Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)

12. Subject has taken a strong inhibitor or inducer of CYP3A4/5 including grapefruit, St.
John*s Wort or related products within two weeks prior to dosing and during the course
of study

13. Creatinine clearance <30 ml /min or requirement of dialysis.

14. 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 arrhythmias; clinically significant pericardial disease)

15. Significant hepatic dysfunction (total bilirubin * 3 times normal value or transaminases * 3 times normal value), unless related to myeloma

16. Subject has any concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, respiratory disease, 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.

17. Subject known to test positive for human immunodeficiency virus (HIV), chronic or
active hepatitis B, or active hepatitis A or C

18. Peripheral neuropathy of >=grade 2.

19. Subjects with gastrointestinal disease that may significantly alter the absorption of
CC-220

20. 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 (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) 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.

21. 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.

22. Subject is a female who is pregnant, nursing or breastfeeding, or who intends to become
pregnant during the participation in the study

23. Subject is unable or unwilling to undergo protocol required thromboembolism prophylaxis

24. Subject has previously received an allogeneic stem cell transplantation within 1 year before the date of registration and has not used immunosuppressive drugs within one month before the date of registration.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-02-2021
Enrollment:	60
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:	Endoxan
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Iberdomide
Generic name:	Iberdomide

Ethics review

Approved WMO Date:	02-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	28-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2023
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
EU-CTR	CTIS2023-508902-66-00
EudraCT	EUCTR2019-004604-35-NL
CCMO	NL72835.029.20