PHASE II STUDY OF IBERDOMIDE (CC220) MAINTENANCE AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENT

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This study has been transitioned to CTIS with ID 2024-512354-21-00 check the CTIS register for the current data. Primary objectivesTo evaluate the efficacy (rate of improvement in response from PR to >= VGPR; from VGPR to >=CR; from CR to sCR...

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

Summary

ID

NL-OMON56318

Source
ToetsingOnline

Brief title
EMN26

Condition

- Plasma cell neoplasms

Synonym
Kahler's disease, MM

Research involving
Human

Sponsors and support

Primary sponsor: Stichting European Myeloma Network
Source(s) of monetary or material Support: Celgene Corporation,European Myeloma Network - EMN

Intervention

Keyword: Maintenance, Multiple Myeloma

Outcome measures

Primary outcome

Response improvement rate within 6 months will be measured as the number of subjects that improve response according to IMWG criteria (from PR to >=VGPR; from VGPR to >=CR; from CR to >sCR) within the end of sixth cycle of treatment.

Dose reductions/discontinuation rate within 6 months will be measured as the number of subjects that discontinued treatment or have a dose modification within the end of sixth cycle of treatment.

Secondary outcome

TTP will be measured by protocol from the date of start of therapy and according to ITT from the date of eligibility confirmation to the date of first observation of PD, or deaths for PD. Subjects who have not progressed or who withdraw from the study or die from causes other than PD will be censored at the time of the last disease assessment. Subjects lost to FU will also be censored at the time of last complete disease assessment.

PFS will be measured by protocol from the date of start of therapy and according to ITT from the date of eligibility confirmation to the date of first

observation of PD, or death from any cause as an event. Subjects who have not progressed or who withdraw from the study or who were lost to FU will be censored at the time of the last disease assessment.

TNT will be measured by protocol from the date of start of therapy and according to ITT from the date of eligibility confirmation to the date of next anti-myeloma therapy. Death due to any cause before starting therapy will be considered an event. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last disease assessment. Subjects lost to FU will also be censored at the time of last contact.

PFS2 will be measured by protocol from the date of start of therapy and according to ITT from the date of eligibility confirmationto the date of observation of second disease progression (i.e. progression after the second line of therapy) or death to any cause as an event. In case of date of second progression is not available, date of start of third line treatment can be used. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to follow-up prior to the end of the study, have not progressed, and are still alive will also be censored at the time of last contact.

OS is defined by protocol from the date of start of therapy and according to ITT from the date of eligibility confirmation to the date of death, regardless cause of death. Subjects who withdraw consent will be censored at the time of

withdrawal. Subjects who are still alive at the cut-off date of final analysis will be censored at the date of last contact. Subjects lost to FU will also be censored at the time of last contact.

Response rate (sCR, CR, VGPR) will be evaluated according to IMWG Response criteria

Rate of NGF Minimal residual disease (MRD) conversion from positive to negative

The MRD conversion rate at 6 months is determined as the proportion of subjects with MRD negativity (>=10-5 sensitivity level, by NGF) after 6 months converted from status as Positive at screening.

The MRD conversion rate at 12 months is determined as the proportion of subjects with MRD negativity (>=10-5 sensitivity level, by NGF) after 12 months converted from status as Positive at screening. Subjects who withdraw from the study or are lost to follow up before post 12 months MRD evaluation, the best MRD assessment will be considered.

The best MRD conversion rate within 12 months is determined as the proportion of subjects with MRD negativity (>=10-5 sensitivity level, by NGF) within 12 months converted from status as Positive at screening. The best MRD assessment will be considered. Subjects who withdraw from the study or are lost to follow up before MRD evaluation, the best MRD assessment will be considered.

The analysis of safety as defined by type, frequency and severity will be done primarily by tabulation of the incidence of AEs as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. In the by-subject analysis, a subject having the same event more than once will be counted only once. AEs will be summarized by worst CTCAE grade

Dose reduction will be done primarily by tabulation of the incidence of subject with at least one dose reduction and causes.

Relative dose will be evaluated consider the ratio between the administered and the planned dose.

Time to discontinuation for toxicity will be measured from the date of first dose of study drugs to the date of discontinuation due to AE or Death for AE/SPM. Subjects who discontinued drugs due to PD, or death for cause other than AE/SPM will be considered a competing event. Subjects has not discontinued and are still alive and on treatment at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

Quality of life defined by EORTC QLQ-C30.

Determine whether tumor response and outcome (PFS, PFS2, TTP, TNT and OS) may

change in subgroups with different prognosis according to current prognostic

factors.

Study description

Background summary

Multiple myeloma (MM) is the second most common hematologic malignancy, characterized by the malignant proliferation of clonal plasma cells in the bone marrow microenviroment, monoclonal protein in blood or urine, and associated organ dysfunction or myeloma defining events (1). The annual incidence rates in Western countries is of 5.6 cases per 100.000 people. The median age at diagnosis is 70 years (2).
High-dose therapy with autologous stem cell transplantation (ASCT) is the standard of care for eligible newly diagnosed MM patients. Induction generally consists of 3-6 cycles of therapy with immunomodulatory agents (thalidomide or lenalidomide) or chemotherapy (cyclophosphamide or doxorubicine) plus proteasome inhibitor (bortezomib). High dose melphalan (200 mg/m2-Mel200) is the standard conditioning myeloablative regimen. Two courses of Mel200 followed by autologous stem cell transplantation (ASCT) can be considered in high-risk patients. Post ASCT consolidation treatment with a regimen similar or equal to the one administered as induction may be considered, according to drug availability, but data on impact on progression free survival (PFS) and overall survival (OS) are conflicting. Post ASCT maintenance with lenalidomide continuous therapy is the current standard of care (3).

Iberdomide
Iberdomide (CC-220) is an orally available agent which binds to the cereblon E3 ubiquitin ligase complex, resulting in proteasomal degradation of Ikaros and Aiolos, which are key transcriptional regulators in cells of the immune system, including B cells, T cells, monocytes, and plasmacytoid dendritic cells.
Iberdomide is a potent antiproliferative agent in B cell-derived tumors, including MM and lymphoma tumor cell lines.
Thus, iberdomide, sharing a similar mechanism of action with lenalidomide and thalidomide, but with greater potency and unique pharmacokinetic (PK) properties, may show clinical benefit in a similar set of hematological diseases.
Iberdomide is being studied in an ongoing Phase 1b/2a study in subjects with MM, MM-001, which consists of 2 parts: Part 1 dose escalation of iberdomide in relapsed and refractory multiple myeloma (RRMM) as monotherapy (Cohort A), iberdomide in combination with dexamethasone (Cohort B; Iber + dex), iberdomide in combination with dexamethasone and daratumumab (Cohort E; IberDd),

iberdomide in combination with dexamethasone and bortezomib (Cohort F; IberVd), and iberdomide in combination with dexamethasone and carfilzomib (Cohort G; IberKd); and Part 2 expansion of the recommended phase 2 dose (RP2D), Iber + dex in RRMM subjects (Cohort D), Iber + dex in RRMM subjects previously exposed to B cell maturation antigen (BCMA)-targeted therapies (Cohort I), IberVd in subjects with newly diagnosed multiple myeloma (NDMM) who are not eligible for autologous stem cell transplant (ASCT) (Cohort J1), IberVd in NDMM subjects who are eligible for ASCT (Cohort J2), and IberDd in subjects with NDMM who are not eligible for ASCT (Cohort K).

As of the clinical cutoff date of 02 Jun 2021, a total of 342 subjects have been enrolled in the MM-001 study: 209 subjects in Part 1 (dose escalation) and 133 patients in Part 2 (dose expansion). At the time of data extract, dose escalation was ongoing in all cohorts in Part 1 with the exception of the Iber monotherapy cohort, where 1 mg dose level was deemed tolerable in subjects with RRMM, the Iber + dex cohort, where a 1.6 mg dose of iberdomide was selected as the RP2D, and the IberDd cohort, where a 1.6 mg dose was selected as the RP2D. Dose expansion in Part 2 was also ongoing with Iber + dex in RRMM subjects (Cohort D) and in RRMM subjects previously exposed to BCMA-targeted therapies (Cohort I).

The Iber + dex cohorts are the most advanced cohort in terms of enrollment and data availability. In Cohort B in part 1, 90 subjects were enrolled and treated with Iber+ dex at doses ranging from 0.3 to 1.6 mg. A total of 89 (98.9%) subjects treated in cohort B experienced at least 1 TEAE.

The most frequently reported TEAEs (occurring in >= 20% of all subjects in Cohort B) were neutropenia, (47.8%), thrombocytopenia (40.0%), anemia, (38.9%), fatigue, (36.7%), insomnia, (32.2%), leukopenia (30%), diarrhea, (23.3%), back pain, muscle spasms, and pyrexia (22.2% each), and arthraligia, cough, and dyspnea (21.1% each). Infections occurred in 56 (62.2%) subjects. Grade 3 or 4 TEAEs were reported in 83.3% of subjects and the most common Grade 3 or 4 TEAEs were neutropenia, (42.2%), anemia, (26.7%), thrombocytopenia, (14.4%), leukopenia (13.3%), pneumonia, (11.1%), and lymphopenia (10.0%).. Five subjects had TEAEs that led to death, 4 of which were related to progression of MM and 1 subject experienced sudden death with unknown causes. Serious TEAEs occurred in 53.3% of subjects. In the Infections and Infestations SOC were the most commonly reported, with a total of 23 (25.6%) subjects, reporting a TEAE within this SOC. Pneumonia was the only PT within this SOC reported for more than 2 subjects. TEAEs reported for more than 2 subjects in other SOCs included back pain (4 subjects, 4.4%), acute kidney injury (4 subjects, 4.4%), febrile neutropenia, (3 subjects, 3.3%), and pyrexia (3 subjects, 3.3%) The TEAEs that led to iberdomide dose discontinuation were anemia, progressive multifocal leukoencephalopathy, lower respiratory tract infection, pyrexia, neutropenia, and thrombocytopenia.

In Cohort A, 29 subjects were enrolled and treated with Iber monotherapy in 6 dose levels (from 0.3 mg to 1.0 mg). The MTD was not reached; however, given the better clinical efficacy and availability of iberdomide in combination with other agents in RRMM, further dose escalation was not continued with iberdomide monotherapy. The most frequently reported all-causality TEAEs were hematologic

in nature or general conditions, including neutropenia and fatigue (55.2% each), anemia and back pain (37.9% each), thrombocytopenia, arthralgia, and constipation (27.6% each), muscle spasms and nausea (24.1% each), and upper respiratory tract infection and musculoskeletal chest pain (20.7% each). Among all Cohort A subjects, the most common Grade 3/4 TEAEs were hematologic in nature (neutropenia, 48.3%; anemia, 20.7%; thrombocytopenia, 17.2%). Grade 3/4 TEAEs in the SOC of Infections and Infestations were reported in 27.6% of all subjects in Cohort A. As of the data cutoff date of 02 Jun 2021, 1 (3.4%) subject in Cohort A died while on treatment due to plasma cell myeloma. SAEs were reported for approximately half of the subjects in Cohort A (13 subjects, 44.8%), with Infections and Infestations SOC the most commonly reported, with a total of 8 (27.6%) subjects. The pharmacokinetics (PK) of iberdomide were characterized in clinical studies in healthy subjects. Following oral administration of iberdomide in healthy subjects, systemic exposure increased in a doseproportional manner. The median time to reach the maximum observed plasma concentration (Cmax) was 2.5 to 4 hours. After repeated QD oral doses, steady state appeared to have been achieved by Day 7 with an approximately 2-fold accumulation ratio (AUC). Following single oral dose administration of iberdomide to healthy subjects, the geometric mean terminal half-life (t1/2) was approximately 9 to 13 hours. Co-administration with a high-fat meal did not change the overall exposure of iberdomide.
Based on results from a radiolabeled human mass balance study, intact parent molecule in urine and feces constitute 16% and 11% respectively, indicating the absorbed drug is extensively metabolized and excreted mostly as metabolites. Iberdomide and metabolite M12 were the predominant components in human plasma comprising approximately 59% and 14% of circulating total radioactivity exposure, respectively. Single-dose PK of iberdomide was characterized in subjects with normal, mild, moderate, a

Study objective

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Primary objectives
To evaluate the efficacy (rate of improvement in response from PR to >= VGPR; from VGPR to >=CR; from CR to sCR) of three different dose levels of Iberdomide in maintenance treatment after ASCT

Secondary objectives
To determine:
• Rate of NGF MRD conversion from positive to negative
• Rate of adverse events
• Safety and efficacy in different subset of subjects with different prognostic features
• Time to Progression (TTP)
• Progression Free Survival (PFS)

• Time to next therapy (TNT)
• Progression Free Survival 2 (PFS2)
• Overall survival (OS)
• Pharmacokinetics (PK) of iberdomide

Study design

This is a non-randomized phase II trial evaluating three dose levels of Iberdomide (1.3 mg, 1.0 mg and 0.75 mg). Newly diagnosed MM subjects who achieved at least a partial response after induction with protesome inhibitor and immunomodulatory agents followed by ASCT +/- consolidation will be assigned to the three different dose levels. Patients will be allocated in a 1:1:1 ratio to each cohort with a fixed sequence: Cohort 1, Cohort 2 and Cohort 3. Subjects will be allocated using a web-based, computer generated, procedure completely concealed to study participants An interim analysis will be conducted when the first 20 patients in each cohort have received at least 3 cycles of maintenance treatment or discontinued treatment. In case of excess toxicity IDMC could recommend to preliminary stop enrollment in cohort.
Details of all treatments (dose and schedule) are given in Section 9.

Intervention

Iberdomide will be given orally, from day 1 to 21 of a 28-day cycle, continuously, until progressive disease (PD) or unacceptable toxicity.

The trial will start by enrolling 3 parallel cohorts of subjects, receiving the following doses of iberdomide:
1. 1.3 mg/day
2. 1.0 mg/day
3. 0.75 mg/day

Study burden and risks

By participating in this study patients will not be asked to deviate significantly from the standard practice in terms fo their disease follow up. In particular visits to the hospital are confined to once per month to monitor the study activities and of course their status and safety of the medication. Furthermore the investigations to be performed during those visits do not differ from the standard practice for Multiple Myeloma.
By receiving iberdomide thyere is a possibility that patients may experience some adverse reactions. Very common adverse reactions with ibedomide treatment include neturopenia, thrombocytopenia, anemia and infections and common ones include skin rash. Treating physician will always safeguard the health and best interested of the patients in the study and, furthermore, as per local requirement, an independent physician will be available to provide independent

advice to the patients.

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

• Subjects with newly diagnosed MM, requiring therapy due to the presence of CRAB symptoms or myeloma defining events and measurable disease (sPEP >=0.5 g/dL and/or uPEP >= 200 mg/24h and/or FLC involved >= 10 mg/dL with abnormal FLC ratio) before induction therapy with a PI and IMID-containing regimen-
• Subjects with complete baseline evaluation at the time of diagnosis according to revised International Staging System (R-ISS) (cytogenetic profile, ISS and LDH)
• Subjects treated with proteasome inhibitor plus immunomodulatory drug-based induction (3-6 cycles), followed by single or double autologous stem cell

transplant (ASCT) with melphalan as condItioning regimen +/- consolidation.
• Subjects within 15 months from diagnosis and 120 days after last ASCT or consolidation treatment, if performed, who achieved at least a partial response (PR) after ASCT, according to IMWG criteria
• Subjects willing and able to follow the trial procedures
• Subjects must understand and voluntary sign an ICF prior to any study related assessment/procedurs being conducted
• Age >=18 years
• ECOG performance status 0-1
• 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. Contraception requirements are detailed in Appendix H.
• 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.]
• 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.
• 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.
• All male and female subjects must follow all requirements defined in the Pregnancy Prevention Program (v5.1). See Appendix I for CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials.
• Subject agree to refrain from donating blood while on iberdomide, during dose interruption and for at least 28 days following the last iberdomide dose

• Baseline values:
ANC >=1.0 x 109/L without use of growth factors;
PLTs>=75 x109/L (transfusions within 14 days from Day1 cycle 1 to achieve this cut off are not allowed);
Hb >8 g/dL (transfusions within 14 days from Day1 cycle 1 to achieve this cut off are not allowed);
• Life expectancy >= 3 months

Exclusion criteria

• Systemic AL amyloidosis or plasma cell leukemia (>2.0x109/L circulating plasma cells by standard differential) or Waldenstrom*s macroglobulinemia
• Subject has known meningeal involvement of multiple myeloma
• History of active malignancy during the past 5 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.
• Subject with any one of the following: clinically significant abnormal electrocardiogram (ECG) findings at screening; congestive heart failure (New York Heart Association Class III or IV); myocardial infarction within 12 months prior to starting iberdomide; unstable or poorly controlled angina pectoris, including Prinzmetal variant; clinically significant pericardial disease
• Peripheral neuropathy of >=grade 2.
• Subject has any concurrent severe and/or uncontrolled medical condition or psychiatric disease 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 or that confounds the ability to interpret data from the study.
• Subjects with gastrointestinal disease that may significantly alter the absorption of iberdomide
• Subject with known history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, pomalidomide
• Subject with known or suspected hypersensitivity to excipients contained in the formulation of iberdomide
• Subjects has current or prior use of immunosuppressive medication within 14 days prior to starting therapy with iberdomide (exceptions are intranasal, inhaled, topical or local steroids injections; systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent; steroids as premedication for hypersensitivity reactions)
• Subject has taken a strong inhibitor or inducer of CYP3A4/5 including grapefruit, St John*s wort or related products within 2 weeks prior to dosing and during the course of study

• Subject known to test positive for HIV or have active hepatitis A, B or C
• Subjects is unable or unwilling to undergo protocol required thromboembolism prophylaxis
• Subject is a female who is pregnant nursing or breastfeeding or who intends to become pregnant during the participation
• Baseline lab values:
- Creatinine clearance <=30 ml/min.
- Significant hepatic dysfunction (total bilirubin > 1.5x ULN or AST/ALT > 2.5x ULN), or > 3.0 mg/dL for subjects with documented Gilbert*s syndrome unless related to myeloma
- Corrected serum calcium>13.5 mg/dL (3.4 mmol/L)
• Any clinical condition at screening that would preclude subject from completing the study

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):	08-12-2021
Enrollment:	24
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	CC-220
Generic name:	iberdomide

Ethics review

Approved WMO Date:	02-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2024

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2024
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
Other	2020-003091-40
EU-CTR	CTIS2024-512354-21-00
EudraCT	EUCTR2020-003091-40-NL
CCMO	NL75594.029.20