A PHASE 1B/2A MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE, ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF CC-220 AS MONOTHERAPY AND IN COMBINATION WITH OTHER TREATMENTS IN SUBJECTS WITH MULTIPLE MYELOMA

Published: 12-10-2016
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This study has been transitioned to CTIS with ID 2024-510799-19-00 check the CTIS register for the current data.

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

Summary

ID

NL-OMON54734

Source
ToetsingOnline

Brief title
Celgene 0451/0204

Condition

- Plasma cell neoplasms

Synonym
bone marrow cancer, Multiple myeloma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: multiple myeloma, safety, tolerability

Outcome measures

Primary outcome

Recommended Dose and Regimen in Part 1:
Establish the maximum tolerated doses (MTDs) and or Recommended Phase 2 doses (RP2D) of CC-220 monotherapy, in combination with DEX, and in combination with DEX and daratumumab (C220Dd), in combination with DEX and bortezomib (C220Vd), and in combination with DEX and carfilzomib (CC-220Kd).

Overall response rate (ORR) in Cohort D:
Tumor response, including progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) in CC-220 in combination with DEX

Secondary outcome

Secondary
Safety: Type, frequency, seriousness and severity of adverse events (AEs) (and AEs of special interest) and relationship of AEs to investigational product

Very good partial response or better rate (VGPR): Tumor response, including progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) for subjects who achieved VGPR or better

Overall response rate (ORR): Tumor response, including progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016) for subjects who achieved partial response (PR) or better

Time to response (TTR): Time from enrollment to the first documentation of response (partial response [PR] or greater)

Duration of response (DOR): Time from the first documentation of response (PR or greater) to the first documentation of PD

Progression-free Survival (PFS): Time from the first dose of investigational product (IP) to the first documentation of PD or death from any cause, whichever occurs first

Overall Survival (OS) in Part 2 RRMM cohorts: Time from first dose of IP to death due to any cause

Pharmacokinetic parameters : PK of CC-220, and as appropriate, it's R-enantiomer CC-17195 in plasma, eg, (AUC(TAU), Cmax, Tmax.

Exploratory
For Exploratory parameters refer to protocol, table 8.

Study description

Background summary

This study has been transitioned to CTIS with ID 2024-510799-19-00 check the CTIS register for the current data.

Study objective

This study has been transitioned to CTIS with ID 2024-510799-19-00 check the CTIS register for the current data.

Study design

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Intervention

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Study burden and risks

This study has been transitioned to CTIS with ID 2024-510799-19-00 check the CTIS register for the current data.

Contacts

Public
Celgene Corporation

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US
Scientific
Celgene Corporation

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is >=18 years of age the time of signing the informed consent form (ICF)

2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted

3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements

4. All subjects in RRMM cohorts must have a documented diagnosis of MM and have

measurable disease defined as a) M-protein (serum and/or urine protein electrophoresis (sPEP or uPEP)): sPEP >=0.5 g/dL or uPEP >=200 mg/24 hours and/or b) Light chain MM without measurable disease in the serum or urine: serum immunoglobulin free light chain >= 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio

5. Subjects in Cohorts A, B, C, E, G1 and G2 must have received at least 2 prior myeloma regimens (note: induction with or without bone marrow transplant and with or without maintenance therapy is considered one regimen). Subjects in Cohort F must have received at least 1 prior myeloma regimen. Subjects in Cohorts D and I must have received at least 3 prior myeloma regimens.

6. All subjects in RRMM cohorts must have received prior treatment with at least 2 consecutive cycles of a lenalidomide or pomalidomide-containing regimen. Subjects in Cohort D must have received at least 3 prior myeloma regimens.

7. All subjects in RRMM cohorts must have received prior treatment with at least 2 consecutive cycles of a proteasome inhibitor or a proteasome inhibitor-containing regimen

8. For Part 2 RRMM cohorts (Cohorts C, D and I), all subjects must have received prior treatment with at least 2 consecutive cycles of a CD38 antibody or a CD38 antibody-containing regimen

9. All subjects in RRMM cohorts must have documented disease progression on or within 60 days from the last dose of their last myeloma therapy. Subjects who had CAR T therapy as their last myeloma therapy must have documented disease progression.

10. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2

11. 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 (ie, 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 DARA (for Cohorts E and K), or 7 months after last dose of BTZ (for Cohorts F, J1 and J2), or 6 months after the last dose of CFZ (for Cohorts G1 and G2) whichever is longer.

12. 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, 4 months after the last dose of BTZ (for Cohort F, J1 and J2) or 3 months after the last dose of CFZ (for Cohorts G1 and G2), whichever is longer, 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.]

13. 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.

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

15. All male and female subjects must follow all requirements defined in the Pregnancy Prevention Program. See Appendix D for CC-220 Pregnancy Prevention Plan for Subjects in Clinical Trials.

16. Subjects in Cohort D must have received prior treatment with at least 2 consecutive cycles of a glucocorticoid-containing regimen.

17. Subjects in Cohort D must be refractory to an immunomodulatory agent, a proteasome inhibitor, a glucocorticoid and a CD38 antibody. Refractory is defined as disease that is nonresponsive on therapy (failure to achieve minimal response or development of progressive disease while on therapy) or progresses within 60 days of last dose.

18. Subjects in Cohort I must have received prior treatment with a BCMA targeted therapy.

Additional Inclusion Criteria for Part 2 Cohorts J1 and J2 (CC-220 + BTZ + DEX in NDMM and K (CC-220 + DARA + DEX in NDMM):
19. Subject must have documented diagnosis with previously untreated

symptomatic MM as defined by the criteria below (Rajkumar, 2016):
• MM diagnostic criteria;
- Clonal bone marrow plasma cells >= 10% or biopsy-proven bony or extramedullary plasmacytoma
- And any one or more of the following myeloma defining events:
o one or more of the following myeloma-related organ dysfunction (at least one of the following);
* [C] Calcium elevation (serum calcium > 0.25 mmol/L [> 1 mg/dL] higher than the upper limit of laboratory normal or > 2.75 mmol/L [> 11 mg/dL])
* [R] Renal insufficiency (serum creatinine > 2 mg/dl [> 177 µmol/L] or creatinine clearance < 40 ml/min)
* [A] Anemia (hemoglobin < 10 g/dl or > 2 g/dL below the lower limit of laboratory normal)
* [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)/CT
o one or more of the following biomarkers of malignancy:
* Clonal bone marrow plasma cell percentage* >= 60%
* Abnormal serum free light-chain (FLC) ratio >= 100 (involved kappa) or < 0.01 (involved lambda) and involved FLC level must be >= 100 mg/L
* >1 focal lesion detected by magnetic resonance imaging (MRI) (at least 5 mm in size)
AND have measurable disease, as assessed by central laboratory, defined by any of the following:
• Immunoglobulin (Ig)G myeloma: serum M-protein level >= 1.0 g/dL or urine M-protein level >= 200 mg/24 hours; or
• IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level >= 0.5 g/dL or urine M-protein level >= 200 mg/24 hours; or
• Light chain multiple myeloma without measurable disease in serum or urine: serum FLC >= 100 mg/L and abnormal kappa lambda (*/*) ratio

20. Subjects in Cohorts J1 and K are those for who ASCT (autologous stem cell transplant) is not planned for initial therapy or are not considered by the investigator as eligible for high-dose chemotherapy and autologous stem cell transplantation due to:
• Age >=65 years, OR
• In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with autologous stem cell transplantation.

21. Subjects in Cohort J2 are considered by the investigator as eligible for high-dose chemotherapy and autologous stem cell transplantation according to the institution's criteria based on age, medical his

Exclusion criteria

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study

2. Subject has 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. Subject has any condition that confounds the ability to interpret data from the study

4. Subject has nonsecretory multiple myeloma

5. Subjects with Plasma Cell leukemia or amyloidosis

6. Any of the following laboratory abnormalities · Absolute neutrophil count (ANC) <1,000/µL · Platelet count < 75,000/µL for Part 1. For Part 2; platelet count < 75,000/µL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; otherwise platelet count < 50,000/µL (transfusions are not permitted to achieve minimum platelet counts) · Corrected serum calcium >13.5 mg/dL (>3.4 mmol/L) · Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) or serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) >=2.0 x upper limit of normal (ULN) · Serum total bilirubin and alkaline phosphatase >1.5 x ULN · Subjects with serious renal impairment (creatine clearance [CrCl] <30 mL/min) or requiring dialysis would be excluded

7. Subjects with peripheral neuropathy >=Grade 2

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

9. Subjects with a prior history of malignancies, other than MM, unless the subject has been free of the disease for >=5 years with the exception of the following noninvasive malignancies: · Basal cell carcinoma of the skin · Squamous cell carcinoma of the skin · Carcinoma in situ of the cervix · Carcinoma in situ of the breast · Incidental histological findings of prostate cancer such as T1a or T1b using the Tumor/Node/Metastasis (TNM) classification of malignant tumors or prostate cancer that is curative

10. Subject has a history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, pomalidomide, DEX, daratumumab (for Cohorts E and K), bortezomib (for Cohorts F, J1 and J2), or carfilzomib (for Cohorts G1 and G2). Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-220, DEX, daratumumab (for Cohorts E and K), bortezomib (for Cohorts F, J1 and J2)), or carfilzomib (for Cohorts G1 and G2)

11. Contraindications to the other treatment regimens, as per local prescribing information

12. Subject has received any of the following within the last 14 days of initiating IP: · 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

13. 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 IP. Not applicable for subjects who had CAR T as last prior regimen.

14. Subject has any one of the following: · Clinically significant abnormal electrocardiogram (ECG) finding at Screening · Congestive heart failure (New York Heart Association Class III or IV) · Myocardial infarction within 12 months prior to starting IP · Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris

15. 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)

16. 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.

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

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

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

Additional Exclusion Criteria for Cohorts E and K (CC-220 + DARA + DEX):
20. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. Note that forced expiratory testing (FEV1) is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal
21. Subject has received previous allogeneic stem cell transplant; or received autologous stem cell transplantation within 12 weeks prior to enrollment
22. Subject has known moderate or severe persistent asthma, or currently has uncontrolled asthma of any classification

Additional Exclusion Criteria for Cohorts F, J1 and J2 (CC-220 + BTZ + DEX):
23. Subject with acute diffuse infiltrative pulmonary and pericardial disease

Additional Exclusion Criteria for Cohorts G1 and G2 (CC-220 + CFZ + DEX):
24. Left ventricular ejection fraction (LVEF) < 45% as determined by echocardiogram (ECHO) or multigated acquisition (MUGA) scan and/or an ECG with corrected QT interval (QTc) of > 470 milliseconds at Screening
25. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment
26. Subject has symptomatic ischemia, pericardial disease, history of severe coronary artery disease, sick sinus syndrome, uncontrolled arrhythmias, Grade 3 conduction system abnormalities not mitigated by a pacemaker, hypertrophic cardiomyopathy, or restrictive cardiomyopathy
27. Subject has mild hepatic impairment defined as elevated bilirubin > 1.0 but < 1.5 x ULN or normal bilirubin with any elevation of AST

Additional Exclusion Criteria for Part 2 Cohorts C (MonoT) and D (DoubleT):
28. Previous history of treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or BCMA targeted therapy

Additional Exclusion Criteria for Part 2 Cohorts J1 and J2 (CC-220 + BTZ + DEX in NDMM) and K (CC-220 + DARA + DEX in NDMM):
29. Previous treatment with anti-myeloma therapy, including treatment for smoldering myeloma (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of initiating study treatment]).

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):	13-07-2017
Enrollment:	56
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CC-220 capsule 0,15 mg
Generic name:	Iberdomide
Product type:	Medicine
Brand name:	CC-220 capsule 0,30 mg
Generic name:	Iberdomide
Product type:	Medicine
Brand name:	CC-220 capsule 0,45 mg
Generic name:	Iberdomide
Product type:	Medicine
Brand name:	Dexamethasone tablets BP 2 mg
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dexamethasone-ratiopharm 4 mg tablets
Generic name:	Dexamethasone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-10-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-12-2018
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Not approved

Date:	21-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	12-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	02-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	06-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	15-03-2024
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
EU-CTR	CTIS2024-510799-19-00
EudraCT	EUCTR2016-000860-40-NL
ClinicalTrials.gov	NCT02773030
CCMO	NL59269.078.16