




Essai Clinique

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Titre	Étude multicentrique de phase 1/2 à doses croissantes et d'expansion de la cohorte sur le traitement d'association par le vénétoclax, le daratumumab et la dexaméthasone (avec ou sans bortézomib) chez des sujets atteints d'un myélome multiple récidivant ou réfractaire
Protocole ID	M15-654
ClinicalTrials.gov ID	NCT03314181
Type(s) de cancer	Myélome
Phase	Phase I-II
Stade	Maladie réfractaire
Type étude	Traitement
Médicament	Vénétoclax + Daratumumab + Dexaméthasone avec ou sans Bortézomib
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But étude	<p>This is a study of venetoclax, daratumumab, and dexamethasone with and without bortezomib combination therapy to evaluate safety, tolerability, and efficacy of these combinations in participants with relapsed or refractory multiple myeloma. The study will consist of 2 distinct parts: Part 1 includes participants with t(11;14) positive relapsed/refractory (R/R) multiple myeloma who will receive venetoclax in combination with daratumumab and dexamethasone (VenDd); Part 2 includes participants with R/R multiple myeloma who will receive venetoclax in combination with daratumumab, bortezomib, and dexamethasone (VenDBz). Each Part will be initiated with a dose-escalation phase. During the open-label, escalation phases, increasing doses of venetoclax with fixed doses of daratumumab and dexamethasone (Part 1a) or daratumumab, bortezomib, and dexamethasone (Part 2a) will be administered. The dose-escalation phases will be followed by either a randomized, and blinded (Part 1b) expansion phase or single-arm and open-label (Part 2b) expansion phase.</p>
Critères d'éligibilité	<ul style="list-style-type: none">• Subject ≥ 18 years of age.• Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.• Subject has relapsed or refractory multiple myeloma with documented evidence of progression that occurred during or after the subject's last treatment regimen based on investigator's determination of IMWG criteria.• Measurable disease confirmed by central lab at Screening, defined by at least 1 of the following:<ul style="list-style-type: none">• Serum M-protein ≥ 1.0 g/dL (≥ 10 g/L), OR• Urine M-protein ≥ 200 mg/24 hours, OR• Serum free light chain (FLC) ≥ 10 mg/dL, provided serum FLC ratio is abnormal in subjects who do not have measurable disease by SPEP or UPEP criteria.• Part 3: Subject must have received at least one prior line of therapy including an IMiD. For subjects in Part 3, prior treatment with bortezomib or other PIs is allowed provided ALL the following criteria are met:

- Disease is NOT refractory to any proteasome inhibitor, defined as no disease progression (i.e., PD, per IMWG criteria) while receiving proteasome inhibitor therapy or within 60 days after the last dose, AND
- Best response achieved with any proteasome inhibitor therapy (alone or in combination) was at least a partial response (PR), AND
- Subject did not discontinue bortezomib or ixazomib due to intolerance or \geq Grade 3 related toxicity.
- Bone marrow aspirate samples have been collected
 - To qualify for Parts 1 and 3, the subject must be t(11;14) positive as determined by an analytically validated FISH assay per central laboratory testing.
- Subjects must meet the following laboratory parameters, at least once during screening:
 - ANC \geq 1000/ μ L within 2 weeks prior to first dose of study treatment; subject may use growth factor support to achieve ANC eligibility criteria;
 - Platelets: \geq 75,000/mm³ for subject with \leq 50% myeloma involvement in the bone marrow; \geq 50,000/mm³ for subject with $>$ 50% myeloma involvement in the marrow (subject may not have received a platelet transfusion within 72 hours prior to the platelet count used for eligibility);
 - Hemoglobin \geq 8.0 g/dL within 2 weeks prior to first dose of study treatment; subject may receive red blood cell (RBC) transfusions in accordance with institutional guidelines to meet this criteria;
 - AST and ALT \leq 3 \times upper limit of normal (ULN);
 - Total bilirubin \leq 1.5 \times ULN (subjects with documented Gilbert's syndrome may have bilirubin $>$ 1.5 \times ULN);
 - Creatinine clearance \geq 30 mL/min, measured by 24-hour urine collection or calculated using the Cockcroft-Gault formula;
 - Serum calcium corrected for albumin \leq 14.0 mg/dL (\leq 3.5mmol/L).
- Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
- If female, subject must be either
- Postmenopausal defined as:
 - Age $>$ 55 years with no menses for 12 or more months without an alternative medical cause **OR**
 - Age \leq 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level $>$ 40 IU/L; **OR**
 - Permanently surgical sterile (bilateral tubal ligation at least 3 months before study participation, bilateral oophorectomy and/or hysterectomy); **OR**
 - Women of Childbearing Potential (WOCBP) practicing two protocol specified methods of birth control (Section 5.2.5), starting at Study Day 1 (or earlier) through at least 3 months after the last dose of daratumumab or 30 days after the last dose of venetoclax, whichever is longer.
- Females of childbearing potential must have a negative serum pregnancy test performed:
 - At Screening on a serum sample obtained within 28 days prior to first dose.
 - Prior to first dosing if study drug on a urine sample obtained on Day 1, if it has been $>$ 24 hours since obtaining the serum pregnancy test results.

Critères d'exclusion

1. Previous treatment with venetoclax or other BCL-2 inhibitor. 2. For Subjects in Part 3: Prior daratumumab or other anti-CD38 antibody therapy exposure that meets ANY of the following criteria:
 - Failure to achieve at least a PR to most recent therapy with daratumumab or other anti-CD38 therapy
 - Daratumumab or other anti-CD38 antibody therapy was discontinued due to toxicity
 - Relapse within 60 days of intensive treatment (at least every other week) of daratumumab or other anti-CD38 antibody therapy
 - Prior treatment with daratumumab or other anti-CD38 antibody within 6 months prior to first dose of study drug
3. For subjects in Parts 2 and 3:
 - Subject is refractory to any proteasome inhibitor, defined as progression on or within 60 days of the last dose of a proteasome inhibitor-containing regimen.
 - Subject has had prior treatment with proteasome inhibitor within 60 days prior to first dose of study drug.
4. Treatment with anti-myeloma chemotherapy, radiotherapy, biological, immunotherapy or an investigational therapy, including targeted small molecule agents within 2 weeks or 5 half-lives (whichever is longer and/or applicable) before first dose⁵. Treatment with anti-myeloma monoclonal antibodies within 6 weeks prior to first dose⁶. Recent corticosteroid therapy at a cumulative dose equivalent to \geq 140 mg of prednisone, cumulative dose equivalent to \geq 40 mg of dexamethasone, or a single dose equivalent to \geq 40 mg of dexamethasone within 2 weeks prior the first dose of study drug⁷. Subject has a hypersensitivity or allergy to any of the components of study therapy, excipient or boron.
8. Known allergies, hypersensitivities, or intolerance to monoclonal antibodies or human proteins, or their excipients, or known sensitivity to mammalian-derived products (see daratumumab prescribing information)⁹. Known central nervous system involvement of multiple myeloma
10. Significant history of renal, neurologic, psychiatric, endocrinologic (diabetes mellitus), metabolic, immunologic, cardiovascular, pulmonary or hepatic disease within the last 6 months that, in the Investigator's opinion,

would adversely affect the subject's participation. 1. Any of the following conditions:

- Non-secretory multiple myeloma;
- Active plasma cell leukemia i.e., either 20% of peripheral white blood cells or $> 2.0 \times 10^9$ /L circulating plasma cells by standard differential; ? Waldenström's macroglobulinemia;
- Primary amyloidosis;
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes);
- Known chronic obstructive pulmonary disease (COPD) with forced expiratory volume in 1 second (FEV1) $< 50\%$ of predicted normal;
- Acute diffuse infiltrative pneumopathy;
- Known moderate or persistent chronic asthma within the last 2 years, or uncontrolled asthma of any classification. (Note: subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate.);
- Active hepatitis B (HBsAg positive) infection based on screening blood testing;

o Subjects with resolved infection (HBsAg negative, but antiHBc or antiHBs positive) must be screened using real-time PCR of HBV DNA. Those with positive PCR will be excluded. o Exception: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR

- Active hepatitis C infection based on screening blood testing; o Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
- Known human immunodeficiency virus (HIV) infection;
- Major surgery within 4 weeks prior first dose or planned during study participation;
- Acute infections requiring antibiotics, antifungal, or antiviral therapy within 28 days prior first dose;
- Active viral infections (including viral hepatitis, herpes, chicken pox, shingles);
- Significant cardiovascular or pericardial disease, including uncontrolled angina, arrhythmia, recent myocardial infarction within 6 months of first dose, congestive heart failure NYHA Class ≥ 3 ;
- Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) > 470 msec. (For subjects in Parts 1 and 2 only);
- Uncontrolled diabetes or hypertension within 14 days prior first dose;
- Peripheral neuropathy \geq Grade 3 or \geq Grade 2 with pain within 2 weeks prior to first dose;
- Known active SARS-CoV-2 infection.

o Subjects with signs/symptoms suggestive of SARS-CoV-2 infection should undergo molecular (e.g., PCR) testing to rule out SARS-CoV-2 infection. If applicable, a negative test result is required prior to enrollment. b Subjects with confirmed SARS-CoV-2 infection must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria and do not have any other COVID-19 related medical condition that, in the opinion of the Investigator, would impact the risk/benefit ratio of the subject's participation in the study:

- At least 14 days since first PCR test result have passed in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- Any other medical condition that, in the opinion of the Investigator, would adversely affect the subject's participation in the study.

12. History of other active malignancies including myelodysplastic syndromes (MDS) within the past 3 years with the following exceptions:

- Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
- Prostate cancer Gleason grade 6 or lower AND with stable Prostate Specific Antigen (PSA) levels off treatment;
- Previous malignancy with no evidence of disease confined and surgically resected (or treated with other modalities) with curative intent and unlikely to impact survival during the duration of the study.

13. Previous allogenic SCT 14. Autologous SCT within 12 weeks prior to first dose 15. Immunization with live vaccine within 8 weeks prior to first dose 16. Consumption of grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days prior to first dose.

17. Use of a strong or moderate CYP3A inhibitor or inducer within 1 week prior to first dose 18. Anticipated use of excluded medications or foods during study participation 19. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study and for approximately 90 days after the last dose of study drug.