A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor.

The APOLLO Study

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4.2 ENDPOINTS

4.2.1 Primary Endpoint

- Progression free survival

4.2.2 Secondary Endpoints

- Overall response rate
- VGPR or better
- Complete response (CR) or better
- MRD negativity rate
- Time to response
- Duration of response (DoR)
- Time to next therapy
- Overall survival
- Safety (adverse events)
- Scale and domain scores of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) (global health status, physical functioning, emotional functioning, fatigue, pain) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20) (disease symptoms, side effects of treatment)
- European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) health utility values
- Immunomodulatory effects of daratumumab on T cells
- Daratumumab pharmacokinetic concentrations (Dara IV and Dara SC)
- Daratumumab and rHuPH20 immunogenicity in subjects who receive Dara SC

5 STUDY ENROLLMENT AND WITHDRAWAL

All criteria MUST be met to be included in the study.

5.1 SUBJECT INCLUSION CRITERIA

1. Males and females at least 18 years of age.
2. Voluntary written informed consent before performance of any study-related procedure.
3. Subject must have measurable disease of MM as defined by the criteria below:

    - IgG multiple myeloma: Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours, or
    - IgA, IgD, IgE, IgM multiple myeloma: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
    - Light chain multiple myeloma, for subjects without measurable disease in the serum or urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

4. Subjects must have received prior anti-myeloma treatment. The prior treatment must have included both a PI- and lenalidomide-containing regimens. The subject must have had a response (ie, PR or better based on the investigator's determination of response as defined by the modified IMWG criteria) to prior therapy.
5. Subjects must have documented evidence of PD based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen.
6. Subjects who received only 1 line of prior treatment must have demonstrated PD on or within 60 days of completion of the lenalidomide-containing regimen (ie, lenalidomide refractory).
7. Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
8. Willingness and ability to participate in study procedures.
9. For subjects experiencing toxicities resulting from previous therapy, the toxicities must be resolved or stabilized to ≤Grade 1.
10. All of the following laboratory test results during Screening:

a) Absolute neutrophil count ≥1.0 × 10^9/L;
b) Hemoglobin level ≥7.5 g/dL (≥4.65 mmol/L) (transfusions are not permitted to reach this level);
c) Platelet count ≥75 × 10^9/L in subjects in whom <50% of bone marrow nucleated cells are plasma cells and platelet count ≥50 x 10^9/L in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells (transfusions are not permitted to reach this level);
d) Alanine aminotransferase (ALT) level ≤2.5 times the upper limit of normal (ULN);
e) Aspartate aminotransferase (AST) level ≤2.5 x ULN;
f) Total bilirubin level ≤1.5 x ULN, (except for Gilbert Syndrome: direct bilirubin ≤1.5 × ULN);
g) Creatinine clearance ≥30 mL/min (Appendix 6);
h) Serum calcium corrected for albumin ≤14.0 mg/dL (≤3.5 mmol/L), or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

11. Criterion (letter "g") modified per Amendment 2:

11.1 Reproductive Status

a) Women of childbearing potential (WOCBP) must have 2 negative serum or urine pregnancy tests, one 10-14 days prior to start of study treatment and one within 24 hours prior to the start of study treatment. Females are not of reproductive potential if they have been in natural menopause for at least 24 consecutive months, or have had a hysterectomy and/or bilateral oophorectomy.
b) Women must not be breastfeeding.
c) WOCBP must agree to follow instructions for methods of contraception for 4 weeks before the start of study treatment, for the duration of study treatment, and for 3 months after cessation of daratumumab or 4 weeks after cessation of pomalidomide, whichever is longer.
d) Males who are sexually active must always use a latex or synthetic condom during any sexual contact with females of reproductive potential, even if they have undergone a successful vasectomy. They must also agree to follow instructions for methods of contraception for 4 weeks before the start of study treatment, for the duration of study treatment, and for a total of 3 months post-treatment completion.
e) Male subjects must not donate sperm for up to 90 days post-treatment completion.
f) Female subject must not donate eggs for up to 90 days post-treatment completion.
g) Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However, WOCBP will still undergo pregnancy testing as described in this section.

Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly. Subjects must agree to the use of 2 methods of contraception, with 1 method being highly effective and the other method being additionally effective.

Because of the embryo-fetal risk of pomalidomide, all subjects must adhere to the pomalidomide pregnancy prevention program applicable in their region. Investigators should comply with the local label for pomalidomide for guidance on subject education and ensure that all subjects adhere to the local Pomalidomide Risk Evaluation Mitigation Strategy (REMS) program. When no local pomalidomide REMS program exists, subjects must adhere to the pomalidomide Global Pregnancy Prevention Plan.

5.2 SUBJECT EXCLUSION CRITERIA

1. Previous therapy with any anti-CD38 monoclonal antibody.
2. Previous exposure to pomalidomide.
3. Subject has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) for palliative treatment before Cycle 1, Day 1 (C1D1).
4. Previous allogenic stem cell transplant; or autologous stem cell transplantation (ASCT) within 12 weeks before C1D1.
5. History of malignancy (other than MM) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).
6. Clinical signs of meningeal involvement of MM.
7. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal. (Appendix 4).
8. Clinically significant cardiac disease, including:
   a) Myocardial infarction within 6 months before C1D1, or unstable or uncontrolled condition (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).
   b) Cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher) or clinically significant electrocardiogram (ECG) abnormalities.
   c) Electrocardiogram showing a baseline QT interval as corrected QTc >470 msec.
9. Criterion modified per Amendment 2:
   9.1 Known:
   a) Active hepatitis A
   b) To be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. 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.
   c) To be seropositive for hepatitis C (except in the setting of a sustained virologic response, defined as aviremia at least 12 weeks after completion of antiviral therapy).

10. Criterion Revised per Amendment 2
    10.1 Known to be seropositive for human immunodeficiency virus.
11. Gastrointestinal disease that may significantly alter the absorption of pomalidomide.
12. Subject has plasma cell leukemia (>2.0 × 10^9/L circulating plasma cells by standard differential) or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.
13. Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results or that, in the opinion of the investigator, would constitute a hazard for participating in this study.
14. Ongoing ≥Grade 2 peripheral neuropathy.
15. Subject had ≥Grade 3 rash during prior therapy.
16. Subject has had major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.
17. Pregnant or nursing women.
18. Subject has known allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, monoclonal antibodies, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products.
19. Subject was vaccinated with live vaccines within 4 weeks prior to randomization.

Sponsor will review and approve (through eCRF) the subject eligibility data submitted by the investigational site before randomization.

5.3 SUBJECT WITHDRAWAL OR TERMINATION

5.3.1 REASONS FOR WITHDRAWAL OR TERMINATION

Every subject has the right to discontinue study participation at any time, for any reason, and every subject may be discontinued from the study for any reason beneficial to his/her well-being.

Subjects MUST discontinue investigational product(s) for any of the following reasons:

- Withdrawal of informed consent.
- Any AE, laboratory abnormality or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy.
- Progressive disease.
- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis related to pomalidomide.
- Grade 4 IRRs to daratumumab (see *Section 6.1.5*).
- When the study ends/is terminated.

For subject whose daratumumab treatment is discontinued, they may continue to receive pomalidomide/dexamethasone. For subjects whose pomalidomide/dexamethasone treatment is discontinued, daratumumab treatment may be continued.