SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-54767414 Daratumumab

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Status: Approved

Date: 21 May 2018

Prepared by: Janssen Research & Development, LLC

Protocol No.: 54767414MMY1003

Title of Study: A Phase 1, Open-label, Dose Escalation Study of JNJ-54767414 (Daratumumab) in Chinese Subjects With Relapsed or Refractory Multiple Myeloma Who Failed at Least 2 Prior Lines of Systemic Therapy

NCT No.: NCT02852837

Clinical Registry No.: CR108180

Principal Investigator(s): Lugui Qiu, MD; Junyuan Qi, MD - PPD China; Hongmei Jing, MD; Li Yang, MS - PPD China; Jie Jin, MD - PPD

Study Center(s): 3 sites in China.

Publication (Reference): None

Study Period: 20 October 2016 (Date first subject signed informed consent) to 22 December 2017 (Data cutoff date, study is ongoing; Date of last observation for last subject recorded as part of the database for primary analysis)

Phase of Development: Phase 1

Objectives:

The primary objective of Part 1 and Part 2 was:

- To evaluate the tolerability, safety and the PK profile of daratumumab in Chinese subjects with relapsed or refractory multiple myeloma (MM) who failed at least 2 prior lines of systemic therapy

Secondary Objectives

The secondary objectives of Part 1 and Part 2 were:

- To evaluate the immunogenicity of daratumumab
- To evaluate preliminary clinical outcomes

Exploratory Objective

The exploratory objective of Part 1 and Part 2 was:

- To explore the pharmacokinetics (PK)/pharmacodynamics relationship of daratumumab

Methodology: This was an open-label, non-randomized, phase 1 study to evaluate the tolerability, safety and PK of daratumumab in Chinese subjects with relapsed or refractory MM who failed at least 2 prior lines of systemic therapy in Part 1 and Part 2, and tolerability and safety of daratumumab in Chinese subjects whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) and who have demonstrated disease progression on the last therapy in Part 3. The study consisted of 3 parts: a dose escalation part (Part 1), a PK expansion part (Part 2), and a safety expansion part (Part 3).

In Part 1, 8 mg/kg was chosen as the starting dose, followed by dose escalation to 16 mg/kg if 8 mg/kg was determined safe and tolerated. No further dose beyond 16 mg/kg was to be studied. The study was to enter Part 2 if 16 mg/kg was determined safe and tolerated in Part 1.

No interim analysis was planned for the study. The first (primary) data cutoff was to be for the primary analysis, which was estimated to be performed after approximately 20 subjects had received at least 3 months of follow-up, or alternative appropriate cutoffs were to be considered if needed. Primary efficacy, safety, and PK data, were to be summarized and the results were to be reported in a Clinical Study Report and submitted to the health authority. In addition, a PK data cutoff was to be performed for PK analysis, which was estimated to be approximately 8 cycles (5 months) after the last subject in Part 2 received the first dose of daratumumab.

Number of Subjects (planned and analyzed): An approximately total of 20 subjects with relapsed or refractory MM who failed at least 2 prior lines of systemic therapy were planned to be enrolled in Part 1 and Part 2 to meet the requirement of China Food and Drug Administration. Twenty-two (22) subjects were treated with daratumumab in this study; 3 subjects were treated with 8 mg/kg and 19 subjects were treated with 16 mg/kg.

Diagnosis and Main Criteria for Inclusion: In Part 1 and Part 2, Chinese subjects who were ≥20 years of age with documented relapsed or refractory MM, and had previously received at least 2 prior lines of therapy, were enrolled.**Error! Reference source not found.**

Test Product, Dose and Mode of Administration, Batch No.: Daratumumab drug product was supplied as a colorless to yellow liquid at a concentration of 20 mg/mL in glass vials for intravenous (IV) administration (Batch numbers: FDS6U, GHS61). Daratumumab was administered in 2 doses (8 mg/kg and 16 mg/kg).

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: In Part 1 and Part 2, subjects were to be treated with daratumumab until disease progression, intolerability, or any other reasons for treatment discontinuation. The Follow-up Phase was to begin once a subject discontinued the study drug, and was to continue until death, lost to follow-up, consent withdrawal for study participation, or study end (defined as 30 days after the last subject discontinues study treatment or when there is commercial availability of daratumumab in China if subjects are still receiving daratumumab treatment), whichever occurred first.

Criteria for Evaluation: Subject response and disease progression were evaluated based on computerized algorithm following the International Myeloma Working Group (IMWG) response criteria. Disease evaluations included measurements of myeloma proteins, bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin, and β2-microglobulin and albumin. Survival status and subsequent anticancer treatment data were also collected.

Serum samples were obtained from all subjects in Part 1 and Part 2 for evaluation of drug exposure of daratumumab and generation of anti-daratumumab antibodies.

Safety evaluations included dose-limiting toxicity evaluation, adverse events (AEs) monitoring, clinical laboratory tests, electrocardiograms (ECGs), vital sign measurements, physical examinations, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status.

Statistical Methods: Efficacy analyses (overall response rate [ORR], time to response, duration of response, progression-free survival [PFS], overall survival [OS]) were performed based on the evaluation of response and disease progression using a validated computerized algorithm following the modified IMWG consensus recommendations for MM treatment response criteria. The safety profiles of daratumumab were evaluated by the incidence of AEs, deaths, laboratory results, vital signs, physical examination findings, ECG results, and ECOG status scores. The severity of AEs and the toxicity of laboratory parameters were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. AEs were coded using the latest version of Medical Dictionary for Regulatory Activities. Descriptive statistics was used to summarize daratumumab serum concentrations at each sampling time point and PK parameters of daratumumab.

RESULTS:

STUDY POPULATION:

Of the 22 treated subjects, 3 subjects received 8 mg/kg and 19 subjects received 16mg/kg. It is noteworthy that, all the 3 subjects in the 8 mg/kg group had their doses escalated into 16 mg/kg after 8 mg/kg and 16 mg/kg were determined safe by SET as no DLT were observed on both dose levels. The results from all the 3 subjects in the 8 mg/kg group who crossed over to receive 16 mg/kg daratumumab were included in their original 8 mg/kg group for all analyses and not included in the 16 mg/kg group. Nine (40.9%) subjects discontinued the study treatment. For the 16 mg/kg group, 7 (36.8%) of 19 subjects discontinued the study treatment. The most common reason for study treatment discontinuation was progressive disease (3 [15.8%] subjects), followed by physician decision (2 [10.5%] subjects). For the 8 mg/kg group, 2 (66.7%) subjects discontinued the study treatment due to progressive disease.

Half (50.0%) of the all treated subjects were male. The median age was 60.5 years (range: 35 to 80 years). For the 16 mg/kg group, the median age was 58.0 years (range: 35 to 80 years); 52.6% of subjects were female. More than half (63.2%) of subjects had a baseline ECOG performance score of 0, 6 (31.6%) subjects had a baseline ECOG performance status score of 1, and one (5.3%) subject had a baseline ECOG performance score of 2. For the all treated subjects, the most common type of myeloma was immunoglobulin G (IgG; 13 [59.1%] subjects), followed by immunoglobulin A (4 [18.2%] subjects). The median time since the initial diagnosis of MM was 3.53 years (range: 0.5 to 10.1 years). For the 16 mg/kg group, the majority of subjects had IgG myeloma (13 [68.4%] subjects). The median time since the initial diagnosis of MM was 3.50 years (range: 0.5 to 10.1 years). More than half (10 [51.6%] subjects) of the subjects had measurable disease in serum only. In the 16 mg/kg group, amplification 1q21 was reported in 13 (68.4%) subjects, and deletion 13q was reported was reported in 6 (31.6%) subjects. High risk cytogenetic abnormality was only observed in 1 subject with deletion 17p in the 8 mg/kg group.

For the 16 mg/kg group, the median number of prior lines of MM therapy was 4.0 (range: 2 to 9); 73.7% of subjects had ≥3 prior lines of therapy. Eighteen (94.7%) subjects received both prior PI and IMiD. Eighteen (94.7%) subjects received a prior PI: all of them received prior bortezomib and 1 (5.3%) subject received prior ixazomib. Nineteen (100%) subjects received a prior IMiD: 17 (89.5%) subjects received prior lenalidomide and 13 (68.4%) subjects received prior thalidomide. For the 8 mg/kg group, all the 3 (100%) subjects received both prior PI and IMiD.

For the 16 mg/kg group, the median duration of treatment is 5.09 months (range: 0 to 9.7 months). The median number of treatment cycles received was 7.0 (range: 1 to 12); 9 (47.4%) subjects received at least 8 cycles of daratumumab treatment. For the 8 mg/kg group, the median duration of treatment is

11.30 months (range: 5.8 to 12.2 months). The median number of treatment cycles received was 14.0 (range: 8 to 15). The median relative dose intensity was 99.94% in the 16 mg/kg group and 99.30% in the 8 mg/kg group.

EFFICACY RESULTS:

For the 16 mg/kg group, the ORR was 42.1% (8 of 19 subjects; 95% confidence interval [CI]: 20.3%, 66.5%), with 3 (15.8%) subjects achieving very good partial response and 5 (26.3%) subjects achieving partial response. The median time to first response was 1.4 months (range: 0.7 to 1.9 months). The median time to best response was 1.6 months (range: 1.4 to 3.5 months). With a median follow-up of 6.7 months, the median duration of response was not reached; the median PFS was not reached and the estimated 6-month PFS rate was 64.8% (95% CI: 34.0%, 84.0%); the median OS was not reached and the estimated 6-month survival rate was 86.1% (95% CI: 53.3%, 96.5%). The ORR, time to response, duration of response, PFS, and OS results in the 16 mg/kg group from the relapsed and refractory MM population are consistent with those from the all treated population.**Error! Reference source not found.**

PHARMACOKINETIC RESULTS:

Daratumumab exposure increased with increasing dose. Daratumumab elimination showed decreasing clearance following multiple doses in both dose groups. Following the 16 mg/kg dose regimen, accumulation of daratumumab continued throughout the weekly dosing, and decreased slightly as subjects entered the biweekly dosing period and the subsequent once every 4 weeks dosing period.

SAFETY RESULTS:

- All but 1 subject had at least one treatment-emergent AE (TEAE; 95.5%). Half of the subjects (50%) experienced Grade 3 or 4 TEAEs. Serious TEAEs were reported in 7 (31.8%) subjects. The most frequently reported TEAEs were leukopenia (16 [72.7%] subjects), neutropenia (14 [63.6%] subjects), anemia (12 [54.5%] subjects), lymphopenia (8 [36.4%] subjects), hypokalemia, upper respiratory tract infection (both for 7 [31.8%] subjects), hypercalcemia, alanine aminotransferase increased, aspartate aminotransferase increased, thrombocytopenia (6 [27.3%] subjects for each), hypoalbuminemia, and pyrexia (both for 5 [22.7%] subjects). The most frequently reported Grade 3 or 4 TEAEs for all treated subjects were leukopenia (5 [22.7%] subjects), anemia, thrombocytopenia (both for 4 [18.2%] subjects), neutropenia, hypercalcemia, and lung infection (3 [13.6%] subjects for each).
- Seven (31.8%) subjects had serious TEAEs (6 [31.6%] in the 16 mg/kg group and 1 [33.3%] subject in the 8 mg/kg group). The most frequently reported serious TEAE in the 16 mg/kg group was thrombocytopenia (2 [10.5%] subjects); other serious TEAEs were all single occurrences. One (33.3%) subject in the 8 mg/kg group had a serious Grade 4 lung infection.
- No deaths due to TEAEs were reported in the study. Two (9.1%) subjects in the 16 mg/kg group died due to progressive disease. No TEAEs leading to treatment discontinuation were reported in the study.
- Seven (31.8%) subjects had treatment-emergent infusion-related reactions (IRRs; 6 [31.6%] subjects in the 16 mg/kg group and 1 [33.3%] subject in the 8 mg/kg group). Most of the IRRs occurred during the first infusion. All IRRs were Grade 1 or 2 in severity. None of the IRRs were considered serious.
- Eleven (50.0%) subjects experienced TEAEs of infections and infestations (10 [52.6%] subjects in the 16 mg/kg group and 1 [33.3%] subject in the 8 mg/kg group). The most frequent reported TEAEs of infections and infestations were upper respiratory tract infection (7 [31.8%] subjects) and lung

infection (4 [18.2%] subjects). Grade 3 or 4 TEAEs of infections and infestations were reported for 3 (15.8%) subjects in the 16 mg/kg group and 1 (33.3%) subject in the 8 mg/kg group.

- No dose-limiting toxicities (DLTs) were observed in either dose level during the study.
- Three (13.6%) subjects (all in the 16 mg/kg group) had a total of 11 transfusions during treatment: 2 (9.1%) subjects had 9 packed red blood cell transfusions. No transfusion-related reactions were reported during the study.
- No additional safety signal was identified from the analyses of hematology and biochemistry laboratory data, vital signs, ECG findings, and ECOG status scores.
- Daratumumab administered as an IV infusion at the dose levels of 8 mg/kg and 16 mg/kg was well tolerated with a favorable safety profile in Chinese subjects with relapsed or refractory MM who failed at least 2 prior lines of systemic therapy. The safety profile demonstrated in this study is consistent with the known safety profile of single agent daratumumab.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): Daratumumab was well-tolerated in Chinese subjects at both 8 mg/kg and 16 mg/kg dose levels and did not result in any new safety signals. PK characteristics of daratumumab observed in Chinese subjects behaved as expected. The administration of single-agent daratumumab demonstrated compelling clinical activity, with an ORR of 42.1% in the 16 mg/kg group. Collectively, the data demonstrates a favorable benefit/risk profile of single agent daratumumab for the treatment of Chinese subjects with relapsed or refractory MM who failed at least 2 prior lines of systemic therapy, as well as the Chinese subjects whose prior therapy included a PI and an IMiD and who had demonstrated disease progression on the last therapy.

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