SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.*
Name of Investigational Product	JNJ-54767414 (Daratumumab)

* This study was conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the report to represent Janssen Pharmaceutical K.K.

Status: Approved

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Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: 54767414MMY1005

Title of Study: A Phase 1b Study of JNJ-54767414 (Daratumumab) in Combination With Bortezomib and Dexamethasone (D-Vd) in Japanese Patients With Relapsed or Refractory Multiple Myeloma (MM)

NCT No.: NCT02497378

Clinical Registry No.: CR107666

Principal Investigator: Shinsuke Iida, MD, PhD, [redacted], Japan

Study Centers: 5 sites in Japan

Publication (Reference): Iida S, Ichinohe T, Shinagawa A, et al. Safety and efficacy of daratumumab in combination with bortezomib and dexamethasone in Japanese patients with relapsed or refractory multiple myeloma. Int J Hematol. 2018 Apr;107(4):460-467.

Study Period: 05 August 2015 (Date of first subject signed informed consent) to 06 March 2018 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 1b

Objectives:

Primary Objective

The primary objective of this study was to evaluate the tolerability and safety of daratumumab combined with bortezomib and dexamethasone (D-Vd) in Japanese subjects with relapsed or refractory multiple myeloma (MM).

Secondary Objectives

The secondary objectives of this study were:

- To assess the pharmacokinetics (PK) of daratumumab in combination with bortezomib and dexamethasone.
- To assess the immunogenicity of daratumumab.
- To evaluate the overall response rate (ORR).
- To evaluate the proportion of subjects with a response of complete response (CR) or better.
- To evaluate the proportion of subjects with a response of very good partial response (VGPR) or better.

- To evaluate the time to response.

Exploratory Objectives

The exploratory objectives of this study were:

- To explore biomarkers predictive of response to daratumumab.
- To evaluate the duration of response (DOR).

Methodology:

This was an open-label, nonrandomized, multicenter, Phase 1b study to evaluate the safety and tolerability of D-Vd in Japanese subjects with relapsed or refractory MM. A minimum of 6 subjects were planned to be enrolled in this study.

The study included a screening phase, a treatment phase, and a follow-up phase. Study phases and critical study events are described below.

Screening Phase

The screening phase was up to 21 days prior to Cycle 1 Day 1. Screening procedures were to be performed within 21 days before Cycle 1 Day 1, except for disease evaluations, laboratory tests, and pregnancy tests. Serum and urine tests were to be performed within 14 days before Cycle 1 Day 1. Results from skeletal survey and radiologic plasmacytoma assessments performed as a routine follow-up for subject's disease within 42 days before Cycle 1 Day 1 and bone marrow aspirate/biopsy within a maximum of 42 days before Cycle 1 Day 1 could be used without these tests being repeated. During screening, a urine or serum pregnancy test had to be performed within 7 days prior to Cycle 1 Day 1. If approved by the sponsor, subjects who were screen failures could be rescreened if their condition changed.

Treatment Phase

The treatment phase started on Cycle 1 Day 1 by administration of any component of the study treatment (ie, daratumumab, bortezomib, or dexamethasone) and extended until study treatment discontinuation.

Cycles 1 through 8 were 21-day cycles. Cycle 9 and onwards were 28-day cycles. The dose-limiting toxicity (DLT) evaluation period began with the first administration of daratumumab and ended at the end of Cycle 1 (including the safety evaluation before daratumumab infusion on Cycle 2 Day 1).

Daratumumab was administered at a dose of 16 mg/kg intravenous (i.v.) infusion weekly for the first 3 cycles, on Day 1 of Cycles 4 to 8, and then on Day 1 of every 4 weeks thereafter. Each subject's dose was calculated based on the subject's weight rounded to the nearest kilogram. Recalculation of daratumumab dose was not required for weight changes <10% from baseline. For all daratumumab infusions, subjects received preinfusion and postinfusion medications (as needed) to reduce the risk of infusion-related reactions (IRRs). Treatment with daratumumab was to be continued until disease progression, unacceptable toxicity, or other study treatment discontinuation criteria.

Bortezomib was administered at a dose of 1.3 mg/m^2 subcutaneously (SC) on Days 1, 4, 8, and 11 of Cycles 1 through 8. For subjects who experienced injection site reactions, bortezomib was administered by i.v. infusion.

Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of the first 8 bortezomib treatment cycles. Additionally, in Cycles 1 to 3, a 20-mg dose of dexamethasone was administered as a preinfusion medication on Day 15. During weeks when the subject received an infusion of daratumumab, dexamethasone was administered at a dose of 20 mg i.v. or orally (only if i.v. was not available) before daratumumab infusion as a preinfusion medication.

Subjects were hospitalized from Cycle 1 Day 1 to Cycle 1 Day 8, to allow close clinical monitoring for adverse events (AEs), laboratory abnormalities, and clinical response in the treatment phase. Clinical evaluations and laboratory assessments could be repeated more frequently, if clinically indicated. If disease progression was confirmed, the study treatment was discontinued. The end-of-treatment (EOT) visit was completed for such a subject, after which the subject entered the follow-up phase.

The EOT visit occurred 4 weeks (±3 days) after the last dose of study treatment, or as soon as possible before the start of subsequent therapy, unless the subject withdrew consent for study participation or was lost to follow-up. Every effort was made to conduct the EOT visit before the subject started subsequent treatment. If a subject was unable to return for the EOT visit, he/she was contacted to collect information on AEs that occurred up to 30 days after the last dose of study treatment.

After daratumumab was approved by the Ministry of Health, Labour and Welfare (MHLW) on 27 Sep 2017, the market products of daratumumab were delivered to the study site. The subjects visited the study site at the next dosing timing and all applicable procedures scheduled for the EOT visit were performed. Daratumumab was switched from the study agent to market products. Daratumumab was available to continue the postmarketing study after getting approval until market products were delivered to the study site and the terms ‘clinical study’ and ‘study’ were interpreted as the ‘postmarketing study’ (hereinafter the same applies).

Follow-up Phase

The follow-up phase began immediately following the EOT visit and was to continue until 8 weeks after the last dose of study treatment, death, lost to follow-up, subject withdrawal of consent, or study end, whichever occurred first. Samples for PK evaluations and immunogenicity assessments were collected during the follow-up phase.

Number of Subjects (Planned and Analyzed):

Subjects	Vd+Daratumumab (16 mg/kg)
Planned	Minimum 6 subjects and maximum 20 subjects
Enrolled	8
Treated	8 (100.0%)
Included for efficacy analyses (response-evaluable analysis set)	8 (100.0%)
Included for safety analyses (all-treated analysis set)	8 (100.0%)
Included for pharmacokinetic analyses (pharmacokinetic analysis set)	8 (100.0%)
Included for immunogenicity assessment (immunogenicity analysis set)	8 (100.0%)
Included for DLT assessment (DLT evaluable set)	8 (100.0%)

Keys: DLT=dose-limiting toxicity; Vd=bortezomib and dexamethasone

Diagnosis and Main Criteria for Inclusion:

Japanese men and nonpregnant women, ≥20 years of age with symptomatic MM (International Myeloma Working Group [IMWG] diagnostic criteria), who had received at least 1 prior line of therapy for MM, and had documented evidence of progressive disease (PD) based on investigator’s determination of response by the IMWG criteria on or after their last regimen were included in the study. Subjects were required to have measurable disease defined by serum or urine M-proteins or serum free-light chains (FLCs).

Test Product, Dose and Mode of Administration, Batch No.:

Daratumumab was supplied as a colorless to yellow sterile liquid concentrate of 20 mg/mL in a vial (Batch Numbers: EJS4F and FFS2F for clinical study and FLS2V for postmarketing clinical study). Daratumumab was diluted in a sterile, pyrogen-free, physiologic saline solution (0.9% NaCl) prior to i.v. administration.

Bortezomib was administered at a dose of 1.3 mg/m^2 SC by the treating physician. For subjects who experienced injection site reactions, bortezomib was administered by i.v. infusion.

Dexamethasone 20 mg was given as single dose vials and/or tablets for oral dosing or as prescribed by the treating physician. For subjects who were >75 years of age, who were underweight (body mass index of <18.5 kg/m^2), had poorly controlled diabetes mellitus, or had prior intolerance/AE to steroid therapy, dexamethasone was administered at a dose of 20 mg weekly (on Days 1 and 8 [additionally, on Day 15 in Cycles 1-3]).

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

Duration of Treatment:

The treatment phase started on Cycle 1 Day 1 by administration of any component of the study treatment (ie, daratumumab, bortezomib, or dexamethasone) and extended until study treatment discontinuation. Cycles 1 through 8 were 21-day cycles. Cycle 9 and onwards were 28-day cycles.

Daratumumab was administered at a dose of 16 mg/kg by i.v. infusion weekly for the first 3 cycles, on Day 1 of Cycles 4 to 8, and then on Day 1 of every 4 weeks thereafter. Bortezomib was administered at a dose of 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of Cycles 1 through 8. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of the first 8 bortezomib treatment cycles. Additionally, in Cycles 1 to 3, 20-mg dose of dexamethasone was administered as a preinfusion medication on Day 15.

Criteria for Evaluation:

Pharmacokinetics

The PK parameters summarized for serum daratumumab were minimum observed serum concentration (C_{min}) and maximum observed serum concentration (C_{max}). Blood samples to assess the PK of daratumumab were obtained on Day 1 of Cycles 1, 3, 6, 9, and 12, at EOT visit, and at follow-up visit (posttreatment Week 8).

Immunogenicity

Anti-daratumumab antibodies were assessed predose on Cycle 1 Day 1, at EOT visit, and at follow-up visit.

Biomarkers

Assessments for biomarkers (natural killer [NK], T cells, and B cells) were performed. Blood samples for biomarker evaluations were collected at Cycles 1, 2, 3, 8, and EOT visit.

Efficacy

Efficacy was not the primary objective of the study. However, efficacy endpoints included ORR and time to response (defined as the time from the first dose of daratumumab to the first efficacy evaluation that the subject had met all criteria for partial response [PR] or better). Other efficacy endpoints included DOR, time to disease progression, progression-free survival (PFS), overall survival (OS), and serum and urine M-protein response. Efficacy assessments included response to treatment in accordance with the

IMWG criteria. The proportion of subjects with response to treatment (stringent complete response [sCR], CR, VGPR, and PR) and clinical benefit (overall response+minimal response [MR]) were summarized.

Safety Evaluations

Safety evaluations were based on the incidence of treatment-emergent AEs (TEAEs), clinical laboratory results, vital signs, physical examination findings, electrocardiograms (ECGs), and Eastern Cooperative Oncology Group (ECOG) performance status score.

Dose-limiting Toxicity

DLT criteria were based on daratumumab-related AEs and were defined as any of the following events occurring in the DLT-evaluation period: IRRs and hematologic and nonhematologic toxicities.

Statistical Methods:

Analysis Sets

- All-treated Analysis Set: All subjects who received at least 1 dose of daratumumab. This population was used for all safety analyses as the safety population and for efficacy analyses unless otherwise stated.
- Response-evaluable Analysis Set: All subjects who received at least 1 dose of daratumumab and had a disease assessment during the treatment phase to allow for comparison to the baseline assessment.
- Pharmacokinetic Analysis Set: All subjects who received at least 1 dose of daratumumab and had at least 1 daratumumab concentration data after administration.
- Immunogenicity Analysis Set: All subjects who received at least 1 dose of daratumumab and had at least 1 daratumumab immunogenicity data after administration.
- Dose-limiting Toxicity Evaluable Set: All subjects in the all-treated analysis set who did not meet the subject replacement rule for dose-escalation decision.

Planned Analyses

Pharmacokinetics

Descriptive statistics were used to summarize serum daratumumab concentrations at each sampling time point.

Immunogenicity

The incidence of anti-daratumumab antibodies was summarized for all subjects who received a dose of daratumumab and had appropriate samples for detection of anti-daratumumab antibodies.

Biomarkers

The counts of CD3+CD4+, CD3+CD8+, CD3-CD16+CD56+, and CD19+ were summarized by visit.

Efficacy

Overall response rate, time to response, and other efficacy endpoints (DOR, time to disease progression, PFS, OS, and serum and urine M-protein responses) were summarized. The response-evaluable analysis set was used for all response-related analyses.

Safety

Safety analyses included the descriptive statistics and frequency tabulations of all reported TEAEs, deaths, serious TEAEs, other significant AEs (TEAEs leading to treatment discontinuation, TEAEs leading to

dose delay, TEAEs leading to dose reduction, and TEAEs leading to infusion interruption), and AEs of special interest (IRRs, cytopenic AEs, infections and infestations, tumor lysis syndrome, and second primary malignancies). Adverse events were graded for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Laboratory data were summarized as shift tables and time series plots for creatinine, hemoglobin, platelets, white blood cells (WBC), neutrophils, and lymphocytes. Lists of abnormal laboratory observations were presented. The effect of daratumumab on ECG was evaluated by means of descriptive statistics and frequency tabulation. All other safety data (vital signs and physical examination) were presented in listings or tables.

RESULTS:

STUDY POPULATION:

The study was conducted at 5 study sites in Japan. On receiving marketing approval of daratumumab, the clinical study was considered as a postmarketing study and delivery of market products to the study sites marked the completion of postmarketing study.

Eight subjects were enrolled in the study and received at least 1 dose of daratumumab. Six subjects (75.0%) completed the study, while 2 subjects (25.0%) were withdrawn from the study due to disease progression after the response. All 8 subjects (100.0%) discontinued the study treatment. The most common reason for discontinuation of study treatment was the completion of postmarketing study (5 subjects [62.5%]). Two subjects (25.0%) discontinued the study treatment due to AEs and 1 subject (12.5%) discontinued the study treatment due to disease progression after the response.

Demographics

Six subjects (75.0%) were men and 2 subjects (25.0%) were women. The median age of the subjects was 74.5 years (range, 54-82 years), with 4 subjects (50.0%) ≥75 years of age. The mean (SD) weight was 57.40 (10.281) kg and mean (SD) BSA was 1.583 (0.1859) m^2.

Six subjects (75.0%) had an ECOG performance status score of 0 and 2 subjects (25.0%) had an ECOG performance status score of 1.

Baseline Disease Characteristics

Four subjects (50.0%) had immunoglobulin G (IgG) type of myeloma confirmed by immunofixation assay (IFE). Two subjects (25.0%) each had immunoglobulin A (IgA) and kappa light chain type of myeloma. Five subjects (62.5%) had measurable disease in the serum with IgG being the most common isotype (3 subjects [37.5%]), followed by IgA (2 subjects [25.0%]). In 1 subject (12.5%), the disease was measurable in urine only and in the remaining 2 subjects (25.0%), it was measurable by serum FLC only. The majority of the subjects (7 subjects [87.5%]) had International Staging System (ISS) Stage I MM and 1 subject (12.5%) had ISS Stage II MM. The median duration between initial diagnosis of MM and administration of the first dose of study treatment was 3.74 years (range, 2.3-11.5 years).

Prior and Concomitant Therapies

All 8 subjects (100.0%) had received prior systemic therapy for MM and 2 subjects (25.0%) had received autologous stem cell transplant (ASCT). Six subjects (75.0%) had received 2 lines of therapy as prior treatment. All subjects had a prior exposure to corticosteroids, while 4 subjects (50.0%) had a prior exposure to bortezomib. Three subjects (37.5%) each had received the immunomodulatory agents lenalidomide and thalidomide, while 7 subjects (87.5%) had received at least 1 alkylating agent. None of the subjects underwent a cancer-related surgery or received radiotherapy prior to the study participation.

Exposure

All 8 subjects (100.0%) received at least 8 cycles of study treatment and the majority of subjects (6 subjects [75.0%]) received at least 20 cycles of study treatment during the study. The median number of treatment cycles received was 27.5 (range, 8-31 cycles). The median duration of study treatment was 23.08 months (range, 5.3-25.9 months). Based on Kaplan-Meier product limit estimate, the median duration of follow-up of subjects was 24.90 months (range, 11.2-27.7 months).

EFFICACY RESULTS:

Response to Study Treatment

All 8 subjects (100.0%) were evaluable for responses to the study treatment. Overall response rate (sCR+CR+VGPR+PR) was 100.0% (8 subjects), with 3 subjects (37.5%) each achieving sCR and VGPR, and 2 subjects (25.0%) achieving CR. Five subjects (62.5%) had CR or better response and all 8 subjects (100.0%) had VGPR or better response. None of the subjects were reported to have PD during the study as a best response.

Time to Response

The median time to first response (PR or better) was 0.9 months (95% CI [confidence interval], 0.8-1.5 months).

Duration of Response

The median DOR for all 8 subjects was 24.11 months (range, 8.5-27.0 months).

Time to Disease Progression

As 6 subjects (75.0%) were censored and only 2 subjects (25.0%) developed disease progression during the study, the Kaplan-Meier estimate for median time to disease progression was not evaluable.

Progression-free survival

The 6-month PFS rate was 100.0% and the 24-month PFS rate was 75.0% (95% CI, 31.5%-93.1%). As 6 subjects (75.0%) were censored and only 2 subjects (25.0%) developed disease progression during the study, the Kaplan-Meier estimate for median PFS was not evaluable.

Overall Survival

No deaths were reported in the study.

M-component

Progressive decrease from baseline in serum M-proteins was noted at all time points, with a maximum median decrease of 100.0% (range, 80.0%-100.0%) noted at Weeks 21 and 24. Five subjects had measurable M-proteins in serum at baseline. The M-protein response (≥50% reduction from baseline) in serum was seen in all 5 subjects (100%) with a 100.0% reduction from baseline in serum M-proteins. One subject (12.5%) had measurable M-proteins only in urine at baseline which were not detectable at any postbaseline visit. Two subjects had measurable M-proteins only in dFLC at baseline. Response based on dFLC was reported in both subjects and they achieved ≥90.0% reduction from baseline in serum dFLC.

PHARMACOKINETIC, BIOMARKER, AND IMMUNOGENECITY RESULTS:

Pharmacokinetics

All 8 subjects (100.0%) received daratumumab on Days 1, 8, and 15 of Cycles 1, 2, and 3 (weekly), Day 1 of Cycles 4 to 8 (every 3 weeks), and Day 1 of every cycle thereafter (every 4 weeks). The

mean (SD) peak concentration after the first dose (Cycle 1 Day 1 postinfusion) was 354.10 (61.757) µg/mL. Accumulation of daratumumab continued through at least the first 7 doses of weekly dosing (the last PK sampling time point in weekly dosing), resulting in a 2.4-fold increase in postinfusion daratumumab peak concentration to 864.98 (167.806) µg/mL on Cycle 3 Day 1. The mean (SD) preinfusion trough concentration after 6 weekly doses on Cycle 3 Day 1 was 512.87 (137.972) µg/mL. The mean trough concentrations of daratumumab in serum gradually decreased over time after Cycle 6 Day 1 reaching a mean (SD) peak concentration of 710.39 (114.688) µg/mL on Cycle 9 Day 1 and 675.41 (95.627) µg/mL on Cycle 12 Day 1.

Immunogenicity

All 8 subjects (100.0%) were tested for anti-daratumumab antibodies at least once after the first daratumumab infusion. None of the subjects were positive for anti-daratumumab antibodies at any time after their first infusion.

Biomarkers

Whole blood analysis for biomarkers was performed at baseline (Cycle 1 Day 1) and subsequently on Day 1 of Cycles 2, 3, and 8. The levels of CD3-CD16+CD56+ cells showed a decrease from baseline at all time points. A similar trend was observed for CD3+CD4+ and CD19+ cells. No trend was observed with respect to CD3+CD8+ lymphocytes. A decrease from baseline in total NK cells was observed at all time points.

SAFETY RESULTS:

All 8 subjects (100.0%) had at least 1 TEAE. There were no deaths or any Grade 5 TEAEs reported during the study.

Treatment-emergent Adverse Events

The most frequently reported TEAEs by preferred term (PT) were thrombocytopenia (7 subjects [87.5%]), viral upper respiratory tract infection and lymphopenia (5 subjects [62.5%] each).

All 8 subjects (100.0%) had at least 1 TEAE related to any component of the study treatment (daratumumab, bortezomib, or dexamethasone). The most frequently reported TEAEs related to daratumumab were thrombocytopenia (6 subjects [75.0%]) and lymphopenia (5 subjects [62.5%]). The most frequently reported TEAEs related to bortezomib were thrombocytopenia (7 subjects [87.5%]) and lymphopenia (4 subjects [50.0%]). The most frequently reported TEAE related to dexamethasone was lymphopenia (5 subjects [62.5%]).

Grade 3 or 4 TEAEs

All 8 subjects (100.0%) had at least 1 Grade 3 or 4 TEAE. The most frequently reported Grade 3 or 4 TEAEs by PT were thrombocytopenia (6 subjects [75.0%]) and lymphopenia (5 subjects [62.5%]). Grade 4 thrombocytopenia was reported in 3 subjects (37.5%) and Grade 4 lymphopenia was reported in 1 subject (12.5%).

Serious Adverse Events

Serious TEAEs were reported in 3 subjects (37.5%): Prostate cancer and viral upper respiratory tract infection were reported in 1 subject (12.5%) each, and herpes zoster and femoral neck fracture were reported in 1 subject (12.5%). The events of herpes zoster and viral upper respiratory tract infection were related to the study treatment.

Other Significant Adverse Events

Two subjects (25.0%) had TEAEs leading to study treatment discontinuation (1 subject discontinued study treatment due to a serious TEAE of prostate cancer, which was not related to study treatment; and 1 subject discontinued study treatment due to TEAEs of aortic dissection and blood creatine phosphokinase increased, both of which were possibly related to daratumumab and not related to dexamethasone and bortezomib).

Treatment cycle delays or dose modifications due to TEAEs were reported in all 8 subjects (100.0%), most frequently due to a TEAE of thrombocytopenia (4 subjects [50.0%]).

Adverse Events of Special Interest

Five subjects (62.5%) experienced at least 1 IRR. All IRRs occurred during the first daratumumab infusion and resolved within 24 hours of onset. All IRRs were of toxicity Grade 1 or 2. The most common IRRs were hypoxia, wheezing, and chills reported in 2 subjects (25.0%) each. The median time to onset of IRRs during the first daratumumab infusion was 85.0 minutes (range, 20-184 minutes).

All 8 subjects (100.0%) had at least 1 cytopenic TEAE. The most frequently reported cytopenic TEAEs were thrombocytopenia (7 subjects [87.5%]) and lymphopenia (5 subjects [62.5%]). The majority of subjects (7 subjects [87.5%]) had at least 1 Grade 3 or 4 cytopenic TEAE. Of the 7 subjects with thrombocytopenia, these events led to dose modification or cycle delay in 4 subjects (50.0%). Grade 3 thrombocytopenia with bleeding, which was classified as a DLT, was reported in 1 subject (12.5%). Grade 1 hemorrhage subcutaneous was reported in 1 subject (12.5%).

Six subjects (75.0%) had at least 1 treatment-emergent infection and infestation. Grade 3 or 4 treatment-emergent infections and infestations were reported in 2 subjects (25.0%): 1 subject (12.5%) each had a TEAE herpes zoster and viral upper respiratory tract infection. Of the 7 subjects who received prophylactic antivirals, 5 subjects (71.4%) had at least 1 infection and 1 subject (14.3%) had an opportunistic infection of herpes zoster. Of the 5 subjects who received prophylactic antibacterials, none of the subjects had an opportunistic infection.

There were no events of tumor lysis syndrome reported in the study.

One subject (12.5%) had a serious TEAE of Grade 3 prostate cancer, which was a second primary malignancy.

Other Adverse Events

One subject (12.5%) with a prior exposure to bortezomib developed Grade 2 peripheral sensory neuropathy during Cycle 1 which improved to Grade 1 in Cycle 9 (after completing dosing of bortezomib up to Cycle 8).

Dose-limiting Toxicities

Three DLT events (Grade 3 thrombocytopenia, Grade 3 gamma glutamyl transferase increased, and Grade 3 AST increased) were observed in 2 subjects (25.0%). The DLT of thrombocytopenia required platelet transfusion. None of the subjects discontinued the study treatment due to the DLTs. The study evaluation team reviewed the DLTs and concluded that the 16 mg/kg dose of daratumumab in combination with Vd was safe and tolerable.

Clinical Laboratory Evaluations

A gradual improvement in the mean hemoglobin values was seen from Cycle 9 through Cycle 21 Day 1 (more than 5 evaluable subjects) in comparison to baseline levels. A transient cyclical decrease and recovery in platelet count was observed from Cycle 1 through Cycle 9 with some values below the lower limit of normal (LLN) laboratory range. The platelet count recovered to baseline levels on Cycle 9 Day 1

and showed a steady increase through Cycle 21 Day 1 (more than 5 evaluable subjects) and the end of study. A sharp decrease in the mean WBC and neutrophil counts was noted on Cycle 2 Day 1, followed by the recovery to baseline levels on Cycle 2 Day 15. Thereafter, the mean WBC and neutrophil counts remained stable until Cycle 8 Day 11 (all 8 subjects). Again, intermittent decrease in the mean WBC and neutrophil counts was noted from Cycle 9 Day 1 onwards and from Cycle 14 Day 1 onwards, respectively, compared to baseline levels, showing minor fluctuations through Cycle 21 Day 1 (more than 5 evaluable subjects), with the values above LLN. A sharp decrease in the mean lymphocyte count was noted on Cycle 1 Day 8, followed by gradual recovery to baseline levels until Cycle 3 Day 15. The mean lymphocyte count remained stable until Cycle 7 Day 11, and showed a sharp decrease on Cycle 8 Day 1, followed by a gradual recovery to baseline levels until Cycle 13 Day 1. Thereafter, the mean values showed improvement through Cycle 21 Day 1 (more than 5 evaluable subjects) and the end of study with the values above LLN.

The mean aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increased sharply from baseline to Cycle 2 Day 1 (39.0 U/L and 30.6 U/L, respectively). The mean AST and ALT values recovered to near baseline levels on Cycle 4 Day 1 and were maintained with minor fluctuations until Cycle 21 Day 1.

Other Safety Observations

In general, the majority of the subjects did not report any clinically significant abnormal vital signs or clinically meaningful ECG during the study.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

Daratumumab at a dose of 16 mg/kg in combination with bortezomib and dexamethasone (Vd) was tolerable in Japanese subjects with relapsed or refractory MM who had received at least 1 prior therapy. The study also showed favorable safety and efficacy profiles of daratumumab at a dose of 16 mg/kg in combination with Vd in this population.

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