SYNOPSIS

Study Title: Phase 2, Randomized, Open-Label Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) Versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects With Newly Diagnosed Multiple Myeloma Eligible for High-Dose Chemotherapy and Autologous Stem Cell Transplantation

Study Number: 54767414MMY2004

Study Phase: 2

Name of Study Intervention: JNJ-54767414 (daratumumab)

Trade Name: DARZALEX®

Name of Sponsor/Company: Janssen Scientific Affairs, LLC

Status:	Approved
Date:	1 March 2023
Prepared by:	Janssen Scientific Affairs, LLC

Study Name: GRIFFIN

NCT No.: NCT02874742

Clinical Registry No.: CR108195

Number of Study Centers and Countries: This study was conducted in the United States at 35 centers that enrolled participants.

Publications:

Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020;136(8):936-945.

Voorhees PM, Rodriguez C, Reeves B, et al. Daratumumab plus RVd for newly diagnosed multiple myeloma: final analysis of the safety run-in cohort of GRIFFIN. Blood Adv. 2021;5(4):1092-1096.

Nooka AK, Kaufman JL, Rodriguez C, et al. Daratumumab plus lenalidomide/bortezomib/dexamethasone in Black patients with transplant-eligible newly diagnosed multiple myeloma in GRIFFIN. Blood Cancer J. 2022; 12:63.

Sborov DW, Baljevic M, Reeves B, et al. Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma: Analysis of vascular thrombotic events in the GRIFFIN study. Br J Haematol. 2022;199(3):355-365.

Chhabra S, Callander N, Watts NL, et al. Stem Cell Mobilization Yields with Daratumumab- and Lenalidomide-Containing Quadruplet Induction Therapy in Newly Diagnosed Multiple Myeloma: Findings from the MASTER and GRIFFIN Trials. Transplant Cell Ther. 2022;S2666-6367(22)01802-4.

Study Period: 29 August 2016 (date of first site was opened) to 8 April 2022 (date of last participant last visit)

Rationale: Targeted immunotherapy based on monoclonal antibodies against relevant tumor antigens has shown to be not only feasible, but also an effective approach in treating hematological malignancies when combined with chemotherapy agents. The future of successful multiple myeloma treatment lies in both the development of novel agents targeting the multiple myeloma cells or the bone marrow microenvironment, and the development of rationally based combination therapies. As the RVd regimen is the most commonly utilized treatment regimen for patients in the US with transplant-eligible newly diagnosed multiple myeloma, the addition of daratumumab to RVd induction therapy (D-RVd) could potentially improve initial disease control and long-term outcomes. In addition, although daratumumab was approved in combination with VTd for the treatment of patients with newly diagnosed multiple myeloma who are eligible for ASCT, thalidomide as part of the VTd regimen is rarely used in the US. Based upon pre-clinical synergism, promising clinical data in the relapsed/refractory setting, and the limited use of VTd in US clinical practice, the D-RVd combination was investigated in this study in newly diagnosed, transplant-eligible patients.

Objectives:

Primary Objective

The primary objective was to determine if the addition of daratumumab to lenalidomide, bortezomib, and dexamethasone (RVd) increased the proportion of participants achieving stringent complete response (sCR), as defined by the International Myeloma Working Group (IMWG) criteria, by the time of completion of post-autologous stem cell transplant (ASCT) consolidation treatment, compared with RVd alone.

Secondary Objectives

The secondary objectives were:

- To evaluate complete response (CR) and sCR rate following induction, ASCT, post-ASCT consolidation, and maintenance treatment
- To evaluate overall response rate (ORR) and rate of very good partial response (VGPR) or better following induction, ASCT, post-ASCT consolidation, and maintenance treatment
- To evaluate duration of and time to sCR and time to CR
- To evaluate time to VGPR or better
- To evaluate time to partial response (PR) or better
- To assess the negative minimal residual disease (MRD) rate following induction, post-ASCT consolidation, and maintenance treatment
- To evaluate clinical outcomes including:

  Time to progression (TTP)

  Progression-free survival (PFS)

  Overall survival (OS)

  Duration of response (DOR)
- To assess the safety and tolerability of daratumumab plus lenalidomide-bortezomib-dexamethasone (D-RVd)
- To assess the pharmacokinetics of daratumumab
- To assess the immunogenicity of daratumumab
- To evaluate patient-reported outcomes (PROs)
- To evaluate stem cell yield after mobilization

- To assess time to absolute neutrophil count (ANC) recovery, defined as the date from transplant to the first of 3 consecutive laboratory values (obtained on different days) where the ANC was > 0.5 x 10^9/L
- To assess time to platelet count recovery, defined as the date from transplant to the first of 3 consecutive laboratory values (obtained on different days) where the platelet count was > 20 x 10^9/L and at least 7 days after the most recent prior platelet transfusion
- To evaluate the tolerability of daratumumab when administered as a rapid infusion during maintenance treatment (ie, an accelerated infusion rate whereby 20% of the daratumumab dose was administered over 30 minutes and the remaining 80% was administered over 60 minutes for a total dose administration time of 90 minutes)
- To evaluate the tolerability of daratumumab when administered with rHuPH20 as a 3- to 5-min subcutaneous (SC) injection

Exploratory Objectives

The exploratory objectives were:

- To evaluate progression-free survival (PFS) on next line therapy (PFS2)
- To evaluate the clinical efficacy of D-RVd in high-risk cytogenetic subgroups: del(17p), t(4;14), and t(14;16)
- To explore immune modulatory effects of D-RVd as compared with RVd through immune profiling (NK, T, and B cells) and T-cell receptor sequencing
- To collect medical resource utilization (MRU) data that was used in future economic modeling (the construction and reporting of the economic model was conducted separately from this study)
- To evaluate serum concentrations and potential immunogenicity of daratumumab with respect to IRRs in the setting of rapid infusion during maintenance.

Methodology: This was a multicenter, randomized, open-label, active-controlled, Phase 2 study in participants 18 to 70 years of age with newly diagnosed multiple myeloma eligible for high-dose therapy (HDT) and ASCT. Initially, there was a safety run-in phase in up to 16 participants at selected study sites to assess potential dose-limiting toxicities (DLTs) that were associated with the addition of daratumumab to the RVd regimen.

The main study consisted of 4 phases:

- A 28-day screening phase during which screening procedures were performed to determine study eligibility.
- An induction/consolidation phase (which was inclusive of four 21-day induction treatment cycles followed by stem cell mobilization, HDT, and ASCT, followed by two 21-day consolidation treatment cycles).
- A 24-month maintenance phase that started after the post-ASCT consolidation disease evaluation.
- A long-term follow-up phase. All participants were followed in the long-term follow-up phase for at least 1 year after last dose of study treatment and continued until death, withdrawal of consent for study participation, or the end-of-study definition was met. The end-of-study was defined as when all participants have completed at least 1 year of long-term follow-up, or until death or withdrawal of consent for study participation, whichever occurs first.

Participants who experienced a DLT during the safety run-in were withdrawn from the study (based on investigator's judgment and best clinical practice). If, after review of the safety data by a Data Review Committee, the stopping boundaries were crossed after 8, 12, or 16 participants, all participants were to be

withdrawn from the study, and the study was to be stopped. Unless the study was stopped due to DLTs, participants enrolled in the safety run-in phase continued in the study and followed the visit schedule and procedures described for the main study (except PRO assessments and MRU data collection). An interim safety analysis was done for the safety run-in after all participants were treated for at least 4 cycles or discontinued study participation.

Following successful completion of the safety run-in phase, approximately 200 participants were randomly assigned to 1 of 2 treatment groups (100 per treatment group) in the main study:

- D-RVd group: RVd with daratumumab 16 mg/kg intravenous (IV) weekly during induction treatment (Days 1, 8, and 15 of Cycles 1 through 4) and every 3 weeks during consolidation treatment (Day 1 of Cycles 5 and 6). During maintenance treatment (Cycle 7 and beyond for 24 months), daratumumab IV (16 mg/kg) or, following implementation of the protocol Amendment 4, daratumumab SC (1800 mg flat dose) was administered every 4 or 8 weeks.
- RVd group: RVd alone as induction and consolidation treatment (Cycles 1 through 6: lenalidomide 25 mg orally on Days 1 through 14, bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11, and oral dexamethasone 40 mg weekly [20 mg on Days 1, 2, 8, 9, 15, and 16]) followed by maintenance treatment with oral lenalidomide 10 mg daily on Days 1-21 throughout each 28-day cycle on Cycles 7 through 9. Beginning at Cycle 10, the lenalidomide dose was increased to 15 mg unless there was a tolerability concern.
- Stem cell mobilization was performed with G-CSF, with or without plerixafor according to institutional standards of dose and schedule. Use of cyclophosphamide was only allowed if G-CSF with or without plerixafor was not successful. Participants were then to proceed to HDT and ASCT. Melphalan 200 mg/m^2 were to be used as the conditioning regimen which could either be given on a single day or divided into 2 days depending on local practice.
- In Protocol Amendment 2, daratumumab administration was changed from every 8 weeks to every 4 weeks during the maintenance phase, based on pharmacokinetic results from Study SMM2001 in participants with smoldering multiple myeloma showing that dosing every 8 weeks is insufficient to maintain target daratumumab saturation. Following protocol Amendment 2, daratumumab was administered every 4 weeks during the maintenance phase. While Q4w dosing was the preferred treatment schedule, participants who did not elect to receive daratumumab every 4 weeks received daratumumab every 8 weeks during maintenance, as originally planned.
- Following Protocol Amendment 3, accelerated infusion of daratumumab (rapid infusion) was allowed during the maintenance phase (beginning Cycle 7), if clinically feasible.
- All participants randomized to the D-RVd group in this study initially received daratumumab IV formulation; however, following implementation of the protocol Amendment 4, participants still receiving treatment with daratumumab IV had the option to switch to daratumumab SC on Day 1 of any cycle during maintenance phase, at the discretion of the investigator. Participants with a known allergy/intolerance to any of the components of the SC formulation, including sorbitol, were not eligible to switch to daratumumab SC. Note: throughout this document, text has been added to highlight any differences between daratumumab IV and daratumumab SC dosing, and where there was no clarification, it was implied that the descriptions were the same for daratumumab IV and daratumumab SC.

Participants were stratified at randomization by International Staging System Stage I, II, or III disease (β-2 microglobulin and albumin) and creatinine clearance (CrCl [30-50 mL/min and >50 mL/min]).

Daratumumab and RVd were administered as described in Dosage and Administration. After 4 cycles of induction study treatment, participants underwent stem cell mobilization and then proceeded to HDT and ASCT, which was performed according to institutional standards. If the decision was made by the investigator not to pursue HDT and ASCT, participants were discontinued from study treatment and entered

the long-term follow-up phase; participants who did not undergo HDT and ASCT did not receive consolidation or maintenance treatment on protocol.

Consolidation treatment commenced after engraftment and when in the opinion of the investigator the participant was fit enough to tolerate subsequent systemic therapy (60-100 days post-ASCT). At the start of consolidation treatment, both groups received the same dosages of lenalidomide, bortezomib, and oral dexamethasone that were tolerated at the end of induction treatment. Participants were evaluated for the primary endpoint (post-ASCT consolidation sCR). MRD was assessed by next-generation sequencing, regardless of treatment group. After the post-ASCT consolidation disease evaluation, participants entered the 24-month maintenance phase of the study. Following completion of the last cycle of the maintenance phase, participants were allowed to continue lenalidomide per local standard of care.

Participants received study treatment through completion of the 24-month maintenance phase, or until confirmed disease progression, discontinuation of study treatment due to an unacceptable drug toxicity, or other reasons. After completion of the EOT visit, participants entered the long-term follow-up phase of the study. Participants who entered the long-term follow-up phase before disease progression returned to the site every 12 weeks for disease evaluation and other follow-up assessments, until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end-of-study, whichever occurred first. After confirmed disease progression or the start of a new treatment for multiple myeloma, participants returned to the site or were contacted by telephone every 12 weeks for follow-up assessments. Following disease progression on the next line therapy, participants were only followed for survival.

Throughout the study, participants were monitored closely for adverse events, laboratory abnormalities, and clinical response.

To measure functional status, well-being, and symptoms, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L instruments were completed by participants throughout the study. Medical resource utilization data were also collected.

An independent Data Monitoring Committee (DMC) met periodically to review interim safety data during the main study. One planned interim safety analysis occurred after at least 50 participants were treated for at least 4 cycles and underwent stem cell mobilization (or were evaluated for mobilization feasibility) in the main study or had discontinued before completing 4 cycles / stem cell mobilization feasibility.

Number of Participants (planned and analyzed): Approximately 216 participants were planned to be enrolled in the study (16 participants in the safety run-in and 100 participants each in the D-RVd and RVd treatment groups).

A total of 223 participants (16 participants in the safety run-in, 104 participants in the D-RVd treatment group and 103 participants in the RVd treatment group) were enrolled/randomized.

Diagnosis and Main Criteria for Inclusion and Exclusion: Participants ≥18 to ≤70 years of age, with documented multiple myeloma as defined at study entry by the IMWG 2014 criteria, measurable disease as defined by i) serum monoclonal paraprotein (M-protein) ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours); or ii) for immunoglobulin (Ig) A, IgD, IgE, or IgM multiple myeloma, serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or iii) light chain multiple myeloma without measurable disease in serum or urine, serum Ig free light chain [FLC] ≥10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio); and Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 were enrolled in the study. The key criteria for exclusion in the study included: Participant diagnosed or treated for malignancy other than multiple myeloma, except i) malignancy treated with curative intent with no known active disease present for ≥3 years before randomization or ii) adequately treated non-melanoma skin cancer, lentigo maligna or in situ malignancies (including but not limited to, cervical, breast) with no evidence of disease; Participants who had a known history of meningeal or central nervous system involvement by multiple myeloma, chronic obstructive pulmonary disease (a forced

expiratory volume in 1 second <50% of predicted normal), known moderate or severe persistent asthma within the past 2 years or currently uncontrolled asthma of any classification, clinically significant cardiac disease or plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes), or light chain amyloidosis.

Study Interventions, Dose, Mode of Administration, and Batch Numbers: Daratumumab was administered at a dose of 16 mg/kg through intravenous infusion weekly on Cycles 1 to 4 (Days 1, 8, and 15) during the induction phase and every 3 weeks on Cycles 5 and 6 (Day 1) during the consolidation phase. During maintenance treatment (Cycle 7 and beyond for 24 months), daratumumab IV (16 mg/kg) or, following implementation of the protocol Amendment 4, daratumumab SC (1800 mg flat dose) was administered every 4 or 8 weeks. Batch numbers (expiry dates) for daratumumab IV were: 4372761 (10 October 2016), 4373623 (15 June 2018), 4375176 (21 November 2018), 4376495 (26 April 2019), 4377536 (20 December 2020), 4378501 (20 May 2021), and for daratumumab SC was: 4380218 (02 December 2021).

Reference Therapy, Dose and Mode of Administration, Batch No.: Lenalidomide was self-administered orally at a dose of 25 mg each day on Days 1 to 14 of each 21-day cycle during Cycles 1 to 6 of induction/consolidation phase (for participants with CrCl >50 mL/min during the induction phase; or at the start of the consolidation phase [Cycle 5, Day 1], at the same dose that was tolerated at the end of the induction phase). Lenalidomide dose adjustments were requested to be instituted for participants with a CrCl ≤50 mL/min and were in accordance with the approved lenalidomide labeling. During the maintenance phase (Cycles 7 to 9), lenalidomide was given at a dose of 10 mg orally, which could be increased to 15 mg at the beginning ofCycle 10 unless there was a tolerability concern. Following completion of the last cycle of the 24-month maintenance phase (end-of-study treatment), participants could continue lenalidomide per local standard of care. Commercially available lenalidomide was used in the study.

Bortezomib was administered at a dose of 1.3 mg/m^2 subcutaneously twice weekly (Days 1, 4, 8, and 11) during the 21-day cycles (Cycles 1 to 6) of the induction and consolidation phases; or at the start of the consolidation phase (Cycle 5 Day 1) at the same dose that was tolerated at the end of the induction phase. For participants who experienced injection-site reactions at the subcutaneous administration site, bortezomib could be administered by intravenous injection. On daratumumab infusion days, bortezomib was administered at the end of the daratumumab infusion. Neither group received bortezomib after the first 6 cycles of D-RVd or RVd. Commercially available bortezomib was used in the study.

Dexamethasone was self-administered orally at a total dose of 40 mg weekly (ie, 20 mg on Days 1, 2, 8, 9, 15, and 16) during the induction and consolidation phases (Cycles 1 to 6); or at the start of the consolidation phase (Cycle 5 Day 1) at the same dose that was tolerated at the end of the induction phase. For participants in the D-RVd group, the dexamethasone 20 mg oral or IV (only if oral was not available) dose administered as a pre-infusion medication on daratumumab infusion days (Days 1, 8, and 15) replaced the oral dexamethasone dose for that day. Dexamethasone was to be administered until the participant experiences disease progression or unacceptable toxicity during the induction/consolidation phase. Dexamethasone, 20 mg orally or intravenously (only if oral was not available) was administered as a pre-infusion/administration medication to participants in the D-RVd treatment group during the induction/consolidation phase (daratumumab infusion Days 1, 8, and 15) and the maintenance phase. Commercially available dexamethasone was used in the study. After Cycle 4, the dose of dexamethasone could be reduced at the investigator's discretion. The 20 mg oral dose of dexamethasone administered as a pre-infusion medication on the day of daratumumab infusions/administration was not to be decreased.

Duration of Study Intervention:

A 12-week induction phase followed by autologous stem cell mobilization, HDT and ASCT; a 6-week consolidation phase; and an approximately 104-week maintenance phase (until disease progression or up to a maximum of 2 years).

Criteria for Evaluation:

Efficacy: Assessments of tumor response and disease progression were conducted in accordance with the IMWG 2016 response criteria. For data analysis and reporting, the sponsor used a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to the IMWG 2016 criteria. Disease evaluations included M-protein measurements (serum and urine), immunofixation (IFE; serum and urine), serum FLC, serum calcium corrected for albumin, examination of bone marrow aspirate or biopsy, skeletal survey (assessment of lytic bone disease), and documentation of extramedullary plasmacytomas. Minimal residual disease in the bone marrow aspirate was also assessed.

Pharmacokinetics: For all participants who received daratumumab (D-RVd during induction/consolidation and daratumumab plus lenalidomide during maintenance), blood samples were collected to determine the concentration of daratumumab at specified timepoints (pre- and post-infusion on Day 1 of Cycles 1, 4, 5 and 6, and at 4 weeks and 8 weeks post-treatment [after D-RVd/daratumumab-lenalidomide treatment has been discontinued]), and for estimation of the following pharmacokinetics (PK) parameters of daratumumab: minimum observed concentration (C_{min}) and maximum observed concentration (C_{max}).

Immunogenicity: Samples drawn from all participants who received daratumumab (D-RVd during induction/consolidation, and daratumumab plus lenalidomide during maintenance) were assessed for the generation of anti-daratumumab antibodies.

Biomarkers: Blood and bone marrow aspirate samples for biomarker studies were drawn from all participants at screening and following treatment at pre-specified timepoints after protocol Amendment 2. Biomarker evaluations focused on the assessment of MRD (in bone marrow aspirates). Baseline bone marrow aspirate samples were subjected to DNA and RNA sequencing to establish the myeloma clone for MRD monitoring. Minimal residual disease was evaluated in participants who achieved CR or sCR (including participants with VGPR or better and suspected daratumumab interference), after induction/before stem cell collection, at post-ASCT consolidation disease evaluation, and at 12 and 24 months during maintenance. In addition to evaluating MRD, biomarker assessments could also monitor changes in immune cell subpopulations in bone marrow aspirates and whole blood.

Safety: Safety assessments included adverse event (AE) monitoring, clinical laboratory tests (hematology and serum chemistry), vital sign measurements, physical examinations, 12-lead ECGs, pregnancy tests, and ECOG performance status.

Patient-reported Outcomes: Functional status, well-being, and symptoms were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30), EORTC Quality-of-Life Questionnaire-Multiple Myeloma 20 (QLQMY20), and the 5-level EuroQoL-5-Dimension (EQ-5D-5L) questionnaires. PRO assessments were not performed for participants enrolled in the safety run-in.

Medical Resource Utilization: MRU data, associated with protocol-driven medical encounters and safety monitoring, were collected in the electronic case report form (eCRF) by the investigator and study site personnel for participants in the D-RVd and RVd treatment groups throughout the study. MRU data were not collected for participants enrolled in the safety run-in.

Statistical Methods: Sample size determination was based on historical data that suggested the post-consolidation sCR rate was approximately 35% for RVd therapy. To detect an absolute 15% increase in post-consolidation sCR rate with 80% power using a 1-sided likelihood ratio test at the 10% significance level, 200 participants were needed to be randomized with a 1:1 randomization ratio, assuming a 5% non-evaluable rate.

Analyses

The primary hypothesis was tested at 1-sided 0.1 significance level (equivalent to 2-sided 0.2 significance level). All the secondary and exploratory analyses were tested at a 2-sided 0.05 significance level with p-values reported as 2-sided. Response to study treatment and progressive disease was evaluated by a validated computer algorithm per IMWG 2016 criteria. The primary efficacy endpoint was the proportion of participants achieving a sCR by the end of post-ASCT consolidation treatment. The proportion of sCR response was compared between the 2 randomized treatment groups using the stratified Cochran Mantel-Haenszel (CMH) test. A Mantel-Haenszel odds ratio, along with its 2-sided 95% CI and the p-value from the CMH chi-square test, was reported.

Secondary efficacy endpoints: All binary endpoints, including sCR, CR or better, ORR, VGPR or better rate following induction, ASCT, post-ASCT consolidation, maintenance, and MRD-negative rate, were analyzed similarly as the primary endpoint. Time-to-event efficacy endpoints, such as PFS, time to response, duration of response, time to progression, PFS2, and OS, were descriptively summarized using the Kaplan-Meier method. They were compared between the 2 randomized treatment groups using a stratified log-rank test. The p-value from the stratified log-rank test was reported. Hazard ratio and its 95% confidence interval were estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable.

Stratification factors used in the analyses include ISS stage (I, II or III), and creatinine clearance (CrCl [30-50 mL/min or >50 mL/min]) from Interactive Web Response System (IWRS) at randomization.

SUMMARY OF RESULTS AND CONCLUSIONS:

Study 54767414MMY2004 was a multicenter, randomized, open-label, active-controlled, Phase 2 study to evaluate whether the addition of daratumumab to RVd could increase the proportion of participants achieving sCR, as defined by the IMWG 2016 criteria, by the time of completion of post-ASCT consolidation treatment, compared with RVd alone. A safety run-in phase, including 16 participants who all received D-RVd, was evaluated by a Data Review Committee. The pre-specified stopping criteria of the study were not met, and therefore the randomized phase of the study proceeded to compare D-RVd versus RVd.

The first participant was consented on 29 August 2016. The clinical cutoff for the primary analysis was 25 January 2019. This CSR provides the final end-of-study updates after 24-month maintenance treatment following the post-ASCT consolidation disease evaluation and a subsequent 1-year long-term follow-up phase after the end-of-study therapy.

Of the 292 participants screened for the study, 223 participants were enrolled/randomized (16 participants in the safety run-in, 104 participants randomized to the D-RVd treatment group, and 103 participants to the RVd treatment group). Among the 207 randomized participants, 201 participants received treatment (D-RVd: 100 [96.2%] participants; RVd: 101 [98.1%] participants). Four participants in the D-RVd treatment group and 2 participants in the RVd treatment group were randomized but did not receive any treatment. One participant randomized to the D-RVd treatment group received RVd treatment. The participant was counted in the D-RVd treatment group for the intention to treat (ITT) analysis and RVd treatment group for the safety analysis.

Disposition:

Safety Run-in Participants

All (16 [100%]) participants completed the induction and consolidation phases and entered the maintenance phase. Fifteen (93.8%) participants completed maintenance phase and one (6.3%) participant discontinued study treatment during the maintenance phase due to progressive disease. The median duration of follow-up was 59.47 (range: 20.6-61.5) months.

Randomized Participants

A total of 26 (25.0%) participants in the D-RVd treatment group discontinued study treatment, compared with 53 (51.5%) participants in the RVd treatment group. The most common reasons for discontinuation were progressive disease (per investigator assessment) (D-RVd: 7.7%; RVd: 14.6%), AEs (D-RVd: 7.7%; RVd: 12.6%), withdrawal by participant (D-RVd: 4.8%; RVd: 10.7%), and other reasons (D-RVd: 1.9%; RVd: 9.7%). The majority of "other" reasons for discontinuation were physician decision not to proceed with the study therapy. The median duration of follow-up was 49.84 (range: 0-57.9) months for the D-RVd group and 49.41 (range: 0-59.4) months for the RVd group.

Of the 100 (96.2%) participants randomized to the D-RVd treatment group, 96.2%, 90.4%, and 88.5% of participants received induction treatment, transplant, and consolidation treatment, respectively; and 94.2% and 87.5% of participants completed induction and consolidation treatment, respectively. In the D-RVd treatment group, 1.9% of participants discontinued induction treatment, 2.9% completed induction but did not proceed to transplant, and 1.0% of participants discontinued consolidation treatment. The reasons for discontinuation of induction were progressive disease (1.0%) and withdrawal by participant (1.0%). The reasons for completing induction but not proceeding to transplant were withdrawal by participant (1.9%) and adverse event (1.0%), while progressive disease (1.0%) was the only reason for not completing consolidation. In the D-RVd treatment group, 91.3% of participants underwent stem cell mobilization and 90.4% of participants received transplant. Of the 90 (86.5%) participants treated in the maintenance phase, 74 (71.2%) participants completed the maintenance treatment. There were 16 (15.4%) participants who discontinued study treatment during the maintenance phase. The reasons for discontinuation were AEs (6 [5.8%] participants), progressive disease (3 [2.9%] participants), loss to follow-up, withdrawal by participant, and other reasons (2 [1.9%] participants each), and death (1[1%] participants, the cause of death was a TEAE of bronchopneumonia).

Of the 101 (98.1%) participants randomized to RVd treatment group, 98.1%, 75.7%, and 70.9% of participants received induction treatment, transplant, and consolidation treatment, respectively; and 91.3% and 69.9% of participants completed induction and consolidation treatment, respectively. In the RVd treatment group, 6.8% of participants discontinued induction treatment, 13.6% completed induction but did not proceed to transplant, and 1.0% of participants discontinued consolidation treatment. The reasons for discontinuation of induction treatment were AEs (4 [3.9%] participants), other (2 [1.9%] participants), and progressive disease (1 [1.0%] participant). The reasons for completing induction but not proceeding to stem cell transplant were progressive disease (per investigator assessment) (6 [5.8%] participants), other reasons (4 [3.9%] participants), withdrawal by participant (3[2.9%] participants) and participant refusal of further study treatment (1 [1.0%] participant). One (1.0%) participant discontinued the study treatment during consolidation phase due to withdrawal of consent. In the RVd treatment group, 77.7% of participants underwent stem cell mobilization and 75.7% of the participants received transplant. Of the 70 (68.0%) participants treated in the maintenance phase, 48 (46.6%) completed the maintenance treatment. There were 22 (21.4%) participants who discontinued study treatment during the maintenance phase. The reasons for discontinuation were progressive disease (8 [7.8%] participants), AEs (7 [6.8%] participants), withdrawal by participant (4 [3.9%] participants), other reason (2 [1.9%] participants), and death (1[1%] participant, the cause of death was unknown).

Fewer participants in the D-RVd treatment group than in the RVd treatment group discontinued during induction (D-RVd: 1.9% versus RVd: 6.8%), after induction but before stem cell mobilization (D-RVd: 2.9% versus RVd: 13.6%), and during maintenance (D-RVd: 15.4% versus RVd: 21.4%). Progressive disease was more common as the reason for not proceeding to stem cell collection in the RVd treatment (7 participants) while this was the reason for the 1 participant in the D-RVd treatment group.

Demographic and Other Baseline Characteristics:

Safety Run-in Participants:

Half of the participant population were male (8 [50.0%] participants) and the majority of participants were white (11 [68.8%] participants) followed by black or African American (4 [25.0%] participants). The median age was 62.5 years (range: 46 to 65 years) and median weight was 82.9 kg (range: 61.5 to 110.9 kg). The majority of participants (10 [62.5%] participants) had an ECOG score of 1 at baseline. The majority of participants had IgG type of multiple myeloma (11 [68.8%] participants) and measurable disease by serum only (10 [62.5%] participants). The majority of participants (12 [75.0%] participants) had standard cytogenetic risk while high-risk cytogenetic abnormalities (del[17p], t[4;14] and/or t[14;16]) were reported for 4 (25.0%) participants. Median time since initial diagnosis was 1.6 months (range: 0 to 5 months) and the majority of participants (12 [75.0%] participants) had ISS stage I disease.

Randomized Participants:

Overall, demographics and baseline characteristics were balanced between the 2 randomized treatment groups. The majority of participants were male (118 [57.0%] participants) and white (161 [78.2%] participants). A total of 32 (15.5%) participants were black or African American. The median age was 60 years (range: 29 to 70 years) and the median weight was 82.0 kg (range: 37.4 to 158.6 kg). Approximately half of the participants (103 [50.7%]) had an ECOG score of 1 at baseline.

In both the D-RVd and RVd treatment groups, the majority of participants had IgG type of multiple myeloma (D-RVd: 58 [58.0%] participants; RVd: 55 [55.0%] participants) and measurable disease by serum only (D-RVD: 53 [51.0%] participants; RVd: 60 [58.3%] participants). Median time since diagnosis was 0.7 months (range: 0 to 12 months) in the D-RVd treatment group and 0.9 months (range: 0 to 61 months) in the RVd treatment group. Approximately half of the participants (D-RVd: 49 [47.1%] participants; RVd: 50 [48.5%] participants) had ISS stage I disease. As assessed by fluorescence in situ hybridization (FISH), the majority of participants (D-RVd: 82 [83.7%] participants; RVd: 83 [85.6%] participants) had standard cytogenetic risk. High cytogenetic risk disease (del[17p], t[4;14] and/or t[14;16]) was seen in 14 (14.4%) participants in the D-RVd treatment group and 16 (16.3%) in the RVd treatment group.

Exposure:

Safety Run-in Participants

All participants (100%) received ≥7 cycles of treatment. The median relative dose intensity for daratumumab was 100.1% (range: 97% to 103%). The median duration of study treatment was 32.9 months. Eleven participants received at least one rapid daratumumab infusion. The median number of rapid infusion cycles received by safety run-in participants was 6 and median daratumumab rapid infusion time was 1.7 hours. None of the safety run-in participants received daratumumab SC injection. Cycle delays for at least once were reported for 12 (75.0%) participants and the most common reason for delay was AE (11 [68.8%] participants). Daratumumab doses were skipped at least once for 6 (37.5%) participants, with AE as the primary reason. All (100%) participants underwent stem cell mobilization and received stem cell transplant. The median number of CD34+ stem cells collected and transplanted was 8.1×10^6/kg and 4.7×10^6/kg, respectively. Median time to neutrophil engraftment and platelet engraftment was 14 days (range: 11 to 29 days) and 13.5 days (range: 10 to 29 days) respectively.

Randomized Participants:

The median daratumumab relative dose intensity was 99.4% (range: 92.2% to 113.9%). The median duration of treatment was 32.5 months in the D-RVd treatment group and 27.5 months in the RVd treatment group. Eighty-one participants received at least one rapid infusion of daratumumab. Among those who received rapid infusions of daratumumab, the median number of rapid infusion cycles received by

participants in the D-RVd treatment group was 12 and median daratumumab rapid infusion time was 1.6 hours. Nineteen participants received at least one SC daratumumab injection, all during maintenance therapy. Among those who received SC daratumumab injections, the median total number of daratumumab SC injections or cycles received by participants in the D-RVd treatment group was 3.0 and median administration time of daratumumab SC injection was 4.0 minutes. A total of 175 randomized participants (D-RVd: 95 [91.3%] participants; RVd: 80 [77.7%] participants) underwent stem cell mobilization. The median number of CD34+ stem cells collected was lower in the D-RVd treatment group (8.2×10^6/kg) compared with the RVd treatment group (9.4×10^6/kg). Three participants did not receive stem cell transplant due to the following reasons: consent withdrawal (1 participant in the RVd treatment group), "other" reason (physician's discretion [1 participant in the RVd treatment group] and AE sequelae [1 participant in the D-RVd treatment group]). A total of 172 participants (D-RVd: 94 [90.4%] participants; RVd: 78 [75.7%] participants) received stem cell transplant. The median number of CD34+ stem cells transplanted was lower in the D-RVd treatment group (D-RVd: 4.2×10^6/kg; RVd: 4.8×10^6/kg). Median time to neutrophil engraftment and platelet engraftment was 12 days (range: 3 to 31 days) and 13 days (range: 2 to 31 days), respectively, in the D-RVd treatment group and 12 days (range: 2 to 23 days) and 12 days (range: 1 to 23 days), respectively, in the RVd treatment group.

Cycle delays were reported for 63 (63.6%) participants in the D-RVd treatment group and 51 (50.0%) participants in the RVd treatment group. The most common reason for delay was AE (D-RVd: 48.5%; RVd: 43.1%). At least 1 dose of daratumumab was skipped for 55 (55.6%) participants in the D-RVd treatment group and the main reason for skipped daratumumab doses was 'other'.

Efficacy Results:

The clinical cutoff for the primary analysis was 25 January 2019 after all randomized participants had completed the post-ASCT consolidation disease evaluation or discontinued from the study treatment by this timepoint. The final analysis was performed on the data after database lock on 18 May 2022.

Safety Run-in Participants:

By the end of maintenance, all (100%) participants achieved a response (overall response = sCR + CR + VGPR + PR) as assessed by the computerized algorithm. CR or better (sCR + CR) response by end of the maintenance phases was achieved by 15 (93.8%). Per assessment by the computerized algorithm, 2 (12.5%) participants had progressive disease at the time of the final analysis. At the end of the study, the majority of responders (14 [87.5%] participants) had not had disease progression and the median DOR was not reached. The median time to first response, time to a response of VGPR or better, time to a response of CR or better, and time to a response of sCR were 0.8, 2.1, 7.7, and 8.4 months, respectively. The estimated 48-month survival rate was 93.8%. MRD negativity rates (sensitivity threshold 10^{-5}) by the end of induction, by the end of consolidation, and by the end of maintenance phase were 18.8%, 50.0% and 81.3% respectively. Among the 15 participants who achieved CR or better at the end of maintenance phase, MRD (10^{-5}) was achieved by 13 (86.7%) participants. Sustained (6-month) MRD negativity rate at the sensitivity threshold of 10^{-5} was achieved in 9 (56.3%) participants and sustained (1-year) MRD negativity rate at the sensitivity threshold of 10^{-5} was achieved in 8 (50.0%) participants.

Randomized Participants:

Primary Endpoint:

The study met its primary endpoint. The addition of daratumumab to RVd improved efficacy outcomes in participants with newly diagnosed multiple myeloma compared with the RVd regimen alone. The primary efficacy analysis of sCR by the end of post-ASCT consolidation phase, as assessed by the computerized algorithm, observed an sCR rate of 42.4% in participants in the D-RVd treatment group and 32.0% in participants in the RVd treatment group (odds ratio [D-RVd versus RVd] 1.57 with 95% CI: 0.87, 2.82; 2-sided p-value=0.1359 equivalent to 1-sided p-value=0.068) which was statistically significant at the pre-set 1-sided alpha level of 0.1. Pre-specified subgroup analyses of sCR demonstrated that the treatment effect

of D-RVd over RVd across subgroups was generally consistent with the primary efficacy endpoint in all participants. Point estimates are in favor of D-RVd except in the cytogenetic high-risk subgroup and ISS stage III subgroup, both with a wide confidence interval.

Secondary Endpoints:

Results of secondary efficacy analyses also demonstrated improved benefit for the addition of daratumumab to the standard regimen of RVd.

Eleven (10.6%) and 18 (17.5%) PFS events per computerized algorithm occurred in the D-RVd and RVd treatment groups, respectively, leading to a 55% reduction in the risk of disease progression or death for the D-RVd group versus the RVd group (HR, 0.45; 95% CI, 0.21-0.95; p-value=0.0324). The median PFS was not reached in either of the treatment groups. The estimated 48-month PFS rate was 87.2% in the D-RVd treatment group and 70% in the RVd treatment group. Estimated 48-month overall survival rates were high for both groups (D-RVd, 92.7%; RVd, 92.2%), with 7 deaths in each treatment group.

TTP events occurred in 10 (9.6%) and 17 (16.5%) participants in the D-RVd and RVd treatment groups, respectively. The median TTP was not reached in either of the treatment groups.

Per assessment by the computerized algorithm, the rates of overall response (D-RVd: 99.0%; RVd: 91.8%), sCR (D-RVd: 67.0%; RVd: 48.0%), CR or better (D-RVd: 83.0%; RVd: 60.2%), and VGPR or better (D-RVd: 96.0%; RVd: 77.6%) were higher in the D-RVd treatment group by the end of the maintenance phase, compared with the RVd treatment group.

At the time of the final analysis, with a median follow-up time of 49.6 months, the median DOR was not reached for either treatment group.

Median time to sCR was shorter in the D-RVd group than in the RVd group (10.2 months versus 14.3 months); median time to CR or better (8.9 months versus 9.6 months) and median time to VGPR or better (2.2 months versus 3.0 months) were also shorter with D--RVd than RVd.

Greater depth of response in favor of the D-RVd treatment group was also demonstrated by improvement in MRD negativity rate. The MRD negativity rate at the sensitivity threshold of 10^{-5} in the ITT population by the end of maintenance phase was higher in the D-RVd treatment group (64.4%) compared with the RVd treatment group (30.1%). The results for MRD negativity rates at 10^{-4} and 10^{-6} were consistent with the sensitivity threshold of 10^{-5}. The proportion of participants who achieved MRD negativity at 10^{-5} and CR or better response by the end of maintenance phase in the ITT population was higher in the D-RVd treatment group (61.5%) compared with the RVd treatment group (27.2%) (odds ratio=4.20; 95% CI: 2.34, 7.56; p-value<0.0001). The median time to MRD negativity (10^{-5}) in bone marrow was 8.5 months in the D-RVd treatment group and 34.6 months in the RVd treatment group.

The sustained (≥6-month) MRD negativity rate at the sensitivity threshold of 10^{-5} in the ITT population was higher in participants in the D-RVd treatment group (48.1%) compared with the participants in the RVd treatment group (15.5%). These results were consistent with the data seen for ≥1-year sustained MRD negativity rate at the sensitivity threshold of 10^{-5} in the ITT population (D-RVd: 44.2%, RVd: 13.6%).

Exploratory Endpoint:

Data of the exploratory analysis on progression-free survival after next line of therapy (PFS2) showed that 9 (8.7%) and 11 (10.7%) PFS events occurred after next line of therapy in the D-RVd and RVd treatment groups, respectively. The median PFS2 was not reached in either treatment group. The exploratory objective to explore immune modulatory effects of D-RVd as compared with RVd has not been investigated and will not be part of this final CSR.

Safety Results:

Safety Run-in Participants

All (100%) participants experienced at least 1 TEAE. The most frequently reported TEAEs (≥30.0%) by preferred term were lymphopenia and neutropenia (13 [81.3%] participants each); cough (12 [75.5%] participants); upper respiratory tract infection (11 [68.8%] participants); fatigue, diarrhea, and leukopenia, (10 [62.5%] participants each); thrombocytopenia, hypokalemia, and hypocalcaemia (8 [50.0%] participants each); anemia, pyrexia, and nausea, (7 [43.8%] participants); edema peripheral, constipation, vomiting, abdominal pain, peripheral sensory neuropathy, pain in extremity, insomnia, and hypertension (6 [37.5%] participants each); and pneumonia, back pain, nasal congestion, hypophosphatemia, and hypomagnesemia (5 [31.3%] participants each).

Fifteen (93.8%) participants experienced at least 1 Grade 3/4 TEAE; 13 (81.3%) participants experienced Grade 3 TEAEs and 2 (12.5%) participants experienced Grade 4 TEAEs. The most frequently reported Grade 3/4 TEAEs (≥10.0%) by preferred term were neutropenia (7 [43.8%] participants), pneumonia (5 [31.3%] participants), lymphopenia (5 [31.3%] participants), thrombocytopenia (4 [25.0%] participants), hypertension (3 [18.8%] participants), and leukopenia, febrile neutropenia, bronchitis, hypophosphatemia, diarrhea, and rash (2 [12.5%] participants each).

One participant died due to progressive disease. No TEAEs had an outcome of death.

Twelve (75.0%) participants experienced treatment-emergent SAEs. Treatment-emergent SAEs reported by more than 1 participant were pneumonia (5 [31.3%] participants) and febrile neutropenia (3 [18.8%] participants).

One (6.3%) participant experienced TEAEs leading to study treatment discontinuation (neuralgia and thrombocytopenia). Fourteen (87.5%) participants had a TEAE leading to treatment cycle delays or dose modifications, including 10 (62.5%) participants who had at least 1 Grade 3/4 TEAE leading to treatment cycle delays or dose modifications. The most common TEAEs (all grades; ≥10.0%) leading to treatment cycle delays or dose modifications were neutropenia (7 [43.8%] participants), peripheral sensory neuropathy (3 [18.8%] participants), and thrombocytopenia (2 [12.5%] participants).

Five (31.3%) participants in safety run-in phase had Infusion-related reactions (IRRs) associated with daratumumab administration. None of the participants had Grade ≥3 IRRs. Most participants experienced an IRR associated with the first infusion. The median duration of daratumumab infusion was 6.7 hours for the first infusion, 4.2 hours for the second, and 3.4 hours for all subsequent infusions.

Eleven participants received at least 1 rapid daratumumab infusion and none received daratumumab SC. No participants reported IRRs associated with daratumumab rapid infusion.

Fourteen (87.5%) participants had at least 1 TEAE in the SOC of infections and infestations. The infections reported in more than 1 participant were upper respiratory tract infection (11 [68.8%] participants), pneumonia (5 [31.3%] participants), bronchitis (4 [25.0%] participants), sinusitis (3 [18.8%] participants), and urinary tract infection, cellulitis, nasopharyngitis, gastroenteritis viral, laryngitis, ear infection, and viral infection (2 [12.5%] participants each). The Grade 3/4 infection TEAEs reported in >1 participant were pneumonia (5 [31.3%] participants) and bronchitis (2 [12.5%] participants). No COVID-19 infections were reported.

Nine (56.3%) participants had at least 1 TEAE of peripheral neuropathy. All TEAEs of peripheral neuropathy were Grade 1 or 2.

A second primary malignancy was reported for 3 (18.8%) participants (1 [6.3%] participant during the consolidation phase and 2 [12.5%] participants during the maintenance phase).

There were no clinically meaningful findings related to safety in vital sign measurements, laboratory tests, physical examination assessments, ECOG PS, or ECG observations. No new safety concerns were identified based on locally reported abnormal hematology and biochemistry values during treatment. Clinically significant abnormalities in laboratory tests, vital signs, post-baseline physical examination and post-baseline ECGs were collected as AEs.

Randomized Participants:

The safety results from this study demonstrated that the safety profile of D-RVd treatment was consistent with the known safety profiles of daratumumab and the RVd regimen. The tolerability of this combination is supported by the similar frequency of study treatment discontinuation due to TEAEs between treatment groups (D-RVd: 33.3%; RVd: 31.4%).

All (100%) participants in the D-RVd and RVd treatment groups experienced at least 1 TEAE. The most common TEAEs (incidence rate ≥20%) that occurred at ≥10% higher frequency in the D-RVd treatment group compared with the RVd treatment group were pyrexia, chills, upper respiratory tract infection, diarrhea, constipation, abdominal pain, paresthesia, muscle spasms, neutropenia, leukopenia, cough, decreased appetite, and insomnia. Treatment-emergent adverse events reported in at least 20% of participants that occurred at a ≥10% higher frequency in the RVd treatment group compared with the D-RVd treatment group was neuropathy peripheral.

The incidence of Grade 3/4 TEAEs in the D-RVd and RVd treatment groups were 85.9% and 79.4%, respectively. The most frequently reported Grade 3/4 TEAEs (≥10% in either treatment group) in the D-RVd and RVd treatment groups were neutropenia (D-RVd: 46.5%; RVd: 22.5%), lymphopenia (D-RVd: 23.2%; RVd: 22.5%), leukopenia (D-RVd: 17.2%; RVd: 7.8%), thrombocytopenia (D-RVd: 16.2%; RVd: 8.8%), pneumonia (D-RVd: 12.1%; RVd: 13.7%), and hypophosphatemia (D-RVd: 10.1%; RVd: 10.8%).

The incidence of treatment-emergent SAEs was lower in the D-RVd treatment group (46.5%) compared with the RVd treatment group (52.0%). Pneumonia (D-RVd: 15.2%; RVd: 13.7%) and pyrexia (D-RVd: 11.1%; RVd: 9.8%) were the most common (≥5.0%) treatment-emergent SAEs and were generally similar in frequency in both the D-RVd treatment group and the RVd treatment group.

Discontinuation of study treatment (ie, all study drugs) due to a TEAE was similar in the D-RVd treatment group (33.3%) and the RVd treatment group (31.4%). Most of the TEAEs that resulted in study treatment discontinuation were Grade 1 or 2.

A higher proportion of participants in the D-RVd treatment group (88.9%) had a TEAE leading to treatment cycle delays or dose modifications for any study drug compared with the RVd treatment group (68.6%).

A total of 14 deaths were reported in randomized (D-RVd: 7 and RVd: 7) participants. In the D-RVd treatment group, 5 participants died due to progressive disease after treatment discontinuation, 1 participant died because of respiratory failure due to influenza A virus (outside TEAE reporting period per the protocol), and 1 participant died due to a TEAE of pneumonia (bronchopneumonia). In the RVd treatment group, 4 participants died due to progressive disease after treatment discontinuation, 1 participant due to spontaneous subdural hemorrhage in the setting of thrombocytopenia and aggressively relapsed multiple myeloma (outside TEAE reporting period per the protocol), 1 participant due to acute respiratory failure and hypoxia followed by subsequent septic shock (outside TEAE reporting period per the protocol), and 1 participant had a TEAE of death (cause of death was unknown).

Infusion-related reactions associated with daratumumab administration were reported in 49.5% of participants; none of the participants discontinued therapy due to IRRs. Most IRRs were Grade 1 or 2 and were experienced following the first infusion of daratumumab, consistent with the known IRR characteristics for daratumumab. Among 81 participants who received rapid daratumumab infusions, IRRs after rapid daratumumab infusion were reported for 2 (2.5%) participants, both with Grade 1 IRRs. Among 19 participants who received daratumumab SC administrations, IRRs after daratumumab SC administration

were reported for 9 (47.4%) participants. Two (10.5%) participants had Grade 3 IRRs, 4 (21.1%) participants had Grade 2 IRRs, and 3 (15.8%) participants had Grade 1 IRRs. None of the participants had Grade ≥4 IRRs.

Infections were more common in the D-RVd treatment group (92.9% versus 65.7%), due to a greater incidence of Grade 1 or 2 infections. The incidence of Grade 3/4 infections was similar between the D-RVd treatment group (29.3%) and the RVd treatment group (26.5%), and the incidence of treatment-emergent SAEs of infection was similar between both treatment groups (D-RVd: 26.3%; RVd: 26.5%). Furthermore, 2.0% of participants in the D-RVd treatment group and 2.9% of participants in the RVd treatment group discontinued study therapy due to infections. Thus, infections were clinically manageable and did not result in an increase in treatment discontinuation or death.

The incidence of peripheral neuropathies was lower in the D-RVd treatment group (62.6%) compared with the RVd treatment group (76.5%). Grade 3/4 TEAEs of peripheral neuropathy were reported for 7 (7.1%) participants in the D-RVd treatment group and 9 (8.8%) participants in the RVd treatment group.

A second primary malignancy was reported for 6 (6.1%) participants (2 [2.0%] participants with first onset during the induction phase and 4 [4.5%] participants during the maintenance phase) in the D-RVd treatment group and 3 (2.9%) participants (all with first onset during the maintenance phase) in the RVd treatment group.

TEAEs of hemorrhagic events were reported for 30 (30.3%) participants in the D-RVd treatment group and 21 (20.6%) participants in the RVd treatment group, all Grade 1 or 2.

COVID-19 infection was reported in 5 (5.1%) participants in the D-RVd treatment group and 2 (2.0%) participants in the RVd treatment group. One (1.0%) participant, in the D-RVd treatment group, had a serious TEAE COVID-19 infection of Grade 3 severity. There were no reported COVID-19 infection-related deaths.

There were no clinically meaningful findings related to safety in vital sign measurements, laboratory tests, physical examination assessments, ECOG PS, or ECG observations in this study. In addition, no new safety concerns were identified based on locally reported abnormal hematology and biochemistry values during treatment. Clinically significant abnormalities in laboratory tests, vital signs, post-baseline physical examination and post-baseline ECGs were collected as AEs.

Pharmacokinetic and Immunogenicity Results:

Pharmacokinetics

These findings were consistent with observations from previous monotherapy and combination therapy studies following administration of daratumumab IV using similar dosing regimen and schedule. The post-infusion serum daratumumab concentrations (C_{max}) on Cycle 4 Day 1 following weekly doses of daratumumab increased to 3.27- and 2.99-fold in the randomized D-RVd and safety run-in groups, respectively (ie, to 890 µg/mL and 938 µg/mL for the randomized D-RVd and safety run-in participants, respectively) compared with the concentrations at the end of the first infusion on Cycle 1 Day 1 (ie, 272 µg/mL and 314 µg/mL for the randomized D-RVd and safety run-in participants, respectively). The mean [SD] pre-infusion serum daratumumab concentrations (129 [77.4] µg/mL and 120 [46.4] µg/mL in the randomized D-RVd and safety run-in participants, respectively) and post-infusion serum daratumumab concentrations (461 [125] µg/mL and 477 [61.6] µg/mL in the randomized D-RVd and safety run-in participants, respectively) on Cycle 6 Day 1 decreased following less frequent dosing of daratumumab (every 3 weeks) compared with the pre-infusion concentrations (554 [185] µg/mL and 573 [134] µg/mL in the randomized D-RVd and safety run-in participants, respectively) and post-infusion concentrations (890 [236] µg/mL and 938 [162] µg/mL in the randomized D-RVd and safety run-in participants, respectively) following weekly dosing on Cycle 4 Day 1. Due to the long half-life of daratumumab, daratumumab concentrations were quantifiable at 4 weeks (261 [132] µg/mL and 233 [98.1] µg/mL in the randomized D-

RVd and safety run-in participants, respectively) and 8 weeks (152 [92.1] µg/mL and 109 [85.4] µg/mL in the randomized D-RVd and safety run-in participants, respectively) after the last dose of daratumumab in both groups. The pre- and post-infusion serum daratumumab concentrations were comparable between participants in the randomized D-RVd treatment group and those in the safety run-in group at each specified time point from Cycles 1-6, and at 4 weeks and 8 weeks post-treatment (after D-RVd/daratumumab-lenalidomide treatment has been discontinued).

Immunogenicity

The immunogenicity results for participants in the randomized D-RVd and safety run-in groups were based on the immune responsible-evaluable analysis set and 2 different analytical methods (initial drug tolerance [DT] method and enhanced DT method). The incidence of anti-daratumumab antibodies was low and not associated with any safety findings in the combination of daratumumab with RVd. Cumulatively, 2 out of 98 (2.0%) participants in the randomized D-RVd treatment group tested positive for anti-daratumumab antibodies. The participants who tested positive for anti-daratumumab antibodies also tested positive for neutralizing antibodies. No participants in the safety run-in group were positive for anti-daratumumab antibodies.

Medical Resource Utilization and Health Economics:

Sixty-one (61.6%) participants in the D-RVd treatment group and 68 (66.7%) participants in the RVd treatment group had a hospitalization or an outpatient visit (including physician or emergency room visits other than study related visits for tests and procedures, and medications). The most common (≥10.0%) hospitalization or outpatient units visited by participants in the D-RVd treatment group were other physician or clinic (50.0%), study physician or study site (20.6%), and other (10.6%). The most common (≥10.0%) hospitalization or outpatient units visited by participants in the RVd treatment group were other physician or clinic (54.4%), emergency room (14.8%), and study physician or study site (11.5%). Among the participants with a hospitalization or an outpatient visit, the most common reason for hospitalization or an outpatient visit were adverse events (D-RVd: 83.6% versus RVd: 75.0%).

Patient-Reported Outcomes (Functional Status and Well-being):

The functional status and well-being results from the PRO endpoints, including the cancer-specific EORTC QLQC30, EORTC QLQ-MY20, and the general health EQ-5D-5L, indicated improvements in health-related quality-of-life for participants who remained in the study in both the D-RVd and RVd treatment groups.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

Conclusions:

- A safety run-in phase, including 16 participants who all received D-RVd, was evaluated by a Data Review Committee. The pre-specified stopping criteria of the study were not met, and therefore the randomized phase of the study proceeded to compare D-RVd versus RVd.
- The study met its primary endpoint. The addition of daratumumab to RVd improved the sCR rate by the end of post-ASCT consolidation in participants with newly diagnosed multiple myeloma compared with the RVd regimen alone. The odds ratio of (D-RVd versus RVd) 1.57 with 95% CI: 0.87, 2.82; 1-sided p-value=0.068, was statistically significant at the pre-set 1-sided alpha level of 0.1.
- This study was done in study sites across various geographical regions in the United States. Fifteen percent of randomized study participants were black, which marks a more accurate representation of this racial group in the general population as well as among multiple myeloma patients.

- Secondary analysis results demonstrated improved benefit, supporting the addition of daratumumab to the standard regimen of RVd. Daratumumab in combination with RVd showed clinically meaningful PFS benefit compared with RVd (HR, 0.45; 95% CI, 0.21-0.95; p-value=0.0324), with a 55% reduction in the risk of disease progression or death for the D-RVd group versus the RVd group. Also, the addition of daratumumab to RVd showed improved efficacy in comparison with RVd alone as assessed by overall response rate (sCR + CR + VGPR + PR), CR or better rate , and VGPR or better rate.
- MRD negativity rates improved with prolonged therapy and were consistently higher for the D-RVd group versus the RVd group. At the time of final analysis, MRD negativity rates were more than 2-fold higher for the D-RVd group versus the RVd group at the sensitivity thresholds of 10^{-5} and 10^{-6}. In participants who achieved a best response of CR or better, MRD negativity rates were also higher for D-RVd versus RVd at both sensitivity thresholds. Similarly, D-RVd was associated with higher rates of sustained MRD negativity lasting ≥6 months and ≥12 months, versus RVd. Median time to MRD negativity was also shorter with D-RVd versus RVd at both 10^{-5} and 10^{-6} sensitivity thresholds.
- The addition of daratumumab to RVd-based induction therapy had minimal impact on stem cell mobilization after four 3-week cycles of induction therapy, with a numerically lower yield of stem cells. None-the-less, participants were able to undergo CD34+ mobilization and collection with no impact on time to neutrophil or platelet engraftment after ASCT.
- Median OS was not reached for either D-RVd or RVd. At the time of this final analysis, 7 participants died in each treatment group.
- The incidence of Grade 3/4 TEAEs in the D-RVd group (85.9%) was higher than the RVd group (79.4%), while the incidence of treatment-emergent SAEs was lower in the D-RVd treatment group (46.5%) compared with the RVd treatment group (52.0%). A similar proportion of participants between the 2 groups had TEAEs leading to treatment discontinuation. TEAEs that resulted in death were reported in 1 patient in each of the treatment groups, and neither was related to study treatment.
- Infusion-related reactions associated with daratumumab administration were reported in 49.5% of participants, mostly Grade 1 or 2, and mostly associated with the first infusion of daratumumab, consistent with the known IRR profile for daratumumab. The same trend was seen for IRRs that occurred when daratumumab was given as a rapid infusion or through SC injection.
- The overall incidence of TEAEs in the SOC of infections and infestations was higher in the D-RVd treatment group (92.9%) compared with the RVd treatment group (65.7%), which was attributable to a higher incidence of Grade 1 or 2 infections in the D-RVd group. The incidences of Grade 3 and 4 infections, infections leading to treatment discontinuations and SAEs of infections were comparable between treatment groups.
- In summary, the study met its primary endpoint. The addition of daratumumab to RVd improved the sCR rate by the end of post-ASCT consolidation phase in participants with newly diagnosed multiple myeloma compared with the RVd regimen alone. In the final analysis, at a median follow-up of 49.6 months, the addition of daratumumab to RVd led to a clinically meaningful PFS benefit favoring the D-RVd treatment group. Response rates as well as MRD negativity rates continued to deepen throughout the course of the study. No new safety concerns were identified with extended follow-up. D-RVd treatment had a safety profile consistent with the known safety profile of daratumumab and the RVd regimen. These data support the use of frontline daratumumab as part of RVd induction/consolidation and daratumumab/lenalidomide maintenance in participants with transplant-eligible NDMM.