Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial

Overall survival with daratumumab, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma (MAIA): a randomised, open-label, phase 3 trial

Thierry Facon, Shaji K Kumar, Torben Plesner, Robert Z Orlowski, Philippe Moreau, Nizar Bahlis, Supratik Basu, Hareth Nahi, Cyrille Hulin, Hang Quach, Hartmut Goldschmidt, Michael O'Dwyer, Aurore Perrot, Christopher P Venner, Katja Weisel, Joseph R Mace, Noopur Raje, Mourad Tiab, Margaret Macro, Laurent Frenzel, Xavier Leleu, Tahamtan Ahmadi, Jianping Wang, Rian Van Rampelbergh, Clarissa M Uhlar, Brenda Tromp, Maria Delioukina, Jessica Vermeulen, Saad Z Usmani

University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France (Prof T Facon MD); **Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA** (Prof S K Kumar MD); **Vejle Hospital and University of Southern Denmark, Vejle, Denmark** (Prof T Plesner MD); **Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (R Z Orlowski MD); **Hematology, University Hospital Hôtel-Dieu, Nantes, France** (Prof P Moreau MD); **Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada** (Prof N Bahlis MD); **Royal Wolverhampton NHS Trust and University of Wolverhampton, Wolverhampton, UK** (Prof S Basu MD); **Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden** (H Nahi MD); **Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France** (C Hulin MD); **University of Melbourne, St Vincent's Hospital, Melbourne, Australia** (H Quach MD); **University Hospital Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany** (Prof H Goldschmidt MD); **Department of**

Medicine/Haematology, NUI, Galway, Republic of Ireland (Prof M O'Dwyer MD); **CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France** (A Perrot MD); **Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada** (C P Venner MD); **Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany** (Prof K Weisel MD); **Florida Cancer Specialists, St. Petersburg, FL, USA** (J R Mace MD); **Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston, MA, USA** (Prof N Raje MD); **CHD Vendée, La Roche sur Yon, France** (M Tiab MD); **Centre Hospitalier Universitaire (CHU) de Caen, Caen, France** (M Macro MD); **Department of Clinical Haematology, Hopital Necker-Enfants Malades, Paris, France** (L Frenzel MD); **CHU Poitiers, Hôpital la Milétrie, Poitiers, France** (Prof X Leleu MD); **Genmab US, Inc., Plainsboro, NJ, USA** (T Ahmadi MD); **Janssen Research & Development, Raritan, NJ, USA** (J Wang PhD); **Janssen Research & Development, Beerse, Belgium** (R Van Rampelbergh MD); **Janssen Research & Development, Spring House, PA, USA** (C M Uhlar PhD, M Delioukina MD); **Janssen Research & Development, LLC, Leiden, The Netherlands** (B Tromp MSc, J Vermeulen MD); **and Levine Cancer Institute/Atrium Health, Charlotte, NC, USA** (Prof S Z Usmani MD)

Correspondence to:

Prof Thierry Facon, MD

University of Lille, CHU Lille, Service des Maladies du Sang,

2 Avenue Oscar Lambret

59000 Lille, France

+33 (0)3 20 44 57 12

thierry.facon@chru-lille.fr

Abstract word count: 457

Text word count: 5992

Table/Figure Count: 6 tables/figures

Reference Count: 33

SUMMARY

Background

At the primary analysis of the phase 3 MAIA study (median follow-up, 28·0 months), significant progression-free survival benefit was observed with daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed myeloma. We report updated efficacy and safety results from a prespecified interim analysis for overall survival.

Methods

MAIA is an ongoing, multicentre, randomised, open-label, phase 3 trial that enrolled patients between 18 March 2015 and 15 January 2017 at 176 sites in 14 countries. Eligible patients were aged ≥18 years, had newly diagnosed multiple myeloma, had an Eastern Cooperative Oncology Group performance status score of 0–2, and were ineligible for high-dose chemotherapy with autologous stem-cell transplantation due to age (≥65 years) or comorbidities. Patients were randomised 1:1 by an interactive web response system to receive 28-day cycles of Rd with daratumumab (D-Rd group) or without (Rd group). Randomisation was stratified by International Staging System disease stage, geographic region, and age. Patients in both groups received oral lenalidomide (25 mg on days 1–21 of each cycle) and oral dexamethasone (40 mg on days 1, 8, 15, and 22 of each cycle). The D-Rd group also received intravenous daratumumab (16 mg/kg, once weekly during cycles 1–2, once every 2 weeks in cycles 3–6, and once every 4 weeks thereafter). The primary endpoint was progression-free survival, and a secondary endpoint was overall survival (both assessed in the intention-to-treat population). Results presented here are from a prespecified interim analysis for overall survival. ClinicalTrials.gov number, NCT02252172.

Findings

At a median follow-up of 56·2 months (interquartile range, 52·7–59·9), a significant benefit in overall survival was observed for the D-Rd group (hazard ratio [HR] 0·68; 95% CI 0·53–0·86; p=0·0013). The Kaplan-Meier estimate of the 60-month rate of overall survival was 66·3% (95% CI 60·8–71·3) in the D-Rd group and 53·1% (47·2–58·6) in the Rd group. Median progression-free survival in the D-Rd group versus the Rd group was not reached (95% CI 54·8–not reached) versus 34·4 months (95% CI 29·6–39·2; HR 0·53; 95% CI 0·43–0·66; p<0·0001). The most common (>15%) grade 3 or 4 treatment-emergent adverse events were neutropenia (197 [54%] patients in the D-Rd group and 135 [37%] patients in the Rd group), pneumonia (70 [19%] and 39 [11%]), anaemia (61 [17%] and 79 [22%]), and lymphopenia (60 [16%] and 41 [11%]). Serious adverse events occurred in 281 (77%) patients in the D-Rd group and 257 (70%) patients in the Rd group. Treatment-related deaths occurred in 13 (4%) patients in the D-Rd group and 10 (3%) patients in the Rd group (all due to adverse events).

Interpretation

D-Rd prolonged overall survival and progression-free survival in patients ineligible for stem-cell transplantation with newly diagnosed multiple myeloma. There were no new safety concerns.

Funding

Janssen Research & Development.

Research in context

Evidence before this study

We searched PubMed for articles published from database inception to 5 April 2021. All fields were searched for "newly diagnosed" AND "multiple myeloma" AND "overall survival" AND "monoclonal antibody". Our search identified 100 articles published during this timeframe. Of those, 18 articles were published before the first patient was enrolled in the MAIA study in March 2015, with one describing a clinical trial of a monoclonal antibody. In that phase 2 trial, siltuximab, an interleukin-6 monoclonal antibody, in combination with bortezomib, melphalan, and prednisone did not demonstrate a clinical benefit over bortezomib, melphalan, and prednisone alone in transplant-ineligible, newly diagnosed multiple myeloma. Of the 82 articles published after MAIA was initiated, nine reported results of clinical trials with a monoclonal antibody; survival benefit was shown only in the phase 3 ALCYONE study of daratumumab in combination with bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone alone.

Added value of this study

MAIA is, to our knowledge, the first randomised, phase 3 study that showed a significant improvement in overall survival with daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in transplant-ineligible patients with newly diagnosed multiple myeloma. At a median follow-up of 56·2 months, treatment until progression with daratumumab in combination with lenalidomide and dexamethasone showed a reduction in the risk of death versus lenalidomide and dexamethasone alone (hazard ratio 0·68). The daratumumab-containing regimen continued to demonstrate a progression-free survival benefit, with the median progression-free survival still not reached in the daratumumab group

versus 34·4 months in the standard-of-care group. With longer follow-up, daratumumab in combination with lenalidomide and dexamethasone is expected to demonstrate an unprecedented median progression-free survival in transplant-ineligible patients with newly diagnosed multiple myeloma. There were no new safety concerns.

Implications of all the available evidence

This is the second study in which a daratumumab-based regimen has demonstrated a significant improvement in overall survival in transplant-ineligible patients with newly diagnosed multiple myeloma. Together with the findings of the ALCYONE study, the efficacy and safety results of the MAIA study strongly support the frontline use of daratumumab in combination with standard-of-care regimens for transplant-ineligible patients with multiple myeloma.

Introduction

Daratumumab is a human IgGκ monoclonal antibody that targets CD38 with a direct on-tumour[1-4] and immunomodulatory[5-7] mechanism of action. Daratumumab is approved as monotherapy and in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma (RRMM) or newly diagnosed multiple myeloma (NDMM).[8] In the phase 3 POLLUX study in patients with RRMM, daratumumab in combination with lenalidomide and dexamethasone (D-Rd) demonstrated a significant progression-free survival (PFS) benefit over lenalidomide and dexamethasone (Rd) alone.[9]

Two phase 3 studies (ALCYONE and MAIA) demonstrated the superior clinical efficacy of daratumumab in combination with standard-of-care regimens versus standard of care alone for transplant-ineligible patients with NDMM.[10,11] The ALCYONE study demonstrated for the first time that a daratumumab-based combination provides significant improvement in overall survival (OS); at a median follow-up of 40·1 months, adding daratumumab to bortezomib, melphalan, and prednisone (D-VMP) significantly reduced the risk of death versus bortezomib, melphalan, and prednisone (VMP) alone.[12] In ALCYONE, both groups received ≤nine 42-day cycles of VMP; the D-VMP group also received daratumumab until disease progression or unacceptable safety events. In the primary analysis of MAIA (28·0-month median follow-up), D-Rd significantly prolonged PFS versus Rd; both groups received treatment until disease progression or unacceptable safety events.[11] With longer (47·9-month median) follow-up, D-Rd continued to demonstrate a PFS benefit versus Rd alone.[13] A progression-free survival on next line of therapy (PFS2) benefit favouring D-Rd was also observed. At the time of those MAIA analyses, OS data were not mature.

Another regimen shown to improve OS in patients with NDMM is bortezomib in combination with Rd (VRd).[14] In the phase 3 SWOG S0777 study (55-month median follow-up), VRd significantly prolonged PFS and OS versus Rd in patients with NDMM without intent for immediate transplant; the VRd and Rd groups received eight 21-day cycles of VRd and six 28-day cycles of Rd, respectively, after which both groups received Rd until disease progression or unacceptable safety events.[14] With longer (84-month median) follow-up, VRd continued to demonstrate prolonged PFS and OS versus Rd; however, a significant OS benefit was not observed in patients aged ≥65 years.[15] Patients who received VRd had a high incidence of grade ≥3 neurologic and gastrointestinal adverse events.

Here, we report updated efficacy and safety results from a prespecified interim OS analysis of MAIA after approximately 56 months of follow-up (clinical cutoff date, 19 February 2021).

Methods

Study design and participants

MAIA is an ongoing, multicentre, randomised, open-label, active-controlled, phase 3 trial that enrolled patients between 18 March 2015 and 15 January 2017 at 176 sites in 14 countries across North America, Europe, the Middle East, and the Asia-Pacific region. The study design was published previously.[11] Independent ethics committees or institutional review boards at each site approved the protocol (appendix p 28–183). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Complete eligibility criteria were previously published.[11] Briefly, eligible patients were aged ≥18 years, had documented NDMM (appendix p 4), had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, and were ineligible for high-dose chemotherapy with autologous stem-cell transplantation (ASCT) due to age (≥65 years) or substantial comorbidities. Patients were required to have the following clinical laboratory values: a haemoglobin level of ≥7.5 g/dL; an absolute neutrophil count of ≥1.0 x 10^9/L; a platelet count of ≥70 x 10^9/L (>50 x 10^9/L if ≥50% of nucleated bone marrow cells were plasma cells), aspartate aminotransferase and alanine aminotransferase levels of ≤2.5 x the upper limit of the normal range, a total bilirubin level of ≤2.0 x the upper limit of the normal range, a creatinine clearance of ≥30 mL/min, and a corrected serum calcium level of ≤14 mg/dL. Patients were excluded if they had prior or current systemic therapy or stem-cell transplantation for multiple myeloma, monoclonal gammopathy of undetermined significance, smouldering multiple myeloma, primary amyloidosis, Waldenström's macroglobulinemia, plasma cell leukaemia or POEMS syndrome, or malignancy within 5 years prior to randomization.

Randomisation and masking

Eligible patients were randomly assigned (1:1; randomly permuted blocks) by an interactive web response system to receive D-Rd or Rd. Randomisation was stratified by International Staging System (ISS) disease stage (I *vs* II *vs* III), geographic region (North America *vs* other), and age (<75 *vs* ≥75 years). There was no masking to treatment assignments.

Procedures

Patients in both treatment groups received 28-day cycles of oral lenalidomide (25 mg [10 mg recommended if creatinine clearance was 30-50 mL/min] on days 1–21 of each cycle) and oral dexamethasone (40 mg [20 mg if aged >75 years or body-mass index <18·5 kg/m^2] on days 1, 8, 15, and 22 each cycle). Additional details on dose modifications are listed in the appendix (p 4). The experimental group also received intravenous daratumumab (16 mg/kg, once weekly during cycles 1–2, once every 2 weeks in cycles 3–6, and once every 4 weeks thereafter). Pre- and post-infusion medications are listed in the appendix (p 4). Patients received treatment until disease progression or unacceptable safety events.

Patients in the Rd group were given the option to receive daratumumab after confirmation of disease progression according to International Myeloma Working Group (IMWG) criteria,[16,17] if recommended by the investigator, following a protocol amendment issued on 15 January 2019. Patients in the D-Rd group were given the option to switch from intravenous to subcutaneous daratumumab on day 1 of any cycle, at the investigator's discretion, following a protocol amendment issued on 3 April 2020. Subcutaneous daratumumab at a fixed dose of 1800 mg was administered by manual injection over 3–5 minutes in the abdominal subcutaneous tissue once every 4 weeks.

Complete skeletal surveys were performed and evaluated locally by X-ray or low-dose computed tomography for the presence of soft tissue plasmacytoma or bone lesions at screening and as clinically indicated based on symptoms to document response or progression during treatment.

Magnetic resonance imaging was permitted as an additional assessment at the discretion of the investigator.

Disease evaluations of serum and urine samples collected at screening, on day 1 of every cycle for 2 years, and then every 8 weeks thereafter until disease progression, were performed by a central laboratory. Response to study treatment and progressive disease were evaluated based on IMWG criteria using a validated computer algorithm.[9,16-18] Safety was monitored continuously throughout the study until 30 days after the last dose of study treatment. Adverse events were graded in severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4).[19]

Outcomes

The primary endpoint was PFS (the duration from the date of randomisation to either progressive disease or death, whichever came first). Secondary endpoints included time to progression (the time from the date of randomisation to the date of first documented evidence of disease progression), complete response (CR) rate (the proportion of patients achieving complete response), stringent CR (sCR) rate (the proportion of patients achieving stringent complete response), very good partial response (VGPR) or better rate (the proportion of patients achieving VGPR, CR, and sCR), overall response rate (ORR; the proportion of patients who achieved partial response or better), time to response (the time between randomisation and the first efficacy evaluation in which the patient had met all criteria for partial response or better), duration of response (the date of initial documentation of a response [partial response or better] to the date of the first documented evidence of progressive disease), minimal residual disease

(MRD)–negativity rate (the proportion of patients who were negative for MRD at any time point after randomisation), PFS2 (the time from randomisation to disease progression on the next line of therapy or death, whichever occurred first), OS (the time from randomisation to the date of the patient's death), time to next (second-line) treatment (the time from randomisation to the start of the next line of therapy), and safety (adverse events). Efficacy response was determined by IMWG criteria.[16,17] Complete definitions of all efficacy endpoints are included in the appendix (p 4–5). Efficacy assessments were performed as previously described.[11] OS data and updated data on CR or better rate, VGPR or better rate, and ORR are provided in this manuscript; however, MRD data were not updated based on the clinical cutoff for the analyses presented in this manuscript. Updated MRD results based on a shorter duration of follow-up are provided in this manuscript. Cytogenetic risk was assessed locally (no standard cutoff for clonal size) by fluorescence *in situ* hybridisation or karyotype testing; a high-risk cytogenetic profile was defined by a deletion (del)17p and/or translocations t(14;16), or t(4;14).

Statistical analysis

The primary analysis population was the intention-to-treat (ITT) population of all patients who underwent randomisation. The safety population included patients who received any dose of study treatment. Sample size assumptions were previously described;[11] the sample size of 730 was driven by the PFS assumption (HR=0.75) and power (80%). To achieve 80% power for OS with such a sample size, at least 330 deaths and an HR $\leq$0.73 were required. A stratified log-rank test was used to compare distribution of time-to-event variables between the two treatment groups. Time-to-event variables were estimated using the Kaplan-Meier method. A stratified Cox regression model with treatment as the sole explanatory variable and stratified by ISS

staging, geographical region, and patient age as per randomisation was used to estimate treatment effect (hazard ratio [HR]) and two-sided 95% confidence intervals (CIs). Binary endpoints, including ORR, were assessed using the stratified Cochran–Mantel–Haenszel test. For PFS, patients were censored at the date of last disease assessment prior to subsequent anti-myeloma therapy or withdrawal of consent to study participation, whichever occurred first. For PFS2, patients were censored at the start of the next line of therapy if the next line of therapy was started without disease progression on study treatment; or at the date of last follow-up if any of the following occurred: (1) the patient was still alive and the next line of therapy was not started after progression on study treatment or (2) the patient was still alive and had not yet progressed on the next line of therapy. For OS, patients were censored at the last date at which they were known to be alive. Three OS analyses were prespecified: the first interim OS analysis was to occur at the time of the interim PFS analysis; the second interim OS analysis was to occur after approximately 260 deaths (around the same time as the primary PFS analysis); and the third, final OS analysis was to occur after 330 deaths. Following a significant PFS (two-sided alpha level of 0.05) established at the primary PFS analysis,[11] follow-up of OS continued as planned. The current prespecified second interim analysis for OS occurred after 273 deaths (83% of planned events) were observed. A modified linear alpha spending function was used to determine the alpha level at each of the three OS analyses. The alpha level was 0.0001 for the first OS analysis; for the second interim OS analysis (presented in this manuscript), the prespecified stopping boundary was p=0·0414. All key secondary endpoints (CR or better rate, VGPR or better rate, MRD-negativity rate, ORR, and OS) were evaluated with a two-sided alpha level of 0.05 and using a hierarchical testing procedure at the time of the primary PFS analysis; all key secondary endpoints, except for OS, had crossed the prespecified stopping boundaries. OS and

PFS analyses were performed in prespecified subgroups (appendix p 5). Results for subsequent therapies are descriptive. SAS (version 9.4) was used for statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT02252172.

Role of the funding source

Janssen Research and Development sponsored this trial and designed it in collaboration with the academic authors. Data collected by the investigators were compiled and maintained by the sponsor. All authors had access to the data and were not restricted by confidentiality agreements. Professional medical writers who were funded by the sponsor prepared the manuscript. All authors reviewed and revised the manuscript and approved it for submission. The sponsor and authors vouch for the accuracy and completeness of the data from the prespecified interim analysis and for adherence of the trial to the protocol.

Results

Patients were enrolled between 18 March 2015 and 15 January 2017. 737 patients were randomly assigned to receive either D-Rd (n=368) or Rd (n=369). Baseline demographic and clinical characteristics were well balanced between groups (table 1).[11] Median age at randomisation was 73 years (interquartile range [IQR], 70–78), 321 (44%) of 737 patients were aged ≥75 years, 217 (29%) of 737 patients had ISS stage III disease, and 92 (14%) of 642 patients had high-risk cytogenetics. 162 (44%) patients in the D-Rd group and 142 (38%) in the Rd group presented with a creatinine clearance ≤60 mL/min.

Among the patients who were randomly assigned, 729 patients (364 [99%] in the D-Rd group and 365 [99%] in the Rd group) received at least one dose of study treatment (figure 1). At the clinical cutoff date for the updated analysis (19 February 2021), 209 (57%) of 368 patients in the D-Rd group and 298 (81%) of 369 patients in the Rd group had discontinued treatment. The two most common reasons for discontinuation were progressive disease (98 [27%] patients in the D-Rd group *vs* 127 [34%] in the Rd group) and adverse events (49 [13%] patients *vs* 84 [23%] patients). In the D-Rd group, 5 (1%) patients discontinued only daratumumab, 33 (9%) discontinued only lenalidomide, and 38 (10%) discontinued only dexamethasone prior to disease progression. In the Rd group, 14 (4%) patients discontinued only lenalidomide and 46 (12%) discontinued only dexamethasone prior to disease progression. Median duration of study treatment was 47·5 months (IQR, 20·01–56·36) in the D-Rd group and 22·6 months (IQR, 8·18–46·82) in the Rd group; median number of treatment cycles received was 50 (IQR, 22–60) in the D-Rd group and 24 (IQR, 9–49) in the Rd group. Consistent with the primary analysis, median lenalidomide relative dose intensity (RDI) was lower in the D-Rd group (66% [IQR, 46–93]) versus the Rd group (86% [IQR, 61–99]; appendix p 11). 112 (31%) of 364 patients in the D-Rd group and 83 (23%) of 365 patients in the Rd group received a lenalidomide starting dose of ≤10 mg. Lenalidomide dose reductions were reported in 269 (74%) patients in the D-Rd group and 205 (56%) patients in the Rd group. Additional data on lenalidomide dose by time interval are reported in the appendix (p 12). Median cumulative lenalidomide dose was higher in the D-Rd group (9185 mg [IQR, 4054–15275]) versus the Rd group (8040 mg [IQR, 3413–16723]). Median dexamethasone RDI was similar between the D-Rd group (78% [IQR, 56–96]) and the Rd group (86% [IQR, 65–99]). Median intravenous daratumumab RDI was 98% (IQR, 95–101).

At a median follow-up of 56·6 months (IQR, 53·0–60·1) in the D-Rd group and 55·9 months (IQR, 52·5–59·4) in the Rd group, 273 patients (117 [32%] of 368 patients in the D-Rd group and 156 [42%] of 369 patients in the Rd group) had died. 58 patients in the D-Rd group and 89 in the Rd group had disease progression prior to death. The HR for death in the D-Rd group compared with the Rd group was 0·68 (95% CI 0·53–0·86; p=0·0013; figure 2A), crossing the prespecified stopping boundary of p=0·0414. The Kaplan-Meier estimate of the 60-month OS rate was 66·3% (95% CI 60·8–71·3) in the D-Rd group and 53·1% (95% CI 47·2–58·6) in the Rd group. Median OS was not reached (NR) in either group. The prespecified subgroup analyses of OS are shown in figure 3.

377 patients (160 [43%] of 368 patients in the D-Rd group and 217 [59%] of 369 patients in the Rd group) had PFS events. Of the 160 PFS events in the D-Rd group, 48 (30%) were deaths and 112 (70%) were disease progression events. Of the 217 PFS events in the Rd group, 46 (21%) were deaths and 171 (79%) were disease progression events. 208 (57%) of 368 patients in the D-Rd group versus 152 (41%) of 369 patients in the Rd group were censored for PFS. Patients were censored due to study cutoff (179 [86%] of 208 patients in the D-Rd group and 93 [61%] of 152 patients in the Rd group), receipt of subsequent therapy (23 [11%] and 41 [27%]), withdrawal of consent (4 [2%] and 16 [11%]), physician decision (2 [1%] and 0), and lost to follow-up (0 and 2 [1%]). The HR for disease progression or death in the D-Rd group versus the Rd group was 0·53 (95% CI 0·43–0·66; p<0·0001; figure 2B). The Kaplan-Meier estimate of the 60-month PFS rate was 52·5% (95% CI 46·7–58·0) for D-Rd and 28·7% (95% CI 23·1–34·6) for Rd. Median PFS was NR (95% CI 54·8–NR) for D-Rd versus 34·4 months (95% CI 29·6–39·2) for Rd. PFS subgroup analyses demonstrated favourable outcomes for the D-Rd group over the Rd group

across all prespecified subgroups (appendix p 6). Median time to progression was NR in the D-Rd group and 40·9 months (95% CI 35·8–49·2) in the Rd group.

The updated ORR was 92·9% (95% CI 89·8–95·3) for 368 patients in the D-Rd group and 81·6% (95% CI 77·2–85·4) for 369 patients in the Rd group (p<0·0001; table 2). A significantly higher VGPR or better rate (81% in the D-Rd group *vs* 57% in the Rd group) and CR or better rate (51% *vs* 30%) was also observed with D-Rd versus Rd. Median duration of response was NR with D-Rd versus 43·9 months (95% CI 37·7–52·9) with Rd. At a median follow-up of 47·9 months, the MRD-negativity rate was significantly higher with D-Rd than with Rd (31% in the D-Rd group *vs* 10% in the Rd group; table 2).[13] MRD data were not updated based on the clinical cutoff for the OS and PFS analyses presented in this manuscript; however, a formal MRD analysis is planned for a future data cut.

114 (31%) of 364 patients in the D-Rd group and 186 (51%) of 365 patients in the Rd group had received subsequent therapy at the clinical cutoff date. Among patients who had documented disease progression (115 in the D-Rd group and 173 in the Rd group), 91 (79%) in the D-Rd group and 145 (84%) in the Rd group went on to receive a subsequent line of therapy, 9 (8%) in the D-Rd group and 14 (8%) in the Rd group died, 14 (12%) in the D-Rd group and 14 (8%) in the Rd group were on survival follow-up, and 1 (1%) in the D-Rd group was lost to follow-up. Among patients who did not receive subsequent therapy after disease progression (24 patients in the D-Rd group and 28 in the Rd group), median age was consistent with the ITT population. Median time to next treatment was NR with D-Rd versus 42·4 months (95% CI 33·5–50·4) with Rd (HR 0·47; 95% CI 0·37–0·59; p<0·0001). 132 (36%) of 368 patients in the D-Rd group and

181 (49%) of 369 patients in the Rd group had PFS2 events (HR 0·61; 95% CI 0·48–0·76; p<0·0001) (appendix p 7). Of the 132 PFS2 events in the D-Rd group, 77 (58%) were deaths and 55 (42%) were disease progression events. Of the 181 PFS2 events in the Rd group, 113 (62%) were deaths and 68 (38%) were disease progression events. Median PFS2 in the ITT population was NR with D-Rd versus 47·8 months (95% CI 43·9–56·0) with Rd. The Kaplan-Meier estimate of the 60-month PFS2 rate was 60·8% (95% CI 54·9–66·2) with D-Rd and 41·6% (95% CI 35·5–47·7) with Rd.

For all patients who received subsequent therapy, including patients without confirmed disease progression per IMWG criteria beforehand (23 [20%] of 114 patients in the D-Rd group and 41 [22%] of 186 in the Rd group who received subsequent therapy), first subsequent therapies received are summarised in the appendix (p 13). A proteasome inhibitor–containing regimen without an immunomodulatory drug was the most common first subsequent therapy (60 [53%] of 114 patients in the D-Rd group and 100 [54%] of 186 in the Rd group). Among patients who received subsequent therapy, 11 (10%) patients in the D-Rd group and 39 (21%) in the Rd group received a daratumumab-containing regimen as first subsequent therapy, and 17 (15%) patients in the D-Rd group and 85 (46%) patients in the Rd group received a daratumumab-containing regimen as any subsequent line of therapy.

No new safety concerns were identified with longer follow-up. Grade 3/4 treatment-emergent adverse events (TEAEs) were reported in 348 (96%) of 364 patients in the D-Rd group and 322 (88%) of 365 patients in the Rd group. The most common (in >15% of patients in either group) grade 3/4 TEAEs were neutropenia (197 [54%] patients in the D-Rd group and 135 [37%]

patients in the Rd group), pneumonia (70 [19%] and 39 [11%]), anaemia (61 [17%] and 79 [22%]), and lymphopenia (60 [16%] and 41 [11%]) (table 3 and appendix p 14–26). Grade 3/4 infections were reported more frequently in the D-Rd group than in the Rd group (151 [41%] patients *vs* 106 [29%], respectively); the only grade 3/4 infection reported in ≥5% of patients in either group was pneumonia. The most common (in >1 patient in either group) opportunistic infections were oral candidiasis (15 [4%] patients in the D-Rd group and 17 [5%] patients in the Rd group), herpes zoster (11 [3%] and 18 [5%]), oral fungal infection (3 [1%] and 3 [1%]), post herpetic neuralgia (3 [1%] and 1 [<1%]), oesophageal candidiasis (2 [1%] and 2 [1%]), and pneumocystis jirovecii pneumonia (2 [1%] and 0). Infection prophylaxis medication was used in 186 (51%) patients in the D-Rd group and 148 (41%) in the Rd group. The most common (in >5% of patients in either group) infection prophylaxis medications were sulfamethoxazole and trimethoprim (80 [22%] patients in the D-Rd group and 68 [19%] patients in the Rd group), antivirals for herpes zoster reactivation including valaciclovir (76 [21%] and 55 [15%]) and aciclovir (31 [9%] and 18 [5%]), and phenoxymethylpenicillin (22 [6%] and 24 [7%]). 135 (37%) of 364 patients in the D-Rd group switched from intravenous daratumumab to subcutaneous daratumumab; among these patients, no infusion-related reactions and no new safety concerns were reported.

Serious adverse events (SAEs) occurred in 281 (77%) of 364 patients in the D-Rd group and 257 (70%) of 365 patients in the Rd group. Pneumonia was the most common SAE (66 [18%] patients in the D-Rd group and 39 [11%] in the Rd group). Second primary malignancies (SPMs) were reported in 74 (20%) patients in the D-Rd group and 46 (13%) in the Rd group; the majority were cutaneous (52 [14%] patients in the D-Rd group and 26 [7%] in the Rd group),

and the incidences of invasive solid malignancies (21 [6%] and 17 [5%]) and invasive haematologic malignancies (6 [2%] and 3 [1%]) were similar between treatment groups. Invasive hematologic malignancies reported in the D-Rd group were diffuse large B-cell lymphoma (2 [1%] patients), non-Hodgkin's lymphoma (2 [1%]), acute myeloid leukaemia (1 [<1%]), and mantle cell lymphoma (1 [<1%]), and those reported in the Rd group were diffuse large B-cell lymphoma, B precursor type acute leukaemia, and myelodysplastic syndrome (1 [<1%] patient each). When adjusted for exposure to study treatment, the incidence of cutaneous SPMs was similar between the D-Rd (3 events per 100 patient-months at risk) and Rd (4 events per 100 patient-months at risk) groups.

Deaths were reported in 115 (32%) of 364 patients in the D-Rd group and 156 (43%) of 365 patients in the Rd group. The primary causes of death were disease progression (48 [13%] patients in the D-Rd group and 57 [16%] patients in the Rd group), adverse events (38 [10%] and 35 [10%]), and other (29 [8%] and 63 [17%]). Treatment-related deaths occurred in 13 (4%) patients in the D-Rd group and 10 (3%) patients in the Rd group (all due to adverse events). The treatment-related adverse events that led to death in the D-Rd group were pneumonia (n=2) and diffuse large B-cell lymphoma, coronary artery arteriosclerosis, urosepsis, haemorrhagic stroke, cerebrovascular accident, non-Hodgkin's lymphoma, gastric adenocarcinoma, nocardiosis, acute cardiac failure, acute myocardial infarction, and neutropenic sepsis (n=1 each); the treatment-related adverse events that led to death in the Rd group were pneumonia (n=2) and pulmonary embolism, gastrointestinal haemorrhage, cardiac arrest, cerebrovascular accident, septic shock, myocardial infarction, brain neoplasm, and sudden cardiac death (n=1 each). TEAEs with an outcome of death were reported in 34 (9%) patients in the D-Rd group and 32 (9%) patients in

the Rd group. TEAEs leading to treatment discontinuations were reported in 46 (13%) patients in the D-Rd group and 82 (22%) in the Rd group; the incidence of infections leading to treatment discontinuations was similar between treatment groups (5 [1%] *vs* 6 [2%]). The most common (in ≥4 patients in either group) TEAEs leading to treatment discontinuations were fatigue (4 [1%] patients in the D-Rd group and 2 [1%] patients in the Rd group), asthenia (1 [<1%] and 4 [1%]), and diarrhoea (0 and 6 [2%]). TEAEs leading to lenalidomide discontinuation were reported in 125 (34%) patients in the D-Rd group (95 [26%] patients had ≥1 related to lenalidomide) and 84 (23%) in the Rd group (58 [16%] had ≥1 related to lenalidomide). TEAEs leading to dexamethasone discontinuation were reported in 141 (39%) patients in the D-Rd group (91 [25%] patients had ≥1 related to dexamethasone) and 129 (35%) in the Rd group (68 [19%] had ≥1 related to dexamethasone). TEAEs leading to daratumumab discontinuation were reported in 50 (14%) patients (21 [6%] patients had ≥1 related to daratumumab).

Discussion

After approximately 56 months of follow-up, a statistically significant and clinically meaningful improvement in OS was observed with D-Rd versus Rd in transplant-ineligible patients with NDMM. Daratumumab in combination with Rd reduced the risk of death (HR 0·68). Moreover, the significant PFS benefit from the primary analysis was maintained in the D-Rd group over the Rd group, with a reduction in risk of disease progression or death (HR 0·53) and a median PFS not yet reached in the D-Rd group. Considering the estimated 60-month PFS rate was 52·5% in the D-Rd group, a median PFS of around 5 years is anticipated, which, to our knowledge, would be unprecedented among transplant-ineligible patients with NDMM. Responses deepened with continued daratumumab therapy; the CR or better rate in the D-Rd group increased from 48% in

the primary analysis[11] to 51% in the current analysis. A significant PFS2 benefit was observed for the D-Rd group, with a reduction in risk of disease progression or death (HR 0·61), and median PFS2 had not yet been reached in the D-Rd group despite the older age at baseline of patients enrolled in MAIA (median age, 73 years). Notably, patients with a CrCl of 30-50 mL/min were recommended a reduced lenalidomide dose of 10 mg. Overall, despite the lower median lenalidomide RDI in the D-Rd group versus the Rd group, efficacy was improved with D-Rd over Rd.

In the prespecified subgroup analyses of OS, an OS advantage was observed with D-Rd versus Rd for most subgroups, including patients aged <75 and ≥75 years. Although an OS advantage was also observed for patients with high-risk cytogenetics, the benefit was more pronounced in patients with standard-risk cytogenetics. In contrast, in the PFS subgroup analyses, the PFS advantage was similar between patients with high-risk and those with standard-risk cytogenetics.

No new safety concerns were identified for D-Rd, despite the more than double median treatment duration in the D-Rd group (47·5 months) compared with the Rd group (22·6 months) and the higher median cumulative dose of lenalidomide in the D-Rd group (9185 mg) compared with the Rd group (8040 mg). Grade 3/4 infections were reported more frequently in the D-Rd group versus the Rd group, while the incidence of SAEs and incidence of infections leading to treatment discontinuations were similar between treatment groups. Pneumonia was the most common grade 3/4 infection and most common SAE. SPMs were reported more frequently in the D-Rd group versus the Rd group; this imbalance was driven by a higher incidence of cutaneous SPMs. However, when adjusted for exposure to study treatment, the incidence of cutaneous

SPMs was similar between treatment groups. The incidence of SPMs in both treatment groups of our study is higher than the cumulative incidence range of SPMs reported in previous studies conducted in patients with multiple myeloma.[20] The higher incidence of SPMs in our study may result from continuous lenalidomide treatment; previous studies have shown that lenalidomide maintenance therapy may increase the risk of SPMs.[20] However, other studies have demonstrated that Rd treatment does not increase the incidence of SPMs. Future studies are needed to further investigate the impact of multiple myeloma treatment regimens on the risk of SPMs.

These results complement those of the phase 3 ALCYONE study; at a median follow-up of 40·1 months, a significant OS benefit was observed with D-VMP versus VMP (HR 0·60; 95% CI 0·46–0·80; p=0·0003), PFS benefit was maintained, and responses improved from the primary analysis.[12]

Although cross-trial comparisons should be interpreted with caution, these results compare favourably to those of the SWOG S0777 study of VRd versus Rd in patients with newly diagnosed myeloma without intent for immediate transplant.[14] Compared with patients in SWOG S0777, a higher proportion of patients in MAIA were aged ≥65 years (99% in MAIA [median age, 73 years] compared with 43% in SWOG S0777 [median age, 63 years]). All patients in MAIA were transplant-ineligible, whereas 31% of patients in SWOG S0777 were not intended for future transplant). A similar proportion of patients had ISS stage III disease (29% in MAIA compared with 33% in SWOG S0777) and an ECOG performance status score >1 (17% in MAIA compared with 14% in SWOG S0777).[11,14] Additionally, instead of receiving triplet therapy until disease progression as in the D-Rd group in MAIA, patients in the VRd group in

SWOG S0777 received only eight cycles of triplet therapy followed by Rd until disease progression. In SWOG S0777, at a median follow-up of 55 months, median PFS was 43 months with VRd versus 30 months with Rd (HR 0·712; 96% Wald CI 0·560–0·906; one-sided stratified log-rank p=0·0018).[14] The PFS benefit was more pronounced in MAIA (HR 0·53 with D-Rd *vs* Rd) versus SWOG S0777 (HR 0·71 with VRd *vs* Rd). For patients in SWOG S0777 aged >75 years, median PFS was around 3 years (39 months) in the VRd group (approximately 2 years less than the expected median PFS of 5 years in MAIA) versus 20 months in the Rd group. With a longer (84-month) median follow-up, median OS was NR with VRd versus 69 months with Rd (HR 0·709; 95% Wald CI 0·543–0·926; stratified two-sided p=0·0114); a median OS of greater than 84 months with VRd is anticipated.[15] A significant OS benefit was not observed with VRd versus Rd for patients aged ≥65 years (median, 65 vs 56 months, respectively; HR 0·769; stratified two-sided p=0·168).

In the PEGASUS study, an anchored indirect treatment comparison leveraging individual-level patient data was performed between patients treated with D-Rd in MAIA and patients treated with VRd from the Flatiron Health electronic health record-derived database.[21] D-Rd was associated with a significantly lower risk of progression or death compared to VRd (HR 0·68; 95% CI 0·48–0·98; p=0·04).

Overall, given the efficacy evidence, along with the high incidence of grade ≥3 neurologic and gastrointestinal adverse events associated with VRd, D-Rd may be considered as an alternative over VRd for transplant-ineligible patients with NDMM.[14,15,21] D-Rd also compares favourably with other lenalidomide/proteasome inhibitor-based combination regimens, including VRd lite

(median age, 73 years) and ixazomib in combination with Rd (median age, 73 years); both of these regimens have a median PFS of around 3 years.[22-24]

Comparing outcomes of patients in the Rd group in MAIA (56·2-month median follow-up) to those reported for the continuous Rd group in the final analysis of the FIRST trial (67-month median follow-up), median OS was NR (MAIA) versus 59·1 months (FIRST) and median PFS was 34·4 months versus 26·0 months, respectively; these results may be attributed in part to the longer median treatment duration in MAIA (22·6 months) compared with FIRST (18·4 months) and in part to increased clinician familiarity with the Rd regimen over time.[25] Despite the better median OS and PFS associated with Rd in MAIA, D-Rd still demonstrated a significant clinical benefit over Rd.

Results from the phase 3 POLLUX study support the use of D-Rd after first relapse in patients with RRMM who are not refractory to lenalidomide[9,26]; results of the current MAIA OS analysis highlight the role of D-Rd as first-line treatment in transplant-ineligible patients with NDMM. Real-world data from Europe showed high attrition rates that increased with each subsequent line of therapy (95% of patients received first-line therapy, 61% of patients received second-line therapy, and 38% of patients received third-line therapy).[27] Similarly, a retrospective review of three US databases showed high attrition rates (approximately 50%) after the first and each subsequent line of therapy among non-transplant patients; factors associated with high attrition levels were older age and poor comorbidity status.[28] Taken together, these real-world data and the prolonged OS observed with D-Rd versus Rd in transplant-ineligible patients with NDMM in our study support early use of daratumumab to provide deep responses and prolonged disease

control. The ability of the initial treatment regimen patients receive to induce sustained deep responses may delay clonal evolution and associated drug resistance, thereby improving clinical outcomes.[29]

This study has several limitations. The open-label study design may have led to a bias for early patient withdrawals in the Rd group. Additionally, the prespecified subgroup analysis of OS included subgroups with small sample sizes (non-White race, impaired baseline hepatic function, and high-risk cytogenetics); thus, the comparisons of OS in these subgroups should be interpreted with caution. Patients who received subsequent therapy were censored for the PFS and PFS2 analyses to avoid the confounding effect of subsequent therapy; some bias may remain with this method of naïve censoring. Finally, in the Rd group, 39 (21%) patients received a daratumumab-containing regimen as first subsequent therapy and 85 (46%) received a daratumumab-containing regimen as any subsequent line of therapy. Even with this level of crossover, a significant survival advantage was observed for D-Rd compared with Rd, highlighting the importance of using D-Rd as first-line treatment. The limited availability of daratumumab based on location may have contributed to the low percentage of patients who received a daratumumab-based regimen at the time of initial relapse.

There is potential to further optimise D-Rd treatment by using subcutaneous daratumumab, using a reduced lenalidomide dose, and omitting dexamethasone beyond an initial induction period.[30,31] Further analyses are also needed to determine the optimal duration of daratumumab treatment. In the phase 3 CASSIOPEIA study (NCT02541383), transplant-eligible patients with NDMM who received daratumumab in combination with bortezomib, thalidomide and dexamethasone (D-

VTd) induction/consolidation followed by daratumumab maintenance achieved similar PFS to patients who received D-VTd induction/consolidation followed by observation.[32] However, among patients who received bortezomib, thalidomide and dexamethasone induction/consolidation, daratumumab maintenance significantly improved PFS over observation. CEPHEUS (NCT03652064) is an ongoing phase 3 study evaluating D-Rd maintenance following induction with daratumumab in combination with VRd in patients with NDMM for whom transplant is not planned as initial therapy.[33] Further analyses of MAIA are ongoing to investigate the efficacy of daratumumab retreatment and the timing of neutropenia and infections in relation to daratumumab treatment.

In transplant-ineligible patients with NDMM, treatment until disease progression with D-Rd resulted in a significant OS benefit compared with Rd. With longer follow-up, D-Rd is expected to demonstrate an unprecedented median PFS. These results strongly support the frontline use of D-Rd to maximise PFS for optimal long-term outcomes. Overall, daratumumab-based regimens have set new PFS and OS benchmarks for transplant-ineligible patients with NDMM.

Contributors

All authors contributed to study design, study conduct, data analysis, and data interpretation. All authors participated in the drafting and revising of the manuscript and approved the final version for submission. TF and SZU had access to and verified all data.

Declaration of interests

TF received payment or honoraria for lectures, presentations, speakers bureaus, manuscript witing, or educational events from and participated on a data safety monitoring board or advisory board for Janssen, Bristol Myers Squibb, Takeda, Roche, Amgen, Karyopharm, Oncopeptides, and AbbVie. SKK received research funding from AbbVie, Celgene, Janssen, Takeda, Adaptive Biotechnologies, Kite, MedImmune/AstraZeneca, Merck, Novartis, Roche, and Sanofi; participated on an advisory board for AbbVie, Celgene, Janssen, Takeda, Adaptive Biotechnologies, Kite, and MedImmune/AstraZeneca; and participated on an independent review committee for Oncopeptides. TP received consulting fees from Janssen and Celgene; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript witing, or educational events from Janssen; received payment for expert testimony from Takeda, Oncopeptides, and CSL Behring; and holds stock or stock options in Novo Nordisk. RZO received support for the present manuscript from Janssen; received laboratory research funding from Asylia Therapeutics, BioTheryX, and Heidelberg Pharma; received clinical research funding from CARsgen Therapeutics, Celgene, Exelixis, Janssen Biotech, Sanofi-Aventis, and Takeda; received royalties or licenses for, has patents planned, issued or pending for, and holds stock or stock options in Asylia Therapeutics; received consulting fees from EcoR1 Capital; and participated on an advisory board for Amgen, BioTheryX, Bristol Myers Squibb, Celgene, Forma Therapeutics, Genzyme, GSK Biologicals, Ionis, Janssen Biotech, Juno Therapeutics, Karyopharm, Kite, Neoleukin, Oncopeptides AB, Regeneron, Sanofi-Aventis, Servier, and Takeda. PM received honoraria from AbbVie, Amgen, Celgene, Janssen, Oncopeptides, and Sanofi. NB received grants or contracts from Pfizer and received consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events

from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Janssen, Karyopharm, Sanofi, Pfizer, and Takeda. HQ received grants or contracts from Amgen, GlaxoSmithKline, Celgene, Sanofi, and Karyopharm and had a leadership or fiduciary role in advisory boards for Amgen, GlaxoSmithKline, Celgene, Sanofi, Karyopharm, CSL, Janssen, and Takeda. HG received grants or contracts from Amgen, Bristol Myers Squibb, Celgene, Chugai, Dietmar-Hopp-Foundation, Janssen, Johns Hopkins University, and Sanofi; received consulting fees from Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript witing, or educational events from Amgen, Art Tempi, Bristol Myers Squibb, Celgene, Chugai, Janssen, GlaxoSmithKline, Sanofi, and Novartis; received support for attending meetings and/or travel from Adaptive Biotechnologies, Amgen, Art Tempi, Bristol Myers Squibb, Celgene, Chugai, Janssen, Sanofi, and Takeda; and received research support from Amgen, Bristol Myers Squibb, Celgene, Chugai, Janssen, Incyte, Molecular Partners, Merck Sharp & Dohme, Sanofi, MundiPharma, Takeda, and Novartis. MOD served as a consultant for Janssen, AbbVie, Adaptive Biotechnologies, Amgen, and GlycoMimetics. AP received grants or contracts from Sanofi and Takeda; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Sanofi, and Takeda; received support for attending meetings and/or travel from Amgen and Janssen; and participated on a data safety monitoring board or advisory board for Janssen and Sanofi. CPV received honoraria from Amgen, Bristol Myers Squibb, Pfizer, GlaxoSmithKline, Janssen, Sanofi, and Takeda. KW received honoraria from AbbVie, Adaptive Biotechnologies, Amgen, Celgene/Bristol Myers Squibb, GlaxoSmithKline, Janssen, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche, Sanofi,

and Takeda and received grants from Amgen, Celgene/Bristol Myers Squibb, GlaxoSmithKline, and Sanofi. NR served in an advisory role for Amgen, Bluebird Bio, GlaxoSmithKline, Immuneel, and Caribou. MM received research funding from Janssen and Takeda; received honoraria from Janssen, Takeda, GlaxoSmithKline, and Sanofi; and received travel accommodations from Janssen and Takeda. LF received support for attending meetings and/or travel from Amgen and Janssen and received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, Celgene, Takeda, Bristol Myers Squibb, Sanofi, and Janssen. TA is an employee of and holds equity in Genmab. JW and RVR are employees of Janssen. CMU, BT, MD, and JV are employees of Janssen and hold equity in Johnson & Johnson. SZU received grants from Amgen, Bristol Myers Squibb, Celgene, Pharmacyclics, Sanofi, Seattle Genetics, Janssen, SkylineDX, Merck, GlaxoSmithKline, and Takeda and received personal fees from Amgen, AbbVie, Celgene, MundiPharma, Seattle Genetics, Janssen, Sanofi, SkylineDX, Merck, GlaxoSmithKline, Oncopeptides, Gilead, Genentech, and Takeda. All other authors declare no competing interests.

Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Acknowledgments

This study was sponsored by Janssen Research & Development.

We thank the patients who volunteered to participate in this trial, their families, and the staff members at the trial sites who cared for them; the members of the data and safety monitoring committee (Nikhil C. Munshi, MD [chair], Mario DiCato, MD, and Weichung Shih, PhD); representatives of the sponsor who were involved in data collection and analyses; Intergroupe Francophone du Myélome for their strong support and guidance during the trial start-up; and Grace Wang, PharmD, and Kimberly Carmony, PhD, of Cello Health Communications/MedErgy, for medical writing and editorial assistance.

References

1. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 2011; **186:** 1840–8.

2. Overdijk MB, Jansen JH, Nederend M, et al. The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fcgamma receptor-mediated cross-linking. *J Immunol* 2016; **197:** 807–13.

3. Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs* 2015; **7:** 311–21.

4. Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood* 2014; **124:** 3474.

5. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes $CD38^+$ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood* 2016; **128:** 384–94.

6. Adams HC III, Stevenaert F, Krejcik J, et al. High-parameter mass cytometry evaluation of relapsed/refractory multiple myeloma patients treated with daratumumab demonstrates immune modulation as a novel mechanism of action. *Cytometry A* 2019; **95:** 279–89.

7. Casneuf T, Adams HC III, van de Donk NWCJ, et al. Deep immune profiling of patients treated with lenalidomide and dexamethasone with or without daratumumab. *Leukemia* 2020; **35:** 573–84.

8. DARZALEX® (daratumumab) [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2020.

9. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 1319–31.

10. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med* 2018; **378:** 518–28.

11. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med* 2019; **380:** 2104–15.

12. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet* 2020; **395:** 132–41.

13. Kumar SK, Facon T, Usmani SZ, et al. Updated analysis of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM): the phase 3 MAIA study. Poster presented at: 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; 5–8 December 2020; Virtual.

14. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017; **389:** 519–27.

15. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and

dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J* 2020; **10:** 53.

16. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117:** 4691–5.

17. Durie BGM, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006; **20:** 1467–73.

18. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 754–66.

19. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009.

20. Musto P, Anderson KC, Attal M, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. *Ann Oncol* 2017; **28:** 228–45.

21. Durie BGM, Kumar SK, Usmani SZ, et al. Daratumumab-lenalidomide-dexamethasone vs standard-of-care regimens: Efficacy in transplant-ineligible untreated myeloma. *Am J Hematol* 2020; **95:** 1486–94.

22. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol* 2018; **182:** 222–30.

23. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without

intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2020; **21:** 1317–30.

24. Facon T, Venner C, Bahlis N, et al. The phase 3 TOURMALINE-MM2 trial: oral ixazomib, lenalidomide, and dexamethasone (IRd) vs placebo-Rd for transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). Presented at: 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; 5–8 December 2020; Virtual.

25. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. *Blood* 2018; **131:** 301–10.

26. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia* 2020; **34:** 1875–84.

27. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol* 2016; **175:** 252–64.

28. Fonseca R, Usmani SZ, Mehra M, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. *BMC Cancer* 2020; **20:** 1087.

29. Suzuki K, Nishiwaki K, Yano S. Treatment strategies considering micro-environment and clonal evolution in multiple myeloma. *Cancers (Basel)* 2021; **13:** 215.

30. Larocca A, Bonello F, Gaidano G, et al. Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit, newly diagnosed multiple myeloma patients. *Blood* 2021; published online 19 March. DOI:10.1182/blood.2020009507.

31. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) [package insert]. Horsham, PA: Janssen Biotech,; 2021.

32. Moreau P, Hulin C, Perrot A, et al. Daratumumab (DARA) maintenance or observation (OBS) after treatment with bortezomib, thalidomide and dexamethasone (VTd) with or without DARA and autologous stem cell transplant (ASCT) in patients (pts) with newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 2. *J Clin Oncol* 2021; **39** (15 suppl)**:** 8004.

33. Zweegman S, Usmani SZ, Chastain K, et al. Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DARA) in patients (pts) with newly diagnosed multiple myeloma (NDMM) for whom transplant is not planned as initial therapy: A multicenter, randomized, phase III study (CEPHEUS). *Journal of Clinical Oncology* 2019; **37** (15 suppl)**:** TPS8056.

Figure Legends

Figure 1: **Consort patient flow diagram**

ITT=intention-to-treat.

The primary cause of death for the 24 patients in each treatment group who discontinued treatment with death as the primary reason were adverse events (24 [100%] of 24 patients in the D-Rd group and 23 [96%] of 24 patients in the Rd group). The remaining patient in the Rd group died due to an unspecified other cause.

Figure 2: **OS (A) and PFS (B) in the ITT population**

Kaplan-Meier estimates of OS (A) and PFS (B) in the intention-to-treat population, which included all patients who underwent randomisation.

OS=overall survival. PFS=progression-free survival. ITT=intention-to-treat. Rd=lenalidomide and dexamethasone. D-Rd=daratumumab, lenalidomide, and dexamethasone. HR=hazard ratio. CI=confidence interval.

Figure 3: **Prespecified subgroup analysis of OS in the ITT population**

Results of an analysis of OS in prespecified subgroups of the intention-to-treat population defined by baseline characteristics. Impaired baseline hepatic function includes mild impairment (total bilirubin level ≤ the ULN and aspartate aminotransferase level > the ULN, or total bilirubin level > the ULN and ≤1·5 times the ULN), moderate impairment (total bilirubin level >1·5 times and ≤3 times the ULN), and severe impairment (total bilirubin level >3 times the ULN). The International Staging System disease stage is derived based on the combination of serum β_2-microglobulin and albumin levels. Higher stages indicate more severe disease. The subgroup

analysis for the type of multiple myeloma was performed on data from patients who had measurable disease in serum. Hazard ratio and 95% CI were calculated from an unstratified Cox proportional hazards model with treatment as the sole explanatory variable.

OS=overall survival. ITT=intention-to-treat. D-Rd=daratumumab, lenalidomide, and dexamethasone. Rd=lenalidomide and dexamethasone. CI=confidence interval. NE=not estimable. CrCl=creatinine clearance. ISS=International Staging System. IgG=immunoglobulin G. ECOG=Eastern Cooperative Oncology Group. ULN=upper limit of the normal range.

Figure 1: **Consort patient flow diagram**

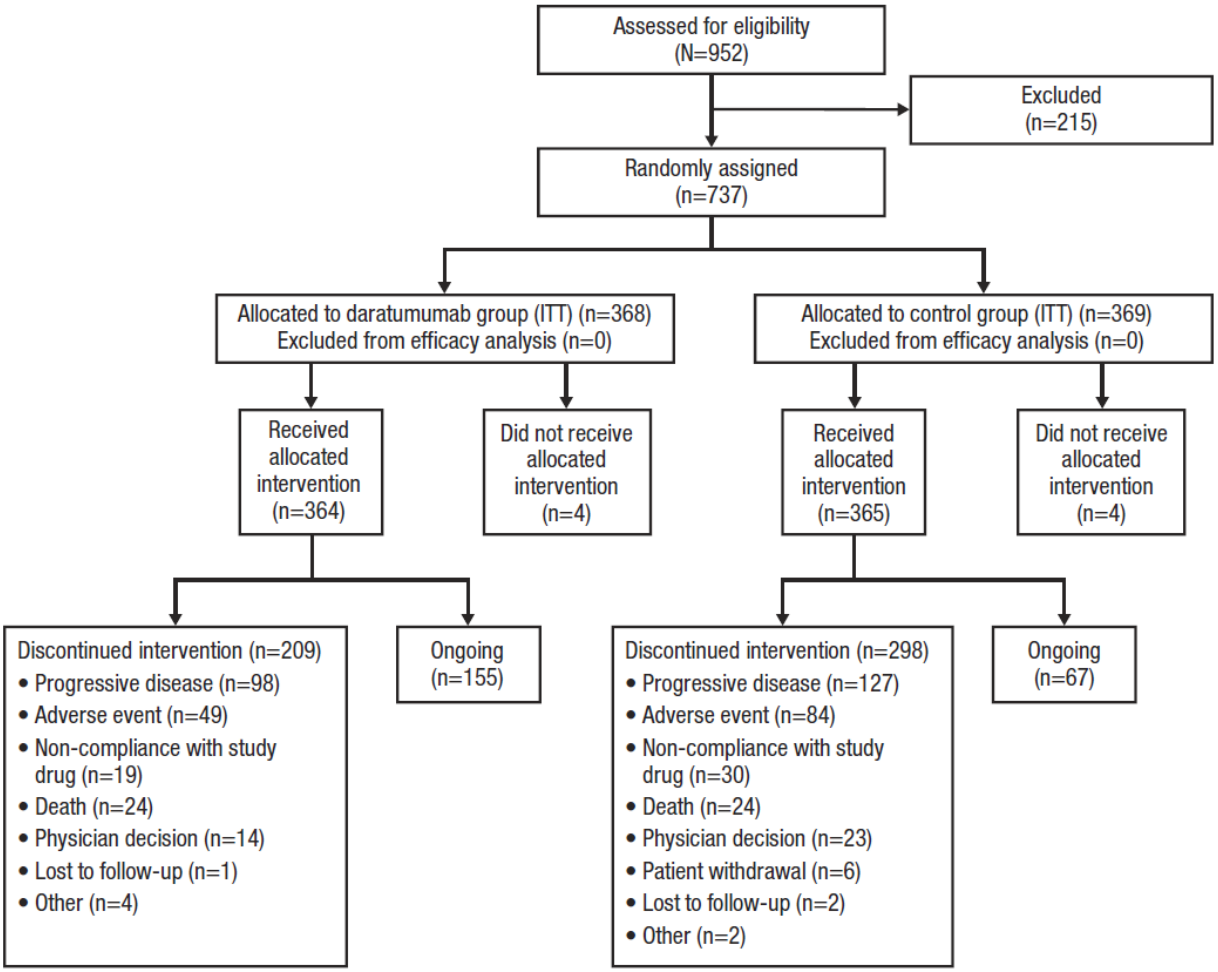
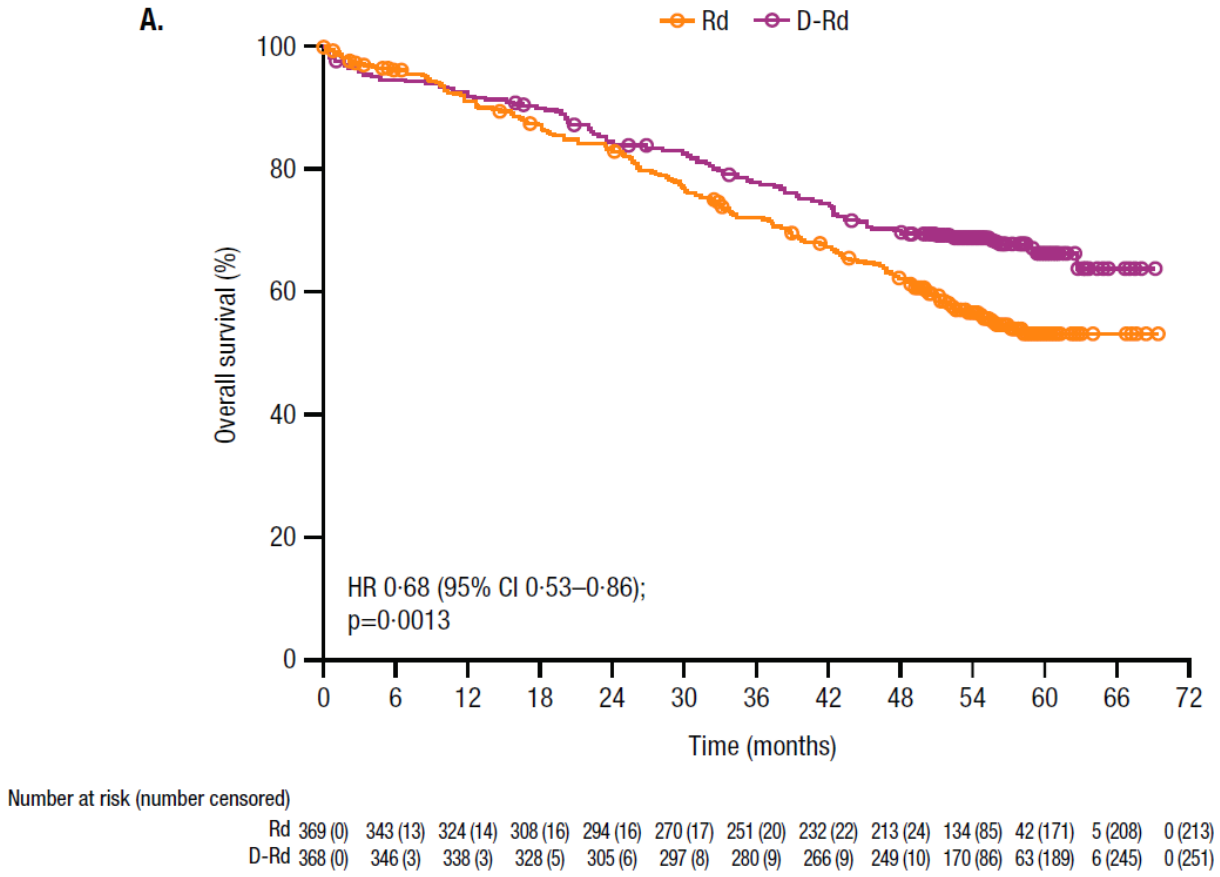
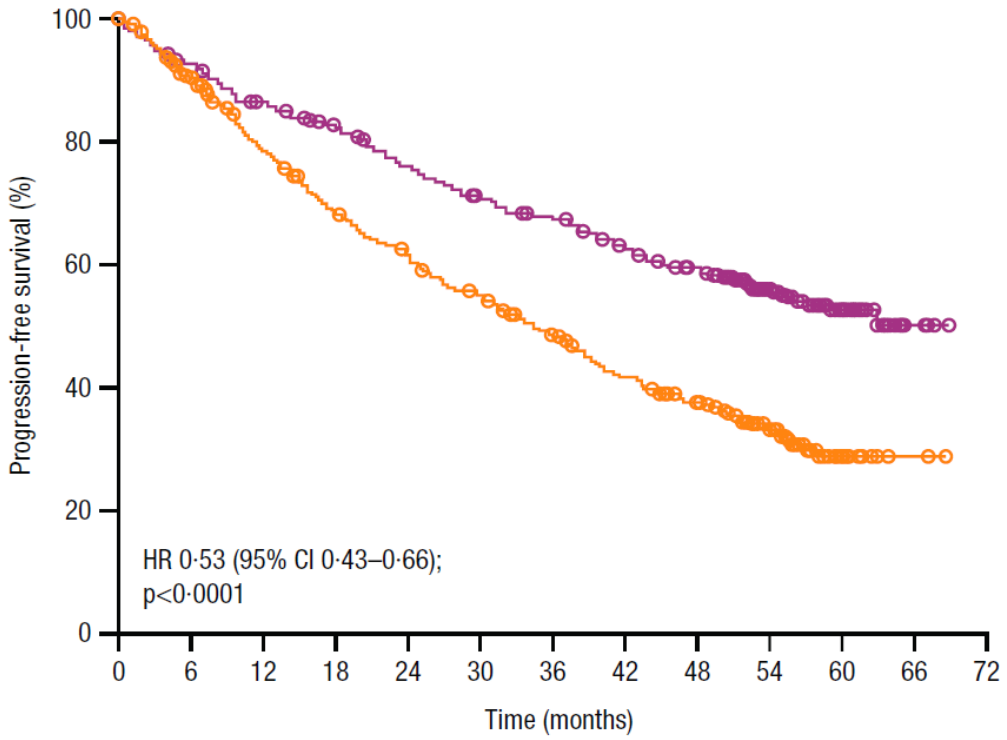


Figure 2: **OS (A) and PFS (B) in the ITT population**



B.



Number at risk (number censored)

Rd	369 (0)	307 (29)	255 (41)	220 (44)	196 (46)	172 (49)	146 (55)	123 (58)	105 (64)	63 (95)	12 (140)	2 (150)	0 (152)
D-Rd	368 (0)	335 (6)	309 (9)	290 (14)	266 (16)	246 (18)	232 (20)	210 (25)	195 (30)	123 (92)	51 (158)	5 (203)	0 (208)

Figure 3: **Prespecified subgroup analysis of OS in the ITT population**

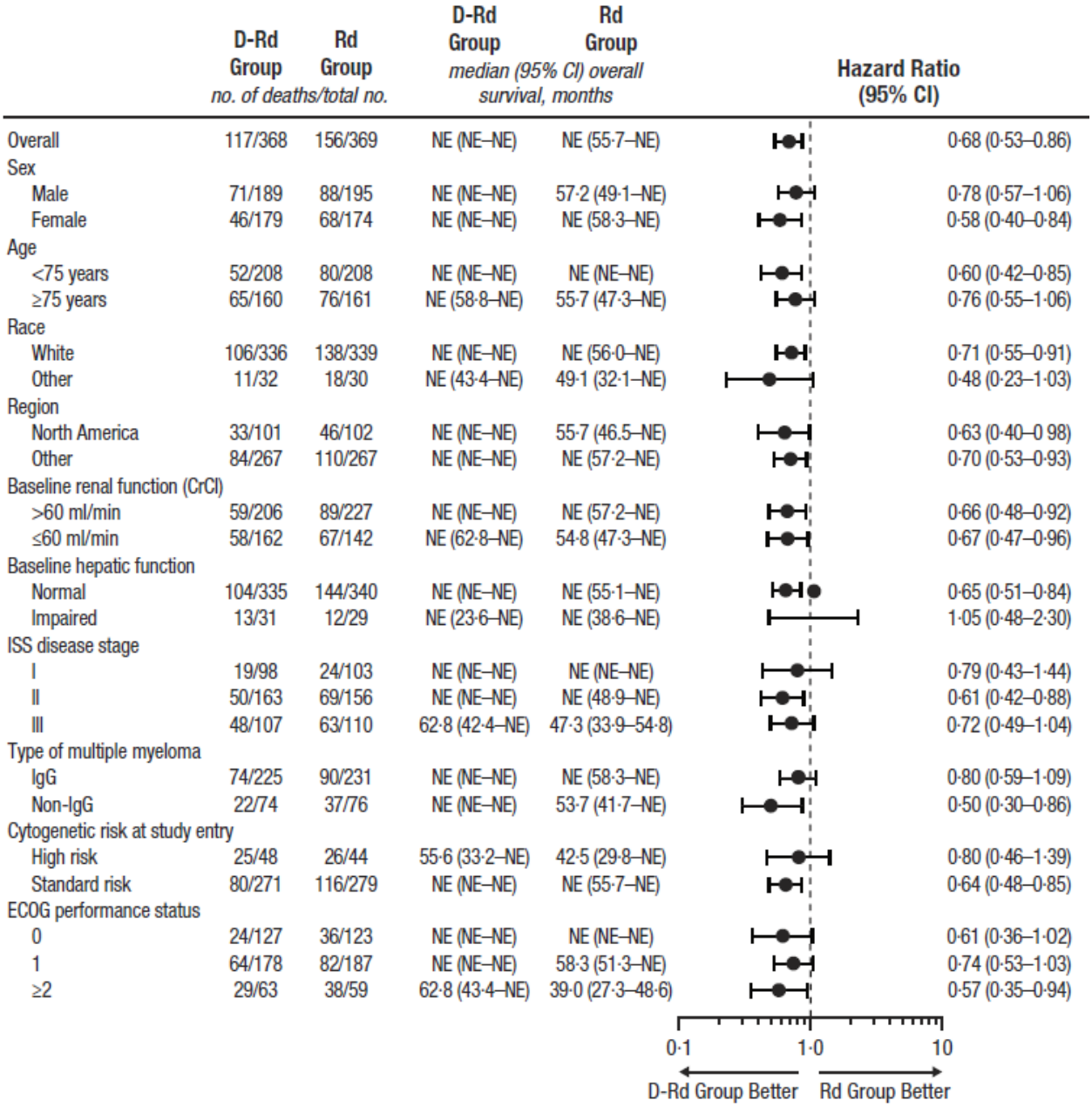


Table 1: **Demographic and baseline disease characteristics in the intention-to-treat population*[,11]**

	D-Rd group (n=368)	Rd group (n=369)
Median age, years	73·0 (70–78)	74·0 (70–78)
Age category		
<65	4 (1%)	4 (1%)
65–<70	74 (20%)	73 (20%)
70–<75	130 (35%)	131 (36%)
≥75	160 (43%)	161 (44%)
ECOG performance status[†]		
0	127 (35%)	123 (33%)
1	178 (48%)	187 (51%)
2[‡]	63 (17%)	59 (16%)
International Staging System disease stage[§]		
I	98 (27%)	103 (28%)
II	163 (44%)	156 (42%)
III	107 (29%)	110 (30%)
Type of measurable disease		
IgG	225 (61%)	231 (63%)
IgA	65 (18%)	66 (18%)
Other[¶]	9 (2%)	10 (3%)
Detected in urine only	40 (11%)	34 (9%)
Detected as serum free light-chain only	29 (8%)	28 (8%)
Cytogenetic profile[‖]		
Standard risk	271/319 (85%)	279/323 (86%)
High risk	48/319 (15%)	44/323 (14%)
Median time since initial diagnosis of multiple myeloma, months	0·95 (0·53–1·46)	0·89 (0·59–1·45)

Data are median (interquartile range), n (%), or n/N (%).

D-Rd=daratumumab, lenalidomide, and dexamethasone. Rd=lenalidomide and dexamethasone. ECOG=Eastern Cooperative Oncology Group. Ig=immunoglobulin.

*The intention-to-treat population included all patients who underwent randomization. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline.
†Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
‡Two patients had a score of greater than 2 (one patient had a score of 3, and another patient had a score of 4).
§The International Staging System (ISS) disease stage, which is derived on the basis of the combination of serum β_2-microglobulin and albumin levels, consists of three stages. Higher stages indicate more severe disease.
¶This category includes IgD, IgE, IgM, and biclonal.
‖Cytogenetic risk was based on fluorescence in situ hybridization or karyotype analysis; patients who had a high-risk cytogenetic profile had at least one high-risk abnormality (del17p, t[14;16], or t[4;14]).

Table 2: **Summary of best confirmed responses and minimal residual disease status in the ITT population**

	D-Rd group (n=368)	Rd group (n=369)	Odds ratio (95% CI)	p value
Overall response (%; 95% CI)	342 (92·9%; 89·8–95·3)	301 (81·6%; 77·2–85·4)	3·00 (1·85–4·86)	<0·0001
Best overall response				
Complete response or better	188 (51%)	111 (30%)	2·44 (1·80–3·30)	<0·0001
Stringent complete response	130 (35%)	56 (15%)	3·06 (2·14–4·38)	<0·0001
Complete response	58 (16%)	55 (15%)		
Very good partial response or better	298 (81%)	210 (57%)	3·28 (2·34–4·59)	<0·0001
Very good partial response	110 (30%)	99 (27%)		
Partial response	44 (12%)	91 (25%)		
Stable disease	11 (3%)	55 (15%)		
Progressive disease	1 (<1%)	0		
Response could not be measured	14 (4%)	13 (4%)		
Negative status for minimal residual disease*[,13]	114 (31%)	38 (10%)	3·91 (2·62–5·84)	<0·0001

ITT=intention-to-treat. D-Rd=daratumumab in combination with lenalidomide and dexamethasone. Rd=lenalidomide and dexamethasone. CI, confidence interval. The p value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. *Minimal residual disease assessments were performed at baseline; at the time of suspected complete response/stringent complete response; and at 12, 18, 24, 30, 36, 48, and 60 months after cycle 1 day 1 (±1 month) if patient response was near complete response/stringent complete response (if one of these time points occurred within 1 month of suspected complete response, a repeat assessment was not requested). These values are from a median follow-up of 47·9 months. The p value was calculated using Fisher's exact test.

Table 3: **Most common TEAEs in the safety population**

	D-Rd group (n=364)				Rd group (n=365)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Haematologic TEAEs								
Anaemia	93 (26%)	60 (16%)	1 (<1%)	0	71 (19%)	79 (22%)	0	0
Thrombocytopenia	47 (13%)	23 (6%)	9 (2%)	0	43 (12%)	23 (6%)	11 (3%)	0
Leukopenia	31 (9%)	37 (10%)	5 (1%)	0	18 (5%)	20 (5%)	3 (1%)	0
Neutropenia	26 (7%)	136 (37%)	61 (17%)	0	30 (8%)	97 (27%)	38 (10%)	0
Lymphopenia	12 (3%)	41 (11%)	19 (5%)	0	7 (2%)	35 (10%)	6 (2%)	0
Nonhaematologic TEAEs								
Diarrhoea	207 (57%)	32 (9%)	0	0	165 (45%)	22 (6%)	0	0
Constipation	151 (41%)	5 (1%)	1 (<1%)	0	135 (37%)	2 (1%)	0	0
Peripheral oedema	146 (40%)	8 (2%)	1 (<1%)	0	112 (31%)	3 (1%)	0	0
Back pain	135 (37%)	13 (4%)	1 (<1%)	0	95 (26%)	13 (4%)	1 (<1%)	0
Fatigue	130 (36%)	32 (9%)	0	0	97 (27%)	17 (5%)	0	0
Nausea	125 (34%)	7 (2%)	0	0	86 (24%)	2 (1%)	0	0
Cough	120 (33%)	2 (1%)	0	0	64 (18%)	0	0	0
Asthenia	115 (32%)	18 (5%)	1 (<1%)	0	83 (23%)	16 (4%)	1 (<1%)	0
Bronchitis	112 (31%)	12 (3%)	0	0	79 (22%)	6 (2%)	0	0
Insomnia	111 (30%)	11 (3%)	0	0	102 (28%)	14 (4%)	0	0
Muscle spasms	108 (30%)	2 (1%)	0	0	80 (22%)	4 (1%)	0	0
Dyspnoea	105 (29%)	11 (3%)	1 (<1%)	0	59 (16%)	4 (1%)	0	0
Weight decreased	101 (28%)	10 (3%)	0	0	58 (16%)	11 (3%)	0	0
Peripheral sensory neuropathy	101 (28%)	9 (2%)	0	0	64 (18%)	1 (<1%)	0	0
Arthralgia	94 (26%)	11 (3%)	0	0	71 (19%)	8 (2%)	0	0
Nasopharyngitis	92 (25%)	0	0	0	66 (18%)	0	0	0
Decreased appetite	90 (25%)	3 (1%)	0	0	63 (17%)	2 (1%)	1 (<1%)	0

Upper respiratory tract infection	89 (24%)	6 (2%)	0	0	50 (14%)	4 (1%)	0	0
Pyrexia	86 (24%)	10 (3%)	0	0	58 (16%)	9 (2%)	0	0
Headache	75 (21%)	2 (1%)	0	0	43 (12%)	0	0	0
Pain in extremity	74 (20%)	6 (2%)	0	0	57 (16%)	1 (<1%)	0	0
Dizziness	74 (20%)	4 (1%)	0	0	64 (18%)	2 (1%)	0	0
Vomiting	71 (20%)	4 (1%)	0	0	48 (13%)	2 (1%)	0	0
Cataract	50 (14%)	40 (11%)	0	0	43 (12%)	39 (11%)	0	0
Hypokalaemia	49 (13%)	41 (11%)	5 (1%)	0	34 (9%)	28 (8%)	8 (2%)	0
Pneumonia	40 (11%)	62 (17%)	5 (1%)	3 (1%)	27 (7%)	31 (8%)	5 (1%)	3 (1%)
Hypertension	30 (8%)	29 (8%)	2 (1%)	0	14 (4%)	16 (4%)	0	0
Hyperglycaemia	25 (7%)	24 (7%)	4 (1%)	0	14 (4%)	12 (3%)	2 (1%)	0
Pulmonary embolism	0	23 (6%)	3 (1%)	0	0	16 (4%)	3 (1%)	1 (<1%)
Second primary malignancy*	74 (20%)	–	–	–	46 (13%)	–	–	–

Grade 1–2 TEAEs occurring in ≥20% of patients and grade 3, 4, and 5 TEAEs occurring in >5% of patients in either treatment group are shown. See appendix p 14–26 for table with grade 1–2 TEAEs occurring in ≥10% of patients in either treatment group and all grade 3, 4, and 5 TEAEs.

D-Rd=daratumumab in combination with lenalidomide and dexamethasone. Rd=lenalidomide and dexamethasone. TEAEs=treatment-emergent adverse events.

*Second primary malignancies were prespecified in the statistical analysis plan as adverse events of clinical interest.