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Daratumumab with lenalidomide as maintenance after transplant in newly diagnosed multiple myeloma: the AURIGA study

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Abstract:
No randomized trial has directly compared daratumumab and lenalidomide (D-R) maintenance therapy versus standard-of-care lenalidomide (R) alone post-transplant. Here, we report the primary results of the phase 3 AURIGA study evaluating D-R versus R maintenance in NDMM patients who were in ≥very good partial response, minimal residual disease (MRD; threshold 10−5) positive, and anti-CD38 naïve post-transplant. Patients were randomized 1:1 to D-R or R maintenance for up to 36 cycles. Two hundred patients were randomized (D-R, n=99; R, n=101). The primary endpoint, MRD-negative (10−5) conversion rate by 12 months from start of maintenance, was significantly higher for D-R versus R (50.5% vs 18.8%; odds ratio [OR], 4.51; 95% confidence interval [CI], 2.37-8.57; P<0.0001). MRD-negative (10−6) conversion rate was similarly higher with D-R (23.2% vs 5.0%; OR, 5.97; 95% CI, 2.15-16.58; P=0.0002). At 32.3 months' median follow-up, D-R achieved a higher overall MRD-negative (10−5) conversion rate (D-R, 60.6% vs R, 27.7%; OR, 4.12; 95% CI, 2.26-7.52; P<0.0001) and ≥complete response rate (75.8% vs 61.4%; OR, 2.00; 95% CI, 1.08-3.69; P=0.0255) versus R alone. Progression-free survival (PFS) favored D-R versus R (hazard ratio, 0.53; 95% CI, 0.29-0.97); estimated 30-month PFS rates were 82.7% for D-R and 66.4% for R. Incidences of grade 3/4 cytopenias (54.2% vs 46.9%) and infections (18.8% vs 13.3%) were slightly higher with D-R versus R. In conclusion, D-R maintenance achieved a higher MRD-negative conversion rate and improved PFS post-transplant versus R alone, with no new safety concerns. This trial was registered at www.ClinicalTrials.gov: #NCT03901963.

Conflict of interest: COI declared - see note

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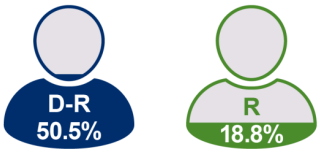
Clinical trial registration information (if any): ClinicalTrials.gov Identifier: NCT03901963

Daratumumab With Lenalidomide (D-R) As Maintenance in Anti-CD38 Naïve, MRD-Positive Patients After Transplant in Newly Diagnosed Multiple Myeloma (NDMM): The AURIGA Study

The phase 3 AURIGA study is the **first randomized study** to directly compare **D-R versus R maintenance in patients with NDMM** who were anti-CD38 naïve and in ≥VGPR and MRD positive post-transplant

D-R maintenance was associated with a significantly higher MRD-negative conversion rate by 12 months after the start of maintenance treatment versus R alone



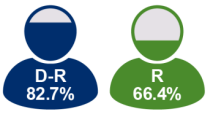
Odds Ratio, 4.51; 95% CI, 2.37-8.57; *P*<0.0001

At a median follow-up of 32.3 months,

PFS favored D-R versus R (HR, 0.53; 95% CI, 0.29-0.97)

47% risk reduction in disease progression or death for D-R

The estimated 30-month PFS rate was higher for D-R versus R



No new safety concerns were observed

Conclusions: Among transplant-eligible patients with NDMM who were anti-CD38 naïve and in ≥VGPR and MRD positive post-ASCT, D-R maintenance improved rates of MRD-negative conversion versus R alone. These results support the addition of daratumumab not only to induction/consolidation, but also to standard-of-care R maintenance.

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blood Visual Abstract

Daratumumab with lenalidomide as maintenance after transplant in newly diagnosed multiple myeloma: the AURIGA study

Short title for running head: Daratumumab-lenalidomide as maintenance in AURIGA

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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.

Key Points

- D-R maintenance improved MRD-negative conversion rate in NDMM patients who were MRD positive post-transplant, versus R maintenance.
- PFS favored D-R maintenance, with an improved 30-month PFS rate versus R alone, and D-R was well tolerated with no new safety concerns.

Abstract

No randomized trial has directly compared daratumumab and lenalidomide (D-R) maintenance therapy versus standard-of-care lenalidomide (R) alone post-transplant. Here, we report the primary results of the phase 3 AURIGA study evaluating D-R versus R maintenance in NDMM patients who were in ≥very good partial response, minimal residual disease (MRD; threshold 10^{-5}) positive, and anti-CD38 naïve post-transplant. Patients were randomized 1:1 to D-R or R maintenance for up to 36 cycles. Two hundred patients were randomized (D-R, n=99; R, n=101). The primary endpoint, MRD-negative (10^{-5}) conversion rate by 12 months from start of maintenance, was significantly higher for D-R versus R (50.5% vs 18.8%; odds ratio [OR], 4.51; 95% confidence interval [CI], 2.37-8.57; *P*<0.0001). MRD-negative (10^{-6}) conversion rate was similarly higher with D-R (23.2% vs 5.0%; OR, 5.97; 95% CI, 2.15-16.58; *P*=0.0002). At 32.3 months' median follow-up, D-R achieved a higher overall MRD-negative (10^{-5}) conversion rate (D-R, 60.6% vs R, 27.7%; OR, 4.12; 95% CI, 2.26-7.52; *P*<0.0001) and ≥complete response rate (75.8% vs 61.4%; OR, 2.00; 95% CI, 1.08-3.69; *P*=0.0255) versus R alone. Progression-free survival (PFS) favored D-R versus R (hazard ratio, 0.53; 95% CI, 0.29-0.97); estimated 30-month PFS rates were 82.7% for D-R and 66.4% for R. Incidences of grade 3/4 cytopenias (54.2% vs 46.9%) and infections (18.8% vs 13.3%) were slightly higher with D-R versus R. In conclusion, D-R maintenance achieved a higher MRD-negative conversion rate and improved PFS post-transplant versus R alone, with no new safety concerns. This trial was registered at www.ClinicalTrials.gov: #NCT03901963.

Introduction

Induction therapy followed by high-dose therapy and autologous stem cell transplant (ASCT), consolidation, and maintenance with lenalidomide (R) is considered the standard of care (SoC) for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM).[1] Despite rapid advancements in multiple myeloma (MM) treatment, most patients ultimately relapse. Therefore, there is a continued need to optimize treatment strategies to improve depth of response and long-term outcomes, especially in the maintenance setting following frontline ASCT.

While long-term clinical endpoints, such as progression-free survival (PFS) and overall survival (OS), remain the gold standard for identifying optimal treatment strategies, surrogate endpoints are used to provide reliable efficacy readouts at an earlier treatment stage, allowing for rapid and informed assessment of treatment options. The achievement of minimal residual disease (MRD) negativity is associated with improved long-term outcomes[2] and has evolved into an important clinical efficacy endpoint in clinical trials.[3,4] In recognition of the increasingly important role of MRD, the Oncologic Drugs Advisory Committee recently voted unanimously in favor of utilizing MRD testing as an early surrogate endpoint in myeloma clinical trials to support the accelerated approval of new treatments.[5]

Daratumumab is a human immunoglobin G kappa monoclonal antibody targeting CD38 and is approved as monotherapy and in combination regimens for the treatment of relapsed or refractory MM, as well as combination therapy for NDMM.[6,7] These approvals are based on many clinical studies of daratumumab combined with SoC regimens and encompass treatment

regimens comprising multiple phases of therapy, including induction/consolidation and maintenance. To date, however, no randomized trial has directly compared daratumumab-based maintenance therapy versus SoC maintenance therapy in transplant-eligible patients with NDMM.

The randomized phase 3 AURIGA study (ClinicalTrials.gov Identifier, NCT03901963) was designed to evaluate whether patients who were anti-CD38 naïve, were MRD positive, and had achieved very good partial response or better (≥VGPR) after induction therapy and ASCT could achieve improved outcomes when daratumumab was added to the standard R maintenance therapy. Herein, we report the primary endpoint and key secondary efficacy and safety endpoints among patients in the AURIGA study.

Methods

Study design and oversight

This multicenter, randomized, open-label, active-controlled, phase 3 study enrolled patients between 4 June 2019 and 4 May 2023 from 52 sites across the United States and Canada. The study protocol and all amendments were approved by the institutional review board or independent ethics committee at each participating site. The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and the principles that originated in the Declaration of Helsinki, and the study abided by all applicable

regulatory and country-specific requirements, including institutional review board approval of the protocol and any required amendments. All patients provided written informed consent.

Patients

Eligible patients were 18 to 79 years of age, had NDMM with a history of ≥4 cycles of induction therapy, had received high-dose therapy and ASCT within 12 months of the start of induction therapy, and were within 6 months of ASCT on the date of study randomization. In addition, eligible patients must have achieved a ≥VGPR as assessed per International Myeloma Working Group (IMWG) 2016 criteria at the time of screening,[8] had an Eastern Cooperative Oncology Group performance status score of 0 to 2, and were MRD positive (threshold 10^{-5}) based on next-generation sequencing (NGS; Adaptive Biotechnologies) post-ASCT at the time of screening. Patients with prior exposure to anti-CD38 therapies were excluded. Additional eligibility criteria are listed in the **Supplementary Methods**.

Study treatments

Patients were randomly assigned in a 1:1 ratio to receive D-R or R maintenance treatment. Randomization was stratified by cytogenetic risk per investigator's assessment (standard risk/unknown versus high risk). High risk was defined as the presence of ≥1 of the following cytogenetic abnormalities: del(17p), t(4;14), and t(14;16).

All patients received R 10 mg daily starting from Day 1 through Day 28 of each 28-day cycle; after 3 cycles, the dose could be increased to 15 mg, if tolerated and at the discretion of the

investigator. Patients in the D-R group also received subcutaneous daratumumab (1800 mg co-formulated with recombinant human hyaluronidase PH20 [2000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA]) weekly during Cycles 1 and 2, every 2 weeks during Cycles 3 through 6, and every 4 weeks from Cycle 7 onwards (all 28-day cycles). Study treatment continued for a planned maximum duration of 36 cycles or until disease progression, unacceptably toxicity, or consent withdrawal. To prevent injection-related reactions, patients receiving daratumumab also received pre- and post-injection medications (**Supplementary Methods**). For the management of drug-related toxicities, R dose reductions or treatment schedule modifications were permitted per institutional standards. No dose modifications were permitted for daratumumab; daratumumab-related toxicities were instead managed using dose delay. After the end of the study treatment period of 36 months, patients benefiting from treatment with daratumumab and/or R could continue receiving treatment per investigator's discretion.

Endpoints and assessments

The primary endpoint was MRD-negative conversion rate by NGS from baseline to 12 months after maintenance treatment, defined as the proportion of patients who achieved MRD-negative status (threshold 10^{-5}) by 12 months after the initiation of maintenance treatment and prior to progressive disease or subsequent antimyeloma therapy. Key secondary endpoints and their complete definitions are provided in the **Supplementary Methods**.

MRD was assessed by NGS of bone marrow aspirate samples by central laboratory (clonoSEQ®; Adaptive Biotechnologies). MRD-negative status was assessed at a minimum sensitivity threshold of 10^{-5} (1 tumor cell per 10^5 nucleated cells). Bone marrow samples were collected at screening and after 12, 18, 24, and 36 months with an accepted ± 30-day window of the scheduled visit. Response and disease progression were assessed with a validated computerized algorithm in accordance with IMWG 2016 response criteria.[8]

Besides determination of cytogenetic risk by investigator assessment for stratification purposes, a separate analysis was done to determine cytogenetic risk at diagnosis using available local fluorescence in situ hybridization/karyotype test. No mixture of central and local cytogenetic data was done to define high cytogenetic risk status for a patient. High-risk cytogenetics were evaluated both per the standard definition (≥1 of the following abnormalities: del[17p], t[4;14], and t[14;16]) as well as per the revised definition (also including t[14;20] and/or gain/amp[1q21]).

Statistical analysis

It was estimated that a sample size of approximately 214 patients (107 patients per group at a 1:1 randomization) would be needed to demonstrate a 20% treatment difference in MRD-negative conversion rate by the end of 12 months of maintenance with a power of ≥85% and a 2-sided alpha of 0.05 using a continuity-corrected chi-squared test. Due to recruitment challenges (eg, the COVID-19 pandemic and increased use of daratumumab during induction), trial enrollment ended after 200 patients had been randomized, providing sufficient power (84%) to detect a 20%

absolute difference in the primary endpoint. The primary analysis was conducted after all randomized patients had completed 12 months of maintenance, had disease progression, died, or discontinued study treatment. The primary analysis was performed in the intent-to-treat population, defined as all patients who were randomized to the study treatment.

The primary endpoint (MRD-negative conversion rate by 12 months of study treatment) was evaluated between treatment groups using a Cochran-Mantel-Haenszel test stratified by the baseline cytogenetic risk per investigator's assessment (high risk vs standard/unknown risk), as used for randomization of the study. Common odds ratios (ORs) were estimated using a Mantel-Haenszel test, and 2-sided 95% confidence intervals (CIs) were calculated. The *P*-value was provided by Fisher's exact test. See the **Supplementary Methods** for information on other categorical endpoints.

Results

Patients and treatment

A total of 200 patients were enrolled and randomly assigned to D-R maintenance (n = 99) or R maintenance alone (n = 101). Baseline demographic and disease characteristics were generally well balanced between treatment groups (**Table 1**). The median age of patients was 62 years (range, 35-78 years), 59.5% were male, 22.0% were Black, and 24.3% had International Staging System stage III disease at diagnosis. Among patients with evaluable cytogenetic risk data at diagnosis of MM, 20.4% (37/181) had high risk per the standard definition (D-R, 23.9% [22/92];

R, 16.9% [15/89]), and 34.1% (62/182) had high risk per the revised definition (D-R, 34.4% [32/93]; R, 33.7% [30/89]). Although treatment randomization was stratified by cytogenetic risk at study entry per investigator's assessment, a higher percentage of patients were identified as having high cytogenetic risk at diagnosis in the D-R arm due to investigators mixing cytogenetic risk assessments; for randomization, some assessments were made on screening cytogenetics and some on cytogenetics from diagnosis. Prior to study entry, patients in both treatment groups received a median of 5 (range, 4-8) induction cycles. Most patients received ≥2 induction cycles in which both bortezomib (V) and R were included as therapy components (D-R, 78.8% [78/99]; R, 83.2% [84/101]). Additional information on induction therapy is provided in the **Supplementary Results**.

Treatment disposition is summarized in **Figure 1**. At the time of this analysis, among those patients who received treatment (D-R, n = 96; R, n = 98), 33.3% (n = 32) in the D-R group and 48.0% (n = 47) in the R group had discontinued ≥1 component of study treatment. Seven patients in the D-R group and 15 patients in the R group discontinued the study (excluding due to death), primarily due to patient withdrawal (D-R, 4.0% [n = 4]; R, 10.9% [n = 11]) and physician decision (D-R, 1.0% [n = 1]; R, 2.0% [n = 2]). Additional information on subsequent therapy is provided in the **Supplementary Results**. At the time of primary analysis (after all patients completed at least 12 months of maintenance, had disease progression, died, or discontinued/withdrew), median follow-up was 32.3 months (D-R, 33.2 months; R, 30.3 months; see **Supplementary Table 1** for additional data on study treatment duration).

The median (range) duration of study treatment was 30.7 (0.7-37.5) months in the D-R group and 20.6 (0-37.7) months in the R group (**Supplementary Table 1**). Patients received a median (range) of 33.0 (1-36) cycles in the D-R group and 21.5 (1-36) cycles in the R group, and 88.5% (85/96) of D-R patients and 78.6% (77/98) of R patients completed ≥12 maintenance cycles. The median (range) relative dose intensity for R was similar across both groups (D-R, 86.7% [29.7-137.3]; R, 87.3% [37.7-145.5]) and was 100% (75.0-100.0) for daratumumab in the D-R group (**Supplementary Table 1**). R dose adjustments occurred in 71.9% (69/96) of D-R patients and 58.2% (57/98) of R patients, the majority of which were due to adverse events (AEs). A summary of treatment cycle delays and dose modifications is provided in **Supplementary Table 2**.

Efficacy

The primary endpoint of MRD-negative (10^{-5}) conversion rate from baseline to 12 months of maintenance treatment was achieved in 50 patients (50.5%) in the D-R group and 19 patients (18.8%) in the R group (OR, 4.51; 95% CI, 2.37-8.57; *P* <0.0001; **Figure 2**), a difference that was statistically significant. Considering only the MRD-evaluable patients (D-R, 88.9% [88/99]; R, 81.2% [82/101]), higher rates of MRD-negative (10^{-5}) conversion by 12 months were also observed for D-R versus R (56.8% [50/88] vs 23.2% [19/82]; OR, 4.40; 95% CI, 2.26-8.58; *P* <0.0001). Among those patients who achieved a complete response or better (≥CR) at any time during the study, similar observations were seen that favored the D-R arm (61.3% [46/75] vs 25.8% [16/62]; OR, 4.62; 95% CI, 2.20-9.70; *P* <0.0001). Among randomized patients, the MRD-negative (10^{-5}) ≥CR conversion rate by 12 months of maintenance treatment was also higher for D-R versus R (44.4% [44/99] vs 14.9% [15/101]; OR, 4.61; 95% CI, 2.34-9.09; *P*

<0.0001). D-R also demonstrated a consistent benefit in MRD-negative (10^{-5}) conversion rate by 12 months across all clinically relevant subgroups, including patients with high cytogenetic risk at diagnosis (per the standard and revised definition) and elderly age (**Figure 3**).

At a median follow-up of 32.3 months, the overall MRD-negative (10^{-5}) conversion rate was greater for D-R than for R (60.6% [60/99] vs 27.7% [28/101]; OR, 4.12; 95% CI, 2.26-7.52; *P* <0.0001). The rate of sustained MRD negativity lasting ≥6 months for D-R was ~2.5 times that of R (35.4% [35/99] vs 13.9% [14/101]; OR, 3.40; 95% CI, 1.69-6.83; *P* = 0.0005), and D-R had a higher rate of sustained MRD negativity lasting ≥12 months compared with R (17.2% [17/99] vs 5.0% [5/101]; OR, 4.08; 95% CI, 1.43-11.62; *P* = 0.0065; **Supplementary Table 3**). MRD analyses at the 10^{-6} threshold showed a similar trend with higher rates of MRD-negative conversion by 12 months for D-R versus R (23.2% [23/99] vs 5.0% [5/101]; OR, 5.97; 95% CI, 2.15-16.58; *P* = 0.0002), as well as higher rates of overall MRD-negative conversion at the time of follow-up for D-R versus R (36.4% [36/99] vs 12.9% [13/101]; OR, 3.91; 95% CI, 1.91-7.99; *P* = 0.0001).

Response by IMWG 2016 criteria favored D-R versus R, with a greater proportion of patients in the D-R group achieving a best overall confirmed response of ≥CR versus the R group (75.8% [75/99] vs 61.4% [62/101]; OR, 2.00; 95% CI, 1.08-3.69; *P* = 0.0255). Among those patients who entered the study with a baseline response of VGPR (D-R, n = 71; R, n = 71), a greater number of patients in the D-R group had their response deepen to ≥CR (n = 21 reached CR; n =

26 reached stringent CR) compared with the R group (n = 14 reached CR; n = 18 reached stringent CR; **Supplementary Table 4**).

At a median follow-up of 32.3 months, 19 PFS events (19.2%) occurred in the D-R group compared with 26 events (25.7%) in the R group. PFS favored D-R versus R (hazard ratio [HR], 0.53; 95% CI, 0.29-0.97), with a 47% risk reduction in disease progression or death; however, the nominal *P*-value of 0.0361 did not cross the stopping boundary of 0.015 for this PFS interim analysis. The estimated 30-month PFS rate was 82.7% (95% CI, 72.8-89.3) for D-R and 66.4% (95% CI, 54.0-76.2) for R (**Figure 4A**). PFS also favored D-R versus R across most clinically relevant subgroups, including those with standard or high cytogenetic risk per both the standard and revised definitions, as well as older patients (**Supplementary Figure 1**). Per **Figure 4B**, a PFS benefit was observed among patients who achieved MRD negativity conversion versus those who remained MRD positive, regardless of treatment. Estimated 30-month PFS rates were higher for those who achieved MRD-negative conversion by 12 months (D-R, 95.2% [95% CI, 81.9-98.8]; R, 94.1% [95% CI, 65.0-99.1]) compared with those who remained MRD positive (D-R, 69.0% [95% CI, 52.2-80.9]; R, 59.3% [95% CI, 45.0-71.0]). Five events (5.1%) of death occurred in the D-R group compared with 9 (8.9%) in the R group, trending favorably for the D-R arm (HR, 0.50; 95% CI, 0.17-1.50; **Supplementary Figure 2**).

Safety

A total of 194 patients (D-R, n = 96; R, n = 98) received ≥1 dose of study treatment and comprised the safety analysis set. Any grade treatment-related AEs were reported in 99.0% of

patients in both treatment groups. Grade 3/4 AEs occurred in 74.0% of patients in the D-R group and 67.3% of patients in the R group. The most common AEs of any grade (occurring in ≥20% of patients in either group) and grade 3/4 treatment-emergent AEs (occurring in ≥5% in either group) are reported in **Table 2**.

Serious AEs were reported in 30.2% and 22.4% of D-R and R patients, respectively; the most frequent across both groups was pneumonia (4.2%; 4.1%, respectively). The proportion of patients with AEs leading to treatment discontinuation of any treatment component was 14.6% in the D-R group and 8.2% in the R group, most commonly due to myelodysplastic syndrome (D-R, 2.1%; R, 1.0%) for D-R and peripheral sensory neuropathy (0; 2.0%) for R. AEs with an outcome of death were reported in 2 patients within the D-R group (COVID-19 pneumonia and pneumonia Legionella, n = 1 each) and 1 patient in the R group (COVID-19 pneumonia).

Cytopenias of any grade were more common for D-R than for R (75.0% vs 69.4%), as was the incidence of grade 3/4 cytopenias (54.2% vs 46.9%). Neutropenia accounted for the majority of grade 3/4 cytopenias reported in both groups (D-R, 46.9%; R, 41.8%). The overall incidence of grade 3/4 infections in the 2 treatment groups was 18.8% versus 13.3%, with the most common being pneumonia (5.2% vs 4.1%). Grade 3/4 COVID-19 occurred in 1.0% of D-R patients versus 3.1% of R patients, with serious COVID-19 infections reported in 2.1% of D-R patients and 3.1% of R patients. In the D-R group, 13.5% of patients had ≥1 infusion-related reaction, none of which were grade ≥3 or serious (**Table 2**). Most infusion-related reactions occurred with the first

injection (11.5%), with incidences decreasing for the second injection (3.1%) and subsequent injections (4.2%).

A complete summary of secondary primary malignancies (SPMs) is provided in **Supplementary Table 5**. A total of 7.3% of patients in the D-R group and 4.1% in the R group had SPMs. Hematologic SPMs were seen in 2.1% of patients in the D-R group and 3.1% of patients in the R group. Noncutaneous and cutaneous SPMs were seen in 3.1% and 2.1% of patients in the D-R group, respectively, and 1.0% and 0% in the R group.

Discussion

In the randomized, phase 3 AURIGA study, the addition of daratumumab to R maintenance resulted in a significantly higher MRD-negative conversion rate among transplant-eligible patients with NDMM who were in ≥VGPR, were MRD positive, and anti-CD38 naïve post-ASCT, compared with R maintenance alone. This increase in MRD-negative conversion was clinically meaningful, as D-R maintenance trended towards improved PFS, higher overall MRD-negative conversion rates, and deeper responses compared with R maintenance alone, with no unexpected safety concerns.

Achieving MRD negativity has been associated with improved disease control and prolonged survival[2,9] and has been demonstrated to be a surrogate marker for PFS.[10] Additionally, a recent meta-analysis of 11 clinical trials reported that a difference of ~12% in MRD-negative rates was

associated with a PFS improvement of ~12 months.[11] In AURIGA, the MRD-negative (10^{-5}) conversion rate by 12 months for D-R maintenance was 2.7 times the rate of R alone (50.5% vs 18.8%, respectively), with improvements also observed at the 10^{-6} threshold and across all clinically relevant subgroups, including patients with high-risk disease. D-R maintenance also led to higher rates of sustained MRD negativity lasting ≥6 months.

At a median follow-up of 32.3 months, PFS favored D-R maintenance compared with R maintenance alone, with an observed 47% reduction in the risk of disease progression or death and estimated 30-month PFS rates of 82.7% in the D-R arm and 66.4% in the R arm. At the time of data analysis, the number of patients who reached the end of study treatment in the ongoing AURIGA study was low, resulting in a low number of patients at risk at this time point. However, given that the Kaplan-Meier curve for D-R was consistently above the curve for R prior to the end of study treatment (Cycle 36) and that the HR for PFS favored D-R, the data demonstrate that PFS favored D-R versus R. A PFS advantage was also observed for patients who achieved MRD-negative conversion compared with those who remained MRD positive, regardless of treatment arm. Thus, the higher MRD-negative conversion rate at 12 months in the D-R arm versus the R arm resulted in a PFS benefit in the D-R arm and demonstrated the value of daratumumab in maintenance therapy.

Although this was the first randomized trial to directly compare daratumumab-based maintenance therapy to SoC maintenance, findings are consistent with those observed in the CASSIOPEIA study. In the CASSIOPEIA study of transplant-eligible patients with NDMM,

patients received bortezomib, thalidomide, and dexamethasone (VTd) with or without daratumumab as induction/consolidation in part 1, followed by part 2, where patients with a partial response or better were rerandomized to receive daratumumab monotherapy every 8 weeks as maintenance or observation.[12,13] After a median follow-up of 70.6 months, daratumumab maintenance significantly reduced the risk of disease progression or death by 51% versus observation. The longest PFS was observed in patients who received daratumumab plus VTd (D-VTd) induction/consolidation followed by the daratumumab maintenance arm, with a substantial difference compared with patients who received D-VTd followed by observation (HR, 0.76; 95% CI, 0.58-1.00; $P = 0.0480$).[14] This PFS benefit for daratumumab maintenance in patients who received D-VTd was not apparent at the primary study readout, but manifested itself with longer follow-up. Thus, the updated CASSIOPEIA data demonstrate the benefit of daratumumab maintenance, both in patients who received VTd as well as in patients who received D-VTd induction/consolidation.

Other studies have included daratumumab as part of the maintenance regimen in transplant-eligible patients with NDMM. Specifically, the phase 2 GRIFFIN study and phase 3 PERSEUS study evaluated the addition of daratumumab to bortezomib/lenalidomide/dexamethasone (D-VRd) induction/consolidation and R maintenance (D-R).[15,16] In both studies, D-VRd induction/consolidation followed by D-R maintenance led to deep and durable responses that improved with maintenance therapy, with both studies reporting a reduced risk of disease progression or death by 55% to 58%.

One critical remaining question is whether the benefit of D-R maintenance, as seen here in AURIGA, is applicable to patients who receive D-VRd or another daratumumab-containing regimen as induction therapy. As discussed previously, the CASSIOPEIA study demonstrated that daratumumab monotherapy improved PFS in patients who received D-VTd, but patients in the control arm did not receive any maintenance therapy. Neither the GRIFFIN nor the PERSEUS studies were designed to isolate the contribution of maintenance therapy to primary and secondary endpoints, as no rerandomization was done prior to maintenance initiation. However, a post hoc analysis of the phase 3 PERSEUS study indicated that D-R maintenance can confer clinical benefit in patients who received D-VRd induction/consolidation. Specifically, 60.2% of patients who were MRD positive following D-VRd induction/consolidation and ASCT successfully converted to MRD negativity (10^{-5}) with D-R maintenance, whereas only 40.5% of patients who were MRD positive following VRd induction/consolidation and ASCT achieved MRD negativity (10^{-5}) conversion with R maintenance alone.[17] This difference was even more pronounced at a threshold of 10^{-6}, with 56.7% of D-VRd patients converting to MRD negativity with D-R maintenance versus 25.2% of VRd patients converting to MRD negativity with R maintenance.[17] However, in the absence of rerandomization, this analysis cannot eliminate the potential impact of daratumumab in induction and consolidation on the MRD-conversion rates during maintenance; further investigations are needed to conclusively isolate the benefit of D-R maintenance versus R alone following daratumumab-based induction regimens. The ongoing DRAMMATIC SWOG1803 study (ClinicalTrials.gov Identifier, NCT04071457) will provide more definitive information on the clinical benefit of D-R versus R maintenance and whether maintenance therapy can be discontinued after attainment of sustained MRD negativity. The

GMMG-HD7 study (ClinicalTrials.gov Identifier, NCT03617731) will also provide information on anti-CD38 therapies in this setting.

The addition of daratumumab to R maintenance did not result in any unexpected or new safety concerns, with a safety profile consistent with that previously known for daratumumab.[12,18,19] Rates of grade 3/4 AEs, serious AEs, and SPMs were slightly greater in the D-R arm than in the R arm alone, as were rates of infections or cytopenias. These higher rates should be interpreted in the light of longer treatment duration for patients randomized to the D-R arm (30.7 months) versus the R arm (20.6 months), leading to a longer AE reporting interval, as well as a longer follow-up time (33.2 months for D-R vs 30.3 months for R) leading to a longer reporting interval for SPMs. The rate of treatment discontinuation of any component of study therapy due to AEs was higher with D-R than R maintenance alone (D-R group, 14.6%; R group, 8.2%).

It is worth mentioning that the AURIGA study eligibility requirement for patients to be anti-CD38 naïve limited the recruitment pool. This was partially due to the D-VRd regimen gaining popularity and increased utilization in the myeloma community for transplant-eligible patients with NDMM, even before the publication of the long-term results of the randomized GRIFFIN and PERSEUS studies.[15,16] An additional limitation was that nearly 10% of patients in each treatment arm had “unknown” cytogenetic risk. Furthermore, there was an imbalance in patients with high cytogenetic risk between the D-R and R maintenance arms at diagnosis (23.9% and 16.9%, respectively), per the standard definition, due to erroneous high-risk assessments used for stratification. Despite these imbalances in favor of the control arm, the current study still met its

primary endpoint, with higher MRD-negative conversion rates observed for the D-R arm, making the AURIGA data more impactful. Of note, many patients have not reached both the 24- and 36-month MRD assessments. Per the study protocol, MRD was assessed after certain numbers of treatment cycles rather than after fixed intervals, and each 28-day cycle was slightly shorter than 1 month. As such, most participants who achieved initial MRD negativity at 12 months were not assessable for ≥6 months or ≥12 months of sustained MRD negativity until they reached the 24-cycle or 36-cycle MRD assessment, respectively. Longer follow-up is needed to determine whether higher sustained MRD-negativity rates are observed at subsequent data cutoffs.

In summary, among transplant-eligible patients with NDMM who were in ≥VGPR, were MRD positive post-ASCT, and anti-CD38 naïve, the addition of daratumumab to SoC R maintenance resulted in improved rates of MRD-negative conversion, deeper responses, and improved PFS rates. No new safety concerns were observed. These results support the addition of daratumumab not only to induction/consolidation, but also to SoC R maintenance for these patients. Future studies should continue to assess the implementation of daratumumab-based maintenance in other patient populations and determine the optimal point of treatment initiation and cessation.

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Authorship

Contribution: A.B. participated in investigation, patient enrollment, analysis of data, writing and reviewing and editing the manuscript. L.F. participated in investigation, acquisition of data, and writing and reviewing and editing the manuscript. L.D.A. participated in investigation, data collection, writing and reviewing and editing the manuscript, and supervision of the investigation and data collection. C.P.C. participated in investigation, patient enrollment, and writing and reviewing and editing the manuscript. E.P. participated in patient enrollment, and writing and reviewing and editing the manuscript. A.J.C. participated in writing and reviewing and editing the manuscript and investigation. C.C. participated in writing and reviewing and editing the manuscript and investigation. S.L. participated in patient enrollment, data collection, and writing and reviewing and editing the manuscript. D.W.S. participated in conceptualization, investigation, writing and reviewing and editing the manuscript, and supervision. K.H.S. participated in patient enrollment and the study steering committee and reviewing and editing the manuscript. R.S. participated in investigation, resources, validation, and writing and reviewing and editing the manuscript. N.S. participated in patient enrollment and the steering committee and writing and reviewing and editing the manuscript. A.C. participated in writing and reviewing and editing the manuscript. M.K. participated in writing and reviewing and editing the

manuscript. H.P. participated in statistical analysis and reviewing and editing the manuscript. S.P. participated in data curation, supervision, project administration, and writing and reviewing and editing the manuscript. V.K. participated in data curation, supervision, project administration, and writing and reviewing and editing the manuscript. A.C. participated in data curation, supervision, project administration, and writing and reviewing and editing the manuscript. R.C. participated in supervision, and writing and reviewing and editing the manuscript. T.S.L. participated in conceptualization, study design, supervision, and writing and reviewing and editing the manuscript. P.V. participated in conceptualization, investigation, resourcing, and writing and reviewing and editing the manuscript.

Conflict of Interest Disclosures

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Table 1. Patient demographic and disease characteristics in the ITT population

	D-R	R
Age, years	n = 99	n = 101
Median (range)	63 (35-77)	62 (35-78)
Category, n (%)		
<65	61 (61.6)	61 (60.4)
65-70	23 (23.2)	21 (20.8)
≥70	15 (15.2)	19 (18.8)
Sex, n (%)	n = 99	n = 101
Male	61 (61.6)	58 (57.4)
Female	38 (38.4)	43 (42.6)
Race, n (%)	n = 99	n = 101
White	67 (67.7)	68 (67.3)
Black or African American	20 (20.2)	24 (23.8)
Asian	5 (5.1)	1 (1.0)
American Indian or Alaska Native	0	1 (1.0)
Other*	5 (5.1)	5 (5.0)
Not reported	2 (2.0)	2 (2.0)
ECOG PS score, n (%)	n = 99	n = 101
0	45 (45.5)	55 (54.5)
1	52 (52.5)	44 (43.6)
2	2 (2.0)	2 (2.0)
ISS disease stage, n (%)	n = 91	n = 98
I	40 (44.0)	38 (38.8)
II	28 (30.8)	37 (37.8)
III	23 (25.3)	23 (23.5)
Number of induction cycles	n = 98	n = 99
Median (range)	5.0 (4.0-8.0)	5.0 (4.0-8.0)
Cytogenetic risk at diagnosis	n = 92	n = 89
Standard risk	63 (68.5)	66 (74.2)
High risk†	22 (23.9)	15 (16.9)
del(17p)	13 (14.1)	3 (3.4)
t(4;14)	10 (10.9)	12 (13.5)
t(14;16)	6 (6.5)	7 (7.9)
Unknown	7 (7.6)	8 (9.0)
Revised cytogenetic risk at diagnosis	n = 93	n = 89
Standard risk	52 (55.9)	53 (59.6)
High risk‡	32 (34.4)	30 (33.7)
del(17p)	13 (14.0)	3 (3.4)
t(4;14)	10 (10.8)	12 (13.5)
t(14;16)	6 (6.5)	7 (7.9)
t(14;20)	1 (1.1)	2 (2.2)
gain/amp(1q21)	16 (17.2)	22 (24.7)

Unknown	9 (9.7)	6 (6.7)

ECOG PS indicates Eastern Cooperative Oncology Group performance status; ISS, International Staging System; ITT, intent-to-treat.

*Patients reporting multiple races are included under other.

[†]High risk is defined as positive for any of del(17p), t(14;16), or t(4;14).

[‡]Revised high-risk cytogenetics is defined as ≥1 abnormality from del(17p), t(4;14), t(14;16), t(14;20), and gain/amp(1q21).

Table 2. Most common* AEs reported in the safety population

	D-R (n = 96)		R (n = 98)	
AE, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Hematologic				
Neutropenia	62 (64.6)	45 (46.9)	60 (61.2)	41 (41.8)
Leukopenia	25 (26.0)	9 (9.4)	29 (29.6)	6 (6.1)
Thrombocytopenia	23 (24.0)	3 (3.1)	28 (28.6)	2 (2.0)
Lymphopenia	23 (24.0)	10 (10.4)	13 (13.3)	5 (5.1)
Anemia	22 (22.9)	4 (4.2)	17 (17.3)	3 (3.1)
Nonhematologic				
Diarrhea	59 (61.5)	3 (3.1)	54 (55.1)	5 (5.1)
Fatigue	44 (45.8)	2 (2.1)	46 (46.9)	3 (3.1)
Upper respiratory tract infection	40 (41.7)	0	26 (26.5)	0
Cough	37 (38.5)	0	36 (36.7)	0
Hypokalemia	33 (34.4)	7 (7.3)	36 (36.7)	6 (6.1)
Arthralgia	32 (33.3)	1 (1.0)	36 (36.7)	1 (1.0)
Back pain	31 (32.3)	0	20 (20.4)	1 (1.0)
COVID-19	28 (29.2)	1 (1.0)	29 (29.6)	3 (3.1)
Nausea	26 (27.1)	0	26 (26.5)	0
Nasal congestion	25 (26.0)	0	19 (19.4)	0
Headache	24 (25.0)	1 (1.0)	17 (17.3)	0
Constipation	22 (22.9)	0	26 (26.5)	0
Muscle spasms	22 (22.9)	0	21 (21.4)	0
Pain in extremity	22 (22.9)	1 (1.0)	17 (17.3)	0
Rash maculopapular	21 (21.9)	1 (1.0)	17 (17.3)	2 (2.0)
Hypertension	14 (14.6)	7 (7.3)	10 (10.2)	4 (4.1)
Pneumonia	10 (10.4)	5 (5.2)	14 (14.3)	4 (4.1)
Infusion-related reactions	13 (13.5)	0	N/A	N/A

N/A indicates not applicable.

*AEs of any grade that occurred in ≥20% of patients and grade 3/4 AEs that occurred in ≥5% of patients in either treatment group.

Figure legends

Figure 1. CONSORT diagram for AURIGA. Summary of treatment disposition in AURIGA.

*3 patients were randomized but not treated due to physician decision, study schedule too intense, and protocol deviation (n=1 each).

†3 patients were randomized but not treated due to study tests being too hard, patient not wanting to be on the lenalidomide only treatment arm, and patient withdrawal of consent (n=1 each).

Figure 2. MRD-negative (10^{-5}) conversion rate from baseline to 12 months of maintenance treatment. ITT indicates intent-to-treat.

*Mantel-Haenszel estimate of the common OR for stratified tables is used. The stratification factor is baseline cytogenetic risk per investigator assessment (high vs standard/unknown) as used for randomization. An OR >1 indicates an advantage for D-R.

†*P*-value <0.0001, from Fisher's exact test.

‡The ITT analysis set was defined as all patients who were randomized to treatment.

§Patients who achieved ≥CR at any time during the study per IMWG computerized algorithm.

‖The MRD-evaluable analysis set includes all randomized patients who had an MRD assessment at baseline and had ≥1 post-baseline MRD evaluation.

Figure 3. Subgroup analysis of MRD-negative (10^{-5}) conversion rate from baseline to 12 months of maintenance treatment.

*High risk is defined as positive for any of the following abnormalities: del(17p), t(14;16), or t(4;14).

†Revised high-risk cytogenetics are defined as ≥1 of the following abnormalities: del(17p), t(4;14), t(14;16), t(14;20), and gain/amp(1q21).

Figure 4. PFS analysis in the ITT population* (A) overall and (B) by MRD-negative (10^{-5}) conversion status by 12 months.†

Estimated 30-month PFS rates are shown.

*At a median follow-up of 32.3 months, median PFS was 37.9 months in the D-R group and was not reached in the R group.

†MRD negative by 12 months refers to patients who were MRD positive at baseline and achieved MRD-negative status (at a threshold of 10^{-5}) by bone marrow aspirate from randomization to 12 months (+2-month window), but prior to progressive disease and subsequent antimyeloma therapy. Otherwise, patients were considered MRD positive.

‡Per study protocol, disease assessments stopped at the end of study treatment (Cycle 36), after which patients were only followed for survival. At the time of this analysis, the number of patients who reached the end of study treatment was low, thus resulting in a low number of patients at risk. Two D-R events occurred at the tail end of study assessments: 1 reported at 1134 days (37.26 months) and 1 at 1153 days (37.88 months). Due to these events, there was a sudden and steep drop in the Kaplan-Meier curve for D-R.

Figure 1

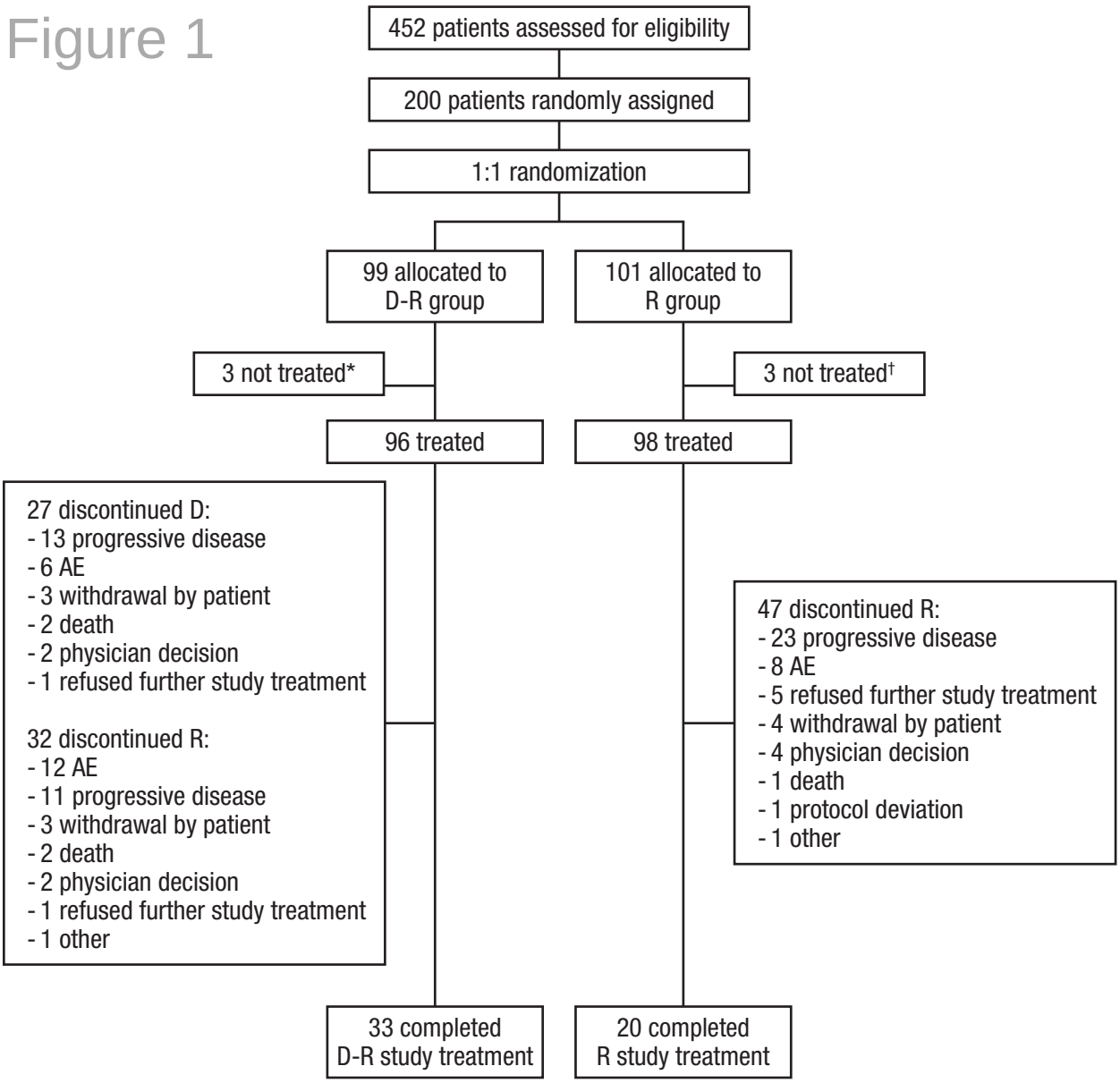

452 patients assessed for eligibility
200 patients randomly assigned
1:1 randomization
99 allocated to D-R group
101 allocated to R group
3 not treated*
3 not treated†
96 treated
98 treated
27 discontinued D:
- 13 progressive disease
- 6 AE
- 3 withdrawal by patient
- 2 death
- 2 physician decision
- 1 refused further study treatment
32 discontinued R:
- 12 AE
- 11 progressive disease
- 3 withdrawal by patient
- 2 death
- 2 physician decision
- 1 refused further study treatment
- 1 other
47 discontinued R:
- 23 progressive disease
- 8 AE
- 5 refused further study treatment
- 4 withdrawal by patient
- 4 physician decision
- 1 death
- 1 protocol deviation
- 1 other
33 completed D-R study treatment
20 completed R study treatment

Figure 2

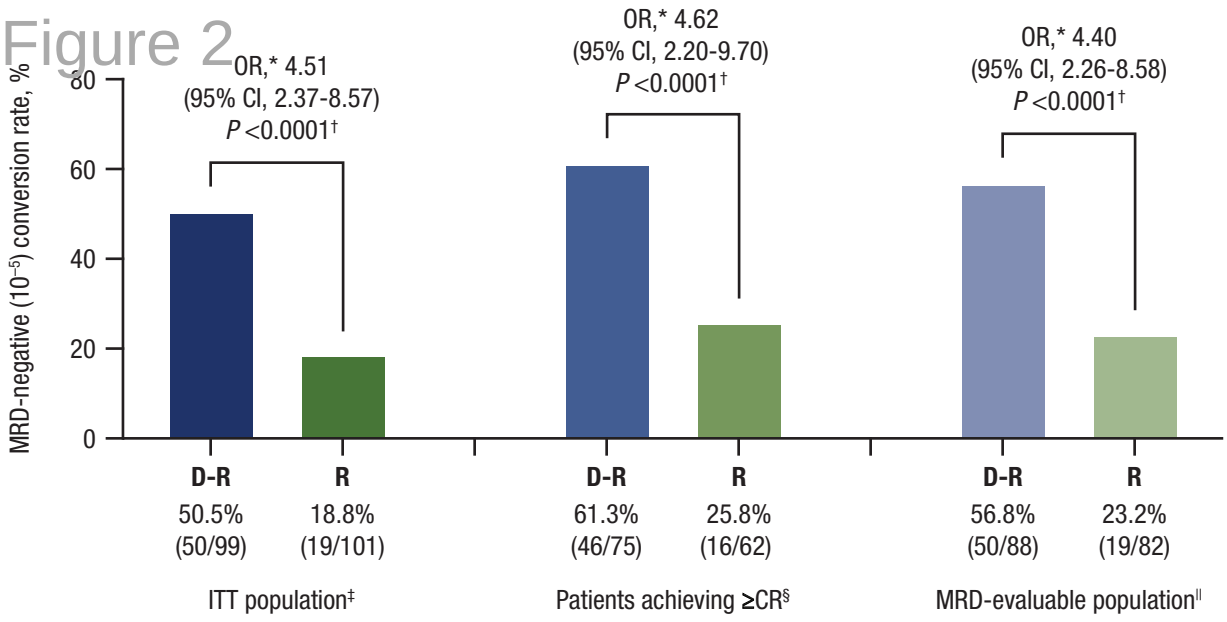

MRD-negative (10^{-5}) conversion rate, %
80
60
40
20
0
OR,* 4.51
(95% CI, 2.37-8.57)
P <0.0001†
OR,* 4.62
(95% CI, 2.20-9.70)
P <0.0001†
OR,* 4.40
(95% CI, 2.26-8.58)
P <0.0001†
D-R
R
50.5%
(50/99)
18.8%
(19/101)
61.3%
(46/75)
25.8%
(16/62)
56.8%
(50/88)
23.2%
(19/82)
ITT population‡
Patients achieving ≥CR§
MRD-evaluable population‖

Figure 3

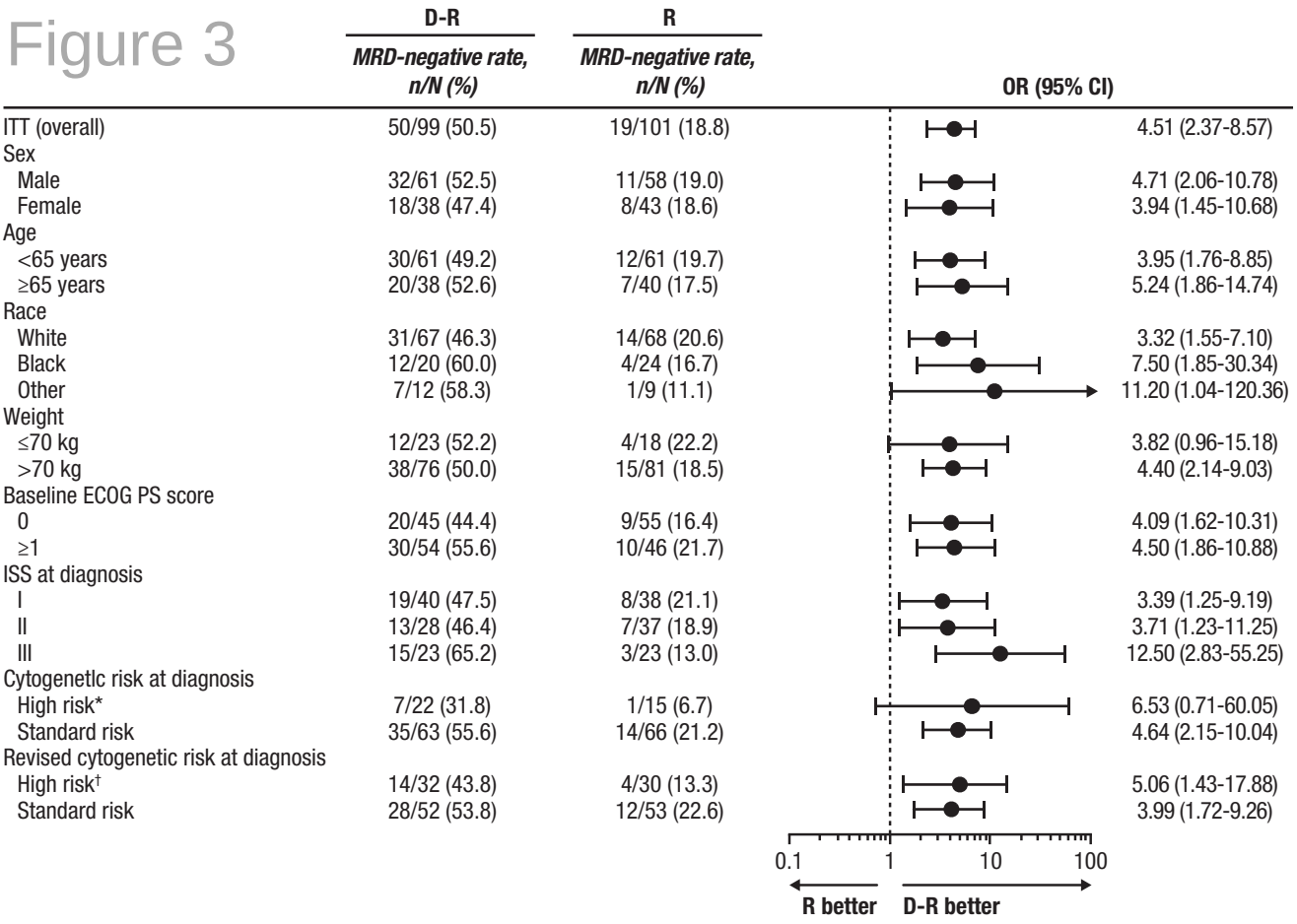
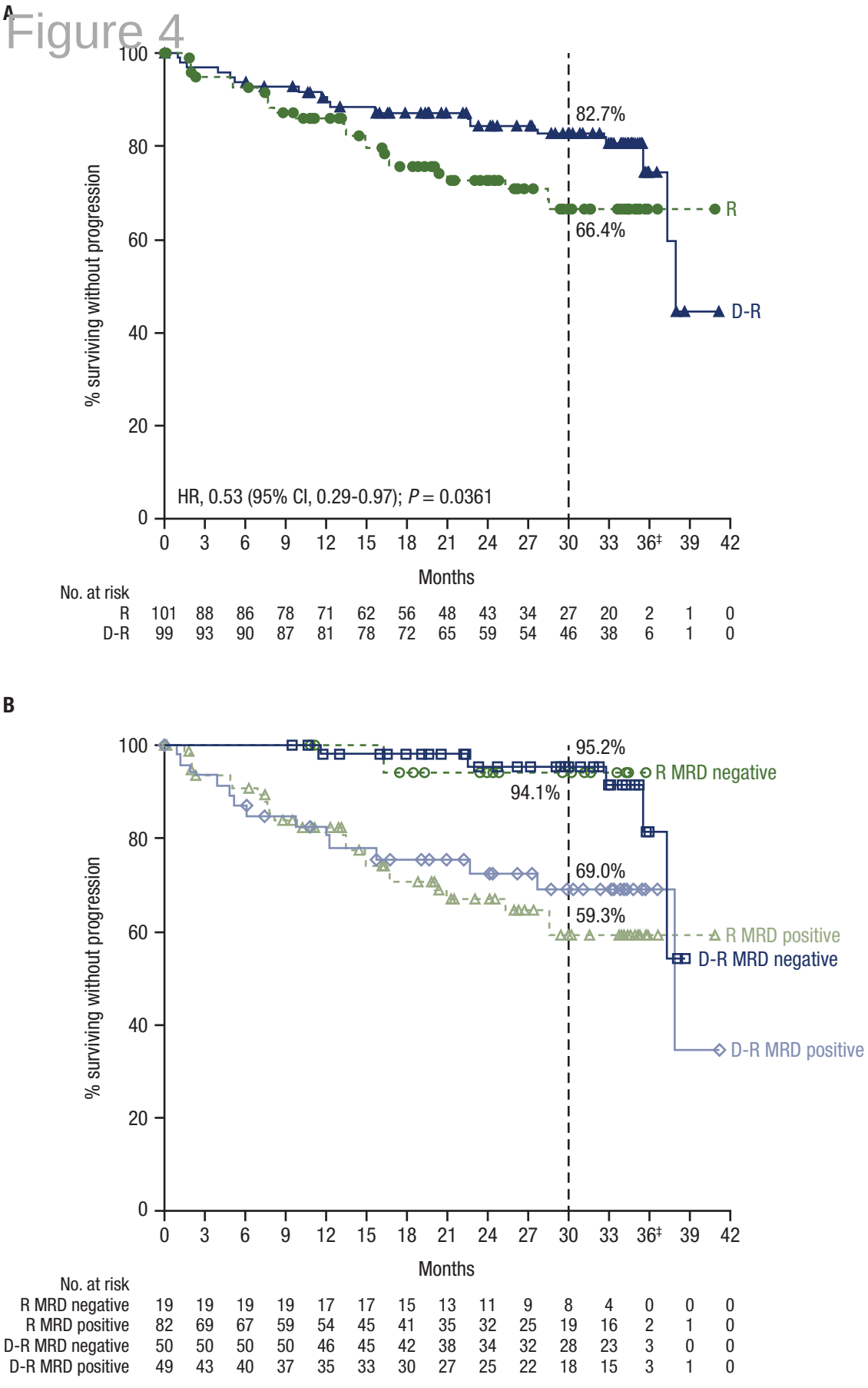

D-R
MRD-negative rate, n/N (%)
R
MRD-negative rate, n/N (%)
OR (95% CI)
ITT (overall) 50/99 (50.5) 19/101 (18.8) 4.51 (2.37-8.57)
Sex
Male 32/61 (52.5) 11/58 (19.0) 4.71 (2.06-10.78)
Female 18/38 (47.4) 8/43 (18.6) 3.94 (1.45-10.68)
Age
<65 years 30/61 (49.2) 12/61 (19.7) 3.95 (1.76-8.85)
≥65 years 20/38 (52.6) 7/40 (17.5) 5.24 (1.86-14.74)
Race
White 31/67 (46.3) 14/68 (20.6) 3.32 (1.55-7.10)
Black 12/20 (60.0) 4/24 (16.7) 7.50 (1.85-30.34)
Other 7/12 (58.3) 1/9 (11.1) 11.20 (1.04-120.36)
Weight
≤70 kg 12/23 (52.2) 4/18 (22.2) 3.82 (0.96-15.18)
>70 kg 38/76 (50.0) 15/81 (18.5) 4.40 (2.14-9.03)
Baseline ECOG PS score
0 20/45 (44.4) 9/55 (16.4) 4.09 (1.62-10.31)
≥1 30/54 (55.6) 10/46 (21.7) 4.50 (1.86-10.88)
ISS at diagnosis
I 19/40 (47.5) 8/38 (21.1) 3.39 (1.25-9.19)
II 13/28 (46.4) 7/37 (18.9) 3.71 (1.23-11.25)
III 15/23 (65.2) 3/23 (13.0) 12.50 (2.83-55.25)
Cytogenetlc risk at diagnosis
High risk* 7/22 (31.8) 1/15 (6.7) 6.53 (0.71-60.05)
Standard risk 35/63 (55.6) 14/66 (21.2) 4.64 (2.15-10.04)
Revised cytogenetic risk at diagnosis
High risk† 14/32 (43.8) 4/30 (13.3) 5.06 (1.43-17.88)
Standard risk 28/52 (53.8) 12/53 (22.6) 3.99 (1.72-9.26)
0.1
1
10
100
R better
D-R better

Figure 4


A
100
80
60
40
20
0
% surviving without progression
82.7%
66.4%
R
D-R
HR, 0.53 (95% CI, 0.29-0.97); P = 0.0361
0 3 6 9 12 15 18 21 24 27 30 33 36‡ 39 42
Months
No. at risk
R 101 88 86 78 71 62 56 48 43 34 27 20 2 1 0
D-R 99 93 90 87 81 78 72 65 59 54 46 38 6 1 0
B
100
80
60
40
20
0
% surviving without progression
95.2%
R MRD negative
94.1%
69.0%
59.3%
R MRD positive
D-R MRD negative
D-R MRD positive
0 3 6 9 12 15 18 21 24 27 30 33 36‡ 39 42
Months
No. at risk
R MRD negative 19 19 19 19 17 17 15 13 11 9 8 4 0 0 0
R MRD positive 82 69 67 59 54 45 41 35 32 25 19 16 2 1 0
D-R MRD negative 50 50 50 50 46 45 42 38 34 32 28 23 3 0 0
D-R MRD positive 49 43 40 37 35 33 30 27 25 22 18 15 3 1 0