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# Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX

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## ABSTRACT

In the POLLUX study, daratumumab plus lenalidomide/dexamethasone significantly reduced risk of progression/death versus lenalidomide/dexamethasone alone in relapsed/refractory multiple myeloma. We provide one additional year of follow up and include the effect on minimal residual disease and in clinically relevant subgroups. After 25.4 months of follow up, daratumumab plus lenalidomide/dexamethasone prolonged progression-free survival versus lenalidomide/dexamethasone alone (median not reached vs. 17.5 months; hazard ratio, 0.41; 95% confidence interval, 0.31-0.53;  $P < 0.0001$ ). The overall response rate was 92.9% versus 76.4%, and 51.2% versus 21.0% achieved a complete response or better, respectively (both  $P < 0.0001$ ). At the  $10^{-5}$  sensitivity threshold, 26.2% versus 6.4% were minimal residual disease-negative, respectively ( $P < 0.0001$ ). *Post hoc* analyses of clinically relevant patient subgroups demonstrated that progression-free survival was significantly prolonged for daratumumab plus lenalidomide/dexamethasone versus

lenalidomide/dexamethasone regardless of number of prior lines of therapy. Patients previously treated with lenalidomide or thalidomide and those refractory to bortezomib received similar benefits (all  $P < 0.01$ ). Treatment benefit with daratumumab plus lenalidomide/dexamethasone was maintained in high-risk patients (median progression-free survival 22.6 vs. 10.2 months; hazard ratio, 0.53; 95% confidence interval, 0.25-1.13;  $P = 0.0921$ ) and patients with treatment-free intervals of  $>12$  and  $\leq 12$  months and  $>6$  and  $\leq 6$  months. No new safety signals were observed. In relapsed/refractory multiple myeloma patients, daratumumab plus lenalidomide/dexamethasone continued to improve progression-free survival and deepen responses *versus* lenalidomide/dexamethasone. Trial Registration: *clinicaltrials.gov* identifier: 02076009.

## Introduction

Novel therapeutics approved during the last decade for relapsed or refractory multiple myeloma (RRMM), including proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), are now standard of care treatments.<sup>1-3</sup> However, patients eventually relapse and subpopulations such as those with high-risk cytogenetic abnormalities may not achieve the same benefits as standard-risk patients.<sup>4</sup> Treatment choices must be based on patient factors (comorbidities, frailty, preferences), disease factors (burden, molecular risk), and treatment factors (prior therapies, refractoriness, and toxicity).

Daratumumab is a human monoclonal antibody targeting CD38, a cell surface receptor highly expressed on multiple myeloma (MM) cells,<sup>5,6</sup> that exerts its effects via direct on-tumor and immunomodulatory mechanisms of action.<sup>7-11</sup> Daratumumab is approved in many countries as monotherapy for patients with heavily treated RRMM.<sup>12,13</sup> In combination with standard of care regimens, including bortezomib/dexamethasone (Vd; CASTOR study)<sup>14</sup> and lenalidomide/dexamethasone (Rd; POLLUX study),<sup>15</sup> daratumumab significantly prolonged progression-free survival (PFS) and deepened responses in patients with RRMM. This led to regulatory approval in many countries for patients with  $\geq 1$  prior line of therapy.<sup>16,17</sup>

In the prespecified interim analysis of POLLUX, after a median follow up of 13.5 months, daratumumab in combination with Rd (D-Rd) resulted in a 63% reduction in the risk of disease progression or death, significantly higher overall response rates (ORRs; 92.9% vs. 76.4%), and significantly higher minimal residual disease (MRD)-negativity rates at multiple sensitivity thresholds *versus* Rd.<sup>15</sup>

To identify patients who may benefit more from D-Rd treatment, we conducted subgroup analyses of POLLUX after a longer follow up of 25.4 months. The efficacy of D-Rd *versus* Rd was compared according to the number of prior lines of therapy received, prior IMiD exposure, bortezomib refractoriness, treatment-free interval after previous treatment line, and cytogenetic risk. We also assessed the ability of daratumumab to drive deep clinical responses beyond complete responses (CRs) through assessment of MRD.

## Methods

### Study Design

POLLUX is an ongoing randomized, open-label, multicenter, phase 3 study conducted in patients with RRMM (*clinicaltrials.gov* identifier: 02076009). An independent ethics committee or institutional review board at each site approved the trial. The study pro-

ocol was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The study design and primary results have been previously published.<sup>15</sup> Briefly, eligible patients had progressive disease according to International Myeloma Working Group (IMWG) criteria<sup>18,19</sup> during or after their last regimen and had received and responded to  $\geq 1$  line of prior therapy; lenalidomide-refractory patients were ineligible. Patients were randomized 1:1 to Rd (lenalidomide: 25 mg orally on Days 1-21 of each 28-day cycle; dexamethasone: 40 mg orally weekly) with or without daratumumab (16 mg/kg intravenously weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks) until progression.

### Endpoints and Assessments

The primary efficacy endpoint was PFS, and secondary efficacy endpoints included ORR, rates of very good partial response (VGPR) or better and CR or better, MRD, time to response, and overall survival.

This exploratory, *post hoc*, secondary analysis examined patient populations according to prior lines of therapy received (1, 2-3, 1-3), prior treatment exposure (bortezomib, lenalidomide, and thalidomide), refractoriness to bortezomib, time since last therapy ( $>12$  months,  $\leq 12$  months,  $>6$  months, and  $\leq 6$  months prior to randomization), and cytogenetic risk. Numbers of prior lines of therapy were determined by investigators according to the IMWG consensus guidelines.<sup>19</sup> Treatment-free interval was defined as the duration between the end date of the last line of prior therapy and randomization. Cytogenetic abnormalities were determined with CD138<sup>+</sup> selected cells at the screening visit prior to randomization by centralized next-generation sequencing. The presence of 1 or more of t(4;14), t(14;16), or del17p (utilizing  $>50\%$  deletion cut-off) defined a patient as high risk. Standard-risk cytogenetic status was assigned to those not meeting the high-risk criteria. Due to limitations with sample quality or quantity, and because cytogenetic evaluation was mandated mid-study, cytogenetic risk was not evaluated in all patients. PFS, ORR, and MRD negativity at sensitivity thresholds of  $10^{-5}$  and  $10^{-6}$  were assessed for each subgroup. PFS based on MRD and cytogenetic risk status was also examined. Health-related quality of life (HRQoL) was assessed using the EuroQol 5-Dimension Questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30).

### Minimal Residual Disease

MRD was assessed (blinded to treatment group) at the time of suspected CR (i.e., CR/stringent CR or VGPR with suspected interference<sup>20,21</sup>), and at 3 and 6 months after suspected CR for patients who maintained this response. The MRD-negativity rate per treatment arm was determined as the proportion of patients with negative MRD at any time point after the first dose and compared using the likelihood-ratio test.

Additional details on assessments for safety, MRD, cytogenetic risk, and HRQoL and statistical analyses are provided in the *Appendix*.

## Results

Of 569 enrolled patients in POLLUX, 286 were assigned to D-Rd and 283 to Rd (*Appendix Figure 1*). Baseline patient demographics and prior treatment history were generally balanced and have been previously reported.<sup>15</sup> Additional baseline clinical and cytogenetic characteristics are summarized in Table 1. The median (range) duration of study treatment was 24.5 (0-32.7) months in the D-Rd group and 16.0 (0.20-32.2) months in the Rd group.

At the clinical cut-off on March 7, 2017, the median (range) duration of follow up was 25.4 (0-32.7) months. Consistent with the primary analysis, D-Rd improved PFS compared with Rd (median not reached [NR] vs. 17.5 months; hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.31-0.53;  $P<0.0001$ ), with 24-month PFS rates of 68.0% versus 40.9%, respectively (Figure 1A). In the response-evaluable population, D-Rd (n=281) compared with Rd alone (n=276) significantly improved the ORR (92.9% vs. 76.4%, respectively;  $P<0.0001$  [Table 2]), and rates of  $\geq$ VGPR and  $\geq$ CR (*Appendix Table 1*). Stringent CRs were achieved by 26.0% and 8.7% of patients receiving D-Rd and Rd, respectively (*Appendix Table 1*). Overall survival data remain immature, and the final analysis is planned after 330 events are observed.

D-Rd significantly improved PFS in RRMM patients who received several prior lines of therapy, a population for whom more effective therapies are needed. In patients who received 1 prior line of therapy, D-Rd significantly prolonged PFS compared with Rd (D-Rd, n=149; Rd, n=146; median NR vs. 19.6 months; HR, 0.39; 95% CI, 0.26-0.58,  $P<0.0001$  [Figure 1B, *Appendix Figure 2A*]), with 24-month PFS rates of 70.3% and 45.0%, respectively. A similar benefit was observed in patients who received 2 to 3 prior lines of therapy (Figure 1B, *Appendix Figure 2B*). ORR was also significantly improved in patients treated with 1 prior line of therapy (D-Rd, n=147; Rd, n=142; 93.2% vs. 80.3%;  $P=0.0003$  [Table 2]) and 2 to 3 prior lines of therapy (D-Rd, n=120; Rd, n=115; 95.0% vs. 73.9%;  $P<0.0001$  [Table 2]). It is considered preferable for MM patients who relapse to switch drug classes for subsequent therapy,<sup>22</sup> and, in bortezomib-refractory patients, D-Rd significantly prolonged PFS compared with Rd (D-Rd, n=59; Rd, n=58; median 26.1 vs. 11.3 months; HR, 0.46; 95% CI, 0.26-0.80;  $P=0.0051$  [Figure 1B]), with 24-month PFS rates of 60.0% and 29.7%, respectively, and improved ORR (D-Rd, n=57; Rd, n=56; 87.7% vs. 67.9%;  $P=0.0113$  [Table 2]).

Patients with high-risk cytogenetic status have had historically poor outcomes, but, regardless of cytogenetic risk status, D-Rd improved outcomes compared with Rd (Figures 1B and 2, Table 2). PFS was longer for D-Rd-treated (n=28) versus Rd-treated patients (n=37) with high cytogenetic risk (median 22.6 vs. 10.2 months; HR, 0.53; 95% CI, 0.25-1.13;  $P=0.0921$ ; 24-month PFS rate, 48.1% vs. 31.7%), and significantly longer for patients with standard-risk disease (D-Rd, n=133; Rd, n=113; median NR vs. 18.5 months; HR, 0.30; 95% CI, 0.20-0.47;  $P<0.0001$ ; 24-month PFS rate, 74.3% vs. 40.0% [Figures 1B and 2]). With D-Rd versus Rd, significantly higher ORRs were

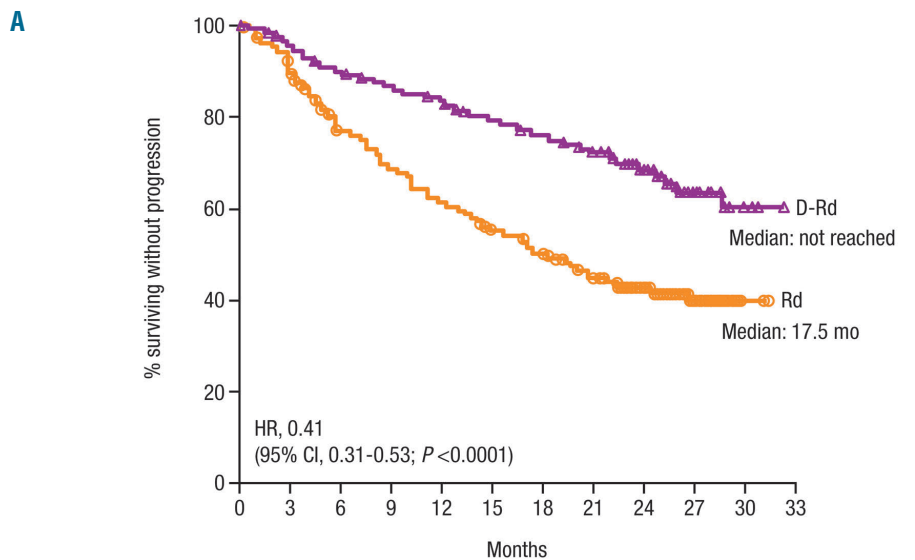
**Table 1. Baseline demographic and clinical characteristics.**

| Characteristic                               | D-Rd<br>(n=286)    | Rd<br>(n=283)      |
|--|--------------------|--------------------|
| Age, years                                   |                    |                    |
| Median (range)                               | 65 (34-89)         | 65 (42-87)         |
| Median (range) time from diagnosis, years    | 3.48<br>(0.4-27.0) | 3.95<br>(0.4-21.7) |
| ECOG performance-status, n (%)               |                    |                    |
| 0  | 139 (48.6)         | 150 (53.0)         |
| 1  | 136 (47.6)         | 118 (41.7)         |
| 2  | 11 (3.8)           | 15 (5.3)           |
| Cytogenetic profile, n (%) <sup>a</sup>      |                    |                    |
| n  | 161                | 150                |
| Standard risk                                | 133 (82.6)         | 113 (75.3)         |
| High risk                                    | 28 (17.4)          | 37 (24.7)          |
| t(4;14)                                      | 16 (9.9)           | 21 (14.0)          |
| t(14;16)                                     | 1 (0.6)            | 3 (2.0)            |
| del17p                                       | 13 (8.1)           | 13 (8.7)           |
| Prior lines of therapy, n (%)                |                    |                    |
| Median (range)                               | 1 (1-11)           | 1 (1-8)            |
| 1  | 149 (52.1)         | 146 (51.6)         |
| 2 to 3                                       | 123 (43.0)         | 118 (41.7)         |
| Time since last prior line of therapy, n (%) |                    |                    |
| >12 months                                   | 140 (49.0)         | 149 (52.7)         |
| ≤12 months                                   | 146 (51.0)         | 134 (47.3)         |
| >6 months                                    | 187 (65.4)         | 188 (66.4)         |
| ≤6 months                                    | 99 (34.6)          | 95 (33.6)          |
| Prior ASCT, n (%)                            | 180 (62.9)         | 180 (63.6)         |
| Prior PI, n (%)                              | 245 (85.7)         | 242 (85.5)         |
| Bortezomib                                   | 241 (84.3)         | 238 (84.1)         |
| Prior IMiD, n (%)                            | 158 (55.2)         | 156 (55.1)         |
| Lenalidomide                                 | 50 (17.5)          | 50 (17.7)          |
| Thalidomide                                  | 122 (42.7)         | 125 (44.2)         |
| Prior IMiD + PI, n (%)                       | 125 (43.7)         | 125 (44.2)         |
| Refractory to bortezomib, n (%)              | 59 (20.6)          | 58 (20.5)          |
| Refractory to last line of therapy, n (%)    | 80 (28.0)          | 76 (26.9)          |

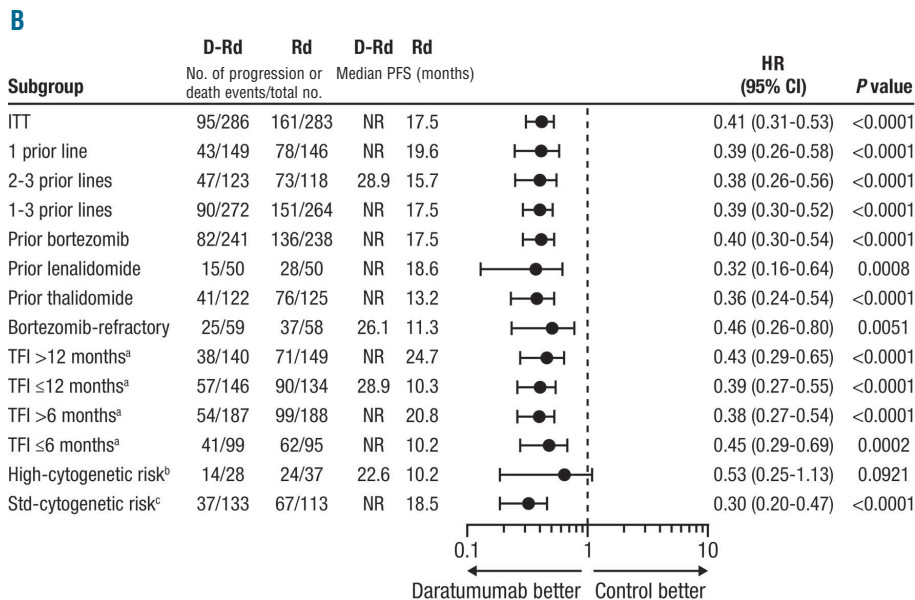
D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; ECOG: Eastern Cooperative Oncology Group; ASCT: autologous stem cell transplantation; PI: proteasome inhibitor; IMiD: immunomodulatory drug. <sup>a</sup>Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

observed for both high-risk (D-Rd, n=27; Rd, n=36; 85.2% vs. 66.7%;  $P=0.0435$ ) and standard-risk patients (D-Rd, n=132; Rd, n = 111; 94.7% vs. 82.0%;  $P=0.0004$  [Table 2]). Further subgroup analyses determined that the clinical benefit of daratumumab was maintained in patients regardless of prior lines of therapy received (1-3), prior treatment exposure (thalidomide or lenalidomide), or time since last therapy (≤12, >12, ≤6, or >6 months [Figure 1B, Table 2, *Appendix Figure 2C*]).

Although D-Rd was associated with a significant treatment benefit in subpopulations that received their last line of prior therapy either ≤12 or >12 months before randomization into the study (Figure 1B, Table 2), the proportion of patients who remained progression-free and alive at 24 months was smaller among patients who relapsed earlier in both the D-Rd (63.6% vs. 72.4%) and Rd (29.2% vs.



| No. at risk |     |     |     |     |     |     |     |     |     |    |   |   |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|
| Rd          | 283 | 249 | 206 | 181 | 160 | 143 | 127 | 109 | 86  | 23 | 2 | 0 |
| D-Rd        | 286 | 266 | 249 | 238 | 229 | 214 | 203 | 189 | 146 | 46 | 8 | 0 |



**Figure 1.** (A) PFS in the ITT population and (B) a forest plot summary of PFS HRs in subgroups by prior lines, prior therapies, treatment-free intervals. Kaplan-Meier analysis of PFS among patients in the ITT population. <sup>a</sup>Treatment-free interval was defined as the duration between the end date of the last line of prior therapy and randomization. <sup>b</sup>High-risk patients had any of t(4;14), t(14;16), or del17p as assessed by next generation sequencing. <sup>c</sup>Standard-risk patients had an absence of high-risk abnormalities. PFS: progression-free survival; ITT: intent-to-treat; HR: hazard ratio; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; CI: confidence interval; NR: not reached; TFI: treatment-free interval; std: standard.

51.4%) treatment groups. However, the ORR and PFS in patients with a shorter treatment-free interval was more severely impacted in patients treated with Rd compared with D-Rd (Figure 1B, Table 2).

MRD status was evaluated to determine the ability of daratumumab to generate deeper responses in patients achieving conventional CR. The IMWG established MRD-negative criteria requiring evaluation by next-generation sequencing to be conducted at a minimum sensitivity threshold of 10<sup>-5</sup>.<sup>23</sup> At this threshold, of the ITT population, 26.2% of patients treated with D-Rd achieved MRD negativity compared with 6.4% of patients who received Rd (*P*<0.000001 [Table 2]). Consistent findings were also observed for D-Rd versus Rd at a sensitivity threshold of 10<sup>-6</sup> (12.9% vs. 2.8%; *P*=0.000003). D-Rd generated deeper responses and higher MRD-negativity rates than Rd in all subgroups evaluated (Table 2), including

patients who received 1 prior line of therapy (D-Rd, n=149; Rd, n=146; 10<sup>-5</sup>: 25.5% vs. 8.2%; *P*=0.000053; 10<sup>-6</sup>: 10.1% vs. 4.8%; *P*=0.08134) and 2 to 3 prior lines of therapy (D-Rd, n=123; Rd, n=118; 10<sup>-5</sup>: 27.6% vs. 4.2%; *P*<0.000001; 10<sup>-6</sup>: 16.3% vs. 0.8%; *P*=0.000003), patients who were bortezomib refractory (D-Rd, n=59; Rd, n=58; 10<sup>-5</sup>: 20.3% vs. 6.9%; *P*=0.0308; 10<sup>-6</sup>: 10.2% vs. 3.4%; *P*=0.1410), and patients who had high-cytogenetic risk at a sensitivity threshold of 10<sup>-5</sup> (D-Rd, n=28; Rd, n=37; 21.4% vs. 0.0%, *P*=0.0009) and 10<sup>-6</sup> (D-Rd, n=28; Rd, n=37; 14.3% vs. 0.0%, *P*=0.0078 [Table 2]). PFS was prolonged in patients who achieved MRD negativity compared with MRD-positive patients in both treatment arms (Figure 3A-B). D-Rd also significantly prolonged PFS compared with Rd in patients with MRD-positive status at the 10<sup>-5</sup> and 10<sup>-6</sup> sensitivity thresholds (*P*<0.001 [Figure 3A-B]). At the time of the analysis, the majority of patients main-

**Table 2. ORR and MRD based on prior treatment history.**

| Subgroup                      | # of patients in group |     | ORR, n (%) <sup>a</sup> |            |                | # of patients in group |     | MRD, n (%) <sup>b</sup> |           |                |                  |         |                |
|-------------------------------|------------------------|-----|-------------------------|------------|----------------|------------------------|-----|-------------------------|-----------|----------------|------------------|---------|----------------|
|                               | D-Rd                   | Rd  | D-Rd                    | Rd         | P <sup>c</sup> | D-Rd                   | Rd  | 10 <sup>-5</sup>        |           | P <sup>d</sup> | 10 <sup>-6</sup> |         | P <sup>d</sup> |
|                               |                        |     |                         |            |                |                        |     | D-Rd                    | Rd        |                | D-Rd             | Rd      |                |
| ITT                           | 281                    | 276 | 261 (92.9)              | 211 (76.4) | <0.0001        | 286                    | 283 | 75 (26.2)               | 18 (6.4)  | <0.000001      | 37 (12.9)        | 8 (2.8) | 0.000003       |
| Prior lines of therapy        |                        |     |                         |            |                |                        |     |                         |           |                |                  |         |                |
| 1                             | 147                    | 142 | 137 (93.2)              | 114 (80.3) | 0.0003         | 149                    | 146 | 38 (25.5)               | 12 (8.2)  | 0.000053       | 15 (10.1)        | 7 (4.8) | 0.081340       |
| 2-3                           | 120                    | 115 | 114 (95.0)              | 85 (73.9)  | <0.0001        | 123                    | 118 | 34 (27.6)               | 5 (4.2)   | <0.000001      | 20 (16.3)        | 1 (0.8) | 0.000003       |
| 1-3                           | 267                    | 257 | 251 (94.0)              | 199 (77.4) | <0.0001        | 272                    | 264 | 72 (26.5)               | 17 (6.4)  | <0.0001        | 35 (12.9)        | 8 (3.0) | <0.0001        |
| Prior therapy                 |                        |     |                         |            |                |                        |     |                         |           |                |                  |         |                |
| Bortezomib                    | 237                    | 232 | 218 (92.0)              | 175 (75.4) | <0.0001        | 241                    | 238 | 63 (26.1)               | 18 (7.6)  | <0.000001      | 32 (13.3)        | 8 (3.4) | 0.000051       |
| Lenalidomide                  | 50                     | 47  | 42 (84.0)               | 32 (64.0)  | 0.0233         | 50                     | 50  | 13 (26.0)               | 2 (4.0)   | 0.0012         | 7 (14.0)         | 2 (4.0) | 0.0729         |
| Thalidomide                   | 119                    | 123 | 109 (91.6)              | 87 (70.7)  | <0.0001        | 122                    | 125 | 26 (21.3)               | 6 (4.8)   | <0.0001        | 16 (13.1)        | 2 (1.6) | 0.0002         |
| Refractory to bortezomib      | 57                     | 56  | 50 (87.7)               | 38 (67.9)  | 0.0113         | 59                     | 58  | 12 (20.3)               | 4 (6.9)   | 0.0308         | 6 (10.2)         | 2 (3.4) | 0.1410         |
| Treatment-free interval       |                        |     |                         |            |                |                        |     |                         |           |                |                  |         |                |
| ≤12 months                    | 143                    | 131 | 129 (90.2)              | 87 (66.4)  | <0.0001        | 146                    | 134 | 34 (23.3)               | 7 (5.2)   | <0.0001        | 16 (11.0)        | 2 (1.5) | 0.0006         |
| >12 months                    | 138                    | 145 | 132 (95.7)              | 124 (85.5) | 0.0038         | 140                    | 149 | 41 (29.3)               | 11 (7.4)  | <0.0001        | 21 (15.0)        | 6 (4.0) | 0.0010         |
| ≤6 months                     | 98                     | 92  | 87 (88.8)               | 57 (62.0)  | <0.0001        | 99                     | 95  | 21 (21.2)               | 6 (6.3)   | 0.0021         | 8 (8.1)          | 2 (2.1) | 0.0514         |
| >6 months                     | 183                    | 184 | 174 (95.1)              | 154 (83.7) | 0.0004         | 187                    | 188 | 54 (28.9)               | 12 (6.4)  | <0.0001        | 29 (15.5)        | 6 (3.2) | <0.0001        |
| Cytogenetic risk <sup>e</sup> |                        |     |                         |            |                |                        |     |                         |           |                |                  |         |                |
| High <sup>f</sup>             | 27                     | 36  | 23 (85.2)               | 24 (66.7)  | 0.0435         | 28                     | 37  | 6 (21.4)                | 0 (0)     | 0.0009         | 4 (14.3)         | 0 (0)   | 0.0078         |
| Standard                      | 132                    | 111 | 125 (94.7)              | 91 (82.0)  | 0.0004         | 133                    | 113 | 42 (31.6)               | 13 (11.5) | 0.0001         | 20 (15.0)        | 6 (5.3) | 0.0109         |

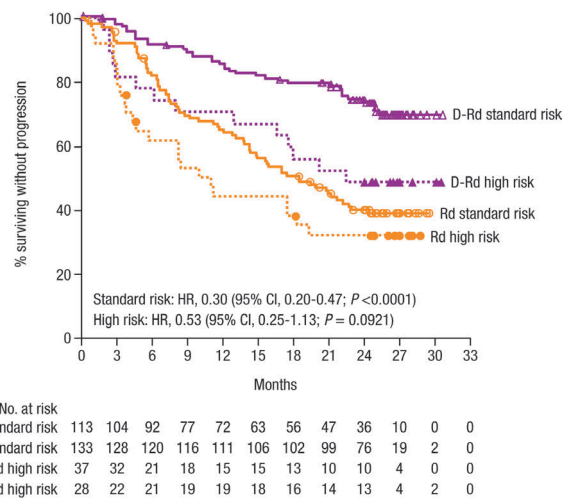
ORR: overall response rate; MRD: minimal residual disease; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; ITT: intent-to-treat. Data are based on computerized algorithm. <sup>a</sup>Response-evaluable population. <sup>b</sup>ITT population. <sup>c</sup>P value was generated using the Cochran-Mantel-Haenszel  $\chi^2$  test. <sup>d</sup>P value was generated using the likelihood-ratio  $\chi^2$  test. <sup>e</sup>Biomarker risk-evaluable population. Includes subjects who have either del17p,t(14;16),t(4;14) or a combination of these.

tained MRD-negative status; patients will continue to be assessed annually.

The safety profile remained unchanged from the primary analysis, with no new safety signals reported in either treatment group with longer follow up (Table 3). The most common treatment-emergent adverse events (≥15%) of any grade included neutropenia, anemia, thrombocytopenia, diarrhea, fatigue, upper respiratory tract infection, cough, constipation, muscle spasms, nasopharyngitis, and nausea (Table 3). The most common grade 3/4 treatment-emergent adverse events (≥5%) included neutropenia, febrile neutropenia, anemia, thrombocytopenia, lymphopenia, diarrhea, fatigue, and pneumonia (Table 3). The percentage of patients with adverse events leading to treatment discontinuation was similar between groups (12.0% for D-Rd, 12.8% for Rd). The most common adverse events (≥1%) leading to treatment discontinuation in D-Rd compared with Rd included pneumonia (1.4% vs. 0.7%), pulmonary embolism (0% vs. 1.1%), general physical health deterioration (1.1% vs. 0%), and renal failure (0.4% vs. 1.1%), respectively.

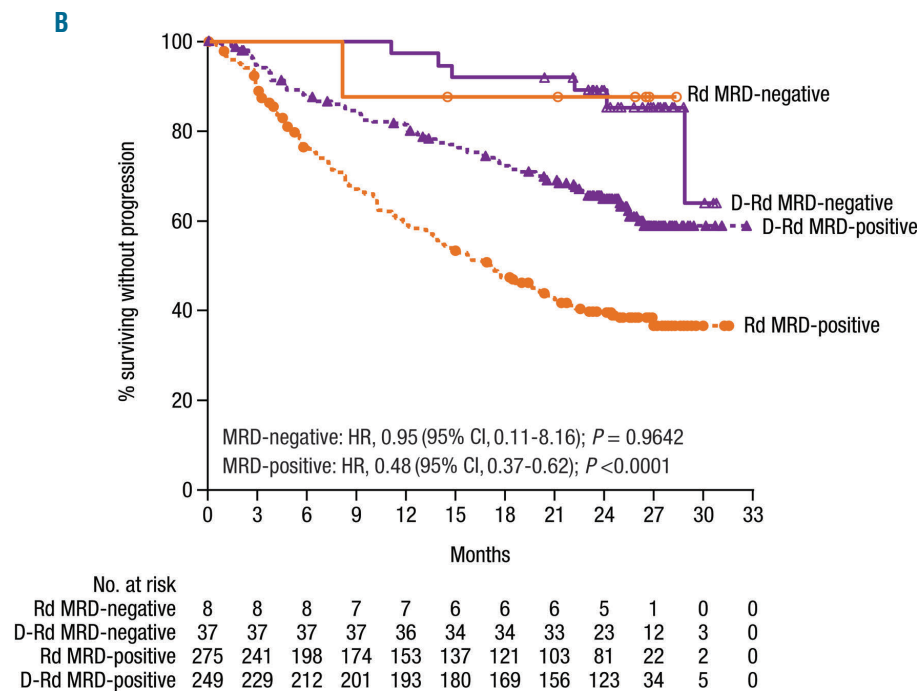
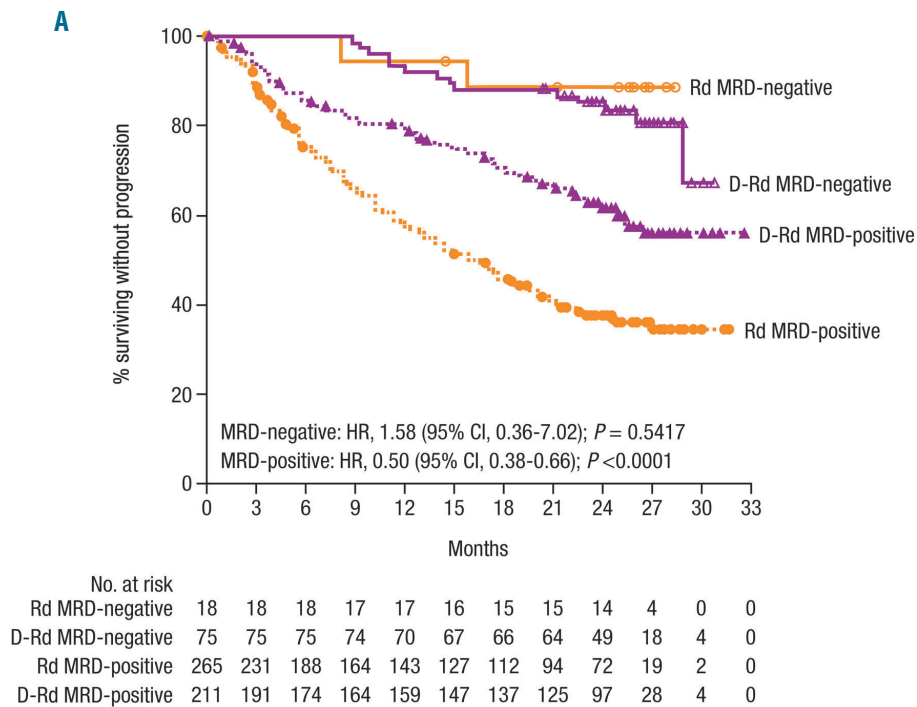
The incidence of second primary malignancies between the D-Rd (n=283) and Rd (n=281) groups was the same (5.7% vs. 5.7%), consistent with previous observations that had no notable differences.<sup>15</sup> The proportion of patients who received transfusions while on study drug was also similar between the D-Rd and Rd groups (24.4% vs. 25.3%).

There was no decline in HRQoL measures with the addition of daratumumab to Rd. Statistically significant differences in the change from baseline were observed in favor of D-Rd at Weeks 48 and 56 with the Utility Score and at



**Figure 2. PFS by cytogenetic risk status.** Cytogenetic risk was assessed via next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities. PFS: progression-free survival; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; HR: hazard ratio; CI: confidence interval.

Weeks 40, 48, and 56 with the Visual Analog Scale Score of the EQ-5D-5L questionnaire. With the EORTC QLQ-C30 Global Health Status Score, statistically significant differences in the change from baseline were observed in favor of D-Rd at Weeks 40, 48, 52, 68, 84, and 116. However, these



**Figure 3. PFS by MRD at sensitivity thresholds of (A)  $10^{-5}$  and (B)  $10^{-6}$ .** Kaplan-Meier estimates of PFS among patients in the intent-to-treat population. MRD-negative status was evaluated at sensitivity thresholds of  $10^{-5}$  and  $10^{-6}$  using bone marrow aspirate samples that were prepared using Ficoll and analyzed by the clonoSEQ™ assay. PFS: progression-free survival; MRD: minimal residual disease; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; HR: hazard ratio; CI: confidence interval.

improvements did not last beyond 3 consecutive assessments in either questionnaire. No significant differences for median time to improvement (6.6 months vs. 6.5 months; HR, 1.03; 95% CI, 0.81-1.30;  $P=0.820$ ) were reported for EORTC QLQ-C30 Global Health Status Scores in the D-Rd and Rd groups. Similarly, no significant differences in median time to improvement were observed between treatment groups for either the EQ-5D-5L Utility Score (6.6 months vs. 10.2 months; HR, 1.23; 95% CI, 0.97-1.57;  $P=0.089$ ) or Visual Analog Scale Score (6.9 months vs. 9.3 months; HR, 1.14; 95% CI, 0.89-1.45;  $P=0.283$ ).

### Discussion

These updated analyses with nearly one further year of follow up reinforce the initial findings of deep and durable responses achieved with D-Rd in RRMM patients.<sup>15</sup> The benefit of D-Rd over Rd was consistently maintained across patients who received 1 or 2 to 3 prior lines of therapy, and the risk of progression or death was reduced by >60%. D-Rd was also superior to Rd regardless of prior treatment exposure (i.e., lenalidomide, thalidomide, bortezomib-refractory), time since last therapy, and cyto-

**Table 3.** Most common all grade ( $\geq 15\%$ ) and grade 3/4 ( $\geq 5\%$ ) treatment-emergent adverse events in the safety population.

| Event, n (%)                      | D-Rd<br>(n=283) |            | Rd<br>(n=281) |            |
|-----------------------------------|-----------------|------------|---------------|------------|
|                                   | All grade       | Grade 3/4  | All grade     | Grade 3/4  |
| Total                             | 281 (99.3)      | 251 (88.7) | 274 (97.5)    | 216 (76.9) |
| <b>Hematologic</b>                |                 |            |               |            |
| Neutropenia                       | 172 (60.8)      | 153 (54.1) | 127 (45.2)    | 112 (39.9) |
| Febrile neutropenia               | 17 (6.0)        | 17 (6.0)   | 8 (2.8)       | 8 (2.8)    |
| Anemia                            | 104 (36.7)      | 44 (15.5)  | 109 (38.8)    | 60 (21.4)  |
| Thrombocytopenia                  | 81 (28.6)       | 39 (13.8)  | 87 (31.0)     | 44 (15.7)  |
| Lymphopenia                       | 18 (6.4)        | 15 (5.3)   | 16 (5.7)      | 11 (3.9)   |
| <b>Nonhematologic</b>             |                 |            |               |            |
| Diarrhea                          | 144 (50.9)      | 20 (7.1)   | 89 (31.7)     | 9 (3.2)    |
| Fatigue                           | 103 (36.4)      | 18 (6.4)   | 85 (30.2)     | 10 (3.6)   |
| Upper respiratory tract infection | 105 (37.1)      | 4 (1.4)    | 74 (26.3)     | 4 (1.4)    |
| Cough                             | 91 (32.2)       | 1 (0.4)    | 40 (14.2)     | 0 (0.0)    |
| Constipation                      | 88 (31.1)       | 3 (1.1)    | 74 (26.3)     | 2 (0.7)    |
| Muscle spasms                     | 81 (28.6)       | 3 (1.1)    | 59 (21.0)     | 4 (1.4)    |
| Nasopharyngitis                   | 84 (29.7)       | 0 (0.0)    | 54 (19.2)     | 0 (0.0)    |
| Nausea                            | 76 (26.9)       | 5 (1.8)    | 50 (17.8)     | 2 (0.7)    |
| Insomnia                          | 67 (23.7)       | 4 (1.4)    | 61 (21.7)     | 4 (1.4)    |
| Pyrexia                           | 67 (23.7)       | 7 (2.5)    | 36 (12.8)     | 5 (1.8)    |
| Dyspnea                           | 59 (20.8)       | 12 (4.2)   | 35 (12.5)     | 2 (0.7)    |
| Back pain                         | 58 (20.5)       | 6 (2.1)    | 53 (18.9)     | 5 (1.8)    |
| Pneumonia                         | 58 (20.5)       | 34 (12.0)  | 42 (14.9)     | 24 (8.5)   |
| Bronchitis                        | 53 (18.7)       | 6 (2.1)    | 46 (16.4)     | 7 (2.5)    |
| Edema peripheral                  | 53 (18.7)       | 2 (0.7)    | 43 (15.3)     | 4 (1.4)    |
| Vomiting                          | 52 (18.4)       | 3 (1.1)    | 19 (6.8)      | 4 (1.4)    |
| Asthenia                          | 51 (18.0)       | 10 (3.5)   | 43 (15.3)     | 8 (2.8)    |
| Headache                          | 43 (15.2)       | 0 (0.0)    | 22 (7.8)      | 0 (0.0)    |

D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone.

genetic risk status. As one of the first studies to prospectively assess MRD in a phase 3 trial of RRMM, MRD-negativity rates were also significantly higher with D-Rd across all patient subgroups, including patients with high cytogenetic risk. These findings reinforce observations that highlight the depth, durability, and robustness of responses achieved with daratumumab-based regimens.<sup>24</sup>

These findings compare favorably with other studies of IMiD-containing regimens with subgroup analyses based on prior lines of therapy and/or prior treatment exposure (*Appendix Table 2*). In a large phase 3 study (ASPIRE) of carfilzomib-Rd (KRd) compared with Rd alone, a consistent PFS benefit was observed with KRd *versus* Rd among patients who received 1 and 2 to 3 prior lines of therapy.<sup>25</sup> Prespecified PFS subgroup analyses showed a modest benefit with KRd over Rd for patients who previously received lenalidomide and patients nonresponsive to bortezomib in any previous regimen.<sup>26</sup> The magnitude of benefit for KRd *versus* Rd was similar in patients with early disease relapse ( $\leq 12$  months from starting the first prior regimen; ORR: 79% vs. 61%).<sup>27</sup> In a phase 3 study of elotuzumab (ELOQUENT-2), the PFS benefit in combination with Rd was maintained among patients who received 2 to 3 prior lines of therapy or had prior exposure

to bortezomib but not among patients who received 1 prior line of therapy or prior lenalidomide.<sup>28,29</sup> Ixazomib in combination with lenalidomide and dexamethasone in the phase 3 TOURMALINE-MM1 study demonstrated a modest PFS benefit *versus* Rd in patients who received 1 or 2 prior lines, were previously treated with an IMiD or a PI, and were refractory to their last line of therapy; interestingly, patients who received 3 prior lines of therapy demonstrated an HR of 0.37.<sup>30</sup>

D-Rd improved responses, including MRD negativity in patients with high-risk cytogenetic status, suggesting that targeting CD38 in combination with Rd may improve outcomes for this challenging-to-treat population. Moreover, despite the small number of patients with high-risk disease, D-Rd demonstrated significantly higher MRD-negativity rates compared with standard-risk patients receiving Rd. While PFS was not statistically different between D-Rd *versus* Rd for patients with high-risk disease, a numerical improvement in PFS was observed in high-risk patients who received D-Rd *versus* Rd. As the magnitude of benefit for D-Rd was lower among high-risk patients, these findings suggest that while D-Rd is able to provide improvements in efficacy, it is not able to overcome the greater risk of progression and poor outcomes associated with high-risk disease. Although cross-

study comparisons should be performed with caution, smaller differences in PFS and ORR between standard- and high-risk patients in the CASTOR study in patients treated with daratumumab and Vd were observed.<sup>31</sup> Daratumumab-based combinations that include both a PI and an IMiD may further improve efficacy in patients with high-risk disease.

Prolonged treatment with D-Rd or Rd did not uncover new safety concerns, and the incidences of second primary malignancies were balanced between study arms. While certain adverse events, such as cough, dyspnea, and pneumonia occurred more frequently with daratumumab, the percentage of patients that discontinued treatment due to adverse events was similar between groups (12.0% for D-Rd, 12.8% for Rd). Additionally, patients in the D-Rd group were treated for longer, with a median duration of 24.5 months *versus* 16.0 months in the Rd group, which likely contributed to the increase in rates for certain adverse events. Finally, the addition of a third drug to the standard of care Rd regimen did not have a negative effect on HRQoL.

Several limitations of the study should be noted. First, although balanced between treatment arms, only a subset of patient samples was collected for central cytogenetic testing as outlined in the Methods. Second, not all eligible patients with suspected CR or CR had available MRD data, and these patients were therefore conservatively classified as MRD positive. Based on the experiences obtained from this phase 3 study, continuous improvements in MRD testing are being implemented across ongoing and future daratumumab studies in multiple myeloma. Finally, based on the limitations of *post hoc*

analyses, the findings presented here require further confirmation in future studies prospectively assessing the efficacy of D-Rd in these clinically relevant patient populations.

In summary, these updated secondary subgroup analyses highlight the benefit of combining daratumumab with the standard of care regimen Rd in RRMM across examined subgroups. The addition of daratumumab to Rd drove deep responses, as shown by achievement of MRD negativity in many patients. These results suggest that D-Rd is a highly effective and well-tolerated regimen that may be recommended for RRMM after first relapse and beyond.

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