Treatment Duration and Long-term Outcomes With Daratumumab in Transplant-ineligible Newly Diagnosed Multiple Myeloma From the Phase 3 MAIA Study

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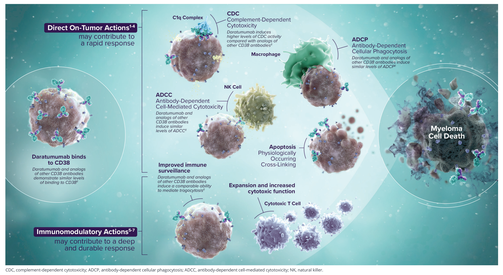
INTRODUCTION

- Daratumumab (DARA) is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor[1-4] and immunomodulatory[5-7] mechanism of action that demonstrates greater cytotoxicity of multiple myeloma (MM) cells ex vivo compared with analogs of other CD38 antibodies[8] (**Figure 1**)

FIGURE 1: Daratumumab mechanism of action



CDC, complement-dependent cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADCC, antibody-dependent cell-mediated cytotoxicity; NK, natural killer.

- Several phase 3 studies demonstrated the clinical benefit of DARA in combination with standard-of-care regimens, including lenalidomide plus dexamethasone (Rd), in patients with MM[9-13]
- DARA plus Rd (D-Rd) is approved for patients with newly diagnosed MM (NDMM) who are ineligible for autologous stem cell transplant based on results from the phase 3 MAIA study[12]
- In the primary analysis of MAIA (median follow-up, 28.0 months), treatment with D-Rd until disease progression improved progression-free survival (PFS) and induced deeper responses versus Rd alone in transplant-ineligible patients with NDMM[12]
  - With longer follow-up (median follow-up, 56.2 months), a significant overall survival (OS) benefit and continued PFS and depth of response benefits were observed with D-Rd versus Rd[14]
- Given the cost of long-term disease control with D-Rd, physicians may look to limit treatment duration while maintaining clinical benefit; however, randomized practice-informing data are lacking
- Post hoc analyses of the MAIA study were performed to determine the impact of treatment duration on long-term clinical outcomes

METHODS

Post hoc analyses

- OS was evaluated in patients who received D-Rd for <18 versus ≥18 months
  - Patients who discontinued D-Rd due to disease progression during the first 18 months were excluded
- PFS and OS were evaluated in the following subgroups:
  - Patients who received D-Rd and discontinued only DARA or only R ± d but continued remaining treatment
  - Patients who received D-Rd or Rd for ≥9 or ≥18 months
  - Patients in both arms who achieved a best response of very good partial response (VGPR) by 6 months and converted to complete response or better (≥CR) by 9 or 18 months (excluding patients who discontinued treatment before 18 months)

Statistical analyses

- A multivariate Cox model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with frailty status and International Staging System disease stage as covariates, for comparisons by treatment duration (<18 vs ≥18 months) within the D-Rd group in the OS analysis
- A log-rank test was used to compare PFS and OS between treatment arms for D-Rd versus Rd analyses
  - A Cox regression model was used to estimate HRs and 95% CIs, with treatment as the sole explanatory variable
- The Kaplan–Meier method was used to summarize and plot time-to-event variables

MULTIPLE MYELOMA

RESULTS

- Patient demographic and disease characteristics are summarized in **Table 1**

TABLE 1: Patient demographic and disease characteristics

Characteristic	ITT population D-Rd (n = 368)	D-Rd treatment <18 months[a] D-Rd (n = 48)	D-Rd treatment ≥18 months[a] D-Rd (n = 283)	Discontinued only R ± d[b] D-Rd (n = 48)
Age, years				
<65, n (%)	4 (1.1)	3 (6.3)	1 (0.4)	0
65-74, n (%)	204 (55.4)	18 (37.5)	167 (59.0)	26 (54.2)
≥75, n (%)	160 (43.5)	27 (56.3)	115 (40.6)	22 (45.8)
Median (range)	73.0 (50-90)	75.0 (50-90)	73.0 (55-88)	74.0 (67-87)
Baseline ECOG PS score, n (%)				
0	127 (34.5)	10 (20.8)	110 (38.9)	15 (31.3)
1	178 (48.4)	25 (52.1)	132 (46.6)	25 (52.1)
≥2	63 (17.1)	13 (27.1)	41 (14.5)	8 (16.7)
ISS disease stage,[c] n (%)				
I	98 (26.6)	8 (16.7)	84 (29.7)	14 (29.2)
II	163 (44.3)	19 (39.6)	129 (45.6)	26 (54.2)
III	107 (29.1)	21 (43.8)	70 (24.7)	8 (16.7)
Cytogenetic abnormalities[d]				
N	319	44	242	45
Standard risk, n (%)	271 (85.0)	38 (86.4)	212 (87.6)	39 (86.7)
High risk, n (%)	48 (15.0)	6 (13.6)	30 (12.4)	6 (13.3)
Frailty status				
Frail	172 (46.7)	30 (62.5)	118 (41.7)	23 (47.9)
Intermediate	128 (34.8)	13 (27.1)	105 (37.1)	19 (39.6)
Fit	68 (18.5)	5 (10.4)	60 (21.2)	6 (12.5)

ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; R, lenalidomide; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.
[a]Patients who discontinued D-Rd due to disease progression during the first 18 months of treatment were excluded.
[b]Patients discontinued lenalidomide with or without dexamethasone but continued remaining treatment.
[c]ISS staging is derived based on the combination of serum β$_2$-microglobulin and albumin.
[d]Cytogenetic abnormalities (del(17p ≥ 0.4) or t(4;14) or t(14;16)) were based on fluorescence in situ hybridization or karyotype testing. Percentages were calculated with the number of patients in each treatment group as the denominator.

- Reasons for lenalidomide discontinuation in the D-Rd arm are shown in **Table 2**
  - Among D-Rd patients who discontinued only R ± d but continued remaining treatment, the median duration of DARA treatment was 58.1 months
    - Estimated 60-month PFS and OS rates were 97.9% and 100.0%, respectively
  - Only 1 patient discontinued DARA treatment (due to adverse events) but continued lenalidomide treatment
    - At the time of analysis, this patient was alive and progression free; therefore, no further analysis was performed for this patient

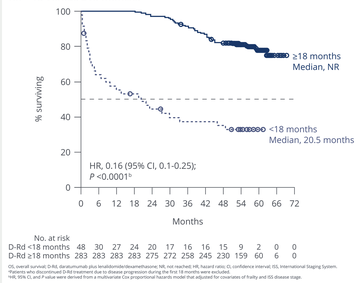
TABLE 2: Reasons for lenalidomide discontinuation in the D-Rd arm

	Discontinued only R ± d[a] D-Rd (n = 48)
Reasons for lenalidomide discontinuation, n (%)	
Adverse event	44 (91.7)
Other[b]	4 (8.3)
Most common (≥5%) reasons for discontinuation of lenalidomide due to adverse events, n (%)	
Diarrhea	9 (18.8)
Peripheral sensory neuropathy	5 (10.4)
Neutropenia	4 (8.3)
Constipation	3 (6.3)

D-Rd, daratumumab plus lenalidomide/dexamethasone; R, lenalidomide; d, dexamethasone.
[a]Patients discontinued lenalidomide with or without dexamethasone but continued remaining treatment.
[b]Other includes patient decision to discontinue, interruption due to adverse events caused by progressive disease or other conditions, or cumulative low-grade adverse events.

- With a median follow-up of 56.2 months, an OS benefit was observed for D-Rd patients who received treatment for ≥18 versus <18 months (HR, 0.16; 95% CI, 0.1-0.25; *P* <0.0001; **Figure 2**)

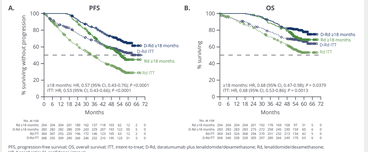
FIGURE 2: OS for patients in the D-Rd arm who received treatment for <18 versus ≥18 months[a]



OS, overall survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; NR, not reached; HR, hazard ratio; CI, confidence interval; ISS, International Staging System.
[a]Patients who discontinued D-Rd treatment due to disease progression during the first 18 months were excluded.
[b]HR, 95% CI, and *P* value were derived from a multivariate Cox proportional hazards model that adjusted for covariates of frailty and ISS disease stage.

- Benefits of D-Rd versus Rd in patients who received treatment for ≥9 months were observed for PFS (HR, 0.49; 95% CI, 0.38-0.62; *P* <0.0001) and OS (HR, 0.63; 95% CI, 0.47-0.85; *P* = 0.0025)
- PFS and OS benefits of D-Rd versus Rd were observed in patients who received treatment for ≥18 months (**Figure 3**)

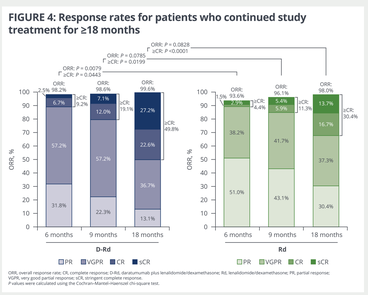
FIGURE 3: (A) PFS and (B) OS for patients who received ≥18 months of treatment versus the ITT population



PFS, progression-free survival; OS, overall survival; ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

- Best response rates deepened over time with continued D-Rd treatment, with ≥CR rates increasing from 9.2% by 6 months to 19.1% by 9 months and 49.8% by 18 months among patients treated for ≥18 months (**Figure 4**)
- ≥CR rates increased over time to a greater extent in the D-Rd arm versus the Rd arm among patients treated for ≥18 months (**Figure 4**)

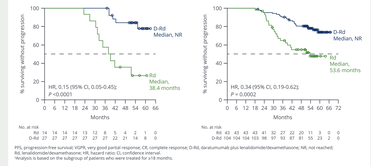
FIGURE 4: Response rates for patients who continued study treatment for ≥18 months



ORR, overall response rate; CR, complete response; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; PR, partial response; VGPR, very good partial response; sCR, stringent complete response.
P values were calculated using the Cochran-Mantel-Haenszel chi-square test.

- A PFS benefit of D-Rd versus Rd was observed in patients who achieved a best response of VGPR by 6 months and converted to ≥CR by 9 months (HR, 0.15; 95% CI, 0.05-0.45; *P* <0.0001; **Figure 5A**) and by 18 months (HR, 0.34; 95% CI, 0.19-0.62; *P* = 0.0002; **Figure 5B**)

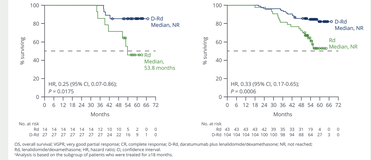
FIGURE 5: PFS for patients who achieved a best response of VGPR by 6 months and converted to ≥CR by (A) 9 or (B) 18 months[a]



PFS, progression-free survival; VGPR, very good partial response; CR, complete response; D-Rd, daratumumab plus lenalidomide/dexamethasone; NR, not reached; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Analysis is based on the subgroup of patients who were treated for ≥18 months.

- An OS benefit of D-Rd versus Rd was observed in patients who achieved a best response of VGPR by 6 months and converted to ≥CR by 9 months (HR, 0.25; 95% CI, 0.07-0.86; *P* = 0.0175; **Figure 6A**) and by 18 months (HR, 0.33; 95% CI, 0.17-0.65; *P* = 0.0006; **Figure 6B**)

FIGURE 6: OS for patients who achieved a best response of VGPR by 6 months and converted to ≥CR by (A) 9 or (B) 18 months[a]



OS, overall survival; VGPR, very good partial response; CR, complete response; D-Rd, daratumumab plus lenalidomide/dexamethasone; NR, not reached; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Analysis is based on the subgroup of patients who were treated for ≥18 months.

- The most common grade 3/4 treatment-emergent adverse events (TEAEs) in patients who received ≥18 months of treatment are shown in **Table 3**
- No new safety concerns were identified
- The rate of grade 3/4 hematologic TEAEs with D-Rd generally decreased over time

TABLE 3. Most common (≥10% in either treatment arm) grade 3/4 TEAEs in patients who received ≥18 months of treatment

	D-Rd (n = 283)	Rd (n = 204)
≥1 grade 3/4 TEAE, n (%)	273 (96.5)	186 (91.2)
Hematologic, n (%)		
Neutropenia	161 (56.9)	84 (41.2)
Anemia	48 (17.0)	37 (18.1)
Lymphopenia	48 (17.0)	25 (12.3)
Leukopenia	33 (11.7)	19 (9.3)
Nonhematologic, n (%)		
Pneumonia	56 (19.8)	22 (10.8)
Hypokalemia	41 (14.5)	24 (11.8)
Cataract	39 (13.8)	38 (18.6)

TEAE, treatment-emergent adverse event; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

KEY TAKEAWAYS

- These results support D-Rd treatment for ≥18 months to achieve deep clinical responses
  - Our findings suggest that stopping D-Rd earlier based on response level may compromise long-term patient outcomes

CONCLUSIONS

- At a median follow-up of >4.5 years, D-Rd improved PFS and OS versus Rd for patients who received ≥18 months of treatment
- For D-Rd patients, discontinuation of R ± d did not appear to compromise efficacy
- No new safety concerns were identified with long-term D-Rd treatment

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DISCLOSURES

PM has served on advisory boards and received honoraria from Celgene/Bristol Myers Squibb, Amgen, Janssen, AbbVie, Sanofi, and Oncopeptides. TF has served on speakers bureaus for Janssen, Celgene/Bristol Myers Squibb, and Takeda; and has served on an advisory board for Janssen, Celgene/Bristol Myers Squibb, Takeda, Roche, Amgen, Karyopharm, Sanofi, and Oncopeptides. SZU has consulted for Amgen, AbbVie, Bristol Myers Squibb, Celgene, EdoPharma, Genentech, Gilead, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, Seattle Genetics, SecuraBio, Skyline Dx, TenecBio, and Takeda; has received research funding from Amgen, Array, BioPharma, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Merck, Pharmacyclics, Sanofi, Seattle Genetics, SkylineDx, and Takeda; and has served on speakers bureaus for Amgen, Bristol Myers Squibb, Janssen, and Sanofi. SKK has received research funding from AbbVie, Amgen, Allogene, AstraZeneca, Bristol Myers Squibb, Cartgen, Glaxosmithkline, Janssen, Novartis, Roche-Genentech, Takeda, Regeneron, and Molecular Templates; and has served as a consultant or on advisory boards for AbbVie, Amgen, Bristol Myers Squibb, Janssen, Roche-Genentech, Takeda, AstraZeneca, bluebird bio, Epizyme, Secura Bio, Karyopharm, Oncopeptides, Promerous Therapeutics, Tyrian, Lava Oncology, K36, Sanofi, ArceRX, Oncopeptides, Beigene, Antengene, and GLH Pharma. TP has served as advisor for Janssen, Celgene, Takeda, Oncopeptides, Genentech, CSL Behring, and AbbVie; and has received research support from Janssen, Genmab, Celgene, Takeda, Oncopeptides, Genentech, AbbVie, and Roche. HG has received grants and/or provisions of investigational medicinal product from Amgen, Bristol Myers Squibb, Celgene, Chugai, Dietmar Hopp Foundation, Janssen, Johns Hopkins University, and Sanofi; has received research funding from Amgen, Bristol Myers Squibb, Celgene, Chugai, Janssen, Incyte, Molecular Partners, Merck Sharp & Dohme, Sanofi, Mundipharma GmbH, Takeda, and Novartis; has served on advisory boards for Amgen, Bristol Myers Squibb, Janssen, Sanofi, and Takeda; has received honoraria from Amgen, Bristol Myers Squibb, Chugai, GlaxoSmithKline, Janssen, Novartis, Sanofi, and Pfizer; and has received meeting and/or travel support from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Novartis, Sanofi, and Pfizer. RZO has served on advisory committees for and received honoraria from AbbVie, BioTheryX, Inc., Bristol Myers Squibb, Janssen Biotech, Karyopharm Therapeutics, Inc., Meridian Therapeutics, Monte Rosa Therapeutics, Neoleukin Corporation, Oncopeptides AB, Regeneron Pharmaceuticals, Inc., Sanofi-Aventis, and Takeda Pharmaceuticals North America, Inc.; has received research funding from Asylia Therapeutics, Inc., BioTheryX, Inc., Heidelberg Pharma, Inc., CARsgen Therapeutics, Celgene/Bristol Myers Squibb, Exelixis, Janssen Biotech, Sanofi-Aventis, and Takeda Pharmaceuticals North America, Inc.; and holds stock in Asylia Therapeutics, Inc. AP has received honoraria from AbbVie, Celgene/Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, and Takeda; has held membership on a board or advisory committee for AbbVie, Celgene/Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, and Takeda; and has received research funding from Takeda. AC has consulted for Janssen, Celgene, Novartis Pharmaceuticals, Amgen, Bristol Myers Squibb, Karyopharm, Sanofi Genzyme, Seattle Genetics, Oncopeptides, Millennium/Takeda, Antengene, GlaxoSmithKline, and Secura Bio; and has received research funding from Janssen, Celgene, Novartis, Amgen, Pharmacyclics, Seattle Genetics, and Millennium/Takeda. GC has received research support from Bristol Myers Squibb/Celgene, Janssen, and Takeda; and has consulted for/received honoraria from Amgen, Bristol Myers Squibb/Celgene, Janssen, Millennium/Takeda, Roche, GlaxoSmithKline, Oncopeptides, and Sanofi. HP, RVR, JBB, CMU, and RC are employees of Janssen and may have equity ownership in Johnson & Johnson. NJB has consulted for, served in an advisory role for, and received honoraria from AbbVie, Celgene/Bristol Myers Squibb, Forus, Genentech, Janssen, Karyopharm, Pfizer, Sanofi, and Takeda; and has received research funding from Pfizer and Celgene/Bristol Myers Squibb.

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REFERENCES:

1. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848. 2. Lammerts van Bueren J, et al. *Blood*. 2014;124(21):3474. 3. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321. 4. Overdijk MB, et al. *J Immunol*. 2016;197(3):807-813. 5. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 6. Adams HC III, et al. *Cytometry A*. 2019;95(3):279-289. 7. Casneuf T, et al. *Leukemia*. 2021;35(2):573-584. 8. Kinder M, et al. *Haematologica*. 2021;106(7):2004-2008. 9. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 10. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 11. Mateos MV, et al. *N Engl J Med*. 2018;378(6):518-528. 12. Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115. 13. Moreau P, et al. *Lancet*. 2019;394(10192):29-38. 14. Facon T, et al. *Lancet Oncol*. 2021;22(11):1582-1596.

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