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Final Survival Analysis of Daratumumab Plus Lenalidomide and Dexamethasone Versus Lenalidomide and Dexamethasone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma: MAIA Study

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Key Takeaway

With long-term follow-up in the MAIA study, the OS benefit observed with the addition of DARA to the Rd standard-of-care regimen continues to support the frontline use of D-Rd to maximize survival in TIE patients with NDMM

Conclusions

In this final analysis of the MAIA study, median OS was finally reached in the D-Rd group after a median follow-up of approximately 7.5 years, and D-Rd continued to demonstrate a clinical OS benefit versus Rd alone in TIE patients with NDMM

D-Rd also prolonged the median time to subsequent antimyeloma therapy, and 28.8% of patients treated with Rd received DARA-based regimens as subsequent antimyeloma therapy, further emphasizing DARA as a standard of care for TIE patients with multiple myeloma

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Poster

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Disclosure
TF served in a consulting or advisory role for Bristol Myers Squibb, Janssen, Roche, and Takeda; and served on a speakers bureau for Bristol Myers Squibb and Janssen.

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, demonstrating greater cytotoxicity toward multiple myeloma cells ex vivo compared with analogs of other CD38 antibodies[8]
- In the primary analysis of the global phase 3 MAIA study, with a median follow-up of 28.0 months, DARA plus lenalidomide and dexamethasone (D-Rd) significantly improved progression-free survival (PFS) compared to lenalidomide plus dexamethasone (Rd) alone in transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM)[9]
  - Updated results at a median follow-up of 64.5 months additionally demonstrated a significant overall survival (OS) benefit with D-Rd versus Rd alone (median, not reached vs 65.5 months; hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.53-0.83; *P* = 0.0003) and a continued PFS benefit (median, 61.9 vs 34.4 months; HR, 0.55; 95% CI, 0.45-0.67; *P* <0.0001)[10]
  - The clinical benefit with D-Rd versus Rd was even more pronounced among patients aged <70 years (OS: HR, 0.50; 95% CI, 0.27-0.90; *P* = 0.0179 and PFS: HR, 0.35; 95% CI, 0.21-0.56; *P* <0.0001)[11]
  - Additionally, the rate of sustained minimal residual disease negativity (10^{-5} threshold) lasting ≥18 months was higher with D-Rd versus Rd (16.8% vs 3.3%, respectively; *P* <0.0001), further substantiating the observed OS and PFS benefit[12]
- DARA is approved in combination with other standard-of-care regimens for patients with NDMM[13] and has been used to treat >518,000 patients worldwide.[14] DARA has consistently demonstrated clinical efficacy as a frontline therapy in pivotal clinical trials[15-18]
- Here, we present updated OS results for D-Rd versus Rd, in addition to new data on subsequent antimyeloma therapies, with a long-term median follow-up of approximately 7.5 years

Methods

Study design

- In MAIA (ClinicalTrials.gov Identifier: NCT02252172), patients with NDMM who were ineligible for high-dose chemotherapy and autologous stem cell transplant (due to age ≥65 years or the presence of comorbidities) were randomized 1:1 to received D-Rd or Rd
- Patients received 28-day cycles of Rd (R: 25 mg orally once daily on Days 1-21; d: 40 mg orally on Days 1, 8, 15, and 22) with or without DARA (16 mg/kg intravenously weekly during Cycles 1-2, every 2 weeks during Cycles 3-6, and every 4 weeks thereafter) until disease progression or unacceptable toxicity

Assessments

- The primary endpoint was PFS; key secondary endpoints presented in this analysis include OS and time to subsequent antimyeloma therapy
- Time-to-event endpoints were compared between treatment groups using a stratified log-rank test
  - The Kaplan–Meier method was used to estimate distributions
  - For the whole intent-to-treat (ITT) population, HRs and 95% CIs were estimated using a stratified Cox regression model with treatment as the sole variable and stratified with the following randomization stratification factors: International Staging System disease stage (I vs II vs III), region (North America vs other), and age (<75 years vs ≥75 years)
  - For subgroups of patients in the ITT population, HRs and 95% CIs were estimated using a nonstratified Cox regression model with treatment as the sole variable
- Data on classes of subsequent therapies, subsequent regimens, rate of study treatment discontinuation, and causes of death were reported descriptively

Results

Patients

- In total, 737 patients were randomized in MAIA (D-Rd, n = 368; Rd, n = 369)
- Baseline patient characteristics were balanced between groups; the median (range) age was 73 (45-90) years, with 43.6% of patients aged ≥75 years (**Table 1**)

Table 1: Demographic and baseline disease characteristics of the ITT population[a]

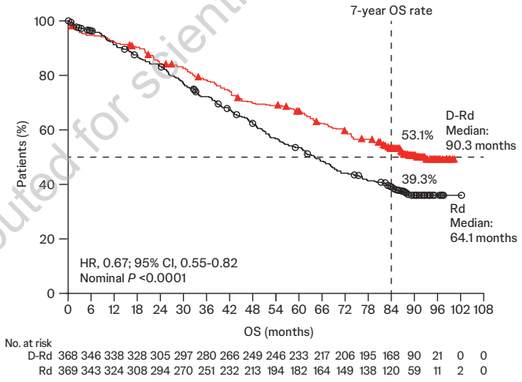
Characteristic	D-Rd (n = 368)	Rd (n = 369)
Age		
Median (range), years	73 (50-90)	74 (45-89)
≥75, n (%)	160 (43.5)	161 (43.6)
Male, n (%)	189 (51.4)	195 (52.8)
ECOG PS, n (%)		
0	127 (34.5)	123 (33.3)
1	178 (48.4)	187 (50.7)
≥2	63 (17.1)	59 (16.0)
ISS disease stage, n (%)		
I	98 (26.6)	103 (27.9)
II	163 (44.3)	156 (42.3)
III	107 (29.1)	110 (29.8)
Type of measurable disease, n (%)		
IgG	225 (61.1)	231 (62.6)
IgA	65 (17.7)	66 (17.9)
Other[b]	9 (2.4)	10 (2.7)
Detected in urine only	40 (10.9)	34 (9.2)
Detected as serum FLC only	29 (7.9)	28 (7.6)
Cytogenetic risk,[c] n (%)		
n	319	323
Standard risk	271 (85.0)	279 (86.4)
High risk	48 (15.0)	44 (13.6)

ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; Ig, immunoglobulin; FLC, free light chain.
[a]The ITT population included all randomized patients.
[b]Inclusive of IgD, IgE, IgM, and biclonal disease.
[c]Cytogenetic risk was based on fluorescence in situ hybridization or karyotype analysis; patients who had a high-risk cytogenetic profile had ≥1 of the following high-risk abnormalities: del(17p), t(14;16), or t(4;14).

Overall survival

- With a median (range) follow-up of 89.3 (0-102.2) months, a 33% reduction in the risk of death was observed with D-Rd versus Rd
- Median OS was reached for the D-Rd group and was prolonged for patients in the D-Rd group versus those in the Rd group (90.3 vs 64.1 months, respectively; **Figure 1**)

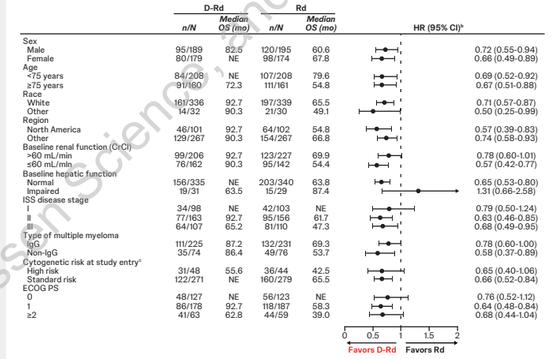
Figure 1: OS with D-Rd and Rd in the ITT population[a]



OS, overall survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval.
[a]The ITT population included all randomized patients.

- Additionally, the OS benefit with D-Rd versus Rd was generally consistent across pre-specified patient subgroups (**Figure 2**)

Figure 2: Analysis of OS in pre-specified patient subgroups[a]

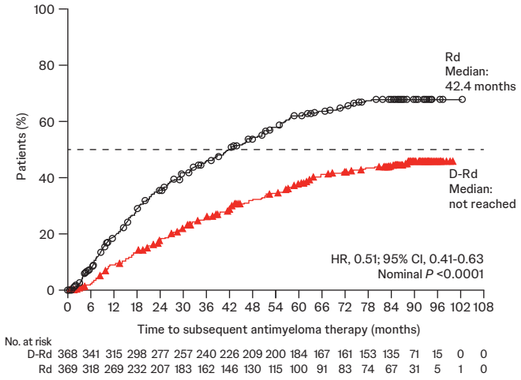


OS, overall survival; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NE, not estimable; CrCl, creatinine clearance; ISS, International Staging System; Ig, immunoglobulin; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat.
[a]In the ITT population, which included all randomized patients.
[b]HRs and 95% CIs were from a Cox proportional hazards model with treatment as the sole explanatory variable. HRs <1 indicate an advantage for D-Rd.
[c]Cytogenetic risk was based on fluorescence in situ hybridization or karyotype analysis; patients who had a high-risk cytogenetic profile had ≥1 of the following high-risk abnormalities: del(17p), t(14;16), or t(4;14).

Subsequent antimyeloma therapy

- Median time to subsequent antimyeloma therapy was not reached in the D-Rd group versus 42.4 months in the Rd group (**Figure 3**)

Figure 3: Time to subsequent antimyeloma therapy in the ITT population[a]



ITT, intent-to-treat; Rd, lenalidomide/dexamethasone; D-Rd, daratumumab plus lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]The ITT population included all randomized patients.

- Among treated patients, 140/364 (38.5%) patients in the D-Rd group and 201/365 (55.1%) patients in the Rd group received ≥1 subsequent antimyeloma therapy
  - Across subsequent therapy lines, the most common antineoplastic agents after D-Rd and Rd, respectively, were bortezomib (27.7% vs 41.9%), DARA (6.3% vs 28.8%), and carfilzomib (7.7% vs 12.3%)
  - No patient in either group reported the use of BCMA- or GPRC5D-targeted therapy
  - Two patients in the D-Rd group and 2 patients in the Rd group received investigational drugs in subsequent therapy lines
- A summary of first subsequent antimyeloma therapy is provided in **Table 2**
  - Proteasome inhibitor–based therapy was the most common first subsequent therapy class in both the D-Rd and Rd groups (69/140 [49.3%] and 101/201 [50.2%], respectively)
  - DARA-containing regimens were received by 15/140 (10.7%) and 49/201 (24.4%) patients in the D-Rd and Rd groups, respectively, as their first subsequent therapy
- Among patients in the D-Rd and Rd groups who were evaluable for their best response to first subsequent antimyeloma therapy, 6/130 (4.6%) and 8/193 (4.1%), respectively, achieved a complete response or better and 18/130 (13.8%) and 46/193 (23.8%) achieved a very good partial response or better

Table 2: Summary of first subsequent antimyeloma therapy in the safety population[a]

n (%)	D-Rd	Rd
Patients who received subsequent therapy, n	140	201
First subsequent therapy class[b,c]		
PI only	69 (49.3)	101 (50.2)
IMiD only	22 (15.7)	25 (12.4)
PI + IMiD	25 (17.9)	16 (8.0)
DARA monotherapy or combination	15 (10.7)	49 (24.4)
Other	9 (6.4)	10 (5.0)
Most common first subsequent therapy regimens[b,d]		
Bortezomib/cyclophosphamide/dexamethasone	19 (13.6)	29 (14.4)
Bortezomib/dexamethasone	20 (14.3)	28 (13.9)
Bortezomib/melphalan/prednisone	14 (10.0)	28 (13.9)
DARA/bortezomib/dexamethasone	4 (2.9)	27 (13.4)
Lenalidomide/dexamethasone	13 (9.3)	16 (8.0)
Bortezomib/pomalidomide/dexamethasone	9 (6.4)	3 (1.5)
Bortezomib/lenalidomide/dexamethasone	8 (5.7)	3 (1.5)
DARA/lenalidomide/dexamethasone	4 (2.9)	6 (3.0)
Pomalidomide/dexamethasone	2 (1.4)	6 (3.0)

D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; PI, proteasome inhibitor; IMiD, immunomodulatory drug; DARA, daratumumab.
[a]The safety population included all randomized patients who received ≥1 dose of study treatment.
[b]Percentages were calculated with the number of patients who received subsequent therapy in each treatment group as the denominator.
[c]Therapy classes are mutually exclusive. Patients in any therapy class subgroup may have received additional agents (other than PI, IMiD, or DARA), such as dexamethasone.
[d]Regimens received by ≥3% of patients in either treatment group.

Safety and tolerability

- Among the safety population, 285 (78.3%) and 345 (94.5%) patients in the D-Rd and Rd groups, respectively, discontinued study treatment
  - The primary reason for discontinuation in both the D-Rd and Rd groups was progressive disease (32.7% and 38.6%, respectively)
  - A lower proportion of patients in the D-Rd group versus the Rd group discontinued study treatment due to adverse events (16.5% and 25.8%, respectively)
- Deaths were reported for 173 (47.5%) patients in the D-Rd group and 218 (59.7%) patients in the Rd group, most frequently due to disease progression (**Table 3**)

Table 3: Summary of death and causes of death in the safety population[a]

n (%)	D-Rd (n = 364)	Rd (n = 365)
Total number of patients who died during the study	173 (47.5)	218 (59.7)
Primary cause of death		
Disease progression	76 (20.9)	88 (24.1)
Adverse events	44 (12.1)	40 (11.0)
Related to study treatment[b]	14 (3.8)	10 (2.7)
Unrelated to study treatment	28 (7.7)	29 (7.9)
Other[c]	53 (14.6)	90 (24.7)
Infections/infestations	9 (2.5)	30 (8.2)
General disorders/administration site conditions[d]	11 (3.0)	5 (1.4)
Neoplasms (benign, malignant, or unspecified)	11 (3.0)	4 (1.1)
Cardiac disorders	1 (0.3)	8 (2.2)
Nervous system disorders	3 (0.8)	5 (1.4)
Unknown	13 (3.6)	27 (7.4)
Deaths within 30 days of last study treatment dose	31 (8.5)	35 (9.6)
Primary cause of death		
Disease progression	1 (0.3)	1 (0.3)
Adverse events	29 (8.0)	32 (8.8)
Related to study treatment[b]	11 (3.0)	10 (2.7)
Unrelated to study treatment	18 (4.9)	22 (6.0)
Other[c]	1 (0.3)	2 (0.5)

D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; DARA, daratumumab.
[a]The safety population included all randomized patients who received ≥1 dose of study treatment.
[b]Adverse events were related to ≥1 of the 2 components of study treatment: DARA, lenalidomide, and dexamethasone.
[c]Other reasons were reported in ≥1% of patients in either treatment group.
[d]All events were related to the general health condition of the patient.
[e]Includes a nervous system disorder in 1 patient in the D-Rd group and a blood and lymphatic system disorder and general disorder/administration site condition in 1 patient each in the Rd group.

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