Time to Response, Duration of Response, and Patient-reported Outcomes With Daratumumab Plus Rd vs Rd Alone in Transplant-ineligible Patients With NDMM: Subgroup Analysis of 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, demonstrating greater cytotoxicity of multiple myeloma cells ex vivo compared with analogs of other CD38 antibodies[8]
  - DARA induces higher levels of complement-dependent cytotoxicity, similar levels of antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis, and, in the presence of Fc receptor crosslinking, which occurs naturally in vivo, DARA elicits similar levels of cell death[8]
  - DARA is approved in combination with standard-of-care regimens for patients with newly diagnosed multiple myeloma (NDMM), is approved as monotherapy and in combination with standard-of-care regimens for patients with relapsed/refractory multiple myeloma,[9,10] and has been used to treat >270,000 patients worldwide[11]
- The phase 3 MAIA trial (ClinicalTrials.gov Identifier: NCT02252172) compared DARA plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with NDMM
  - Adding DARA to Rd improved progression-free survival (PFS) and depth and duration of response[12]
    - At a median follow-up of 28 months, D-Rd was associated with faster and sustained clinically meaningful improvements in patient-reported outcomes (PROs) compared with Rd[13]
  - Updated results at a median follow-up of 56.2 months showed a significant overall survival benefit, continued PFS benefit, higher rates of complete response or better (≥CR) and very good partial response or better (≥VGPR),[14] and improvement in PROs[15] with D-Rd versus Rd
- Here, we present a subgroup analysis of time to response, duration of response, and PROs in MAIA

METHODS

Study design

- In MAIA, transplant-ineligible patients aged ≥18 years with NDMM were randomized 1:1 to receive D-Rd or Rd until disease progression or unacceptable toxicity[12]
  - Patients received 28-day cycles of Rd (R 25 mg orally on Days 1-21; d 40 mg orally weekly) ± DARA (16 mg/kg intravenously weekly in Cycles 1-2, every 2 weeks in Cycles 3-6, and every 4 weeks thereafter)

Patient subgroups

- Renal impairment was defined as having a baseline creatinine clearance (CrCl) ≤60 mL/min
- Patients with high cytogenetic risk had a del17p, t(4;14), or t(14;16) abnormality

Assessments

- The primary endpoint was PFS; secondary endpoints included time to response and duration of response
  - Response and disease progression were assessed via a validated computerized algorithm according to the International Myeloma Working Group criteria[16,17]
  - Time to response was defined as the time between the date of randomization and the first efficacy evaluation at which the patient met the response level in the response-evaluable population; patients who did not reach the response level were censored
    - The response-evaluable population included patients who had a confirmed diagnosis of multiple myeloma, had measurable disease at baseline or screening, had received ≥1 component of study treatment, and had adequate post-baseline disease assessments
  - Duration of response was defined as the time between the first documentation of the response level and disease progression or death due to disease progression, whichever occurred first; responders without disease progression were censored
  - Time to response and duration of response were analyzed via the Kaplan–Meier method and Cox model
- PROs were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30)[18]
  - Treatment effects on changes from baseline in EORTC QLQ-C30 pain, fatigue, and nausea and vomiting symptom scores were assessed via a mixed-effects model with repeated measures

MULTIPLE MYELOMA

RESULTS

Patients

- In total, 368 patients were randomized to the D-Rd group and 369 patients to the Rd group
- Patient demographic and baseline characteristics were reported previously[12]; data on baseline renal function and cytogenetic risk status are provided in **Table 1**

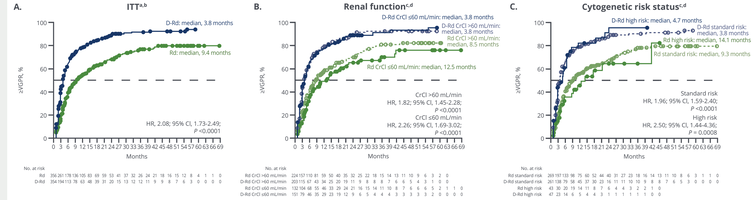
Efficacy

- At a 56.2-month median follow-up, median time to ≥VGPR was shorter with D-Rd versus Rd in the overall study population and in patient subgroups based on renal function and cytogenetic risk status (**Figure 1**)
- Median time to ≥CR was shorter with D-Rd versus Rd in the overall study population (median, 20.8 vs 47.9 months; hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.36-2.18; *P* <0.0001)
- Median time to ≥CR was shorter with D-Rd versus Rd in patient subgroups based on:
  - Renal function:
    - CrCl >60 mL/min: median, 17.6 versus 43.8 months; HR, 1.80; 95% CI, 1.34-2.41; *P* <0.0001
    - CrCl ≤60 mL/min: median, 23.3 versus 54.6 months; HR, 1.58; 95% CI, 1.07-2.33; *P* = 0.0197
  - Cytogenetic risk status:
    - Standard risk: median, 20.8 versus 42.6 months; HR, 1.69; 95% CI, 1.29-2.21; *P* <0.0001
    - High risk: median, 15.7 versus 47.9 months; HR, 1.74; 95% CI, 0.83-3.63; *P* = 0.1372
- Duration of ≥CR was improved for patients receiving D-Rd versus Rd in the overall study population (**Figure 2**)
- Duration of ≥CR was improved with D-Rd versus Rd in patient subgroups based on:
  - Renal function:
    - CrCl >60 mL/min: HR, 0.41; 95% CI, 0.22-0.77; *P* = 0.0043
      - Estimated 48-month event-free rate: D-Rd, 82.2% versus Rd, 55.3%
    - CrCl ≤60 mL/min: HR, 0.45; 95% CI, 0.20-1.04; *P* = 0.0551
      - Estimated 48-month event-free rate: D-Rd, 81.0% versus Rd, 61.5%
  - Cytogenetic risk status:
    - Standard risk: HR, 0.42; 95% CI, 0.24-0.73; *P* = 0.0015
      - Estimated 48-month event-free rate: D-Rd, 80.0% versus Rd, 55.1%
    - High risk: HR, 0.32; 95% CI, 0.09-1.16; *P* = 0.0694
      - Estimated 48-month event-free rate: D-Rd, 74.7% versus Rd, not estimable
- Duration of partial response or better (≥PR) was improved for patients receiving D-Rd versus Rd in the overall study population (HR, 0.50; 95% CI, 0.39-0.64; *P* <0.0001)
- Duration of ≥PR was improved for patients receiving D-Rd versus Rd in patient subgroups based on:
  - Renal function:
    - CrCl >60 mL/min: HR, 0.50; 95% CI, 0.36-0.70; *P* <0.0001
      - Estimated 48-month event-free rate: D-Rd, 69.8% versus Rd, 48.9%
    - CrCl ≤60 mL/min: HR, 0.50; 95% CI, 0.34-0.74; *P* = 0.0003
      - Estimated 48-month event-free rate: D-Rd, 67.2% versus Rd, 44.4%
  - Cytogenetic risk status:
    - Standard risk: HR, 0.43; 95% CI, 0.32-0.57; *P* <0.0001
      - Estimated 48-month event-free rate: D-Rd, 72.3% versus Rd, 45.7%
    - High risk: HR, 0.65; 95% CI, 0.35-1.19; *P* = 0.1560
      - Estimated 48-month event-free rate: D-Rd, 48.8% versus Rd, 29.9%

PROs

- Among patients with renal impairment, greater improvements from baseline in patient-reported pain scores were observed with D-Rd versus Rd across most time points (**Figure 3**)
  - A notably greater meaningful reduction in pain symptom score was seen with D-Rd versus Rd as early as Cycle 6 Day 1 (least squares [LS] mean change from baseline, −14.9 vs −7.0; *P* = 0.0241) in patients with renal impairment
  - Greater improvements from baseline in pain scores were also observed with D-Rd versus Rd across most time points for patients with standard and high cytogenetic risk
- In patients with renal impairment, greater improvements from baseline in patient-reported fatigue and nausea and vomiting symptom scores were also observed with D-Rd versus Rd across most time points
  - A notably greater reduction in fatigue symptom score was seen with D-Rd versus Rd at Cycle 24 Day 1 (LS mean change from baseline, −2.9 vs 8.1; *P* = 0.0018), Cycle 30 Day 1 (LS mean change from baseline, −3.7 vs 4.4; *P* = 0.0258), and Cycle 36 Day 1 (LS mean change from baseline, −2.6 vs 6.5; *P* = 0.0183) in patients with renal impairment
  - A notably greater reduction in nausea and vomiting symptom score was seen with D-Rd versus Rd at Cycle 36 Day 1 (LS mean change from baseline, −3.7 vs 3.3; *P* = 0.0035) in patients with renal impairment

FIGURE 1: Time to ≥VGPR for the (A) ITT population and in patient subgroups based on (B) renal function and (C) cytogenetic risk status



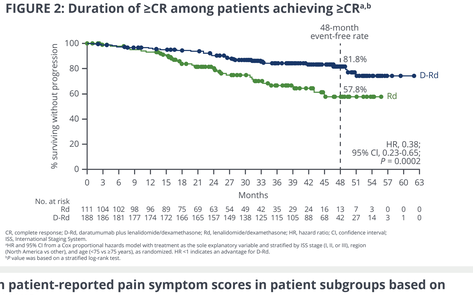
VGPR, very good partial response; ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; CrCl, creatinine clearance; ISS, International Staging System.
[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified by ISS stage (I, II, or III), region (North America vs other), and age (<75 vs ≥75 years), as randomized. HR <1 indicates an advantage for D-Rd.
[b]*P* value was based on a stratified log-rank test.
[c]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. HR >1 indicates an advantage for D-Rd.
[d]*P* value was based on the log-rank test.

TABLE 1: Baseline renal function and cytogenetic risk status in the ITT population

Characteristic, n (%)	D-Rd (n = 368)	Rd (n = 369)
Baseline renal function (CrCl)		
>60 mL/min	206 (56.0)	227 (61.5)
≤60 mL/min	162 (44.0)	142 (38.5)
Cytogenetic risk[a]		
N	319	323
Standard risk	271 (85.0)	279 (86.4)
High risk	48 (15.0)	44 (13.6)

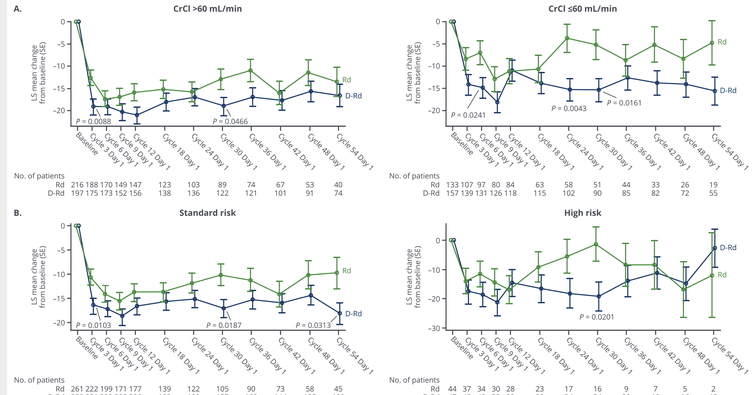
ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; CrCl, creatinine clearance; IMWG, International Myeloma Working Group.
[a]Cytogenetic risk was based on local fluorescence in situ hybridization or karyotype test. Patients with high cytogenetic risk had a del(17p), t(4;14), or t(14;16) abnormality per IMWG 2016 recommendations.[16] Patients with standard cytogenetic risk had an absence of high-risk cytogenetic abnormalities.

FIGURE 2: Duration of ≥CR among patients achieving ≥CR[a,b]



CR, complete response; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; ISS, International Staging System.
[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified by ISS stage (I, II, or III), region (North America vs other), and age (<75 vs ≥75 years), as randomized. HR <1 indicates an advantage for D-Rd.
[b]*P* value was based on a stratified log-rank test.

FIGURE 3: LS mean[a] change from baseline in patient-reported pain symptom scores in patient subgroups based on (A) renal function and (B) cytogenetic risk status



LS, least squares; CrCl, creatinine clearance; SE, standard error; Rd, lenalidomide/dexamethasone; D-Rd, daratumumab plus lenalidomide/dexamethasone.
[a]LS means were derived based on the mixed-effects model with repeated measures, in which the dependent variable was change from baseline in score and the independent variables were baseline value, visit, treatment, and visit by treatment interaction as fixed effects and individual patient as random effect.

KEY TAKEAWAY

Our results support the use of D-Rd in transplant-ineligible patients with NDMM

CONCLUSIONS

In transplant-ineligible patients with NDMM, D-Rd showed more rapid deep responses as well as more durable responses versus Rd, regardless of renal function or cytogenetic risk status

Improvements in patient-reported symptoms were generally greater with D-Rd versus Rd in patients with and without renal impairment and with standard-risk and high-risk cytogenetic status

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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. DARZALEX® (daratumumab) [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2022. 10. European Medicines Agency. DARZALEX 20 mg/mL concentrate for solution for infusion [summary of product characteristics]. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf. Accessed May 6, 2022. 11. Data on file. 12. Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115. 13. Perrot A, et al. *J Clin Oncol*. 2021;39(3):227-237. 14. Facon T, et al. *Lancet Oncol*. 2021;22(11):1582-1596. 15. Perrot A, et al. *Blood*. 2021;138(suppl 1):1655. 16. Durie BGM, et al. *Leukemia*. 2006;20(9):1467-1473. 17. Rajkumar SV, et al. *Blood*. 2011;117(18):4691-4695. 18. Aaronson NK, et al. *J Natl Cancer Inst*. 1993;85(5):365-376. 19. Sonneveld P, et al. *Blood*. 2016;127(24):2955-2962.

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