Adjusted Indirect Treatment Comparison of Progression-free Survival Associated With D-Rd and VRd Based on MAIA and SWOG S0777 Individual Patient-level Data

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INTRODUCTION

- Daratumumab plus lenalidomide and dexamethasone (D-Rd) and bortezomib plus lenalidomide and dexamethasone (VRd) are standard-of-care regimens for the treatment of transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM)[1]
- D-Rd and VRd have each demonstrated superior efficacy relative to lenalidomide and dexamethasone (Rd) alone in patients with NDMM in the MAIA and SWOG S0777 trials, respectively[2-6]
  - In MAIA, D-Rd showed a progression-free survival (PFS) benefit (hazard ratio [HR], 0.55; *P* <0.0001) versus Rd at a median follow-up of 64.5 months[6]
  - In SWOG S0777, VRd showed a PFS benefit (HR, 0.71; one-sided *P* = 0.0018) compared to Rd alone at a median follow-up of 55 months[3]
    - 43% of patients in SWOG S0777 were aged ≥65 years (vs 99% in MAIA)[2,3]; however, a significant PFS benefit in this subgroup was not observed for VRd versus Rd (HR, 0.83; 95% confidence interval [CI], 0.60-1.16)[7]
- D-Rd and VRd have not been compared directly in a head-to-head trial
  - Naïve comparisons of efficacy across the 2 studies may be biased, given that MAIA exclusively enrolled TIE patients (median age, 73 years [interquartile range (IQR), 70-78]) while SWOG S0777 enrolled a mixed population of patients without intent for immediate autologous stem cell transplant (ASCT) that included both TIE patients and patients who chose to defer or refuse frontline transplant (median age, 63 years [IQR, 55-70])[2-4]
- We compared PFS with D-Rd and VRd in TIE patients with NDMM, leveraging individual patient-level data from both trials and adjusting for differences in trial inclusion/exclusion criteria and baseline patient characteristics

METHODS

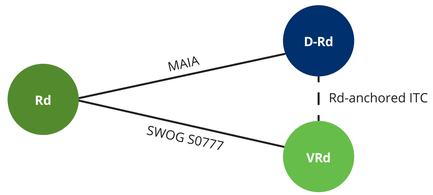
Data sources

- Individual patient-level data from MAIA were based on a median follow-up of 64.5 months[6]
- Individual patient-level data from SWOG S0777 based on the primary data cut (median follow-up, 55 months)[3] were obtained from the National Cancer Institute

Study design

- Harmonized inclusion criteria (NDMM, age ≥65 years, Eastern Cooperative Oncology Group [ECOG] performance status ≤2) were applied to both trial populations. Age ≥65 years served as a proxy for TIE status, as SWOG S0777 enrolled a mixed population of patients without intent for immediate ASCT
- Propensity score (PS) reweighting was used to balance the 2 study populations on key baseline patient characteristics. Missing data were addressed with multiple imputation
- After alignment of inclusion criteria and PS reweighting, an anchored indirect treatment comparison was performed wherein within-trial PFS HRs for D-Rd versus Rd and VRd versus Rd were estimated and used to make an indirect inference regarding PFS for D-Rd versus VRd (**Figure 1**)

FIGURE 1: Anchored ITC study design



ITC, indirect treatment comparison; Rd, lenalidomide/dexamethasone; D-Rd, daratumumab plus lenalidomide/dexamethasone; VRd, bortezomib plus lenalidomide/dexamethasone.

MULTIPLE MYELOMA

RESULTS

Eligible MAIA and SWOG S0777 analysis sets

- In total, 727 MAIA patients and 198 SWOG S0777 patients were eligible for inclusion
- After addressing missing data with multiple imputation and PS reweighting, the trial populations were balanced on the following key baseline patient characteristics: age, sex, International Staging System disease stage, ECOG performance status, hemoglobin, estimated glomerular filtration rate, lactate dehydrogenase level, and cytogenetic risk (**Table 1**)
  - Absolute standardized differences were <0.1 for all covariates, indicating good covariate balance

TABLE 1: Baseline patient characteristics after PS weighting

Covariate	MAIA (n = 727)	SWOG S0777 (n = 198)	Standardized difference
Age, mean (SD), years	72.70 (4.79)	72.67 (5.24)	0.01
Female, %	41	39	0.04
ISS disease stage, %			
I	20	20	0.01
II	45	45	0.00
III	35	35	–0.01
ECOG performance status, %			
0	42	40	0.03
1	50	51	–0.03
2	9	9	0.00
Hemoglobin <10 g/dL, %	31	32	–0.03
eGFR <60 mL/min/1.73 m^2, %	47	47	0.00
LDH ≥190 U/L, %	39	39	0.00
High cytogenetic risk,[a] %	19	17	0.05

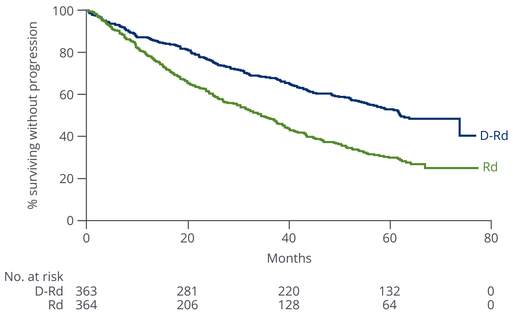
PS, propensity score; SD, standard deviation; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase.
[a]High cytogenetic risk was defined in MAIA and SWOG S0777 as the presence of ≥1 high-risk cytogenetic abnormality (del[17p], t[14;16], or t[4;14]).

PFS

- After PS weighting, the PFS HRs were 0.53 (95% CI, 0.41-0.68) for D-Rd versus Rd based on MAIA data, 0.88 (95% CI, 0.63-1.23) for VRd versus Rd based on SWOG S0777 data, and 0.60 (95% CI, 0.39-0.90) for the Rd-anchored indirect comparison of D-Rd versus VRd (**Figure 2**)

FIGURE 2: PFS results from (A) MAIA, (B) SWOG S0777, and (C) the anchored ITC of D-Rd versus VRd

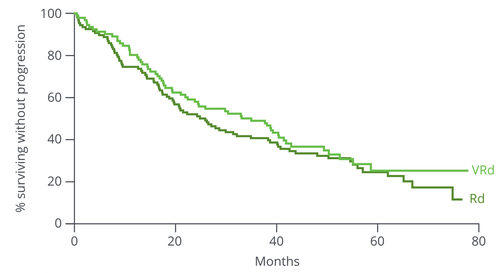
A.



No. at risk

D-Rd	363	281	220	132	0
Rd	364	206	128	64	0

B.



No. at risk

VRd	91	56	37	6	0
Rd	107	60	38	13	0

C.

MAIA: D-Rd vs Rd	SWOG S0777: VRd vs Rd	ITC: D-Rd vs VRd
HR = 0.53 (95% CI, 0.41-0.68; *P* <0.0001)	HR = 0.88 (95% CI, 0.63-1.23; *P* = 0.46)	HR = 0.60 (95% CI, 0.39-0.90; *P* = 0.02)

PFS, progression-free survival; ITC, indirect treatment comparison; D-Rd, daratumumab plus lenalidomide/dexamethasone; VRd, bortezomib plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; PS, propensity score.
PFS Kaplan–Meier plots reflect results after PS weighting for the MAIA (n = 727) and SWOG S0777 (n = 198) patients who met the harmonized inclusion/exclusion criteria. HRs for PFS reflect comparisons after application of harmonized inclusion/exclusion criteria and PS weighting. The anchored ITC of D-Rd versus VRd reflects the ratio of the HRs for D-Rd versus Rd and VRd versus Rd.

KEY TAKEAWAY

Results of this adjusted indirect treatment comparison based on individual patient-level data from the MAIA and SWOG S0777 trials indicate that PFS was superior for D-Rd relative to VRd in TIE patients with NDMM

CONCLUSIONS

Application of harmonized inclusion criteria and PS weighting allowed the treatment effects of D-Rd and VRd to be compared in similar populations of TIE patients with NDMM

In the absence of a head-to-head trial comparing D-Rd and VRd, the results of this indirect treatment comparison may inform treatment selection in TIE patients with NDMM

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DISCLOSURES

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