CO174

Matching-Adjusted Indirect Comparison of Isatuximab-Bortezomib-Lenalidomide-Dexamethasone (IVRd) versus Daratumumab-Based Regimens in Patients with Newly Diagnosed Multiple Myeloma Ineligible for Transplant

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INTRODUCTION

- In the Phase III IMROZ trial, IVRd significantly improved PFS by 40.4% vs VRd in patients with transplant ineligible newly diagnosed multiple myeloma (NDMM)[1]
- DRd showed significant improvement in PFS vs Rd in the Phase III MAIA trial, and DVMp showed significant improvement in PFS vs VMp in the Phase III ALCYONE trial in patients with transplant-ineligible NDMM[2,3]

OBJECTIVE

To estimate the comparative efficacy of IVRd vs DRd and DVMp in patients with transplant-ineligible NDMM in the absence of head-to-head comparisons.

METHODS

Evidence base:

- IPD for IVRd were from IMROZ (median follow-up of 59.7 months)[1]
- Aggregate data for DRd and DVMp were based on publications of the MAIA[2,3] and ALCYONE[4,5] trials, respectively

Statistical methods:

- Unanchored MAIC was required due to the lack of a connected network of evidence
- IPD of the IVRd arm in the IMROZ trial (n = 265) were matched to the aggregated baseline patient characteristics data for DRd from MAIA (n = 368) and DVMp from ALCYONE (n = 350)
- Matching patient characteristics included age, ISS stage, ECOG PS, cytogenetic risk, MM type, and creatinine clearance, which were potential prognostic factors and effect modifiers validated by clinicians and IMROZ IPD
- Cox PH regression and bootstrapping were used to estimate HRs and their 95% CIs
- Mean difference in RMST was calculated by comparing the area under the Kaplan–Meier curves up to the maximum IVRd time

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RESULTS

- Adjusted characteristics were well-balanced between treatments after matching (**Table 1**)
  - When comparing IVRd to DVMp, CrCl was excluded in matching to preserve the ESS, given its lowest rank in the prognostic variables as suggested by clinicians

Table 1: Baseline characteristics before and after matching

	IVRd unadjusted	IVRd weighted to DRd	DRd	IVRd weighted to DVMp	DVMp
N or ESS	265	177.3	368	141.5	350
Age (years)	71.7	73.0	73.0**	71.0	71.0
Male	54%	56%	51%	53%	46%
Race					
White	73%	74%	NR	66%	85%
Other	14%	13%	NR	20%	15%
Missing	13%	13%	NR	14%	0%
ISS stage					
I	34%	27%	27%	20%	20%
II	41%*	44%	44%	40%	40%
III	25%	30%	29%	40%	40%
ECOG PS					
0–1	89%	83%	83%	74%	74%
≥ 2	11%	16%	17%	26%	26%
Cytogenetic risk					
High	15%	15%	15%	17%	17%
Standard	78%	85%	85%	83%	83%
Missing	7%	0%	0%	0%	0%
MM type					
IgG	65%	61%	61%	41%	41%
Non-IgG	35%	39%	39%	59%	59%
CrCl					
≤ 60 mL/min	25%	44%	44%	28%	43%
> 60 mL/min	75%	56%	56%	72%	57%

Notes: Mean reported for continuous variables. * One patient with missing ISS stage was grouped into ISS Stage II as this was the largest group. ** Assumed based on the median due to lack of reported mean age.

Table 2: MAIC HRs and difference in RMST

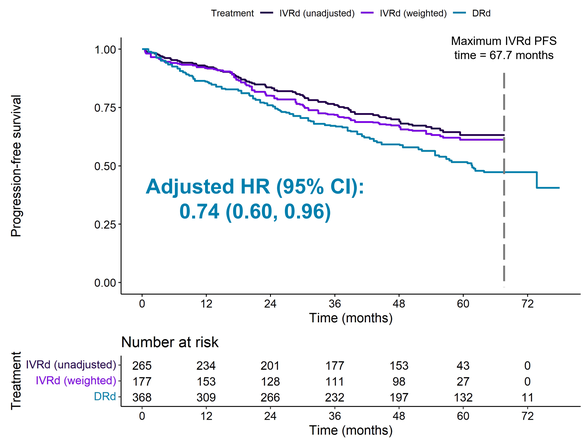
	Endpoint	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Difference in RMST: months (95% CI)*
IVRd vs DRd	PFS	0.67 (0.52, 0.87)	0.74 (0.60, 0.96)	4.25 (-0.05, 8.54)
	OS	0.74 (0.55, 0.99)	0.90 (0.67, 1.15)	1.40 (-2.43, 5.24)
IVRd vs DVMp	PFS	0.43 (0.33, 0.56)	0.52 (0.39, 0.66)	10.85 (5.98, 15.72)
	OS	0.63 (0.47, 0.84)	0.80 (0.57, 1.02)	1.62 (-2.66, 5.90)

Notes: HRs were considered statistically significant if the 95% CI excluded 1. Difference in RMST was considered statistically significant if the 95% CI excluded 0.
* Up to the maximum IVRd event time (PFS = 67.7 months, OS = 69.0 months).

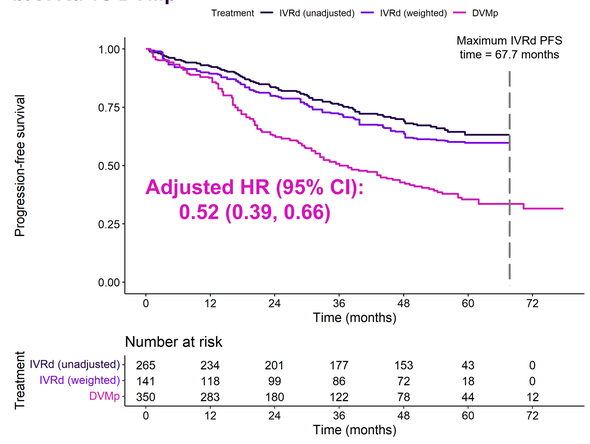
- **The MAICs demonstrated a statistically significant improvement in PFS for IVRd vs DRd and DVMp (Figure 1)**
  - IVRd showed a 26% reduction in the risk of disease progression or death vs DRd: HR (95% CI) = 0.74 (0.60, 0.96) (**Figure 1a**)
  - Mean (95% CI) difference in restricted mean PFS between IVRd and DRd was 4.25 (-0.05, 8.54) months (**Table 2**)
  - IVRd showed a 48% reduction in the risk of disease progression or death vs DVMp: HR (95% CI) = 0.52 (0.39, 0.66) (**Figure 1b**)
  - Mean (95% CI) difference in restricted mean PFS between IVRd and DVMp was 10.85 (5.98, 15.72) months (**Table 2**)

Figure 1: Kaplan–Meier curves before and after matching for PFS

a. IVRd vs DRd



b. IVRd vs DVMp



- **A numerical trend in favor of IVRd vs DRd and DVMp was observed for OS (Table 2)**
  - A reduction in the risk of death was observed for IVRd vs DRd, but the result was not statistically significant: HR (95% CI) = 0.90 (0.67, 1.15)
  - Mean difference (95% CI) in restricted mean OS between IVRd and DRd was 1.40 (-2.43, 5.24) months
  - A reduction in the risk of death was observed for IVRd vs DVMp, but the result was not statistically significant: HR (95% CI) = 0.80 (0.57, 1.02)
  - Mean difference (95% CI) in restricted mean OS between IVRd and DVMp was 1.62 (-2.66, 5.90) months

LIMITATIONS

- Unanchored MAIC assumes that all prognostic factors and effect modifiers have been adjusted for, which is impossible to confirm
- Results may be subject to bias from unmeasured confounders, which is difficult to quantify
- PFS outcomes may not be measured consistently across studies, potentially introducing bias

CONCLUSIONS

- MAICs showed **IVRd significantly improves PFS over DRd and DVMp** for transplant-ineligible NDMM patients
- A **numerical trend suggested improved OS with IVRd**, although IMROZ trial OS data are still immature
- Given IVRd's superior benefit in delaying disease progression or death, **adding isatuximab to standard of care, VRd, represents a valuable treatment option for patients with transplant-ineligible NDMM**

ABBREVIATIONS: CI, confidence interval; CrCl, creatinine clearance; DRd, daratumumab-lenalidomide-dexamethasone; DVMp, daratumumab-bortezomib-melphalan-prednisone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; HR, hazard ratio; IgG, immunoglobulin G; IPD, individual patient-level data; ISS, International Staging System; IVRd, isatuximab-bortezomib-lenalidomide-dexamethasone; MAIC, matching-adjusted indirect comparison; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; NR, not reported; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; Rd, lenalidomide-dexamethasone; RMST, restricted mean survival time; VMp, bortezomib-melphalan-prednisone; VRd, bortezomib-lenalidomide-dexamethasone.

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