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Indirect treatment comparisons of daratumumab-pomalidomide-dexamethasone and pomalidomide-bortezomib-dexamethasone in relapsed/refractory multiple myeloma

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Key Takeaway

This MAIC showed a statistically significant benefit in PFS for DPd vs. PVd in patients with RRMM.

Conclusions

DPd significantly improves PFS compared to PVd and may show a trend towards similar or better improvements in OS in patients with RRMM.

Our conclusion assumes that there were no significant imbalances in important remaining prognostic or effect-modifying variables after adjusting for the selected covariates in the population-adjusted indirect comparisons.

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Poster

Narrated poster video

Supplementary material

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Disclosures

David Bin-Chia Wu, Cathy Kwang-Wei Wu, and Lee Ann Rothwell are employees of Janssen and may hold stock shares in Johnson & Johnson Pte Ltd., Wee Joo Chng and Sung-Hoon Jung declare no conflicts of interest.

Background

- Daratumumab is a monoclonal antibody that targets CD38 which is highly expressed in multiple myeloma. Treatment induces apoptosis of plasma cells via multiple mechanisms of action.[1]
- Daratumumab is a key drug for the treatment of relapsed/refractory multiple myeloma (RRMM), achieving remarkably high and durable response rates with improved progression-free survival vs pomalidomide plus dexamethasone.[2,3]
- However, head-to-head studies of daratumumab in combination with pomalidomide and dexamethasone (DPd) versus recently approved pomalidomide, bortezomib, and dexamethasone (PVd) in patients with RRMM are lacking. Comparative data can help guide clinical decision making and optimize treatment selection.
  - We used population-adjusted comparison methods to compare the effectiveness of DPd vs PVd administered in clinical trials to patients with RRMM.

Objective

- To compare progression-free survival (PFS) and overall survival (OS) associated with DPd from the APOLLO trial[3-4] with PVd from the OPTIMISMM trial[5] in patients with RRMM.

Methods

- We performed an indirect treatment comparison using individual patient-level data from the APOLLO trial and a combination of aggregate data and pseudo-patient level data from the OPTIMISMM trial.
- Comparisons were based on an unanchored Bayesian matching-adjusted indirect comparison (MAIC) in accordance with the NICE Guide to the Methods of Technology Appraisal.
- A harmonized set of inclusion criteria were identified and applied to the APOLLO trial population to account for differences in inclusion criteria between APOLLO and OPTIMISMM.
- Participants in the APOLLO study were re-weighted, such that the treatment effect modifiers (TEMs) and prognostic variables (PVs)* were balanced with those in OPTIMISMM.

*Cytogenetic risk, refractory to IMiD, refractory to PI, refractory to lenalidomide, number of prior lines, refractory to last line, ISS stage, previous autologous stem cell transplant, refractory to bortezomib.

	APOLLO	OPTIMISMM
Design	Phase 3, open, randomized, controlled	Phase 3, open, randomized, controlled
Setting	12 countries in Europe	21 countries worldwide
N	151 received DPd	281 received PVd
Median age	67	67
Previous treatment	Both a proteasome inhibitor and lenalidomide-containing regimen	1–3 previous regimens, including at least 2 cycles of a lenalidomide-containing regimen

Harmonized criteria:

Inclusion:
- Participants had received 1-3 prior lines of anti-myeloma therapy.
- Participants received ≥2 consecutive cycles of lenalidomide.

Exclusion:
- Hemoglobin <8 g/dL (< 4.9 mmol/L)
- Corrected serum calcium >13.5 mg/dL (>3.4 mmol/L)

Results

- In the base-case adjustment, all covariates were balanced (standardized mean difference <0.001), except for the distinct categories of 1 prior line (PVd: 39.5% vs. DPd: 2.1%) and 2 prior line: (PVd: 41.6% vs. DPd: 79.0%) which were matched as 1 or 2 prior line instead of individually (Table 1).
- The proportion of weighted DPd patients who had 1 or 2 prior lines was essentially identical to the proportion of PVd patients who had 1 or 2 prior lines.

Table 1: Patient characteristics for the PVd arm from OPTIMISMM and the DPd arm from APOLLO, before and after application of eligibility criteria and MAIC weighting.

Factor	Level	PVd OPTIMISMM N=281	DPd (APOLLO) Original data N=151	DPd (APOLLO) Additional eligibility criteria N=126	DPd (APOLLO) Weighted base-case ESS=42
Cytogenetic risk	Standard	0.488	0.424	0.437	0.488
	High	0.217	0.258	0.254	0.217
	Missing	0.295	0.318	0.310	0.295
Refractory to IMiD	Yes	0.719	0.828	0.825	0.719
Refractory to protease inhibitor	yes	0.132	0.649	0.659	0.132
Refractory to lenalidomide	yes	0.712	0.815	0.817	0.712
Prior lines of therapy	1, 2	0.811	0.623	0.738	0.811
	1	0.395	0.106	0.127	0.021
	2	0.416	0.517	0.611	0.790
	3	0.189	0.238	0.262	0.189
Refractory to last line	yes	0.701	0.808	0.817	0.701
ISS stage	I	0.530	0.450	0.452	0.530
	II	0.302	0.331	0.333	0.302
	III	0.167	0.219	0.214	0.167
Previous ASCT	yes	0.573	0.603	0.579	0.573
Refractory to bortezomib	yes	0.085	0.497	0.516	0.085

ASCT, autologous stem cell transplant; ESS, effective sample size; IMiD, immunomodulatory drug; ISS, International Staging System; MAIC, matching-adjusted indirect comparison

PFS

- The PFS Kaplan-Meier curve in match-adjusted DPd patients was notably better than the PFS Kaplan-Meier curve for PVd patients (Fig. 1).
- This is further reflected by the match-adjusted HR of 0.59 (95% credible interval [CrI]: 0.36, 0.89) (Table 2, Fig. 3).
- While the naive comparison favored DPd only slightly, the base-case adjustment resulted in a 99% probability that DPd is superior to PVd in terms of PFS.

OS

- The OS Kaplan-Meier curve in match-adjusted DPd patients was notably higher than the OS Kaplan-Meier curve for PVd patients (Fig. 2).
- The HR suggests there was an improvement in OS for DPd patients compared to PVd patients (HR 0.80 [95% CrI: 0.45, 1.30]), although the CrI included the null effect of 1 (Table 3, Fig. 4).
- The corresponding probability of DPd being superior to PVd in terms of OS was 83%.

Figure 1. Kaplan-Meier curves for the PVd, original and match-adjusted DPd patients in terms of PFS

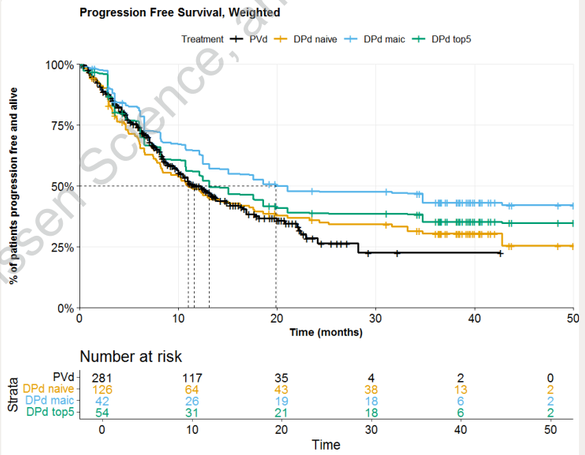
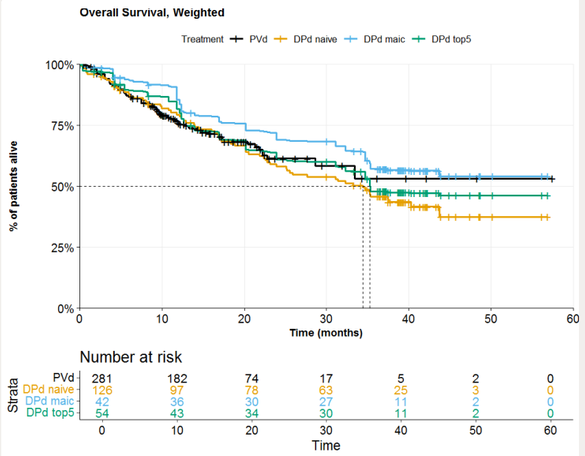


Figure 2. Kaplan-Meier curves for the PVd, original and match-adjusted DPd patients in terms of OS



Top5: The MAIC was carried out twice using 2 different sets of covariates: the base-case adjustment considered the top 10 ranked covariates of concern, and a sensitivity adjustment considered the top 5 ranked covariates. Ranks were determined based on an average of the ranked opinions of 3 clinical experts.

Table 2: Results of Bayesian MAIC for PFS comparison

Indirect comparison	Hazard ratio (95% CrI) DPd vs. PVd	Probability of DPd superiority
Naïve (unadjusted)	0.94 (0.70-1.21)	0.71
Base-case adjustment (all covariates)	0.59 (0.36-0.89)*	0.99

* Credible interval does not contain 1.
CrI, credible interval; DPd, daratumumab, pomalidomide and dexamethasone; PVd, pomalidomide, bortezomib and dexamethasone

Table 3: Results of Bayesian MAIC for OS comparison

Indirect comparison	Hazard ratio (95% CrI) DPd vs. PVd	Probability of DPd Superiority
Naïve (unadjusted)	1.15 (0.81-1.57)	0.24
Base-case adjustment (all covariates)	0.80 (0.45-1.30)	0.83

CrI, credible interval; DPd, daratumumab, pomalidomide and dexamethasone; PVd, pomalidomide, bortezomib and dexamethasone

Summary

- We found evidence that DPd significantly improves PFS compared to PVd and may show a trend towards similar or better improvement in OS.
- Our conclusion assumes that there were no significant imbalances in important remaining TEMs and PVs after adjusting for the selected covariates in the population-adjusted indirect comparisons.
- Compared to OPTIMISMM, APOLLO tends to have more clinically advanced patients in terms of prior lines of therapy, drug resistance and late ISS stage. Therefore, the adjustment made to account for these-differences would make DPd more favorable than PVd.
- Some inclusion/exclusion criteria could not be harmonized across trials; e.g., previous treatment with a proteasome inhibitor.
- In the absence of a randomized controlled trial, these results provide valuable insights with respect to the added clinical benefit of DPd over PVd in RRMM.

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Multiple Myeloma