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905.OUTCOMES RESEARCH-LYMPHOID MALIGNANCIES

Pomalidomide, Dexamethasone, and Daratumumab Versus Other Triplet Regimens in Patients with Relapsed or Refractory Multiple Myeloma: A Population-Adjusted Indirect Treatment Comparison

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Introduction: Multiple myeloma (MM) is an incurable malignant plasma cell disorder in which most patients eventually relapse or become refractory to treatment. Lenalidomide (LEN) is typically administered as part of first-line regimens; however, patients who receive LEN usually relapse, necessitating improved options in later lines of therapy. The phase 2, non-randomized MM-014 trial (NCT01946477) demonstrated promising efficacy of pomalidomide (POM) plus dexamethasone and daratumumab (DPd) among patients with relapsed or refractory MM (RRMM), with an overall response rate of 77.7% and a median overall survival (OS) of 56.7 months at a median follow-up of 41.9 months. With the evolving treatment landscape of RRMM, however, there is limited head-to-head data comparing DPd to other standard of care therapies to inform clinical decision-making.

Objective: To investigate the comparative efficacy of DPd versus non-POM-containing triplets in adult patients with RRMM using population-adjusted indirect comparison (PAIC) approaches.

Methods: A PAIC was conducted using individual patient-level data of 112 adult patients with RRMM who were exposed to LEN (75.9% refractory to LEN) from cohort B of the MM-014 trial. Investigator-assessed OS was the primary endpoint of this analysis. A systematic literature review was performed to identify comparable interventional studies assessing the efficacy of non-POM-containing triplets for RRMM as well as potential prognostic variables (PVs). PVs verified by clinicians were selected for inclusion if significantly associated with OS ($p < 0.1$) in the MM-014 trial based on univariate Cox regression model. The suitability of these potential trials for PAIC was assessed by considering the comparability of study design, inclusion/exclusion criteria, patients' baseline characteristics, and outcomes. A retrospective analysis utilizing Flatiron electronic health record data from Jan 2011 to July 2022 was previously performed to evaluate the effect of LEN-refractory status on OS using multivariable Cox regression. Given the lack of a common comparator, unanchored PAIC was performed for OS using matching-adjusted indirect comparison (MAIC) and confirmatory simulated trial comparison (STC). A sensitivity analysis was conducted to explore the impact of LEN-refractory status as a PV.

Results: Six trials were systematically identified as eligible comparators in initial screening including TOURMALINE-MM1, CANDOR, CASTOR, POLLUX, ASPIRE, and LEPUS. The analyses using Flatiron data showed that patients who were refractory to LEN had significantly shorter OS than those exposed to LEN but not refractory (Hazard ratio: 1.51; 95% CI: 1.17, 1.94), indicating the unsuitability to compare treatments based on studies with large variations in proportion of LEN-refractory patients. Four trials were excluded due to differences violating the transitivity assumption (0% LEN-refractory patients in TOURMALINE-MM1 and POLLUX; LEN-refractory status not reported in ASPIRE; only Chinese patients in LEPUS). The remaining two trials are phase 3 randomized controlled trials investigating carfilzomib plus dexamethasone and daratumumab (DKd) (CANDOR; NCT03158688; Usmani et al. Blood Adv. 2023; Epub ahead of print) and daratumumab plus bortezomib and dexamethasone (DVd) (CASTOR; NCT02136134; Sonneveld et al. J Clin Oncol. 2023; 41:1600-1609). In the base case MAIC adjusting for creatinine clearance, time from diagnosis, International Staging System score, and refractory to LEN, DPd was associated with numerical reduction in the risk of death compared to DKd and DVd (Table). In addition, the base case STC showed significant improvement of OS for DPd over DKd and DVd, confirming the findings from MAIC (Table). In the sensitivity analyses excluding LEN-refractory status, the effect estimates were substantially different from those in the base case analyses (>40% difference), demonstrating the importance of adjusting for LEN refractory status.

Conclusions: In patients with RRMM, consistent OS benefit was found for DPd versus DKd and DVd regardless of the PAIC technique used. These findings support the use of DPd over DKd and DVd in treating patients with RRMM, especially given

the oral route of administration of pomalidomide. This study also highlighted the importance of considering LEN refractory status when comparing efficacy of treatments for RRMM across trials.

Disclosures Lan: *Cytel:* Current Employment; *IQVIA:* Ended employment in the past 24 months. **Dolph:** *Cytel:* Current Employment. **Moradian:** *Cytel:* Current Employment. **Slaff:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Shih:** *Bristol Myers Squibb:* Current Employment; *Janssen:* Other: Spouse current employment; *Novartis:* Ended employment in the past 24 months. **Tang:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.

Table. PAIC results of DPd (MM-014) versus DKd (CANDOR) and DVd (CASTOR) for OS

Comparison	N/ESS in MM-014	ESS %	Hazard ratio (95% CI)
DPd vs. DKd (Ref)			
MAIC	19.71	24.6%	0.70 (0.33, 1.48)
STC	80	NA	0.65 (0.44, 0.97)
DPd vs. DVd (Ref)			
MAIC	23.11	28.9%	0.58 (0.27, 1.24)
STC	80	NA	0.52 (0.36, 0.76)

Note: variables adjusted in PAIC included creatinine clearance, time from diagnosis, International Staging System score, and refractory to lenalidomide. In MM-014 Cohort B, only patients who had data for the four variables were included, i.e., 80 out of 112.
PAIC: population-adjusted indirect comparison; DPd: pomalidomide, dexamethasone, daratumumab; DKd: daratumumab, carfilzomib, dexamethasone; DVd: daratumumab, bortezomib, dexamethasone; MAIC: matching-adjusted indirect comparison; STC: simulated trial comparison; ESS: effective sample size; CI: confidence interval.

Figure 1

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