Project Summary Report

YODA Project Protocol #: 2025-0152

Comparative Outcomes of DVMP, DRd, VMP, and Rd in Older High-Risk Cytogenetic Multiple Myeloma Patients: A Propensity Score Analysis

Objective: To evaluate the comparative effectiveness and safety of daratumumab-lenalidomide-dexamethasone (D-Rd), daratumumab-bortezomib-melphalan-prednisone (D-VMP), lenalidomide-dexamethasone (Rd), and bortezomib-melphalan-prednisone (VMP) in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) and high-risk features, using de-identified patient-level data from the MAIA and ALCYONE phase III trials. A focused subgroup analysis was also performed in patients harboring del(17p13), comparing D-Rd and D-VMP.

Methods: We conducted retrospective comparative analyses using patient-level data obtained through YODA Project #2025-0152. The main analysis included transplant-ineligible NDMM patients with ISS III disease and high-risk cytogenetic abnormalities, including del(17p), amp(1q21), t(4;14), and/or t(14;16). Propensity scores were estimated using multinomial logistic regression based on age, ECOG performance status, sex, and creatinine clearance, and inverse probability of treatment weighting (IPTW) was applied. Progression-free survival (PFS) and overall survival (OS) were evaluated using weighted Kaplan–Meier curves and robust Cox models. Safety outcomes were summarized descriptively. An additional clinically motivated subgroup/sensitivity analysis restricted to patients with del(17p13) used propensity-score matching to compare D-Rd and D-VMP, with balance assessed through standardized mean differences, empirical cumulative distribution function statistics, and variance ratios. The main methods were consistent with the original comparative proposal; the del(17p13) analysis was performed as an additional focused high-risk subgroup analysis using the same approved data source.

Results: The main high-risk cohort included 103 patients: 24 treated with D-Rd, 29 with D-VMP, 21 with Rd, and 29 with VMP. IPTW achieved adequate covariate balance, with maximum standardized mean differences below 0.10. Weighted 3-year PFS was 54.8% for D-Rd, 16.7% for D-VMP, 19.5% for Rd, and 11.0% for VMP. In the robust Cox model for PFS, D-Rd was associated with a significantly lower risk of progression or death compared with VMP (HR 0.29, 95% CI 0.15–0.55; $p<0.001$), whereas D-VMP and Rd did not differ significantly from VMP. Median OS was 59.1, 53.6, 41.0, and 33.0 months for D-Rd, D-VMP, Rd, and VMP, respectively; OS differences were not statistically significant. In the del(17p13) analysis, 86 patients were identified across treatment groups. After matching, 26 patients remained in the D-Rd versus D-VMP comparison. Median PFS was 35.0 months with D-Rd and 20.95 months with D-VMP ($p=0.72$), while 3-year OS was 60.0% and 62.5%, respectively ($p=0.49$). Safety findings were summarized descriptively, without formal comparative safety inference because of the limited subgroup sample size.

Conclusions: Among transplant-ineligible high-risk NDMM patients from MAIA and ALCYONE, D-Rd showed a significant PFS advantage compared with VMP, whereas D-VMP and Rd did not show statistically significant PFS differences versus VMP in the weighted model. OS differences were not statistically significant. In the del(17p13) subgroup, D-Rd and D-VMP showed comparable survival outcomes, with numerically longer PFS for D-Rd but substantial uncertainty due to small sample size. These findings are hypothesis-generating and support the need for prospective head-to-head trials and real-world studies in elderly, high-risk myeloma populations.