REAL-WORLD COMPARATIVE SAFETY AND SURVIVAL OF DARATUMUMAB-BASED REGIMENS IN RELAPSED MULTIPLE MYELOMA: A PROPENSITY-MATCHED TRINETX ANALYSIS OF DRD VS. DPD

F. Khan[1], H. Qadri[2], S. Alsidawi[3]

1. TriHealth Good Samaritan Hospital, Cincinnati, Ohio, USA
2. Memorial Healthcare System, Florida, USA
3. TriHealth Cancer Institute, Cincinnati, Ohio, USA

Introduction

- Daratumumab-based triplets are foundational in relapsed/refractory multiple myeloma (RRMM). In routine care, daratumumab-lenalidomide-dexamethasone (DRd) is commonly chosen earlier, whereas daratumumab-pomalidomide-dexamethasone (DPd) is often used after lenalidomide exposure.
- However, head-to-head real-world comparisons of safety and survival are limited. Given distinct toxicity profiles of lenalidomide and pomalidomide including risks of myelosuppression, infections, renal complications, and venous thromboembolism, clarifying comparative outcomes can guide regimen selection and sequencing in RRMM.

Aim

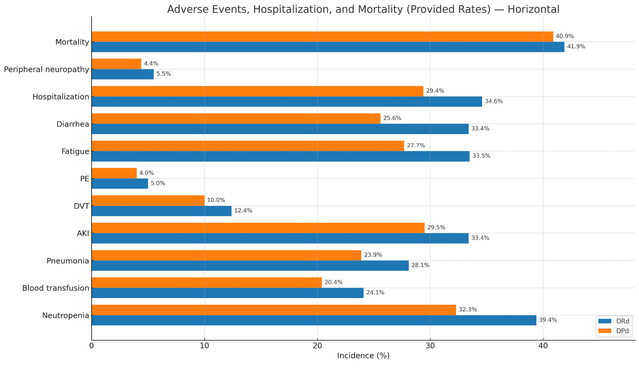
- To compare real-world safety and overall survival between DRd and DPd in adults with RRMM using a large, propensity-matched cohort from the TriNetX Network.

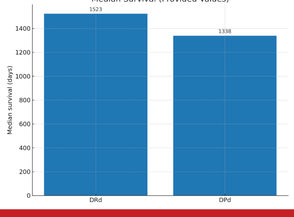
Objectives

- Primary objective: evaluate overall survival (OS) for DPd versus DRd.
- Secondary objectives: compare rates of key toxicities (hematologic, infectious, renal), thromboembolic events, constitutional and gastrointestinal adverse effects, peripheral neuropathy, and healthcare utilization (hospitalizations, outpatient visit frequency).
- Exploratory objective: assess differences in serious complications (e.g., septic shock, stroke, cardiac arrest) and secondary malignancies.

Methods

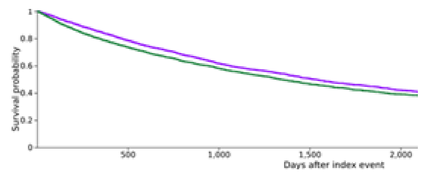
- We conducted a retrospective cohort study within TriNetX, identifying adults (≥18 years) with relapsed or persistent multiple myeloma (ICD-10 C90.00 or C90.02) treated with either DRd or DPd.
- Exposure cohorts were propensity score–matched 1:1 on age, sex, race, comorbidities (chronic kidney disease, congestive heart failure, diabetes), and transplant status to balance baseline characteristics.
- Outcomes included all-cause mortality (primary) and prespecified safety endpoints: neutropenia, transfusions, infections, acute kidney injury (AKI), deep-vein thrombosis (DVT), pulmonary embolism (PE), fatigue, diarrhea, peripheral neuropathy, hospitalizations, and outpatient visit frequency.
- We calculated risk ratios (RR), odds ratios (OR), and hazard ratios (HR) with 95% confidence intervals (CI). Kaplan–Meier curves and HRs compared OS between regimens; two-sided p<0.05 denoted statistical significance





Results

- After matching, 4,206 patients were included per cohort.
- Compared with DPd, the DRd group experienced higher rates of neutropenia (39.4% vs 32.3%; RR 1.22, 95% CI 1.13–1.32; p<0.001), blood transfusion (24.1% vs 20.4%; RR 1.18; p=0.001), pneumonia (28.1% vs 23.9%; RR 1.17; p<0.001), and AKI (33.4% vs 29.5%; RR 1.14; p=0.002).
- DRd was also associated with greater thromboembolic risk—DVT (12.4% vs 10.0%; p=0.001) and PE (5.0% vs 4.0%; p=0.033) and higher rates of fatigue (33.5% vs 27.7%; p<0.001), diarrhea (33.4% vs 25.6%; p<0.001), hospitalization (34.6% vs 29.4%; p=0.001), peripheral neuropathy (5.5% vs 4.4%; p=0.047), and more frequent outpatient visits.
- Mortality proportions were similar (41.9% DRd vs 40.9% DPd), yet time-to-event analysis favored DPd (HR 0.86; 95% CI 0.81–0.92; p<0.001).
- Median survival estimates were numerically longer in DRd (1,523 days) than DPd (1,338 days).
- Several outcomes showed no significant between-group differences, including septic shock, stroke, cardiac arrest, hypogammaglobulinemia, CMV infection, aspergillosis, and secondary malignancies (AML, ALL, or solid tumors)



Summary

- In a large, propensity-matched real-world cohort, DPd was associated with a lower burden of hematologic, infectious, renal, gastrointestinal, and thromboembolic adverse events than DRd, alongside fewer hospitalizations and outpatient encounters.
- While crude mortality proportions were similar, survival curves favored DPd with a statistically significant OS advantage (HR 0.86).
- The pattern of results supports DPd as a safer and potentially more tolerable option for many patients with RRMM, particularly those at risk for cytopenias, infection, VTE, or kidney injury.

Discussion

- These findings align with known pharmacologic differences between lenalidomide and pomalidomide containing backbones and suggest that, in routine practice, DPd may mitigate toxicity and resource utilization compared with DRd.
- The OS advantage for DPd by hazard modeling despite numerically longer median OS in DRd highlights the importance of evaluating the entire survival distribution rather than relying solely on medians, which are sensitive to curve crossing, tail behavior, and censoring.
- Clinically, the observed increases in neutropenia, infection, AKI, and VTE with DRd may influence regimen choice for patients with prior cytopenias, infection risk, renal vulnerability, or thrombosis history, while acknowledging that prior lenalidomide exposure and line of therapy often drive DPd selection.
- Limitations include the retrospective design, potential residual confounding (e.g., disease biology, depth of response, prior therapies), misclassification inherent to EHR/claims coding, and lack of granular dosing/supportive care data.
- Prospective comparative studies and pragmatic trials are warranted to confirm these real-world observations and refine patient selection for optimal daratumumab-based sequencing in RRMM.

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