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Daratumumab-Bortezomib-Lenalidomide-Dexamethasone vs Contemporary Treatment Alternatives in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: Results of a Systematic Literature Review and Network Meta-Analysis

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Introduction

- Numerous treatment regimens have been evaluated in transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM); as the treatment paradigm continues to evolve, there remains a need for comparative evidence across these regimens[1]
- Daratumumab-based regimens such as daratumumab, lenalidomide, and dexamethasone (DRd) are established standards of care in TIE NDMM in the US; daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) is approved in the EU and recommended by the National Comprehensive Cancer Network (NCCN) guidelines in the US, but is not yet FDA approved[2-4]
- Head-to-head comparisons between DVRd and other guideline-endorsed therapies are not available, presenting a gap in evidence to support optimal treatment selection in clinical practice
  - To inform clinical decision making, indirect treatment comparisons such as network meta-analyses (NMAs) may be used to estimate comparative efficacy[5]
- This study presents a systematic literature review (SLR) and Bayesian NMA to assess the relative efficacy of DVRd vs other regimens recommended in current clinical guidelines for the treatment of TIE NDMM

Methods

- An SLR was conducted on November 30, 2020, and updated on August 6, 2024, to identify large randomized controlled trials (RCTs) in the TIE NDMM population; only trials with published efficacy and safety outcomes were included
- Regimens included in the NMA were those endorsed by ASCO/CCO, NCCN, EHA/ESMO, or EMN guidelines and supported by RCT connectivity; regimens required to maintain network connectivity were included (**Figure 1**)
- For trials that enrolled both TIE and transplant-deferred patients with NDMM (eg, CEPHEUS, SWOG S0777, ENDURANCE), subgroup data for TIE patients (or age ≥65 years as a proxy for TIE) were used, if available
- Outcomes assessed included: progression-free survival (PFS), overall survival (OS), and minimal residual disease (MRD) negativity with CR
- A Bayesian NMA was conducted using 10,000 total iterations per network to generate posterior distributions of treatment effects with fixed-effect models selected based on model fit
- A normal likelihood with identity link was applied for time-to-event outcomes; results are reported as posterior probabilities and 95% credible intervals (CrIs)

Figure 1: Regimen selection for NMA base case

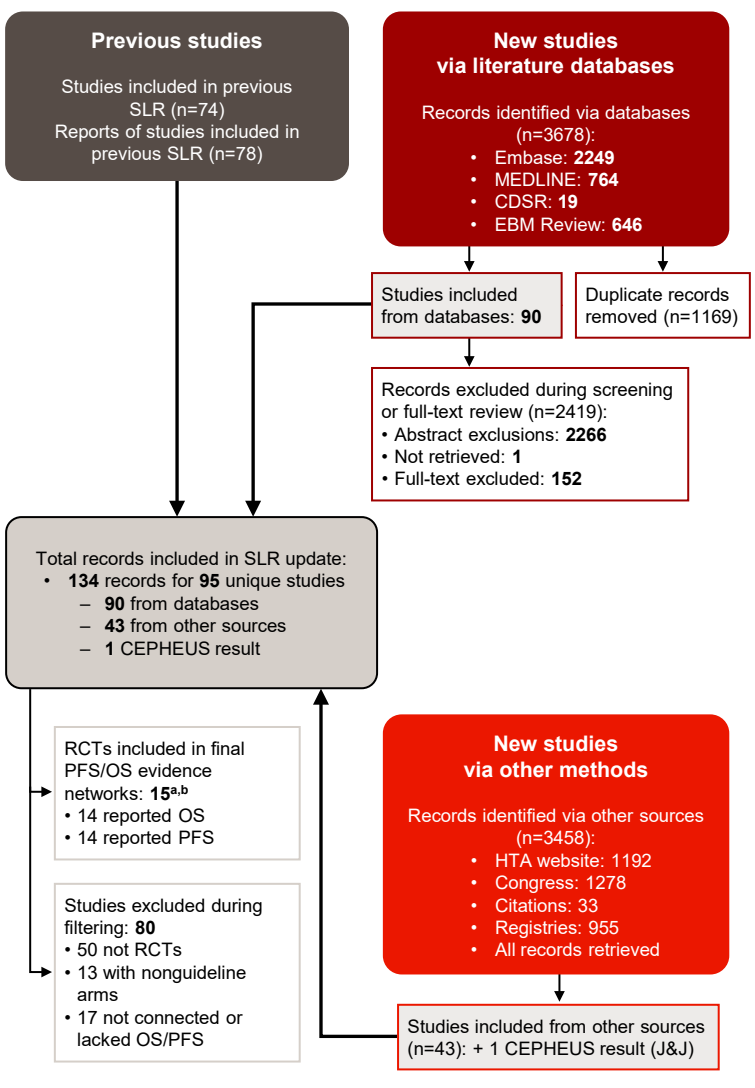
Included in NMA base case:
- CTd[b]
- DRd
- DVMP
- IsaVRd
- KRd
- MP
- MPT
- Rd
- Vd
- VMP
- VRd

Excluded from NMA base case[a]:
- DCVd
- IsaKRd
- KCd
- RCd
- VCd

[a]Excluded due to lack of RCTs that could be connected to the evidence network.
[b]CTd is included in the network due to its evidence loop with the MP and MPT regimens.
CTd, cyclophosphamide, thalidomide, and dexamethasone; DCVd, daratumumab, cyclophosphamide, bortezomib, and dexamethasone; DVMP, daratumumab, bortezomib, melphalan, and prednisone; IsaKRd, isatuximab, carfilzomib, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; KCd, carfilzomib, cyclophosphamide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; MP, melphalan and prednisone; MPR, melphalan, prednisone, and lenalidomide; MPT, melphalan, prednisone, and thalidomide; RCd, lenalidomide, cyclophosphamide, and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd, bortezomib, lenalidomide, and dexamethasone.

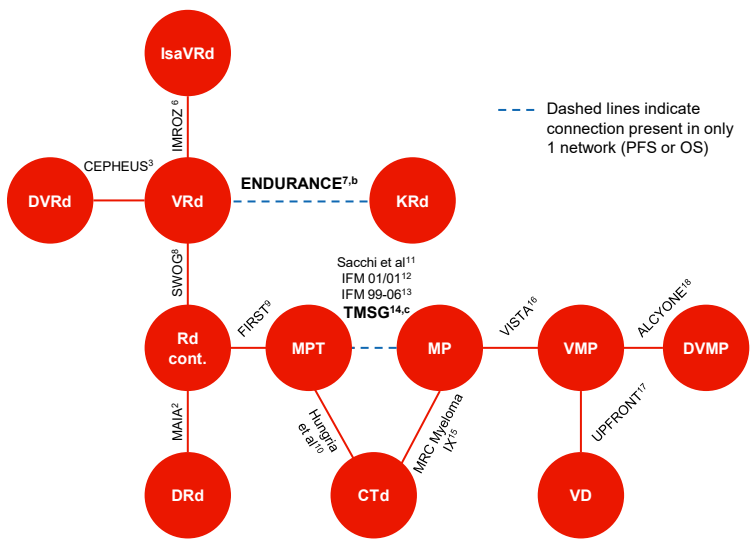
Results

Figure 2: PRIMSA flow diagram for SLR and study selection for inclusion in PFS/OS network



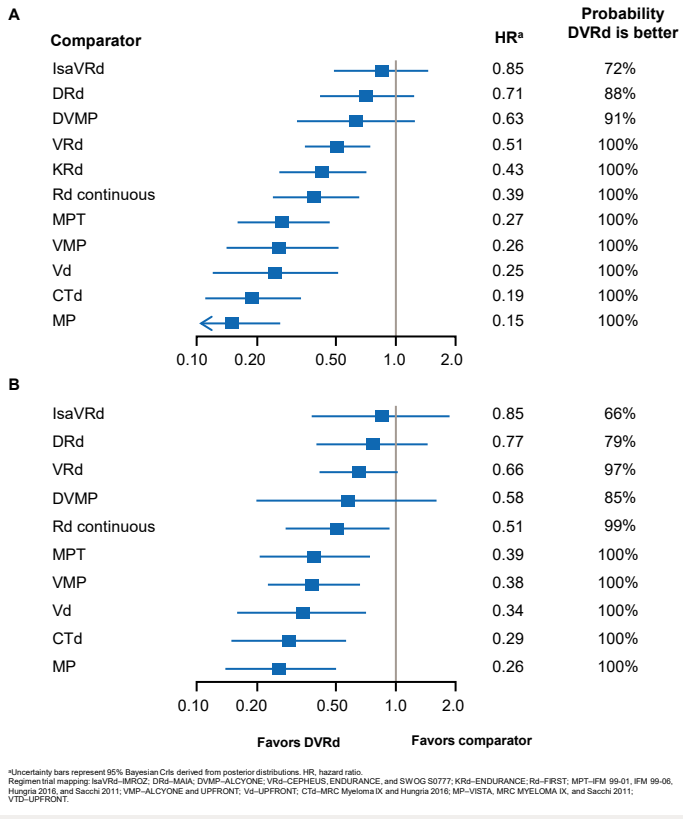
[a]Regimens endorsed by contemporary treatment guidelines, including NCCN (v1.2025), ASCO/CCO, EHA-ESMO 2021, EMN 2014, and EMN 2020. [b]The following regimens were excluded due to network disconnection or lack of comparability within the final PFS/OS networks: VCd, DCVd, IsaKRd, KCd, and RCd.

Figure 3: Network of evidence for DVRd and comparator regimens[a]



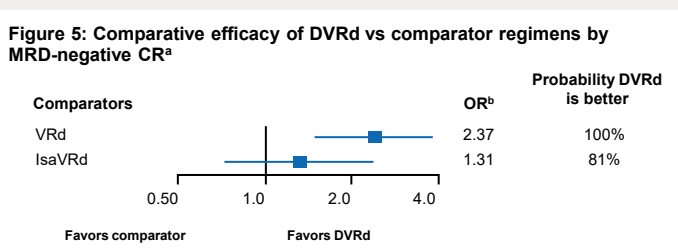
[a]Displayed network reflects PFS data; OS and ORR networks differ slightly in study count and connections. The evidence network for MRD-negative CR includes only the CEPHEUS and IMROZ trials because the S0777 trial (which would connect them to other trials) did not report on MRD-negative CR. [b]ENDURANCE was excluded from the OS network due to lack of results specific to TIE patients but included in the PFS network. [c]TMSG was excluded from the PFS network due to lack of PFS data but included in the OS network due to data availability. CTd, cyclophosphamide, thalidomide, and dexamethasone; TMSG, Turkish Myeloma Study Group.

Figure 4: Comparative efficacy of DVRd vs comparator regimens by (A) PFS and (B) OS



[a]Uncertainty bars represent 95% Bayesian CrIs derived from posterior distributions. HR, hazard ratio.
Regimen trial mapping: IsaVRd–IMROZ; DRd–MAIA; DVMP–ALCYONE; VRd–CEPHEUS, ENDURANCE, and SWOG S0777; KRd–ENDURANCE; Rd–FIRST; MPT–IFM 99-01, IFM 99-06, Hungria 2016, and Sacchi 2011; VMP–ALCYONE and UPFRONT; Vd–UPFRONT; CTd–MRC Myeloma IX and Hungria 2016; MP–VISTA, MRC MYELOMA IX, and Sacchi 2011; VTD–UPFRONT.

Figure 5: Comparative efficacy of DVRd vs comparator regimens by MRD-negative CR[a]



[a]The network of evidence for MRD-negative CR includes 2 studies, allowing for the comparison of 2 treatments; the common comparator was VRd, which was compared to IsaVRd in IMROZ and to DVRd in CEPHEUS. [b]Uncertainty bars represent 95% Bayesian CrIs derived from posterior distributions. OR, odds ratio.

SLR and base case network composition

- The updated 2024 SLR identified 212 relevant publications describing 95 unique studies (**Figure 2**)
- The NMA included 14 studies and 12 regimens for PFS and 14 studies and 11 regimens for OS (**Figure 3**)

PFS

- Heterogeneity was moderate (I^2 = 45.8%; 95% CrI, 0.0–82.0) (**Figure 4A**)
- The probability of DVRd having superior efficacy was 72% vs IsaVRd, 88% vs DRd, 91% vs DVMP, and 100% vs VRd

OS

- Heterogeneity was low (I^2 = 0%; 95% CrI, 0.0–79.2) (**Figure 4B**)
- The probability of DVRd having superior efficacy was 66% vs IsaVRd, 79% vs DRd, 85% vs DVMP, and 97% vs VRd

MRD-negative CR

- The probability of DVRd having superior MRD-negative CR rates was 81% vs IsaVRd and 100% vs VRd (**Figure 5**)

Limitations

- Differences in trial timing may limit comparability, as some regimens reflect outdated clinical practice while others are from more recent studies (eg, DVRd, IsaVRd)
- Certain guideline-recommended regimens were excluded from the network due to insufficient connectivity
- NMAs are limited in their ability to account for baseline heterogeneity across studies; addressing this would require more advanced methods such as multilevel network meta-regression

Key Takeaway

Among SOC regimens reflected in current clinical guidelines for TIE patients with NDMM, DVRd was associated with the highest probability of offering the best PFS, OS, and MRD-negative CR outcomes

Conclusions

DVRd showed the highest probability of superior PFS vs IsaVRd (72%), DRd (88%), DVMP (91%), and VRd (100%)

DVRd also had the highest probability of superior OS vs IsaVRd (66%), DRd (79%), DVMP (85%), and VRd (97%)

The probability of DVRd having superior MRD-negative CR was 81% vs IsaVRd and 100% vs VRd

These comparative efficacy data may inform treatment selection for maximum benefit in the TIE NDMM population; findings should be considered alongside differences in trial timing and baseline characteristics

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Disclosures

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