Assessing Meta-Analyses and Systematic Literature Reviews Comparing Effectiveness of Treatments for Relapsed/Refractory Multiple Myeloma (RRMM): A Targeted Literature Review from 2017-2023

Nishi Yadav M.S., Bhargavi Mahadik M.S., Ambarish Ambegaonkar, Ph.D.
(Corresponding Author: ambi@apperturehealth.com)

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Background

- Multiple Myeloma (MM) accounts for approximately 1.8% of all new cancer cases and 2.1% of all cancer deaths for 2023. As per American Cancer Society's estimates for 2024, about 35,780 new cases and 12,540 deaths are expected to occur for MM in the US. The risk of developing MM increases with age, with a median diagnosis age of around 65 years
- Relapsed Refractory Multiple Myeloma (RRMM) is an incurable disease where patients experience cancer recurrence or poor response to treatment. The main focus of treating RRMM is to control disease progression, manage complications, and improve quality of life

Objective

- To assess the comparative effectiveness of RRMM therapies **(Table 1)** by conducting a review of Network Meta-Analyses (NMA) and pair-wise analyses

Methods

- A search strategy was developed and optimized to extract published articles meta-analyzing effectiveness outcomes for treatments in advanced RRMM
- The search was conducted using PubMed from January 2017 - December 2023
- A total of 36 studies were obtained from the search, of which 33 were screened for title and abstract after deduplication and 29 were screened for full-text. All screening was carried out independently by 2 researchers and discordance was resolved through discussion **(Figure 1)**
- Finally, data were extracted from 19 studies into a pre-finalized workbook using Microsoft Excel
- The data extracted from the included studies were analyzed qualitatively using descriptive and thematic analysis. This involved organizing and synthesizing the data to identify key themes, patterns, and trends across studies. Descriptive summaries, tables, and figures were then used to synthesize and present the findings.

Figure 1. PRISMA Chart for Included Studies

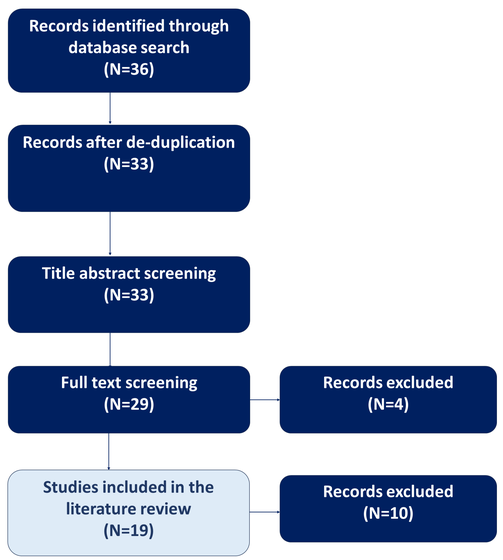


Table 1: RRMM Treatment Classification

Drug Class	Drugs
Monoclonal Antibodies (mABs)	Daratumumab, Elotuzumab, Isatuximab, Siltuximab
Immunomodulatory Drugs (IMiD's)	Lenalidomide, Pomalidomide
Proteasome Inhibitors (PI's)	Bortezomib, Carfilzomib, Ixazomib
Chimeric Antigen Receptor (CAR) T-cell Therapy	B cell maturation antigen (BCMA) therapy, anti-BCMA therapy
B-cell Lymphoma 2 (BCL-2) inhibitors	Venetoclax
Histone Deacetylase Inhibitors (HDACi's)	Panobinostat, Ricolinostat, Vorinostat,
Selective Inhibitors of Nuclear Export (SINE)	Selinexor

Results

Fig 2. Drug Distribution Overall (N=19)

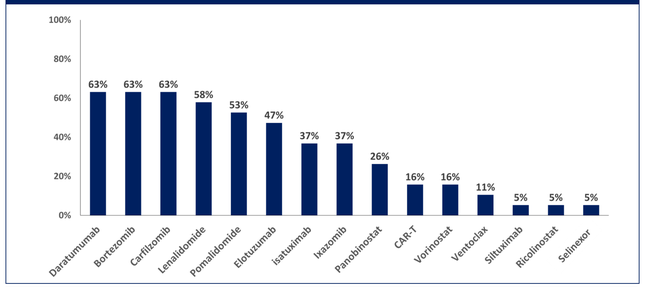
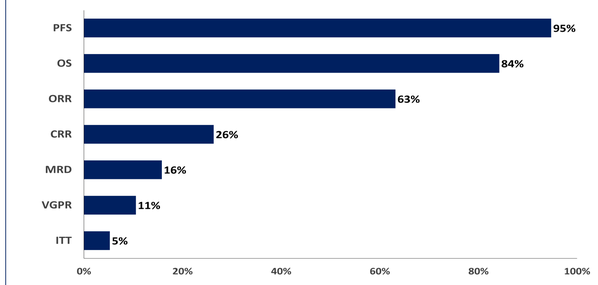


Fig 3. Outcomes measured among various studies (N=19)



CRR: Complete Response Rate, MRD: Minimal Residual Disease, VGPR: Very Good Partial Response, ITT: Intention-to-Treat

- Out of 19 studies, 57% (n=11) were network meta-analyses (MA) and 42% (n=8) were pair-wise meta-analyses with the highest number of studies (N=5) published in 2023
- All pair-wise and network MA included an average of 16 studies (Range: 5-27) and only 11 of them reported the total number of patients included with an average of 3782 patients (Range: 350-9080) who had previously undergone at least 2 or more lines of treatment
- A steady increase was observed in the number of studies published since 2020, most of which were published in the Americas and Asia (N=9, each) while 4 studies were published in Europe
- IMiDs and mABs specifically daratumumab, bortezomib, and carfilzomib were the most assessed treatments in both in pair-wise and network meta-analyses **(Figure 2)**
- Progression-free survival (PFS) and overall survival (OS) and overall response rate (ORR)were the most assessed outcomes of interest **(Figure 3)**
- A total of 8 studies conducted pair-wise meta-analyses of treatments approved for RRMM of which 3 analysed CAR-T, 2 analyzed mABs, 1 analyzed BCL-2i therapy, PI, and HCADi, each **(Table 2)**

Table 2: Synthesis of Pair-wise meta-analyzed studies

Study	No. of Studies	Treatment	Conclusion
Hu, 2023; Zhanga 2021; Yang, 2020	21,22,23	BCMA-targeted CAR-T, non BCMA-targeted CAR-T	Anti-BCMA CAR-T therapy reported significantly higher ORR compared to non-BCMA targeted CAR-T therapy. Anti-BCMA CAR T therapy is effective and safe for patients with R/R MM.
Huang, 2023; Zhang, 2017	5,13	IMiDs, mABs	mAB based doublet/ triplet therapy improved PFS and ORR compared to other regimens. Daratumumab containing regimens had significantly higher ORR and PFS
Xu, 2023	14	Venetoclax	Venetoclax (BCL-2i) when combined with other drugs (mABs, PI, IMiDs,) significantly improves the PFS and ORR. Doublet and triplet therapy have a better response compared to monotherapy
Davies, 2023	12	PI	Pomalidomide-based combination regimens were effective in lenalidomide refractory MM patients
Gao, 2018	19	HDACi	Panobinostat-based PI/IMiD combination regimens had better PFS and ORR compared to vorinostat- and ricolinostat-based regimens

Table 3: Synthesis of NMAs reporting mAB-containing doublet / triplet therapies

Study	No. of Studies	Treatment	Conclusion
Chen, 2023	22	mABs, IMiDs, PI	Daratumumab and isatuximab-based triple combination therapies ranked first in effectiveness in comparison to other therapies
DerSarkissiana, 2022	27	mABs, IMiDs, PI	Daratumumab and Carfilzomib containing triplet therapies reported significantly longer OS and PFS followed by Ixazomib containing triplet therapy
Beurden-Tan, 2022	17	mABs, IMiDs, PI	DRd ranked the first and identified as the treatment with the highest ORR with slightly narrower CrI
Mohyuddin, 2021	7	mABs, PI	Daratumumab containing triplet (DVd/ DKd) therapies were more effective in lenalidomide RRMM
Arcuri, 2021	18	mABs, IMiDs, PI, Others	Triplet regimens containing daratumumab achieve better PFS compared to other triplet and doublet therapies
Weisel, 2019	7	mABs, PI	Daratumumab containing PI triplet therapy has the best treatment for prolonging PFS among all treatments
Dimopoulous, 2018	8	mABs, PI	Triplet combinations of DRd was significantly better in improving progression-free survival in patients with RRMM than were other IMiD-containing doublet/ triplet regimens
Maiese, 2018	27	mABs, IMiDs, PI	Daratumumab containing treatment (DRd/ DVd) have had statistically significant lower risk of progression or death compared to all other treatments
Botta, 2017	19	mABs, IMiDs, PI	Triplet therapy of DRd was the most effective based on SUCRA in terms of PFS, OS, and ORR

DRd: daratumumab/lenalidomide/dexamethasone; DVd: daratumumab/bortezomib/dexamethasone; DKd: daratumumab/carfilzomib/dexamethasone; SUCRA: surface under cumulative ranking curve

- Of the 11 studies that analyzed treatment networks, 9 studies assessed the use of mABs either as monotherapy or in combination with IMiDs and PIs **(Table 3)**
- mAB containing triplet therapy was reported to be more effective in all the 9 studies (100%)
- In NMAs, the most common comparators across all networks were either Dexamethasone/ Lenalidomide or Dexamethasone/ Bortezomib
- Of all available treatment options, daratumumab containing regimens reported high PFS and ORR across all relevant studies

Conclusions

- Our TLR of the comparative effectiveness analysis in RRMM, suggests that mAB + IMiD triplet regimen has better effectiveness than IMiD doublet, followed by mABs or IMiDs or PIs
- Daratumumab –containing triplet therapies, specifically DRd and DVd were the most effective therapies for RRMM

Limitations

- This targeted literature review relies on a relatively limited number of databases for the identification of potentially eligible studies
- There is variation in the inclusion and exclusion criteria across all analyzed studies, therefore any assessment made during the review must be received with caution
- A substantial number of published reviews did not use random effects meta-analysis models; thus, summary estimates may not be generalizable to future studies

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