A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis

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Abstract

A systematic review and network meta-analysis were conducted to compare the clinical efficacy of immunomodulatory drug-containing regimens in patients with relapsed or refractory multiple myeloma. Daratumumab plus lenalidomide and dexamethasone had a significant advantage in improving progression-free survival of patients compared with other immunomodulatory drug-containing regimens.

Background: Previous network meta-analyses combined studies of immunomodulatory drug (IMiD)—containing and IMiD-free regimens, despite a lack of head-to-head randomized controlled trials to robustly link them. However, patients with relapsed or refractory multiple myeloma (RRMM) treated with IMiD-containing regimens differ from those treated with IMiD-free regimens, especially relating to treatment history, which is an important treatment-effect modifier requiring clinical consideration when evaluating the most appropriate subsequent treatment options. A need exists to separately assess the efficacy of treatment regimens for patients who are suitable candidates for IMiD-containing and IMiD-free regimens. The presented analyses will enable clinicians to assess the best regimens to use in patients suitable for IMiD-containing regimens. **Materials and Methods:** We used a Bayesian network meta-analysis to compare IMiD-containing regimens in patients with RRMM. Additionally, subgroup analyses were conducted stratified by previous therapy line, previous bortezomib therapy, and previous lenalidomide therapy. **Results:** The results indicated that triplet combinations are more effective than doublet combinations. Of the triplet combinations, daratumumab, lenalidomide, dexamethasone (DRd) was significantly better in improving progression-free survival in patients with RRMM than were other IMiD-containing regimens (lenalidomide, dexamethasone [Rd]: hazard ratio [HR], 0.37; carfilzomib, Rd: HR, 0.54; elotuzumab, Rd: HR, 0.54; ixazomib, Rd: HR, 0.50). Similar trends were observed for overall survival and overall response. DRd showed the greatest probability of being the best treatment for all clinical efficacy outcomes. The subgroup analyses results were consistent with the base-case results. **Conclusion:** In patients with RRMM who are suitable for an IMiD-containing regimen, DRd showed clear advantages in survival and response outcomes compared with other IMiD-containing regimens.

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Introduction

Multiple myeloma (MM) is an incurable, debilitating disease that accounts for 1% of deaths across all age groups.[1] Because most patients with MM will relapse or develop disease that does not respond to therapy, relapsed or refractory MM (RRMM) also constitutes a major health burden, with an unmet need regarding progressive disease symptoms and treatment-related complications.

Clinicians consider a number of factors before assigning RRMM patients to a specific treatment regimen, including the patient's previous drug exposure and regimen-related toxicity.[2] Previous studies of RRMM have reported that therapeutic outcomes correlate with both the nature and the number of treatment lines to which patients have previously been exposed. For example, Kumar et al[3] found that outcomes deteriorate once a patient's disease has become refractory to previous treatments. These findings suggest that characteristics of previous therapy are important treatment-effect modifiers to consider when evaluating the most suitable regimens for patients with RRMM.

If a patient was previously treated with proteasome inhibitors and their disease continues to progress, current clinical practice suggests a switch in drug class to immunomodulatory drug (IMiD)-containing regimens.[4] New drugs, such as carfilzomib, elotuzumab, ixazomib, and daratumumab, have recently been developed to use in combination with lenalidomide plus dexamethasone (Rd) for treatment of patients with RRMM. To best serve patients' interests in this and other settings in which such a regimen is a suitable choice, clinicians require an evidence-based understanding of how the various Rd treatment options compare with respect to the treatment response and effects on survival.

Previous network meta-analyses (NMAs) combined studies of IMiD-containing and IMiD-free regimens, despite a lack of head-to-head randomized controlled trials (RCTs) to robustly link them.[5-7] This approach could have introduced a potential for bias, because it assumes that all treatment choices for RRMM are equally applicable, regardless of the patient's treatment history and other factors that determine the appropriateness of a particular option. Analyses of such combined networks also require further assumptions to link evidence networks that differ fundamentally with regard to their patient populations and the clinical questions investigated. Given the resulting uncertainty surrounding the findings of NMAs to date, a current unmet need exists with regard to deciding among the IMiD-based regimens for patients for whom such a treatment is appropriate. The objective of the present study was to use an NMA to compare IMiD-based combination regimens for patients with RRMM.

Materials and Methods

Systematic Literature Review

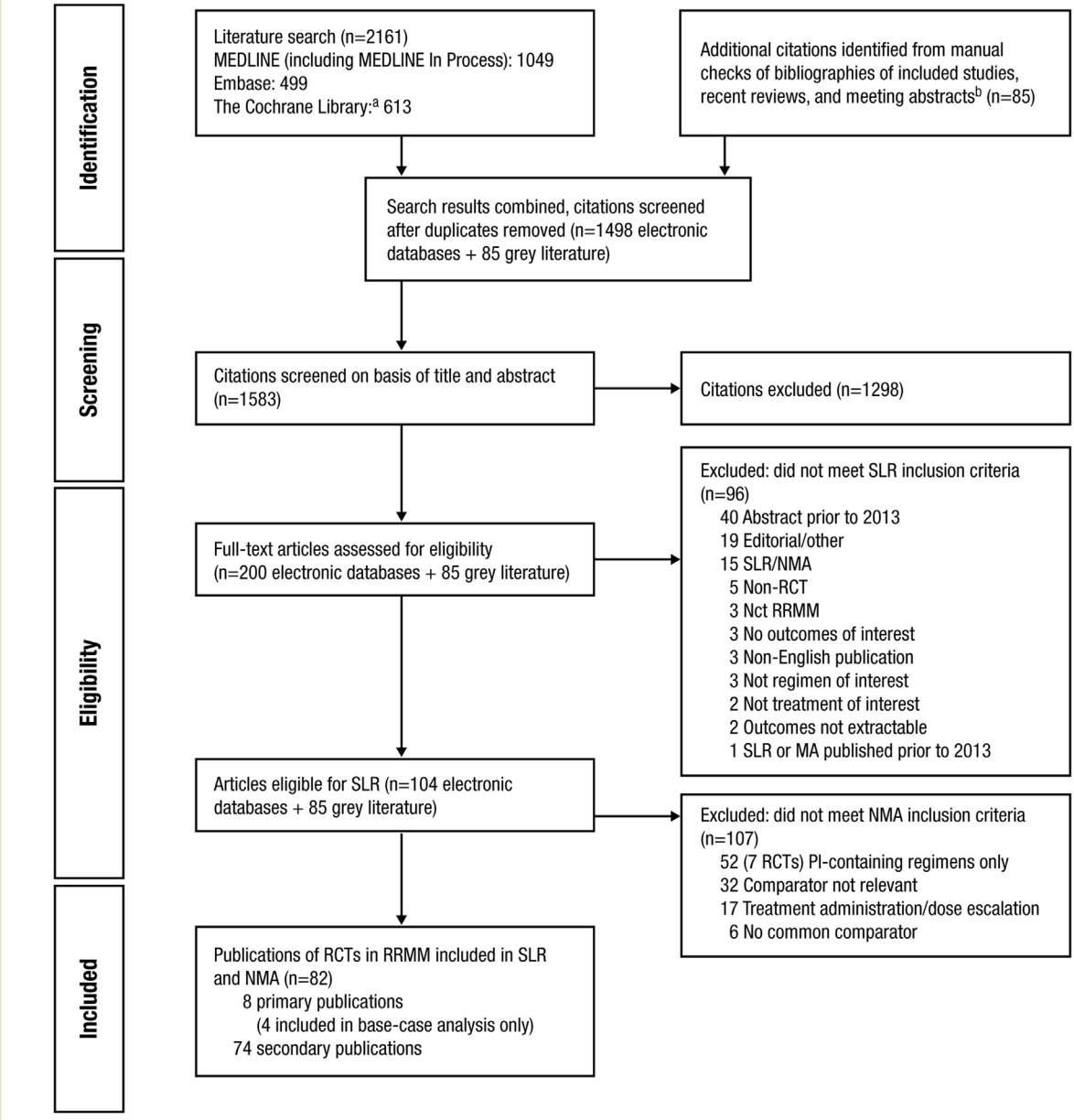
A systematic literature review (SLR) was conducted to identify RCTs reporting efficacy outcome data for patients with RRMM. Indexed databases were searched to identify studies reported in English from January 1, 1995 to November 3, 2016. The strategies used in the database searches are provided in the Supplemental Tables (available in the online version). In addition, the proceedings from key conferences from January 2013 to November 2016 were reviewed for relevant meeting abstracts that met the eligibility criteria. The references of the SLRs and meta-analyses identified by the search were manually reviewed for any additional relevant studies that were not identified by the searches. Also, documents from the European Medicines Agency and US Food and Drug Administration were checked for any missing data. The SLR adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines[8] and followed the study protocol developed for the present review.

Table 1 PICOS-T Criteria

Variable	Inclusion Criteria	Exclusion Criteria
SLR criteria		
Population	Adult patients with primary diagnosis of RRMM	Patients without primary diagnosis of RRMM
Intervention/comparators	Studies that compared ≥ 2 licensed treatments that were considered relevant comparators in RRMM, including treatments undergoing or being prepared for regulatory body prelicensing review, already licensed, or routinely used	Studies examining efficacy of IFN-α, conditioning chemotherapy to prepare for stem cell transplantation, maintenance therapy, preferred sequence of treatments, and treatments aimed at managing complications of RRMM
Outcomes	PFS, OS, ORR	Data that cannot be extracted
Study design	Phase II or III RCTs	Single-arm trials and noninterventional studies
Time point	Publications indexed in literature databases since 1995 and material from key conferences from 2013 to 2016	Publications indexed in or before 1994; conference abstracts presented in or before 2012
Criteria added to NMA		
Population	Trials with similar study design (ie, patients with relapsed and/or refractory disease randomized to treatment)	Studies of patients who had responded to initial treatment in a prerandomized phase and were then randomized to treatment
Intervention/comparators	Studies that compared ≥ 2 active IMiD-containing regimens and studies with a common comparator in the network	Studies that only compared different regimens of the same active drug or compared dose escalations of the same drug; studies assessing treatments that could not be indirectly compared with treatments in the network; and studies that did not have a comparator common to other studies included in the network
Outcomes	PFS and OS: HRs or KM graphs; ORR: number/percentage of patients achieving a response	Data required for NMA not available

Abbreviations: HR = hazard ratio; IFN-α = interferon-α; IMiD = immunomodulatory drug; KM = Kaplan-Meier; NMA = network meta-analysis; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PICOS-T = population, interventions, comparators, outcomes, study design, and time point; RCT = randomized controlled trial; RRMM = relapsed or refractory multiple myeloma; SLR = systematic literature review.

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart for Study Selection and Review. [a]The Cochrane Library includes Cochrane reviews, a database of abstracts of reviews of effects, the Cochrane Central Register of Controlled Trials, and the National Health Services Economic Evaluation Database. [b]Conference searches included American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, International Myeloma Working Group, and International Society for Pharmacoeconomics and Outcomes Research

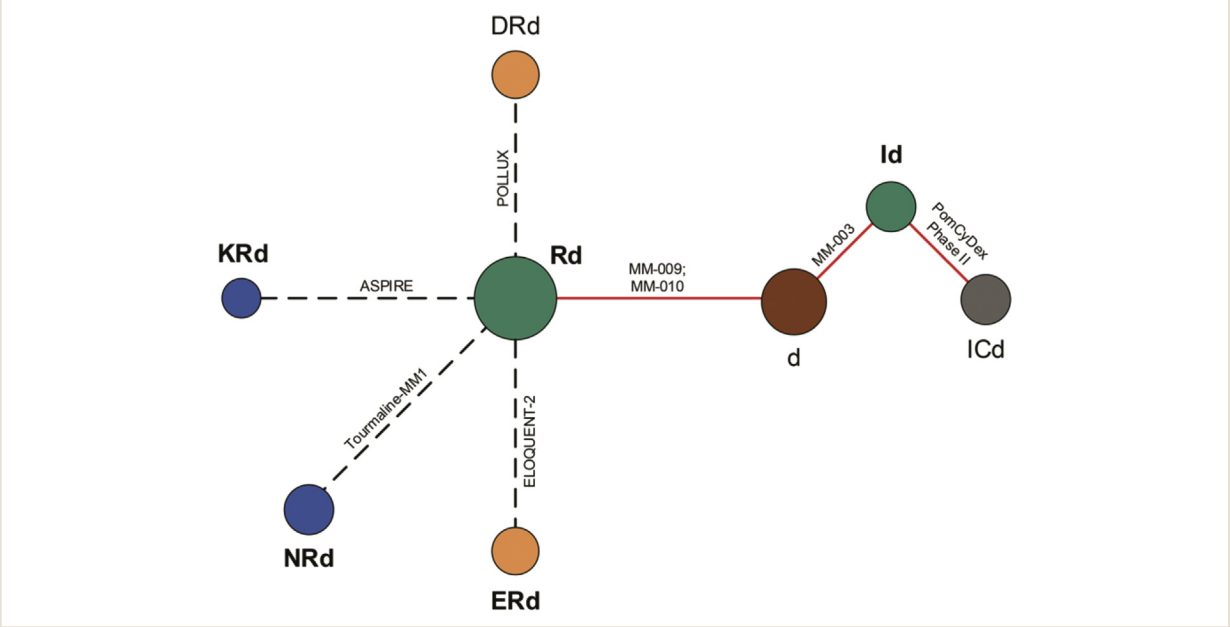


Abbreviations: MA = meta-analysis; NMA = network meta-analysis; PI = proteasome inhibitor; RCT = randomized controlled trial; RRMM = relapsed or refractory multiple myeloma; SLR = systematic literature review.

Eligibility Criteria. Studies were selected for inclusion in the present review using the population, interventions, comparators, outcomes, study design, and time point (PICOS-T) criteria outlined in Table 1.

Study Selection. All abstracts and full-text articles were screened by 2 independent investigators, and any conflicting screening decisions were resolved by a third investigator. Articles reporting studies meeting the inclusion criteria and none of the exclusion criteria were

Figure 2 Network Diagram. Brown indicates glucocorticoid alone; blue, proteasome inhibitor alone or combined; green, immunomodulators with or without a glucocorticoid; gray, immunomodulators and glucocorticoid with or without an alkylating agent; orange, monoclonal antibody alone or combined; bold text, treatments licensed by the US Food and Drug Administration and/or European Medicines Agency; regular text, unlicensed treatments; black dashed lines, trials with incomplete or interim results; and solid red lines, trials removed from the base-case network meta-analysis



Abbreviations: d = dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; ICd = pomalidomide, cyclophosphamide, dexamethasone; Id = pomalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone.

included in the SLR, with additional criteria used to define and explore whether the studies could be included in the NMA (Table 1).

Data Collection and Quality Assessment. The study characteristics, patient characteristics, treatment details, and efficacy outcomes were extracted by 1 investigator (MR or YX) and validated by a second investigator (MR or YX). Any discrepancies between the 2 investigators were resolved by a third investigator (KF). The following clinical efficacy data were extracted: hazard ratios (HRs), including 95% confidence intervals for progression-free survival (PFS), overall survival (OS), and the proportion of patients with an overall response (overall response rate). When the HRs had not been reported, these data were imputed from the Kaplan-Meier curves for PFS and/or OS presented in the reports.

The quality of the included full-text studies was assessed using the checklist described in the Centre for Reviews and Dissemination guidance document,[9] with each trial assigned an overall quality rating of high, moderate, or low.

Geometry of the Network. RCTs were included in the network only if they had $\geq$ 2 arms that allowed the formation of a network of IMiD-containing regimens, regardless of drug class or mechanism of action (additional inclusion criteria for the studies included in the NMA are listed in Table 1). RCTs comparing different administration routes, doses, or schedules of a specific regimen were excluded.

An assessment was undertaken to determine the feasibility of conducting an NMA of the efficacy outcomes in the identified RCTs. The feasibility assessment included a comparison of patient population similarity (eg, number of previous lines of therapy and previous treatment criteria) and intervention similarity (eg, treatment dosing and administration). This included eliciting views from key opinion leaders and clinical experts from North and South America and Europe using an advisory board meeting on the patient eligibility criteria across RCTs.

Analysis

The NMA combined direct and indirect estimates of the relative treatment effect in a single analysis. Specifically, all analyses were conducted within a Bayesian framework using OpenBUGS, version 3.2.2 software.[10] The NMA involved a 50,000 run-in iteration phase for parameter estimation. Because of the limitations of the network (ie, the presence of only 1 study per treatment comparison), only fixed-effects models were fitted. Because only 1 study was present per comparison, it was not possible to test for statistical heterogeneity or inconsistency in effects. To provide hierarchy probabilities, the analysis used ranking probabilities and surface under the cumulative ranking curve, which provides the cumulative ranking (the probability of being that rank or higher) for each treatment assessed.

The output of the NMA included the following:

- Point estimates: HRs for OS and PFS, and odds ratios (ORs) for overall response, with credible intervals (CrIs)
- Bayesian pairwise probability for the treatment of interest being more effective than the other comparators assessed in the

Table 2 Study and Patient Characteristics From RCTs Included in NMA

Trial	Intervention (Dosage); Patients, n	Outcomes	Median (Range) LOT at Baseline	Previous Treatment Criteria	Previous Treatment Exposure at Baseline	Relapsed/Refractory Status
Base-Case Analyses						
ASPIRE[15]	Carfilzomib (20-27 mg/m^2) + lenalidomide (25 mg) + dexamethasone (40 mg); 396	PFS: HR, KM; OS: HR, KM; ORR: sCR, CR, and VGPR	2 (1-3)	Excluding bortezomib or lenalidomide + dexamethasone refractory; previous carfilzomib	Bortezomib, 66%; lenalidomide, 20%; IMiD, 59%; bortezomib + IMiD, 37%	Bortezomib nonresponsive, 15%; lenalidomide refractory, 7%; IMiD refractory, 22%; bortezomib nonresponsive and IMiD refractory, 6%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 396		2 (1-3)		Bortezomib: 66% lenalidomide: 20% IMiD: 58% bortezomib + IMiD: 35%	Bortezomib nonresponsive, 15%; lenalidomide refractory, 7%; IMiD refractory, 22%; bortezomib nonresponsive and IMiD refractory, 7%
ELOQUENT-2[17]	Elotuzumab (10 mg/kg) + lenalidomide (25 mg) + dexamethasone (40 mg); 321	PFS: HR, KM; OS: HR[a,b]; ORR: sCR, CR, VGPR, and PR	2 (1-4)	Including lenalidomide $\leq$ 10% of study sample; excluding lenalidomide refractory	Bortezomib, 68%; thalidomide, 48%; lenalidomide, 5%	Bortezomib refractory, 22%; thalidomide refractory, 9%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 325		2 (1-4)		Bortezomib, 71%; thalidomide, 48%; lenalidomide, 6%	Bortezomib refractory, 21% thalidomide refractory: 11%
POLLUX[16]	Daratumumab (16 mg/kg) + lenalidomide (25 mg) + dexamethasone (40 mg); 286	PFS: HR[a]; OS: HR[a]; ORR: sCR, CR, VGPR, and PR	1 (1-11)	Excluding allogeneic SCT; lenalidomide refractory	PI, 86%; bortezomib, 84%; carfilzomib, 2%; IMiD, 55%; lenalidomide, 18%; thalidomide, 43%	PI refractory, 16%; IMiD refractory, 4%; PI + IMiD refractory, 5%; bortezomib refractory, 21%; carfilzomib refractory; 1%; thalidomide refractory, 9%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 283		1 (1-8)		PI, 86%; bortezomib, 84%; carfilzomib, 2%; IMiD, 55%; lenalidomide, 18%; thalidomide, 44%	PI refractory, 20%; IMiD refractory, 4%; PI + IMiD refractory, 2%; bortezomib refractory, 21%; carfilzomib refractory, 1%; pomalidomide refractory, 0.7%; thalidomide refractory, 6%
Tourmaline-MM1[18]	Ixazomib (4 mg) + lenalidomide (25 mg) + dexamethasone (40 mg); 360	PFS: HR, KM[c]; OS: [a,d]; ORR: sCR, CR, VGPR, and PR	Mean, 1.5 (1-3)	Including thalidomide refractory; excluding PI, lenalidomide refractory	Bortezomib, 69%; carfilzomib, < 1%; lenalidomide, 12%; thalidomide, 44%	PI refractory, 1%; IMiD refractory, 21%
	Lenalidomide (25 mg) + dexamethasone (40 mg); 362		Mean, 1.5 (1-3)		Bortezomib, 69%; carfilzomib, 1%; lenalidomide, 12%; thalidomide, 47%	PI refractory, 2%; IMiD refractory, 25%
Sensitivity Analyses						
MM-003[13]	Pomalidomide (4 mg) + dexamethasone (40 mg); 302	PFS: HR, KM; OS: HR, KM; ORR: [e]	5 (2-17)	Including $\geq$ 2 cycles of lenalidomide and/or bortezomib; previous alkylator; excluding thalidomide, lenalidomide, dexamethasone hypersensitivity; high-dose dexamethasone resistance	ASCT, 69%-71%; bortezomib, 100%; dexamethasone, 98%-99%; lenalidomide, 100%; thalidomide, 57%-61%	Bortezomib refractory, 79%; lenalidomide refractory, 92%-95%; bortezomib and lenalidomide refractory, 74%-75%
	Dexamethasone (40 mg); 153					
MM-009[12,14]	Lenalidomide (25 mg) + dexamethasone (40 mg); 177	PFS: [f]; OS: HR, KM; ORR: [e]	1 previous LOT, 38%; $\geq$ 2 previous LOTs, 62%	NR	Bortezomib, 11%; SCT, 62%; thalidomide, 44%	NR
	Dexamethasone (40 mg); 176					

Table 2 Continued

Trial	Intervention (Dosage); Patients, n	Outcomes	Median (Range) LOT at Baseline	Previous Treatment Criteria	Previous Treatment Exposure at Baseline	Relapsed/Refractory Status
MM-010[12,14]	Lenalidomide (25 mg) + dexamethasone (40 mg); 176	PFS: [f]; OS: HR, KM; ORR: [e]	1 previous LOT, 32%; ≥ 2 previous LOTs, 68%	Excluding thalidomide or dexamethasone intolerance	Bortezomib, 4%; SCT, 55%; thalidomide, 34%	NR
	Dexamethasone (40 mg); 175					
PomCyDex phase II[11]	Pomalidomide (4 mg) + CP (400 mg) + dexamethasone (40 mg); 34	PFS: HR, KM; OS: HR, KM; ORR: [e]	4 (2-12)	Including previous IMiDs and refractory to lenalidomide	HDM/ASCT, 75%-82%; previous alkylating agent, 89%-94%	Bortezomib refractory, 71%-78%; carfilzomib refractory, 38%-44%; lenalidomide refractory, 100%
	Pomalidomide (4 mg) + dexamethasone (40 mg); 36					

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; CP = cyclophosphamide; HDM = high-dose melphalan; HR = hazard ratio; IMiD = immunomodulatory drug; KM = Kaplan-Meier; LOT = line of therapy; NMA = network meta-analysis; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; PR = partial response; RCT = randomized controlled trial; sCR = stringent complete response; SCT = stem cell transplantation; VGPR = very good partial response.
[a]Data not yet mature.
[b]Can be calculated/derived from KM curves.
[c]Events reported in the KM curve were used to derive the HR.
[d]Outcome explored in study but relevant data required for analysis not provided.
[e]Outcome not explored in sensitivity analyses.
[f]Outcome not explored in study; time to progression reported and used in analysis.

network (it is possible that any value > 99.951% would be represented as 100% probability)
- The probability that each treatment ranked in a certain order within the network for each outcome provided; rank probabilities were determined by the location, spread, and overlap of the posterior distributions of the relative treatment effects

When interpreting the analysis findings, a 95% CrI that does not cross the value of 1.00 (for an HR and OR) indicates a treatment can be considered more effective than its comparator (equivalent to a Bayesian pairwise probability of $P \geq 97.5\%$).

Subgroup Analyses

Subgroup analyses for PFS were conducted to confirm the robustness of the results from the base-case analysis by exploring the effect of the clinically meaningful treatment-effect modifiers. The specific analyses included stratification by previous line of therapy (LOT; 1 previous LOT or ≥ 2 previous LOTs), patients with and without previous bortezomib exposure, and patients with and without previous lenalidomide exposure.

Results

Study Selection

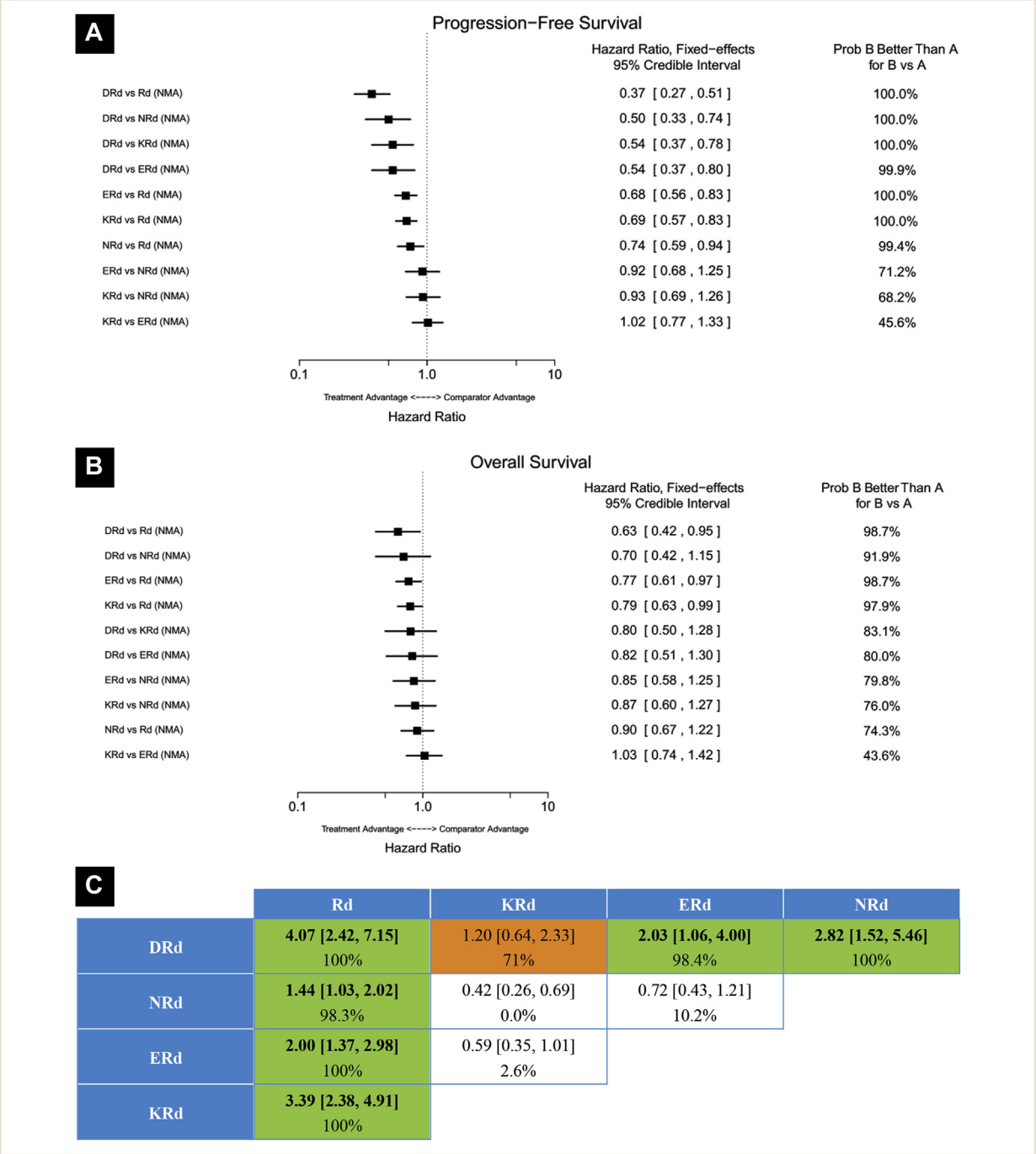
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of RCT selection is shown in Figure 1. The indexed database searches yielded 2161 citations, and an additional 85 meeting abstracts were identified. After removal of the duplicate reports indexed in > 1 database, 1583 unique abstracts were screened, of which 285 full-text articles and conference proceedings were considered for full review. Of these, 203 were excluded: 96 did not meet the SLR inclusion criteria and 107 did not meet the NMA criteria. The remaining 82 studies reported on 8 RCTs, which were included in the NMA. Further details about the RCTs excluded because of the NMA criteria are included in the Supplemental Tables (available in the online version).

Summary of Network Geometry

Eight identified studies were included in the network (Figure 2). However, 4 of these trials[11-14] were excluded from the subsequent base-case analyses because their patient populations differed substantially from those of the other studies (eg, different treatment history; ie, ≥ 2 previous LOTs) or had included an irrelevant comparator not routinely used in clinical practice (eg, dexamethasone monotherapy). However, these trials were included in the sensitivity analyses. The results from the base-case analyses are included in the present report; the results from the sensitivity analyses are included in the Supplemental Tables (available in the online version).

The base-case network included 4 trials evaluating carfilzomib plus Rd (KRd),[15] daratumumab plus Rd (DRd),[16] elotuzumab plus Rd (ERd),[17] and ixazomib plus Rd (NRd),[18] with Rd being the reference treatment. All trials in the base-case analysis had included patients who had received ≥ 1 previous LOT; 3 of the studies had included only patients who had received ≤ 3 previous LOTs. All base-case trials had the same dosing and administration of Rd. Finally, all base-case trials had excluded patients with disease refractory to lenalidomide.

Figure 3 (A) Progression-Free Survival, (B) Overall Survival, and (C) Overall Response Rate With Immunomodulatory Drug (IMiD)-containing Regimens. Hazard ratios for a given treatment compared with another IMiD-containing regimen presented for (A) progression-free survival and (B) overall survival. (C) Comparisons for each treatment versus each of the other treatments; specifically, every combination of A versus B, where A is the treatment at the beginning of each row and B is the treatment at the top of each column. Odds ratios (ORs) > 1 indicate a numerical advantage for the treatment at the end of the row. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. The probability (prob) that the OR for A versus B is < 1 (ie, that regimen A is more Efficacious) is presented under the OR. Interventions with a significant advantage are shown in bold with green shading; interventions with a trend toward improving the overall response (eg, OR > 1.20 but credible intervals crossing 1.0) are shaded in orange. It is possible that 100% probability will appear to represent any value > 99.951%



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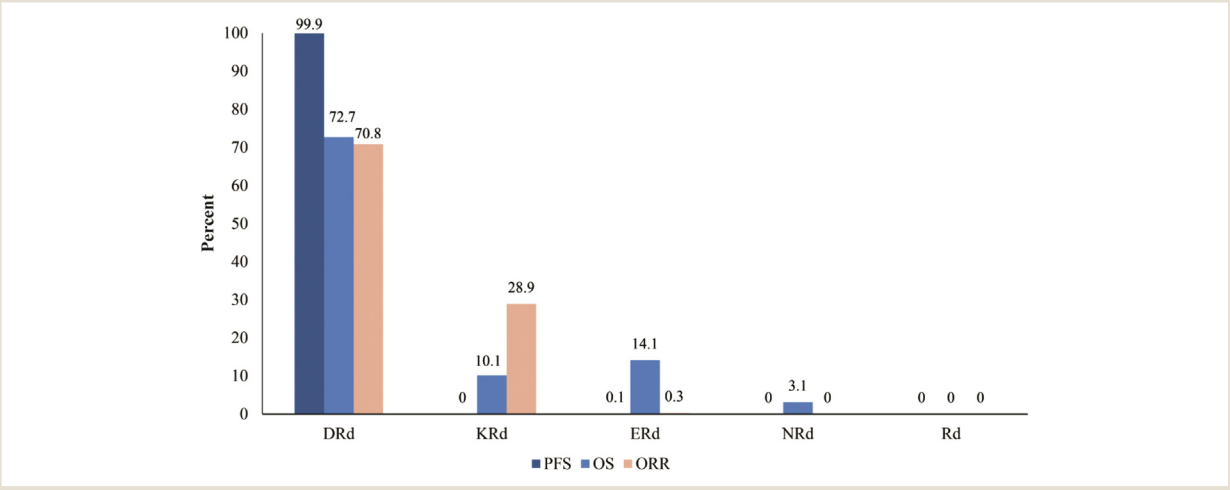
	Rd	KRd	ERd	NRd
DRd	**4.07 [2.42, 7.15]** 100%	1.20 [0.64, 2.33] 71%	**2.03 [1.06, 4.00]** 98.4%	**2.82 [1.52, 5.46]** 100%
NRd	**1.44 [1.03, 2.02]** 98.3%	0.42 [0.26, 0.69] 0.0%	0.72 [0.43, 1.21] 10.2%	
ERd	**2.00 [1.37, 2.98]** 100%	0.59 [0.35, 1.01] 2.6%		
KRd	**3.39 [2.38, 4.91]** 100%			

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone.

Figure 4 Probability of Being the Best Treatment Across Survival and Response Outcomes



Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide, dexamethasone.

The sensitivity analyses included 4 trials evaluating dexamethasone,[12,14] pomalidomide plus dexamethasone,[13] and pomalidomide plus cyclophosphamide and dexamethasone.[11] Two of these trials examined patients who had received ≥ 2 previous LOTs and, accordingly, were not included in the base-case analysis. The remaining 2 trials in the sensitivity analysis involved patients with ≥ 1 LOT but were not a part of the base-case analysis owing the inclusion of an irrelevant comparator (dexamethasone monotherapy) that was no longer needed to form a bridge between DRd and pomalidomide plus dexamethasone once the other 2 trials had been excluded. In addition, 2 of the trials in the sensitivity analyses required participants to have disease refractory to lenalidomide[11,13] or bortezomib,[13] resulting in a large proportion of patients with disease refractory to lenalidomide and bortezomib compared with the rest of the studies in the base-case analysis. Finally, 2 studies comparing dexamethasone to Rd[12,14] presented with heterogeneity related to the patients' International Staging System (ISS) stage and also allowed for crossover between treatment arms, which could have affected the OS estimate. A summary of the patient populations is presented in Table 2.

The primary reports of the trials included in the base-case analysis were of moderate quality. The quality assessment information is available in the Supplemental Tables (available in the online version). The individual trial data from the base-case RCTs input into the NMA are also reported in the Supplemental Tables (available in the online version).

Synthesis of Results

An analysis using a fixed-effects model showed that DRd had a significant advantage in prolonging PFS (ie, an HR < 0.80 with CrIs not crossing 1.0) for patients with RRMM compared with other IMiD-containing regimens (Figure 3A). The probability of DRd providing better results than its comparator ranged from 99.9% (compared with ERd) to 100% (compared with Rd, KRd, and NRd). All other comparators (ERd, KRd, and NRd) demonstrated a significant advantage in prolonging PFS compared with Rd. The results were inconclusive for the comparison of ERd to KRd; however, a trend was found for NRd to reduce PFS compared with KRd and ERd.

A fixed-effects analysis demonstrated that Rd was significantly less effective at extending OS compared with KRd, ERd, and DRd (Figure 3B). NRd was also less effective in improving OS compared with KRd and ERd. A trend was found for DRd to increase OS compared with all comparators.

Patients with RRMM who had received DRd were more likely to achieve an overall response (ie, demonstrated a statistical advantage, with an OR > 1.20 and CrIs not crossing 1.0) compared with those treated with Rd, ERd, and NRd. A trend was seen for DRd to improve the overall response compared with KRd (Figure 3C). Compared with ERd and NRd, the patients treated with KRd were more likely to achieve an overall response, although this advantage was not significant.

DRd had the greatest probability of being the best treatment across all clinical efficacy outcomes compared with the other IMiD-containing regimens (Figure 4). Rd had zero probability of being the best treatment for any outcome.

Results of Subgroup Analyses

The results across all subgroup analyses were generally consistent with the base-case analysis for PFS. For the patients who had received 1 previous LOT, the likelihood of prolonging PFS worsened for NRd compared with Rd, and the HRs improved in favor of DRd compared with ERd and NRd (Figure 5A). No significant HR changes were seen for patients who had received ≥ 2 previous LOTs. The HRs were improved in favor of DRd compared with Rd, KRd, and ERd for patients with no previous bortezomib therapy (Figure 5B). The HRs remained similar to the base-case analyses across all comparators for patients who had received previous bortezomib therapy and for all patients, regardless of whether they had previously received lenalidomide (Figure 5C). Detailed

Figure 5 Subgroup Analyses: Progression-Free Survival (PFS) of Patients With 1 Versus ≥ 2 Previous Lines of Therapy (LOTs; A), With and Without Previous Bortezomib Exposure (B), and With and Without Previous Lenalidomide Exposure (C). Tabular data represent comparisons for each treatment versus each of the other treatments. To obtain hazard ratios (HRs) for comparisons in the opposite direction, reciprocals should be taken. The probability that the HR is < 1 is presented under the HR. (A) For 1 previous LOT, HRs < 1 indicate a numerical advantage for the treatment at the top of the column. For ≥ 2 previous LOTs, HRs < 1 indicate a numerical advantage for the treatment at the beginning of the row. (B) For no previous bortezomib, HRs < 1 indicate a numerical Advantage for the treatment at the top of the column. For previous bortezomib, HRs < 1 indicate a numerical advantage for the treatment at the beginning of the row. (C) For no previous lenalidomide, HRs < 1 indicate a numerical advantage for the treatment at the top of the column. For previous lenalidomide, HRs < 1 indicate a numerical advantage for the treatment at the beginning of the row. It is possible that 100% probability will appear to represent any value > 99.951%. Interventions with a significant advantage are shown in bold with green shading; interventions with a trend toward improving PFS (eg, HR < 0.80 but credible intervals crossing 1.0) are shaded in orange

A

	Two or more prior LOT		
DRd	--	**0.58 [0.35 0.97]** 98.1%	**0.55 [0.34, 0.89]** 99.2%	**0.38 [0.25, 0.58]** 100%
0.43 [0.25, 0.74] 99.9%	**NRd**	--	--	--
0.48 [0.29, 0.80] 99.7%	1.11 [0.71, 1.72] 32.6%	**ERd**	0.95 [0.65, 1.37] 61.6%	**0.65 [0.49, 0.87]** 99.8%
0.52 [0.31, 0.86] 99.4%	1.20 [0.78, 1.84] 20.8%	1.08 [0.72, 1.61] 35.1%	**KRd**	**0.69 [0.54, 0.87]** 99.9%
0.36 [0.23, 0.55] 100%	0.83 [0.59, 1.16] 86.3%	0.75 [0.56, 1.00] 97.4%	**0.69 [0.53, 0.91]** 99.5%	**Rd**
One prior LOT				

B

	Prior bortezomib		
DRd	**0.58 [0.39, 0.85]** 99.7%	**0.56 [0.38, 0.83]** 99.8%	**0.39 [0.28, 0.54]** 100%
0.30 [0.12, 0.79] 99.3%	**ERd**	0.97 [0.71, 1.33] 57.1%	**0.68 [0.55, 0.85]** 100%
0.35 [0.13, 0.88] 98.7%	1.14 [0.69, 1.88] 30.5%	**KRd**	**0.70 [0.56, 0.88]** 99.9%
0.25 [0.10, 0.61] 99.9%	0.83 [0.57, 1.20] 84.1%	0.73 [0.52, 1.02] 96.7%	**Rd**
No prior bortezomib			

C

	Prior lenalidomide		
DRd	0.72 [0.22, 2.31] 70.9%	0.53 [0.22, 1.31] 91.4%	**0.42 [0.19, 0.94]** 98.2%
0.52 [0.35, 0.76] 100%	**ERd**	0.74 [0.28, 1.94] 73.2%	0.59 [0.25, 1.41] 88.5%
0.52 [0.35, 0.77] 100%	1.01 [0.75, 1.38] 46.2%	**KRd**	0.80 [0.52, 1.22] 84.7%
0.36 [0.26, 0.50] 100%	**0.70 [0.57, 0.87]** 100%	**0.69 [0.55, 0.86]** 100%	**Rd**
No prior lenalidomide			

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone.

results from the sensitivity analyses are presented in the Supplemental Tables (available in the online version).

Discussion

Rd-based regimens are 1 of the preferred treatment options for those RRMM patients for whom IMiD treatment is suitable.[19] However, the selection between the available IMiD-containing options has been complicated by the lack of direct comparative evidence and that existing NMAs have not sufficiently acknowledged the important clinical differences among patients with different previous treatment exposures. Thus, the present analysis has offered a more robust approach to estimating the relative effects of these IMiD-containing interventions.

The key findings of the analyses include the superiority of DRd compared with other IMiD-containing regimens for efficacy in RRMM. These results provide an important context for the POLLUX study,[16] which showed that the addition of daratumumab to Rd significantly improved PFS and the overall response rate and demonstrated a trend toward improved OS, compared with Rd alone, in patients with RRMM who had received $\geq$ 1 previous therapy. The results we have presented are also aligned with recent updates to the National Comprehensive Cancer Network guidelines, which have recognized DRd as a category 1 treatment option for previously treated patients with MM,[19] and European Society for Medical Oncology guidelines, which state that daratumumab triplet combination therapies can be considered the standard of care, once licensed.[20] The findings could also help guide the choices that payers and clinicians make between treatments for second or later LOTs in the treatment of patients with RRMM.

The patients enrolled in the trials presented in the Rd network in our analysis had received $\geq$ 1 previous therapy, with a large proportion of these patients having been previously exposed to bortezomib and a smaller subset of patients with disease potentially refractory to bortezomib. In contrast, the trials examining the effect of IMiD-free regimens generally excluded patients with previous bortezomib exposure, with some trials further excluding patients known to have bortezomib-refractory disease. It is clear that the patients in whom Rd regimens were evaluated differed fundamentally from those in whom IMiD-free regimens were evaluated in terms of previous drug exposures. Consequently, the trial data for these patients should be assessed separately in any NMA of RRMM treatments. Previous NMAs have combined IMiD-containing and IMiD-free regimens in 1 network for all RRMM patients, with the assumption that the patient populations were comparable across all treatment combinations. However, key differences were present in the treatment exposure across the studies that could have biased the results of these previous analyses. Further assumptions regarding the equal efficacy of the comparator treatments were also made.[5,6] Despite this, the results of the IMiD-containing network in the present analysis are consistent with previous NMAs in RRMM,[5-7] which have also found DRd to be the best combination of the currently available treatment options. Thus, regardless of the different NMA approaches taken between our analysis and previous reports, daratumumab combined with Rd has consistently been found to be the most clinically efficacious IMiD-containing regimen.

Other important strengths of these analyses should be considered in the context of other reported NMAs. By separating the Rd regimens into a single network for patients who had received $\geq$ 1 previous LOT and conducting relevant subgroup analyses, these analyses provided greater opportunities than the other reported NMAs to eliminate crucial imbalances in treatment-effect modifiers related to previous therapies. In addition, our analysis was limited only to RCT evidence. Given the lack of a published RCT providing a head-to-head comparison of IMiD-containing and IMiD-free regimens, previous NMAs required the use of alternate types of evidence to connect the networks. Analyzing these networks separately provided a more robust approach and holds more strongly to the transitivity and consistency assumptions necessary for the conduct of a valid and reliable NMA. Furthermore, previous NMAs were based on an interim analysis of data from the DRd trials. The present analyses used data from the most recent data-cut of the POLLUX trial. Another advantage of these analyses was the exclusion from the base-case analysis of studies with patient populations that differed substantially from those of the included studies (eg, in terms of treatment exposure or previous LOT). This allowed for the exploration of key potential treatment-effect modifiers in sensitivity analyses, the results of which were then used to validate the results of the base-case analysis.

The present NMA had some limitations. Because each treatment comparison was informed by a single study only (similar to previous NMAs), additional analyses controlling for differences in baseline characteristics using meta-regression techniques were not feasible. Second, the inclusion of PI-refractory patients in the KRd[15] and NRd[18] trials that were included in the base-case network may have impacted the results in the triplet arms of these studies. Third, OS can be affected by the subsequent treatment patients receive after disease progression; however, such data are not available for an NMA. Thus, the potential OS benefit could not be evaluated while accounting for such confounding factors. In addition, these analyses did not consider safety outcomes, focusing instead on the relative efficacy of the licensed treatments as a key determinant of the therapeutic choice for RRMM.

Conclusion

The present study has provided a thorough analysis of the comparative efficacy of IMiD-containing regimens known to improve response and reduce mortality in patients with RRMM. Specifically, the reported NMA results have demonstrated the value of daratumumab as a treatment option combined with Rd in this setting, with efficacy advantages compared with other relevant IMID-containing treatments. In addition, the results from the subgroup analyses were largely consistent with those from the base-case analyses. To the best of our knowledge, the present review includes the most comprehensive evidence base available; therefore, the results can be considered generalizable to the broader RRMM population for whom an IMiD-containing regimen is suitable. These findings provide policymakers and clinicians with important information regarding the comparative effectiveness of different IMiD-containing treatment regimens in patients with RRMM who have received $\geq$ 1 previous LOT. Finally, this analysis compared only regimens that have been investigated in clinical trials; therefore, the results are less informative in situations

in which such regimens cannot be used due to prior treatment exposures, treatment resistance, or reimbursement issues.

Clinical Practice Points

- Previous work has shown a correlation between the number and type of previous treatment exposure and treatment outcomes; thus, clinicians must consider a number of factors before prescribing a specific treatment regimen for patients with RRMM.
- Depending on the treatment history and the response to proteasome inhibitors, patients with RRMM might be suitable candidates for treatment with IMiD-containing regimens.
- The present NMA considered patients suitable for Rd-based regimens.
- Triplet combinations provided a survival and efficacy advantage compared with doublet regimens.
- Daratumumab, combined with lenalidomide and dexamethasone, provides patients with advantages in survival and response outcomes compared with other IMiD-containing regimens.
- These findings align with the recommendation of National Comprehensive Cancer Network and European Society for Medical Oncology guidelines for daratumumab-containing regimens and could help guide treatment choices for patients with RRMM.

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Supplemental Data

The supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2017.12.011.

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Supplemental Table 1 MEDLINE Search Strategy

Search	Search Criteria	Search Algorithm	Search Yield (March 17, 2016)	Update Search Yield (November 3, 2016)
1	1	("Multiple Myeloma"[MeSH] OR ("multiple"[TIAB] AND myelom*[TIAB]) OR "plasma cell myeloma"[TIAB] OR "Kahler's disease"[TIAB] OR "Plasmacytoma"[MeSH] OR plasmacytom*[TIAB])	49,858	51,424
2	2	((relaps*[TIAB] OR refract*[TIAB] OR recurren*[TIAB] OR "resistant"[TIAB] OR "prior treatment"[TIAB] OR "prior treatments"[TIAB] OR "prior therapy"[TIAB] OR "prior therapies"[TIAB] OR "previously treated"[TIAB] OR "second line"[TIAB] OR "third line"[TIAB] OR "2nd line"[TIAB] OR "3rd line"[TIAB] or "fourth line"[TIAB] OR "4th line"[TIAB]))	1,002,907	1,043,924
3	3	("randomized"[TIAB] OR "randomised"[TIAB] OR "controlled trial"[TIAB] OR "clinical trial"[TIAB] OR "cross over"[tiab] OR "cross-over"[tiab] OR "crossover"[tiab] OR (doubl* AND blind*[TIAB]) OR (singl* AND blind*[TIAB]) OR ("open"[TIAB] AND label*[TIAB]) OR "placebo"[TIAB] OR "Clinical Trial" [Publication Type])	1,038,845	1,078,454
4	1 & 2 & 3		1144	1219
5	4 NOT 5	"Animals"[MeSH] NOT "Humans"[MeSH]	1142	1217
6	5 NOT 6	"letter"[PT] OR "editorial"[PT]	1113	1049[a]
7	6 NOT 7	((review[pt]) NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND "treatment comparison")))	975	

The limits for this search included only items with abstracts; we also limited the search to exclude animal-only studies (search row 5), letters and editorials (search 6), and nonsystematic reviews (search 7).
[a]In the update search, rows 6 and 7 were combined.

Supplemental Table 2 EMBASE Search Strategy

Search	Search Criteria	Search Algorithm	Search Yield (March 17, 2016)	Update Search Yield (November 3, 2016)
1	1	"multiple myeloma"/exp OR ("multiple":ab,ti AND myelom*:ab,ti) OR "plasma cell myeloma":ab,ti OR (kahler*:ab,ti AND "disease":ab,ti) OR "plasmacytoma"/exp OR plasmacytom*:ab,ti	72,703	76,064
2	2	relaps*:ab,ti OR refract*:ab,ti OR recurren*:ab,ti OR "resistant":ab,ti OR "prior treatment":ab,ti OR "prior treatments":ab,ti OR "prior therapy":ab,ti OR "prior therapies":ab,ti OR "previously treated":ab,ti OR "second line":ab,ti OR "third line":ab,ti OR "2nd line":ab,ti OR "3rd line":ab,ti OR "fourth line":ab,ti OR "4th line":ab,ti	1,325,287	1,390,716
3	3	"randomized":ab,ti OR "randomised":ab,ti OR "controlled trial":ab,ti OR "clinical trial":ab,ti OR "cross over":ab,ti OR "crossover":ab,ti OR "cross-over":ab,ti OR (doubl* AND blind*:ab,ti) OR (singl* AND blind*:ab,ti) OR ("open":ab,ti AND label*:ab,ti) OR "placebo":ab,ti	869,396	917,965
4	1 & 2 & 3		1623	1721
5	4 NOT 5	"animal"/exp NOT "human"/exp	1605	1702
6	5 NOT 6	letter:it OR editorial:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim	579	631
7	6 NOT 7	review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND "treatment comparison"))	444	499

The limits for this search included only items with abstracts; we also limited the search to exclude animal-only studies (search 5), letters and editorials and conference abstracts (search 6), and nonsystematic reviews (search 7).

Supplemental Table 3 Cochrane Library Search Strategy

Search	Search Criteria	Search Algorithm	Search Yield (March 17, 2016)	Update Search Yield (November 3, 2016)
1	1	MeSH descriptor: [Multiple Myeloma] OR MeSH descriptor: [Plasmacytoma] OR (("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	2316	3485
2	2	(relaps* or refract* or recurren* or "resistant" or "prior treatment" or "prior treatments" or "prior therapy" or "prior therapies" or "previously treated" or "second line" or "third line" or "2nd line" or "3rd line" or "fourth line" or "4th line"):ti,ab,kw	70,006	72,334
3	1 & 2		612	613

The limits for this search included only items in the Cochrane Reviews (reviews only), other reviews, trials, and economic evaluations; the Cochrane Library Search Strategy included (1) Cochrane reviews (reviews only; ie, not including protocols); (2) database of abstracts of reviews of effects (DARE; this has been an archive database only since 2015); (3) the Cochrane Central Register of Controlled Trials (CENTRAL); (4) National Health Services Economic Evaluation Database (NHS-EED; this has been an archive database only since 2015).

Supplemental Table 4 Study and Patient Characteristics From RCTs Excluded From NMA

Trial (Interventions)	Median (Range) LOT at Baseline	Previous Treatment Criteria	Previous Treatment Exposure at Baseline (%)	Relapsed/Refractory Status
CA204-009 (EVd vs. Vd)	NR	Including response to previous PI regimen; progression on last regimen; excluding PI refractory or intolerance	PI: 51%-53%	NR
CASTOR (DVd vs. Vd)	2 (1-10)	Excluding bortezomib refractory; previous daratumumab, allogeneic SCT	ASCT: 61%; bortezomib: 66%; carfilzomib: 4%; dexamethasone: 91%; lenalidomide: 42%; thalidomide: 49%	PI refractory: 1%; IMiD refractory: 33%; PI and IMiD refractory: 3%; bortezomib refractory: 0.6%; carfilzomib refractory: 2%; ixazomib refractory: 2%; lenalidomide refractory: 28%; pomalidomide refractory: 3%; thalidomide refractory: 11%
ENDEAVOR (Kd vs. Vd)	2 (1-4)	Excluding bortezomib or carfilzomib refractory	Bortezomib: 54%; carfilzomib: $<$ 1%; lenalidomide: 38%; thalidomide: 49%	NR
MMVAR-Velcade (TVd vs. Vd)	1 previous ASCT: 53%; $\geq$ 2 previous ASCTs: 47%	Including $\geq$ 1 ASCT; excluding allogeneic SCT	Bortezomib: 20%-21%; thalidomide: 6%-10%	NR
Nordic Myeloma Study (Td vs. Vd)	NR (only required patients were refractory to melphalan)	Excluding previous bortezomib, lenalidomide, thalidomide	High-dose melphalan: 49%-52%	NR
PANORAMA 1 (FVd vs. Vd)	NR	Excluding primary refractory; bortezomib refractory	Bortezomib: 43%; dexamethasone: 81%; lenalidomide: 20%; melphalan (oral): 29%; thalidomide: 51%	NR
VCD Phase III (CVd vs. Vd)	NR	NR	bortezomib: 14%	NR

Abbreviations: ASCT = autologous stem cell transplantation; CVd = cyclophosphamide, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; EVd = elotuzumab, bortezomib, dexamethasone; FVd = panobinostat, bortezomib, dexamethasone; IMiD = immunomodulatory drug; Kd = carfilzomib, dexamethasone; LOT = line of therapy; NMA = network meta-analysis; NR = not reported; PI = proteasome inhibitor; RCT = randomized controlled trial; SCT = stem cell transplantation; Td = thalidomide, dexamethasone; TVd = thalidomide, bortezomib, dexamethasone; Vd = bortezomib, dexamethasone.

Supplemental Table 5 Quality Assessment

Assessment	Details	ASPIRE	ELOQUENT-2	POLLUX	Tourmaline-MM1 Study
Number of patients randomized	Total across groups	792	646	569	722
Was the method of allocation concealment presented? (yes/no)	The process (ie, central telephone service, computer-based system only readable at time of allocation, opaque and sequenced sealed envelopes) used to prevent foreknowledge of which comparison group an individual will be assigned to in a RCT	NA (open-label trial)	NA (open-label trial)	NA (open-label trial)	No
How was allocation concealed?	If applicable, state methods used for allocation concealment: central telephone service, computer-based system only readable at the time of allocation, opaque and sequenced sealed envelopes	NA (open-label trial)	NA (open-label trial)	NA (open-label trial)	NR
Which randomization technique was used?	Simple (single sequence), block (into group that results in equal sample sizes), stratification (by covariates)	Stratified randomization; randomization stratified according to baseline β_2-microglobulin level ($<$ 2.5 mg/L vs. $\geq$ 2.5 mg/L); previous therapy with bortezomib (no vs. yes); previous therapy with lenalidomide (no vs. yes)	Stratified randomization; randomization stratified according to baseline β_2-microglobulin level ($<$ 3.5 mg/L vs. $\geq$ 3.5 mg/L); number of previous therapies (1 vs. 2 or 3); previous immunomodulatory drug therapy (none vs. thalidomide only or other)	Central randomization; randomization was balanced using randomly permuted blocks and stratified according to ISS (I, II, or III); number of previous lines of therapy (1 vs. 2 or 3 vs. $>$ 3); previous lenalidomide treatment (no vs. yes)	Stratified randomization; randomization was stratified according to number of previous treatment lines (1 vs. 2 or 3); previous exposure to proteasome inhibitors (no vs. yes); ISS (I or II vs. III)
Was a justification of the sample size provided?	If yes, copy and paste justification provided	Yes: total of 700 subjects enrolled uniformly over 18-mo period and followed up for an additional 18 mo after planned closure of enrollment expected to result in required 526 events within $\sim$36 mo of first randomized subject; a number of 526 events (disease progression or death) required to provide 90% power to detect a 25% reduction in risk of disease progression or death (HR, 0.75) at 1-sided significance level of 0.025	Yes: it was determined that 640 patients with 466 events would provide a power of 89% to detect an HR of 0.74 for disease progression or death in the elotuzumab group in the final analysis	Yes: total of 295 PFS events provided 85% power (2-sided α=0.05) to detect improvement of 7.7 mo in median PFS (Rd, 18 mo; DRd, 25.7 mo); with a 16-mo accrual and 18-mo follow-up, 560 subjects needed	Yes: total sample size was calculated such that the study would have 80% power to detect a 30% difference in OS (HR, 0.70), at a 2-sided α level of 0.05; study was powered to detect the superiority of intervention over placebo
Was follow-up adequate?	Report latest time point of follow-up results (1-, 2-, 3-year and/or median follow-up) and whether this was interim or final and/or if additional updated analyses are planned	Median follow-up: 32.3 mo; interim analysis for PFS	Minimum follow-up: 2 y; final analysis for PFS	Median follow-up: 17.3 mo; interim analysis for PFS and OS	Median follow-up: 23 mo; interim analysis for OS
Were all care providers blinded?	Was the study open-label, single or double-blinded? Were those providing treatment blinded?	No: open-label trial	No: open-label trial	No: open-label trial	Yes: double-blinded study

Supplemental Table 5 Continued

Assessment	Details	ASPIRE	ELOQUENT-2	POLLUX	Tourmaline-MM1 Study
Were all assessors blinded to treatment allocation?	Was the study open-label, single or double-blinded? Were those assessing outcomes blinded? Did they report outcomes by independent review committee?	Open-label trial: treatment responses and disease progression were assessed centrally in a blinded manner by an independent review committee	Open-label trial: treatment responses and disease progression were assessed centrally in a blinded manner by an independent review committee	Open-label trial; an unblinded independent data monitoring committee reviewed safety data on a regular basis	Unclear: NR whether assessors and care providers are the same
Was the intent-to-treat population used?	That is, all those randomized to treatment included in the efficacy analyses?	Yes	Yes	Yes	Yes
Were the statistical analyses used appropriate?	Was it appropriately powered to detect differences?	Yes: a number of 526 events (disease progression or death) were required to provide 90% power to detect a 25% reduction in risk of disease progression or death (HR, 0.75) at a 1-sided significance level of 0.025	Yes: it was determined that 640 patients with 466 events would provide a power of 89% to detect an HR of 0.74 for disease progression or death in the elotuzumab group in the final analysis; the α level for the analysis of PFS (0.0239) was calculated according to occurrence of 384 of 466 events (82%) at the interim analysis	Yes: a total of 295 PFS events provided 85% power (2-sided α=0.05) to detect improvement of 7.7 mo in median PFS (Rd, 18 mo; DRd, 25.7 mo); with 16-mo accrual and 18-mo follow-up, 560 subjects needed	Yes: total sample size was calculated such that the study would have 80% power to detect a 30% difference in OS (HR, 0.70) at a 2-sided α level of 0.05; the study was powered to detect the superiority of intervention over placebo
	Did the safety analysis include all patients that received $\geq$ 1 dose?	Yes: all subjects who received at $\geq$ 1 dose of any study-specific treatment were included in the safety analysis	Yes: exposure and safety were analyzed for all randomized patients who had received $\geq$ 1 dose of any study medication (all treated patients)	Yes: subjects who received $\geq$ 1 administration of any study treatment used for all safety analyses	Yes: the safety population included all patients who had received $\geq$ 1 dose of a study drug or placebo
	For studies with crossover, did they use rank-preserving structural failure time model?	NA	NA	NA	NA
	For studies with crossover, did they use the inverse probability of censoring weighting model per protocol analyses?	NA	NA	NA	NA
Were all groups similar at baseline in terms of prognostic factors?	Any differences at baseline?	Unclear: *P* value NR; study protocol reported the 2 groups were well balanced at baseline without further information	Unclear: *P* value NR; study reported that baseline characteristics were balanced between 2 study groups	Unclear: *P* value NR; study stated that the 2 treatment groups were generally well balanced in baseline disease characteristics	Unclear: *P* value NR; study reported that the 2 groups were well balanced
Were any confounding factors present that might attenuate the interpretation of the results of the RCTs?	High-risk patients/cytogenetic abnormalities	Yes (high, standard cytogenetic risk)	No	No	Yes (standard, high)
	Previous line of therapy	Yes (1, $\geq$ 2)	Yes (1, 2, 3)	Yes (1, 2, 3, $\geq$ 3)	Yes (1, 2, 3)
	Type of previous therapy	Yes (bortezomib, lenalidomide)	Yes (bortezomib, lenalidomide)	Yes (lenalidomide)	No

Supplemental Table 5 Continued

Assessment	Details	ASPIRE	ELOQUENT-2	POLLUX	Tourmaline-MM1 Study
	ISS stage/ECOG status, etc.	No	Yes: ISS (I, II, III)	Yes: ISS (I, II, III); ECOG performance score (0, ≥1)	Yes: ISS (I, II, III)
Was the RCT conducted in the UK?	Yes, no?	No: international: North America, Europe, and Middle East	No: international: North America (US, Canada, Mexico, Puerto Rico), Europe, Japan, rest of world	No: international: North America (US, Canada), Europe, Russia, Australia, Israel, Korea	No: international
Are dosage regimens within those cited in the summaries of product characteristics?	Available at: https://www.medicines.org.uk/emc/	Yes: unable to find dexamethasone 40 mg in electronic Medicines Compendium	Yes: unable to find elotuzumab 10 mg in electronic Medicines Compendium	Yes: unable to find dexamethasone 40 mg in electronic Medicines Compendium	Yes: unable to find ixazomib 4 mg in electronic Medicines Compendium
Overall quality score	Based on information above, was the trial of high (++), moderate (+), or low (−) quality?	Moderate	Moderate	Moderate	Moderate

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ISS = International Staging System; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; Rd = lenalidomide, dexamethasone.

Supplemental Table 6 Extracted Data From RCTs Included in Base-case Analyses

Study (Comparison)	PFS (HR; 95% CI)	OS (HR; 95% CI)	ORR (OR; *P* Value)
ASPIRE[15] (KRd vs. Rd)	0.69 (0.57-0.83)	0.79 (0.63-0.99)	87.1 vs. 66.7 (< 0.001)
ELOQUENT-2[17] (ERd vs. Rd)	0.70 (0.57-0.85)	0.77 (0.61-0.97)	1.9 (1.4-2.8; < 0.001)
POLLUX[16] (DRd vs. Rd)	0.37 (0.28-0.50)	0.63 (0.42-0.95)	93 vs. 76 (< 0.0001)
Tourmaline-MM1[18] (NRd vs. Rd)	0.742 (0.587-0.939)	0.905 (0.62-1.32)	78.3 vs. 71.5 (0.035)

Abbreviations: CI = confidence interval; DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; HR = hazard ratio; KRd = carfilzomib, lenalidomide, dexamethasone; NRd = ixazomib, lenalidomide, dexamethasone; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; Rd = lenalidomide, dexamethasone.

Supplemental Table 7 Sensitivity Analyses: PFS Results

Treatment	d	Rd	Id	KRd	ERd	NRd	ICd
DRd	0.13[a] (0.09-0.18); 100%	0.37[a] (0.27-0.51); 100%	0.27[a] (0.18-0.41); 100%	0.54[a] (0.37-0.78); 100%	0.54[a] (0.38-0.80); 99.9%	0.50[a] (0.33-0.75); 100%	0.41[a] (0.21-0.79); 99.6%
ICd	0.32[a] (0.18-0.55); 100%	0.91 (0.51-1.60); 63.5%	0.66[b] (0.40-1.09); 94.6%	1.31 (0.72-2.39); 18.5%	1.33 (0.73-2.43); 17.6%	1.22 (0.66-2.26); 26.3%	NA
NRd	0.26[a] (0.20-0.34); 100%	0.74[a] (0.59-0.94); 99.4%	0.54[a] (0.38-0.76); 100%	1.07 (0.79-1.45); 31.7%	1.09 (0.80-1.49); 29.3%	NA	NA
ERd	0.24[a] (0.19-0.30); 100%	0.68[a] (0.56-0.83); 100%	0.50[a] (0.36-0.68); 100%	0.99 (0.75-1.30); 54.1%	NA	NA	NA
KRd	0.24[a] (0.19-0.30); 100%	0.69[a] (0.57-0.83); 100%	0.50[a] (0.37-0.69); 100%	NA	NA	NA	NA
Id	0.48[a] (0.39-0.60); 100%	1.37 (1.07-1.77); 0.60%	NA	NA	NA	NA	NA
Rd	0.35[a] (0.31-0.40); 100%	NA	NA	NA	NA	NA	NA

Data presented as HR (95% confidence interval); probability (it is possible that 100% probability will appear to represent any value > 99.951%).
Comparisons presented for each treatment versus each other treatment; specifically, every combination of A versus B, where A is the treatment at the beginning of each row and B is the treatment at the top of each column; HRs < 1 indicate a numerical advantage for the treatment at the end of the row. To obtain HRs for comparisons in the opposite direction, reciprocals should be taken. The probability that the HR for A versus B is < 1 (ie, that regimen A is more efficacious) is under the HR.
Abbreviations: d = dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; HR = hazard ratio; ICd = pomalidomide, cyclophosphamide, dexamethasone; Id = pomalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NA = not applicable; NRd = ixazomib, lenalidomide, dexamethasone; PFS = progression-free survival; Rd = lenalidomide, dexamethasone.
[a]Interventions with a significant advantage.
[b]Interventions with a trend toward improving PFS (eg, HR < 0.80 but credible intervals crossing 1.0).

Supplemental Table 8 Sensitivity Analyses: OS Results

Treatment	d	Rd	Id	KRd	ERd	NRd	ICd
DRd	0.34[a] (0.21, 0.56) 100%	0.63[a] (0.42, 0.95) 98.7%	0.37[a] (0.27, 0.82) 99.6%	0.80[b] (0.50, 1.27) 82.9%	0.82 (0.51, 1.31) 80.0%	0.70[b] (0.42, 1.16) 91.9%	0.88 (0.34, 2.28) 60.8%
ICd	0.39[a] (0.17, 0.88); 98.9%	0.72[b] (0.31, 1.70); 77.5%	0.54[b] (0.25, 1.17); 94.1%	0.91 (0.37, 2.20); 58.2%	0.93 (0.39, 2.27); 56.0%	0.80[b] (0.32, 1.97); 69.0%	NA
NRd	0.49[a] (0.33, 0.73); 100%	0.90 (0.67, 1.22); 74.5%	0.68[b] (0.41, 1.10); 94.5%	1.14 (0.78, 1.67); 24.0%	1.17 (0.80, 1.72); 20.6%	NA	NA
ERd	0.42[a] (0.29, 0.60); 100%	0.77[a] (0.61, 0.97); 98.6%	0.58[a] (0.37, 0.89); 99.4%	0.98 (0.71, 1.35); 55.9%	NA	NA	NA
KRd	0.43[a] (0.30, 0.61); 100%	0.79[a] (0.63, 0.99); 98.0%	0.59[a] (0.38, 0.92); 99.1%	NA	NA	NA	NA
Id	0.72[a] (0.56, 0.93); 99.6%	1.33 (0.92, 1.92); 6.3%	NA	NA	NA	NA	NA
Rd	0.54[a] (0.41, 0.71); 100%	NA	NA	NA	NA	NA	NA

Data presented as HR (95% confidence interval); probability (it is possible that 100% probability will appear to represent any value > 99.951%).
Comparisons presented for each treatment versus each other treatment; specifically, every combination of A versus B, where A is the treatment at the beginning of each row and B is the treatment at the top of each column; HRs < 1 indicate a numerical advantage for the treatment at the end of the row. To obtain HRs for comparisons in the opposite direction, reciprocals should be taken. The probability that the HR for A versus B is < 1 (ie, that regimen A is more efficacious) is under the HR.
Abbreviations: d = dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; ERd = elotuzumab, lenalidomide, dexamethasone; HR = hazard ratio; ICd = pomalidomide, cyclophosphamide, dexamethasone; Id = pomalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone; NA = not applicable; NRd = ixazomib, lenalidomide, dexamethasone; OS = overall survival; Rd = lenalidomide, dexamethasone.
[a]Interventions with a significant advantage.
[b]Interventions with a trend toward improving OS (eg, HR < 0.80 but credible intervals crossing 1.0).