Randomized Clinical Trial (RCT) Representativeness and Outcomes in Relapsed/Refractory Multiple Myeloma (RRMM) Real-World Patients: Comparison of ASPIRE, TOURMALINE-MM1, POLLUX, and ELOQUENT-2 RCTs

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Background

- Only 3% of patients participate in oncology trials in the United States (US); strict eligibility criteria and high enrollment outside of the US limit the generalizability of trial results and applicability of the benefit/risk treatment profile to real-world patients.^{1,2}
- A retrospective analysis of a US-based multiple myeloma (MM) registry revealed that 44% of newly diagnosed multiple myeloma (NDMM) patients did not meet common RCT eligibility for NDMM studies; survival of those who were RCT-ineligible was inferior to those who were RCT-eligible.³
- RCT representativeness and outcomes in relapsed/refractory MM (RRMM) patients treated in routine care have not been systematically evaluated.
- Due to the increased age of this population and comorbid conditions that come with age, an increase in RCT ineligibility within the real world for RRMM patients is expected.

Objective

- To estimate the proportion of real-world patients meeting eligibility criteria in completed RCTs of triplet lenalidomide/dexamethasone (Rd)-based regimens in RRMM and to compare baseline characteristics and overall survival (OS) between RCT-eligible and RCT-ineligible patients within each trial group.

Materials & Methods

Study Design and Population

- This was a retrospective cohort study of an electronic health record (EHR) database spanning data from 1/1/2007 to 6/30/2017.⁴
- Included patients were adults (≥18 years old) diagnosed with NDMM (identified via ≥1 record with an International Classification of Diseases, 9th/10th Revision [ICD-9/10] code for MM [ICD-9 code: 203.0x; ICD-10 code: C90.0x]) initiating second through fourth line of therapy (LOT) during the study period with 1 of the regimens in the investigational or control arms of the following 4 RCTs for RRMM with an Rd backbone (the LOT in which these regimens occur is the index LOT): 2 proteasome inhibitor (PI)-based triplet regimens: ASPIRE⁵ (NCT01080391) and TOURMALINE-MM1⁶ (NCT01564537); and 2 monoclonal antibody (mAb)-based regimens: POLLUX (NCT02076009) and ELOQUENT-2⁸ (NCT01239797) (Figure 1). Patients were followed until death, loss to follow-up, or end of the study (6/30/2017).
- The index treatment date was the first date that the index LOT (ie, second through fourth LOT and with 1 of the regimens noted above) was initiated. The 6-month period prior to index LOT initiation date, termed the baseline period, was used to characterize the study patients.
- Patients with evidence of anticancer therapy or stem cell transplant (SCT) in the 6-month period prior to the first MM diagnosis date were excluded.
- Patients were categorized into "RCT-eligible" vs "RCT-ineligible" cohorts based on whether eligibility criteria for each of the 4 trials in RRMM were met vs not met; those with missing baseline data rendering the above categorization not possible were excluded from analysis.

Definition of LOTs

- The algorithm for LOT in the EHR was developed in collaboration with several hematology/oncology specialists to proxy the definition of an LOT within the RCTs and in accordance with the National Comprehensive Cancer Network Guidelines v4.2018 for treatment of MM; the following programming rules were applied to define LOTs:
- MM-specific anticancer agents initiated ≤90 days post-index diagnosis date constituted the frontline regimen; for patients with frontline SCT (defined as ≤300 days from frontline therapy initiation), induction therapy was any therapy received prior to SCT. Start of single-agent lenalidomide or bortezomib within 6 months of the end of initial therapy among patients not undergoing frontline SCT, or within 12 months after frontline SCT, was part of first-line maintenance therapy.
- Switch/addition of new drug (other than steroids) compared to initial LOT (or after 60 days from SCT) was 2nd LOT; subsequent LOTs occurred if:
 - There was a switch/addition of a new MM-specific anticancer drug (not including steroids) compared to the prior line, or
 - Re-treatment with same regimen/subset where a gap between the end of the prior LOT and start of re-treatment was ≥6 months.
- Single-agent dexamethasone (but not prednisone) constituted a regimen if it was ≥90 days in duration.
- Time to index LOT (in months) was defined as the time from the index diagnosis date to the start of the index regimen; treatment-free interval (TFI) (in months) was defined as the time from the end of the previous LOT to the start of the index LOT.
- Refractory/intolerant status to any of the PIs or any of the immunomodulators (IMiDs) was defined as follows⁹:
 - The duration of therapy (DOT) of the current regimen was ≤60 days and none of the current drugs were in the next regimen, or
 - The time to the next regimen was ≤60 days and none of the current drugs were in the next regimen.
- For ELOQUENT-2, trial-specific exclusion criteria related to lenalidomide exposure prior to the index regimen were also applied and included prior treatment with lenalidomide for ≥9 months and ≤9 months TFI between the lenalidomide-containing regimen and the next regimen.

Baseline Variables

- Baseline clinical characteristics were assessed in the 6 months prior to the index LOT; measures of interest included the following: Charlson comorbidity index (CCI), CRAB symptoms (hyperCalcemia [identified via ICD-9/10 code or lab value indicating corrected serum calcium >11 mg/dL], Renal insufficiency [defined as lab value indicating serum creatinine >2 mg/dL or creatinine clearance <40 mL/min], Anemia [identified via ICD-9/10 code or hemoglobin level <10 g/dL], and Bone lesions [proven by fracture, radiation, bone-directed surgery, spinal cord compression]).¹⁰ cytogenetic risk (high-risk cytogenetics were defined as the presence of del(17p), t(4;14), t(14;16), and/or 1q21 gain), International Staging System (ISS) stage, and SCT status.
- Evidence of other malignancies was captured via ICD-9/10 codes (1 inpatient code or ≥2 outpatient codes 60–365 days apart).
- Evidence of clinically relevant cardiovascular comorbidities was captured via ICD-9/10 codes (1 inpatient coded as primary or discharge diagnosis or 2 outpatient primary diagnoses that were 60–365 days apart) for arrhythmias, angina, coronary artery disease, congestive heart failure, ischemia, myocardial infarction, prolonged QT interval, and sick sinus syndrome (only those cardiovascular disease comorbidities specified in the exclusion criteria within each individual trial were applied for trial-specific cohorts).

Outcomes

- OS (in months) was defined as the time from the date of the index LOT initiation to the date of death from any cause. Patients alive until study end date or lost to follow-up were censored.

Statistical Analysis

- Characteristics of the study population by treatment category were presented as counts and percentages for categorical variables and means, standard deviations (SDs), medians, and interquartile ranges (IQRs) for continuous variables. Bivariate analyses were conducted using the Chi-square test (for categorical variables) and analysis of variance (for continuous variables).
- OS was estimated using the Kaplan-Meier method and was compared across RCT-eligible vs RCT-ineligible groups for each trial using the log-rank test and Cox proportional hazards model.

Patient Cohorts

Among 3,304 RRMM patients initiating at least second LOT, the following numbers of patients were evaluable for eligibility vs ineligibility in each trial based on use of the control or experimental arm regimen in second through fourth LOT: ASPIRE (n=927), TOURMALINE-MM1 (n=850), POLLUX (n=813), ELOQUENT-2 (n=823) (Figure 1).

Figure 1. Patient Cohort Diagram

Key: 2-4LOT – second- to fourth-line therapy; DRd – daratumumab, lenalidomide, and dexamethasone; ERd – elotuzumab, lenalidomide, and dexamethasone; IRd – ixazomib, lenalidomide, and dexamethasone; KRd – carfilzomib, lenalidomide, and dexamethasone; Rd – lenalidomide, dexamethasone; RRMM – relapsed/refractory multiple myeloma.

- Applying the individual trial criteria, the majority of RRRM patients engaged in routine care did not meet RCT eligibility criteria—specifically, 75% (ASPIRE), 65% (TOURMALINE-MM1), 59% (ELOQUENT-2), and 53% (POLLUX)—and were categorized as RCT-ineligible.
- Primary reasons for ineligibility are detailed in Table 1. Exclusion criteria related to prior treatment history of/refractory status to a PI for the PI-based trials only (ASPIRE and TOURMALINE-MM1, 46% and 35%, respectively) and to lenalidomide (23% [ELOQUENT-2]; 8% [other trials]) were the most common reasons for ineligibility across trials. Due to the recent regulatory approvals of mAbs, less than 1% of patients were RCT-ineligible using the POLLUX and ELOQUENT-2 (mAb-based) trial criterion of prior exposure to a mAb.
- The most common clinical reasons for ineligibility across trial groups were low creatinine clearance (27% [ASPIRE]; 9% [other trials]) and other cancer diagnoses (12% [all trials]). Clinically relevant recent cardiovascular comorbidities accounted for 12% (ASPIRE), 9.2% (TOURMALINE-MM1), 9.0% (ELOQUENT-2), and 5.9% (POLLUX) of RCT-ineligible patients (Table 1).
 - Of note, the definition of adequate renal function and presence of cardiovascular disease varied across trials.

Table 1. Reasons for Ineligibility by RCT^a

Reason for Ineligibility ^a	ASPIRE KRd vs Rd N=927	TOURMALINE-MM1 IRd vs Rd N=850	POLLUX DRd vs Rd N=813	ELOQUENT-2 ERd vs Rd N=823
Renal insufficiency	27%	9%	9%	9%
Refractory/intolerant to a PI	40%	35%	N/A	N/A
Refractory/intolerant to lenalidomide	8%	8%	8%	23%
Prior monoclonal antibody therapy	N/A	N/A	1%	1%
Other malignancy	12%	12%	12%	12%
Cardiovascular disease	12%	9%	6%	9%

^a Ns for each trial reflect the number of patients with an index LOT (ie, 2–4 LOTs) that was the same as the investigational or control arm of each individual trial minus the patients who were initially excluded from analysis within each trial due to missing data (see Figure 1). ^b Definitions of each criterion varied across trials. Key: ERd – elotuzumab, lenalidomide, and dexamethasone; DRd – daratumumab, lenalidomide, and dexamethasone; IRd – ixazomib, lenalidomide, and dexamethasone; KRd – carfilzomib and dexamethasone; KRd – carfilzomib, lenalidomide, and dexamethasone; LOT – line of therapy; N/A – not applicable; PI – proteasome inhibitor; Rd – lenalidomide and dexamethasone.

Results

Patient Characteristics Stratified by RCT Eligibility vs RCT Ineligibility

- Table 2 highlights the differences between RCT-eligible vs RCT-ineligible patients by trial; patients who were RCT-eligible were generally significantly younger, treated in an earlier LOT, more likely to have a history of SCT, and had a lower comorbidity burden. A lower proportion also had known ISS stage III disease vs RCT-ineligible patients.
- In addition, in patients in the PI/IMiD combination trials (ASPIRE and TOURMALINE-MM1), while similar proportions of patients who were RCT-eligible vs RCT-ineligible were IMiD-naïve (ASPIRE, 44.4% vs 48.8%; TOURMALINE-MM1, 43.9% vs 49.1%), a greater proportion of RCT-eligible patients in both trials were PI-naïve compared to RCT-ineligible patients (ASPIRE, 47.8% vs 27.9%; TOURMALINE-MM1, 50.0% vs 29.8%).
 - For the mAb/IMiD-based studies, there was an increase in the proportion of IMiD-naïve patients in the RCT-eligible vs RCT-ineligible cohorts (POLLUX, 52.9% vs 44.3%; ELOQUENT-2, 58.1% vs 39.9%), while the proportion who were PI-naïve was similar across trials and within the RCT-eligible and RCT-ineligible groups (range, 34%–38%).
- The TFI between end of previous line to start of index LOT for each of the trials, with the exception of ELOQUENT-2, was significantly longer for those patients who were RCT-eligible vs those who were RCT-ineligible (Table 2).

Table 2. Baseline Characteristics.

Variable	ASPIRE N=927			TOURMALINE-MM1 N=850			POLLUX N=813			ELOQUENT-2 N=823		
	RCT-eligible N=232 (25%)	RCT-ineligible N=695 (75%)	P-value	RCT-eligible N=296 (35%)	RCT-ineligible N=554 (65%)	P-value	RCT-eligible N=382 (47%)	RCT-ineligible N=431 (53%)	P-value	RCT-eligible N=334 (41%)	RCT-ineligible N=489 (59%)	P-value
Age, median (IQR)	65 (57–73)	70 (61–79)	<0.001	68 (60–75)	71 (62–79)	0.004	68 (61–76)	71 (62–79)	0.019	68 (61–77)	70 (62–78)	0.100
Age group, %												
18–64 years	47	32		38	31		38	30		38	31	
65–74 years	36	30	<0.001	34	31	0.003	33	31	0.008	32	31	0.060
≥75 years	17	38		27	39		30	39		30	37	
CCI score, %												
0	54	28	<0.001	49	27	<0.001	45	27	<0.001	46	27	<0.001
1	15	10		15	9		13	9		12	10	
≥2	31	63		35	64		41	64		42	63	
ISS stage III, %	1	5	0.007 ^a	2	5	0.034 ^a	2	4	0.052 ^a	2	4	0.137 ^a
High-risk cytogenetics ^b , %	15	15	0.922 ^c	13	14	0.618 ^c	13	13	0.855 ^c	14	13	0.712 ^c
CrCl (mL/min), median ^d	83.6	63.1	<0.001	73.8	67.5	0.031	74.0	63.8	0.003	73.0	68.2	0.148
Hgb (g/dL), median ^d	12.4	11.3	<0.001	12.1	11.4	<0.001	12.0	11.4	<0.001	11.9	11.6	0.050
Plts (KL), median ^d	187	175	0.026	184	176	0.150	187	170	0.003	184	172	0.039
Treatment-Related Variables												
SCT prior to index LOT, %	38	21	<0.001	31	21	<0.001	28	23	0.085	28	24	0.206
Time from diagnosis to index LOT (months), median	20.2	19.4	0.531	22.2	20.2	0.250	20.0	20.6	0.549	19.5	21.4	0.212
TFI (months), median	7.3	1.6	<0.001	8.0	2.1	<0.001	6.1	4.1	0.023	5.6	4.6	0.307
Index LOT, %												
2LT	91	70	<0.001	89	69	<0.001	82	71	<0.001	81	73	0.007
3LT	9	22		10	23		15	21		15	20	
4LT	1	7		1	8		3	8		3	7	
PI-refractory, %	0	54	<0.001	0	54	<0.001	31	40	0.014	33	38	0.168
R-refractory, %	0	11	<0.001	0	12	<0.001	0	15	<0.001	0	39	<0.001

^a Stage I and II vs III.

^b High-risk cytogenetics were defined as presence of del(17p), t(4;14), t(14;16), and/or 1q21 gain.

^c High risk vs standard risk/unknown.

^d Baseline levels are relative to 6 months prior to initiation of index LOT, with the level closest to index LOT initiation used.

Key: 2LT – second-line therapy; 3LT – third-line therapy; 4LT – fourth-line therapy; CCI – Charlson comorbidity index; CrCl – creatinine clearance; dx – diagnosis; Hgb – hemoglobin; IQR – interquartile range; ISS – International Staging System; LOT – line of therapy; R – lenalidomide; TFI – treatment-free interval (defined as time from end of previous LOT to index LOT).

Survival Outcomes

- For the 3,304 RRMM patients evaluated for individual trial eligibility criteria, the median follow-up was 15.6 months (interquartile range [IQR]: 6.7–30.3) and the median OS was 45 months (IQR: 42.7–47.9).
- Except in the ELOQUENT-2 group, the 3-year OS rate was significantly higher among RCT-eligible patients vs RCT-ineligible patients, but the difference in OS rate varied across trial groups as shown in Figure 2.

Conclusions

- 53% to 75% of RRMM patients engaged in routine care in the US did not meet the eligibility criteria for the hallmark RCTs of approved, recommended regimens in this setting. Other than prior treatment exposure, the most common reasons for RCT ineligibility were low creatinine clearance, concomitant other cancers, and cardiovascular comorbidities; cardiovascular disease and renal insufficiency excluded more patients in the carfilzomib-containing RCT (ASPIRE) than in other trials.
- The 3-year OS rate was significantly longer for patients classified as RCT-eligible vs RCT-ineligible across trials with the exception of ELOQUENT-2, with the highest differential in OS noted in trials with more stringent eligibility criteria based on creatinine clearance and cardiovascular comorbidities.
 - Notably, the TFI, which has been noted to be a positive prognostic factor for survival in some hematologic malignancies,¹¹ was significantly longer for patients who were RCT-ineligible across all trials except for ELOQUENT-2.
- These results suggest that the outcomes observed in RCTs may not be generalizable to real-world RRMM patients, and greater efforts should be made to broaden eligibility criteria to reflect real-world clinical characteristics.

Limitations

- Limitations of this study include those inherent to any retrospective study. It is possible that some comorbidities were not captured through the use of diagnosis codes, and measures of frailty and performance status were not captured, which may confound outcomes. Also, cytogenetic abnormalities and ISS stage were not available for a majority of patients.
- In addition, refractory/intolerant status to either a PI or IMiD was defined using a proxy⁹ and may over- or underestimate the true proportion of refractory/intolerant patients based on prescribing patterns.
- Finally, across trials, 27% to 30% of patients had missing data, could not be categorized as RCT-eligible or RCT-ineligible, and were excluded from analysis.

References

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Figure 2. Survival Outcomes by RCT Eligibility

^a Based on Cox-proportional hazards model (reference: RCT-ineligible).
Key: CI – confidence interval; HR – hazard ratio; LOT – line of therapy OS – overall survival; RCT – randomized controlled trial.

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