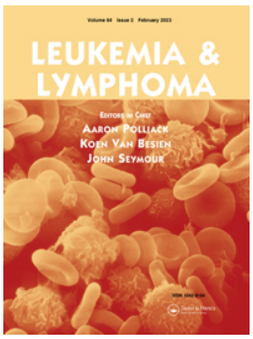

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ORIGINAL ARTICLE

Treatment patterns and overall survival of patients with double-class and triple-class refractory multiple myeloma: a US electronic health record database study

Peter Feng Wang[a], Christopher W. Yee[b], Boris Gorsh[a], Miriam L. Zichlin[b], Prani Paka[a], Rachel H. Bhak[b], Natalie Boytsov[a], Anamika Khanal[b], Ahmed Noman[b], Maral DerSarkissian[b], Shannon Ferrante[a] and Mei Sheng Duh[b]

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ABSTRACT

Patients with relapsed/refractory multiple myeloma (RRMM) resistant to multiple drug classes remain a high unmet need population. This longitudinal retrospective cohort study assessed real-world treatment patterns and outcomes in adults with RRMM. Patients who had three or more prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (double-exposed) were further categorized as refractory to a PI and an immunomodulatory agent (double-class refractory, $n = 381$) or additionally to an anti-CD38 monoclonal antibody (triple-class refractory, $n = 173$). Treatment options are limited for patients with double-class or triple-class refractory disease. Retreatment is a part of standard of care. Bortezomib and lenalidomide had the highest retreatment rates among double-class and triple-class refractory patients. Survival outcomes remain poor among RRMM patients with median overall survival (OS) of 22.3 and 11.6 months for double-class refractory and triple-class refractory patients, respectively. This study highlights the need for novel efficacious therapies in this heavily pretreated RRMM population.

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KEYWORDS
Treatment patterns; myeloma; pharmacotherapeutics

Introduction

Despite substantial improvements in clinical outcomes since the introduction of proteasome inhibitors (PIs), immunomodulatory agents, and monoclonal antibodies (mAbs), most patients with multiple myeloma (MM) eventually relapse and/or become refractory to all available treatments [1–6]. The choice of therapy offered to patients is influenced by its expected efficacy/tolerability, patients' response to previous therapy, number of prior lines of therapy (LOT), and patient and disease characteristics [7]. However, there is no standardized approach to treating patients with relapsed/refractory multiple myeloma (RRMM) [7,8]. In the MAMMOTH study, outcomes for patients with RRMM refractory to anti-CD38 mAbs were investigated in United States (US) academic centers [5]. The median time from MM diagnosis to becoming refractory to anti-CD38 mAbs was 50.1 months, and median (OS) after disease progression was 8.6 months indicating poor outcomes in patients with RRMM following refractoriness to anti-CD38 therapies [5]. While this retrospective observational study identified the unmet need for new treatments after disease progression on anti-CD38 mAbs, the patient population was small and heterogeneous and the exclusively academic setting may not reflect real-world findings [5].

Currently, real-world evidence on treatment patterns and outcomes in heavily pretreated RRMM are limited, especially among those who have developed resistance to multiple classes of therapies. In this study, we investigated the natural history, treatment choices, and outcomes in patients with RRMM who had failed multiple prior LOT and were refractory to multiple drug classes to investigate the need for novel treatment options. We subsequently assessed how patient/disease features and treatment characteristics impacted real-world treatment patient outcomes.

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Methods

This longitudinal retrospective cohort study utilized a subset of the COTA Healthcare de-identified real-world database derived from US electronic health records (EHR) of partnered healthcare providers. Over 1.5 million patients and 1500 oncologists at more than 300 sites (67% academic, 33% tertiary) in the US are included in this database. Patient-level clinical data include patient demographics, diagnoses and disease staging, cytogenetic testing, laboratory values, performance status, treatments, and survival outcomes. Survival data were identified from EHR data (both structured and unstructured/chart review) supplemented with third-party obituary data to improve the completeness of survival data included in this study and accurately represent this outcome [9]. The study included patients of 18 years of age and over at index date (definition provided below) with active RRMM previously exposed to one PI and one immunomodulatory agent who had received at least three prior LOT. Full inclusion and exclusion criteria are shown in Supplementary Table 1. Within this study, refractory status of MM was defined as disease that becomes nonresponsive to therapy (fails to achieve at least a minimal response to therapy) or progresses while on therapy or within 60 days of last therapy by International Myeloma Working Group (IMWG) criteria [10], shown in Supplementary Table 2.

Within the COTA database, patients with active RRMM were identified as double-exposed if they had previously been exposed to one PI and one immunomodulatory agent. Among these patients, those who were refractory to at least one PI and at least one immunomodulatory agent were classified as double-class refractory patients, and those who were refractory to at least one PI, immunomodulatory agent, and anti-CD38 mAb (daratumumab) were classified as triple-class refractory patients. Index dates were defined differently for the double-exposed, double-class refractory, and triple-class refractory cohorts. For the double-exposed cohort, index dates were defined as the date of initiation of the fourth LOT. For the double-class and triple-class refractory cohorts, index dates were defined as the date of initiation of the subsequent LOT after reaching double-class refractory status or triple-class refractory status, respectively. The double-class and triple-class refractory cohorts were distinct due to identification at different time points using different eligibility criteria. All double-class refractory patients were included regardless of whether they became anti-CD38 mAb-refractory at the subsequent line or not. The index LOT was the LOT that began on the index date. The triple-class exposed cohort was not included in the objectives of this study and was not analyzed.

A baseline period of six months was identified prior to the index date in which evidence of clinical activity was required. The follow-up period ran from the index date to the end of data availability (Q1 2020) or death. Evidence of clinical activity or record of death was required within a year of the index date. Data were collected from 1988 through Q1 2020 to ensure the LOT received prior to index date were captured. The design of this retrospective, longitudinal cohort study is shown in Supplementary Figure 1.

Collected variables included patient demographics, therapies received before and during the index LOT, duration of treatment, and treatment discontinuation reasons. High risk cytogenetics were defined as the presence of del[17p], t[4;14], t[14;16], t[14;20], and/or gain of 1q21 at any point during data collection, consistent with other publications [11]. Outcomes measured were OS, duration of therapy (DOT), and time to next treatment (TTNT), which were analyzed using Kaplan–Meier survival analysis methods. Multivariate Cox proportional hazards regression models assessed the relationship between patient or treatment characteristics and OS, DOT, or TTNT with separate models being used for each association.

Data analyses were carried out using SAS Enterprise Guide software Version 7.15 (SAS Institute, Cary, NC). Consent, ethics committee, or Institutional Review Board approval was not required as no direct data collection took place and study results were presented as aggregates in tabular form without identifying information.

Results

Study population, patient demographics/disease characteristics

In total, 650 patients who met inclusion criteria were identified as double-exposed. The double-class refractory cohort included 465 patients (71.5%) while triple-class refractory included 221 (34.0%). Further exclusion of patients without evidence of clinical activity, who participated in a clinical trial or who did not have subsequent therapy resulted in 381 (59.1%) double-class refractory and 173 (26.6%) triple-class refractory patients.

The median time from initial MM diagnosis to the index date for double-exposed was 36.4 months, double-class refractory was 40.8 months, and triple-class refractory was 61.6 months. The earliest index dates, which vary between groups by study design,

Table 1. Patient demographics and disease characteristics.

Characteristic		Double-exposed to PI and immunomodulatory agents $N = 650$	Double-class refractory to PI and immunomodulatory agents $n = 381$	Triple-class refractory to PI, immunomodulatory agents, and anti-CD38 mAb $n = 173$
Index dates	Median	Q2 2015	Q4 2015	Q2 2017
LOT prior to index LOT	Median	3	3	6
Age at index date, years	Median (IQR)	65.2 (57.2, 72.8)	65.0 (57.6, 72.8)	65.5 (59.9, 73.7)
Sex, *n* (%)	Male	348 (53.5)	213 (55.9)	86 (49.7)
Time from initial MM diagnosis to index, months	Median (IQR)	36.4 (23.2, 57.2)	40.8 (25.5, 66.0)	61.6 (40.1, 86.1)
Follow-up time, months	Median (IQR)	24.0 (10.5, 42.2)	14.3 (5.3, 29.2)	8.1 (3.3, 14.9)
Previous SCT, *n* (%)	Autologous SCT	402 (61.8)	237 (62.2)	120 (69.4)
	Allogeneic SCT	23 (3.5)	16 (4.2)	12 (6.9)
ISS disease stage, *n* (%)	Stage I	114 (17.5)	78 (20.5)	50 (28.9)
	Stage II	87 (13.4)	59 (15.5)	35 (20.2)
	Stage III	68 (10.5)	53 (13.9)	27 (15.6)
	Unknown	381 (58.6)	191 (50.1)	61 (35.3)
Cytogenetic abnormalities, *n* (%)	Standard-risk cytogenetics	233 (35.8)	145 (38.1)	65 (37.6)
	High-risk cytogenetics	314 (48.3)	212 (55.6)	114 (65.9)
Performance score, ECOG	Median (IQR)	1.0 (0.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
LDH, μL/mL	Median (IQR)	200.0 (170.0, 280.0)	200.0 (170.0, 272.5)	205.0 (170.0, 257.0)

CD38: cluster of differentiation-38; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; ISS: International Staging System; LDH: lactate dehydrogenase; LOT: lines of therapy; mAb: monoclonal antibody; MM: multiple myeloma; PI: proteasome inhibitor; SCT: stem cell transplant.

were Q4 2003 for double-exposed; Q2 2007 for double-class refractory and Q1 2015 for triple-class refractory. Median ages at the index date were: double-exposed 65.2 years; double-class refractory 65.0 years; triple-class refractory 65.5 years. When defined as the presence of del[17p], t[4;14], t[14;16], t[14;20], and/or gain of 1q21, the majority had high-risk cytogenetics (double-exposed 48.3%; double-class refractory 55.6%; triple-class refractory 65.9%) or prior autologous stem cell transplantation (SCT) (double-exposed 61.8%; double-class refractory 62.2%; triple-class refractory 69.4%). International Staging System stage III: double-exposed 10.5%; double-class refractory 13.9%; triple-class refractory 15.6%. Due to the study design, all patients in the double-exposed cohort had three prior LOT. Median number of prior LOT was three for double-class refractory patients and six for triple-class refractory patients. A summary of patient and disease characteristics are presented in Table 1.

Regimens of choice

Prior to index LOT, bortezomib was the most common PI and 96.9% of patients across all cohorts received bortezomib during the pre-index period (Figure 1(A)). Bortezomib was received with more LOT compared to other PIs across all cohorts (triple-class refractory 2.9 LOT of bortezomib; 2.1 LOT of carfilzomib; 1.2 LOT of ixazomib). Lenalidomide was the most commonly received immunomodulatory agent overall with over 95% of patients receiving lenalidomide prior to index LOT in all cohorts (Figure 1(A)). Lenalidomide was in a similar number of LOT as pomalidomide, and a higher number of LOT compared to thalidomide across all cohorts (triple-class refractory: 2.2 LOT of lenalidomide; 2.5 LOT of pomalidomide; 1.7 LOT of thalidomide). Triple-class refractory patients were more likely to receive carfilzomib (a PI) and pomalidomide (an immunomodulatory agent) compared to double-exposed or double-class refractory patients. Per the study design, all triple-class refractory patients received an anti-CD38 mAb prior to index LOT. At the time of this study, daratumumab was the only anti-CD38 mAb available. Double-class refractory (22.3%) and double-exposed patients (10.9%) also received anti-CD38 mAbs during the baseline period. SCT was common among patients prior to index LOT, although they were less frequently received than PIs or immunomodulatory agents. Triple-class refractory patients were most likely to have received autologous or allogeneic before index LOT (71.7%). Over 40% of patients received investigational agents during their treatment history, with triple-class refractory patients the most likely to receive them (triple-class refractory: 47.4%; double-class refractory: 40.4%; double-exposed: 42.5%).

A higher proportion of double-class refractory (29.9%) and double-exposed patients (20.0%) received anti-CD38 mAbs during index LOT compared to prior to index date, while 28.9% of triple-class refractory patients received anti-CD38 mAbs during index LOT (Figure 1(A,B)). At index LOT, PI/immunomodulatory agent-based and anti-CD38 mAb-based therapies remained the most common therapies. Carfilzomib and pomalidomide were the more commonly received PI and immunomodulatory

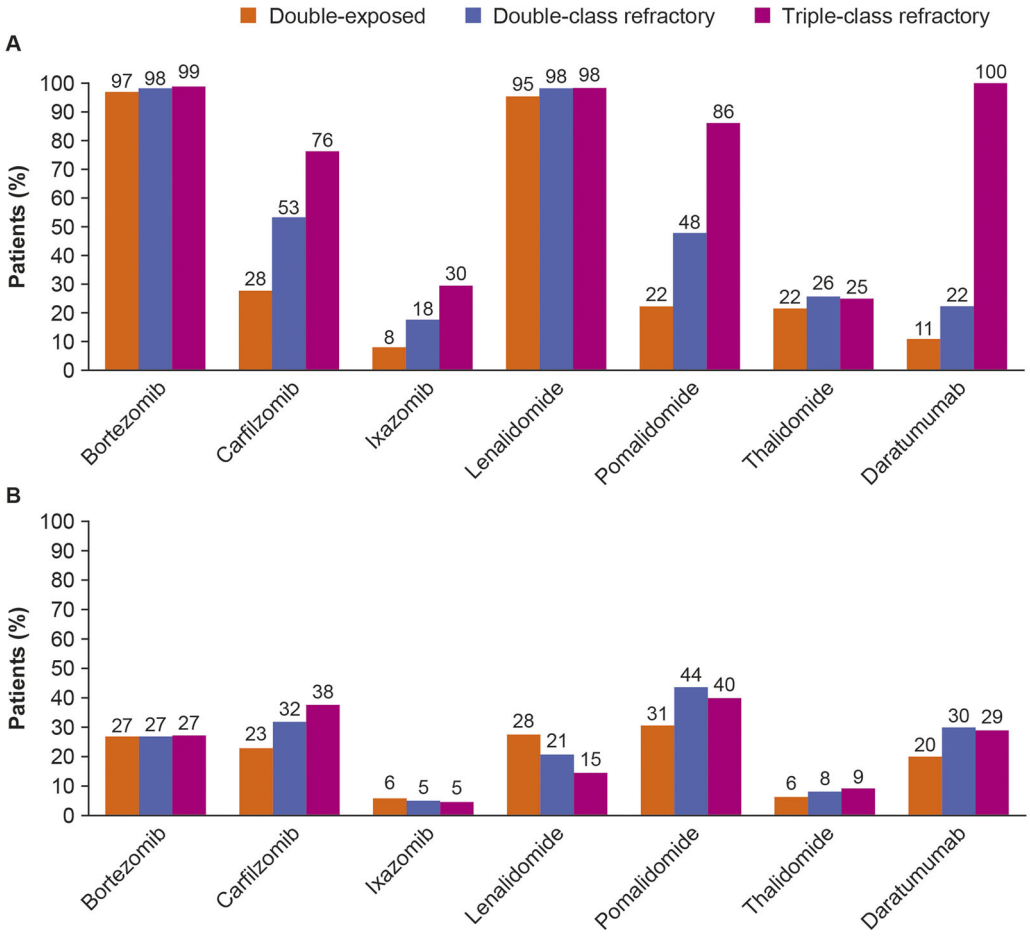

Figure 1. Therapies received by double-exposed, double-class refractory and triple-class refractory patients in (A) baseline period (pre index LOT) and (B) during the index LOT. LOT: line of therapy.

agent received during index LOT by double-class refractory and triple-class refractory patients (Figure 1(B)). In all patient groups, PI or immunomodulatory agent-based therapy and anti-CD38 mAb-based therapies were commonly received during index LOT and two subsequent therapies (Supplementary Figure 2). Triple-class refractory patients were most likely to receive investigational agents before the index LOT. In total, 23.2% of double-exposed 29.9% of double-class refractory, and 41.6% of triple-class refractory patients had no subsequent therapy after index LOT. Seventy-two patients who were triple-class refractory (41.6% of this cohort) did not have additional LOT after index LOT, and 40 (55.6% of this cohort) had a record of death.

Natural history of double-class refractory and triple-class refractory relapsed/refractory multiple myeloma

The median follow-up durations were 24.0 months for double-exposed, 14.3 months for double-class refractory, and 8.1 months for triple-class refractory patients. The duration of gaps between LOT generally decreased with increasing LOT. The gap between second line of treatment (2L) and 3L had the longest median duration (double-exposed: 1.3 months, double-class refractory: 1.0 months, triple-class refractory: 0.9 months). The median gap between all LOT was one month or less. Gaps between LOT were shortest in duration for triple-class refractory patients, ranging from median gaps of 0.9 months between 2L and 3L (double-exposed 1.3; double-class refractory 1.0) down to 0.6 months between 7L–8L (double-exposed 0.6; double-class refractory 0.7) as LOT number increased.

Rates and reasons for treatment discontinuations

The most common reason for treatment discontinuation in all cohorts during index LOT was disease progression (confirmed with laboratory values during treatment and the following 60 days, double-exposed 60.0%; double-class refractory 59.5%; triple-class refractory 60.0%), followed by toxicity (double-exposed 28.4%; double-class refractory 23.0%; triple-class refractory 24.8%). Treatment

Table 2. Reasons for discontinuation of index LOT.

Reasons for treatment discontinuation	Double-exposed to PI and immunomodulatory agents $N = 650$	Double-class refractory to PI and immunomodulatory agents $n = 381$	Triple-class refractory to PI, immunomodulatory agents, and anti-CD38 mAb $n = 173$
Discontinued, *n* (%)			
Reason, n (%)	483 (74.3)	296 (77.7)	125 (72.3)
Progression	290 (60.0)	176 (59.5)	75 (60.0)
Toxicity	137 (28.4)	68 (23.0)	31 (24.8)
Doctor preference	64 (13.3)	42 (14.2)	13 (10.4)
Inadequate response	32 (6.6)	16 (5.4)	5 (4.0)
Patient preference	16 (3.3)	8 (2.7)	2 (1.6)
Death	11 (2.3)	18 (6.1)	11 (8.8)
Unknown	10 (2.1)	10 (3.4)	3 (2.4)
Insurance reason	1 (0.2)	1 (0.3)	1 (0.8)

CD38: cluster of differentiation-38; LOT: line of therapy; mAb: monoclonal antibody; PI: proteasome inhibitor.

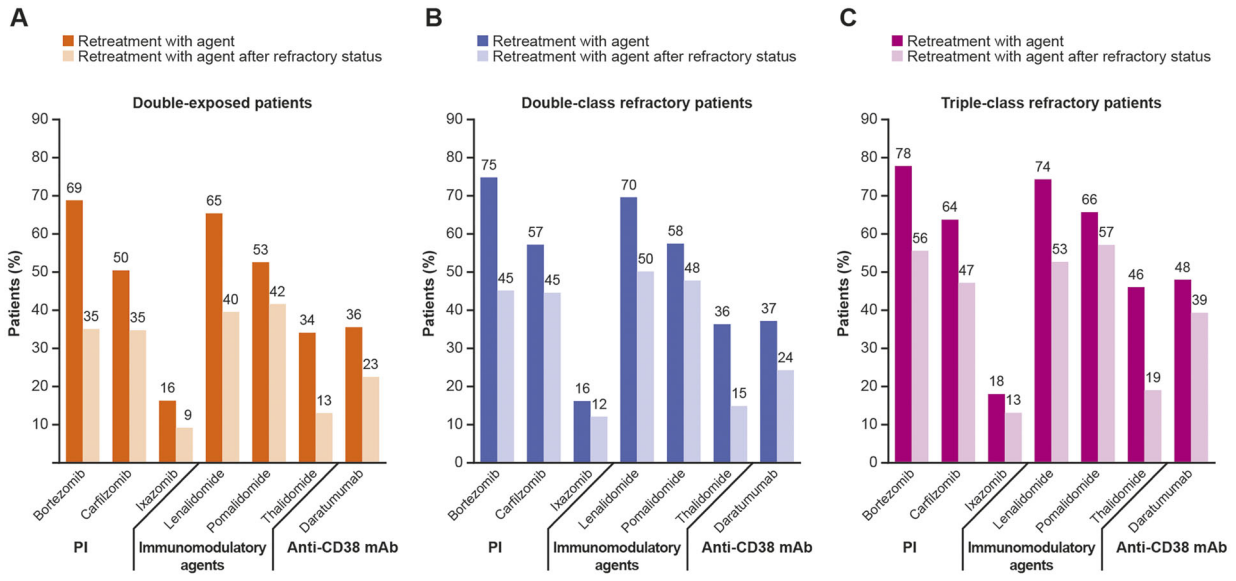

Figure 2. Treatment patterns in double-exposed, double-class refractory and triple-class refractory patients. Levels of overall retreatment (use in more than one line of therapy) and retreatment once refractory to drug in (A) double-exposed, (B) double-class refractory, and (C) triple-class refractory patients. CD38: cluster of differentiation-38; mAb: monoclonal antibody; PI: proteasome inhibitor.

discontinuation was common with double-class refractory patients (77.7%) most likely to discontinue index LOT, followed by double-exposed patients (74.3%), and triple-class refractory patients (72.3%) (Table 2).

Refractory status and retreatment

Compared to other patients, triple-class refractory patients had received more LOT prior to the index LOT and were thus more likely to be refractory to any given therapy. Bortezomib and lenalidomide were the most common PI and immunomodulatory agent, respectively, to which patients were refractory across all cohorts (Figure 2). Among triple-class refractory patients, the refractory rate was 75.7% for bortezomib prior to index LOT and increased to 78.6% when including the follow-up period. Prior to the index LOT, 83.2% of triple-class refractory patients were refractory to lenalidomide which increased to 85% when including the follow-up period.

Retreatment with agents was common, even with treatments to which patients had previously become refractory (Figure 2(A–C)). Triple-class refractory patients were slightly more likely to be retreated with a given agent; retreatment rates were highest with bortezomib in all groups (triple-class refractory patients 55.6%; 45.2% for double-class refractory; 35.1% for double-exposed). Pomalidomide was the most frequent immunomodulatory agent used for retreatment after refractory status (57.1% for triple-class refractory; 47.9% for double-class refractory; 41.6% for double-exposed). Triple-class refractory patients were most likely to be retreated with anti-CD38 mAbs, even after becoming refractory.

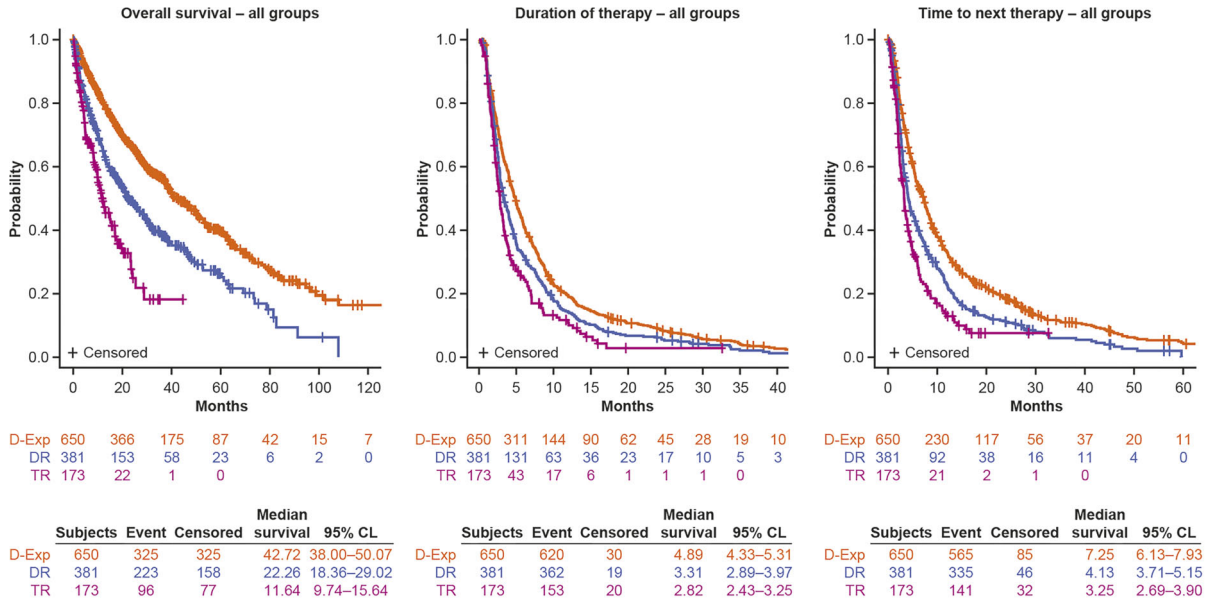

Figure 3. Kaplan–Meier curves showing the overall survival, duration of therapy and time to next treatment for the double-exposed, double-class refractory, and triple-class refractory groups of patients. CL: confidence limits; DR: double-class refractory; D-Exp: double-exposed; TR: triple-class refractory.

Retreatment rates were 39.3% for triple-class refractory, 24.3% for double-class refractory, and 22.5% for double-exposed patients. Refractory status and retreatment characteristics in double-class refractory and triple-class refractory groups are shown in Supplementary Table 3.

Outcomes after developing double-class refractory or triple-class refractory status

Median OS, DOT, and TTNT durations from the index date were shorter in triple-class refractory patients compared to double-class refractory patients and double-exposed patients (Figure 3).

When stratified by LOT, the median OS for triple-class refractory patients generally decreased with increasing index LOT, except for patients with 6L index LOT (triple-class refractory: 10.0 months for 5L ($n = 45$), 25.4 months for 6L ($n = 31$), and 8.1 months for 7L ($n = 27$)). This trend was consistent among double-class refractory patients. Median DOT among triple-class refractory patients was 2.8 months, which was slightly lower than median DOT for double-class refractory (3.3 months) and double-exposed (4.9 months) patients. Median TTNT was the shortest for triple-class refractory (3.2 months) followed by double-class refractory (4.1 months) and double-exposed (7.2 months) cohorts.

In multivariate statistical analyses, worse prognosis (higher risk of death, shorter DOT, and shorter TTNT) in double-class refractory and triple-class refractory patients were associated with inferior baseline Eastern Cooperative Oncology Group performance scores (ECOG-PS). For OS, double-exposed ECOG-PS 3/4, $p < 0.001$, double-class refractory ECOG-PS 3/4, $p < 0.001$, triple-class refractory ECOG-PS 3, $p = 0.004$; ECOG-PS 4 was not available due to small patient numbers. High-risk cytogenetic abnormalities were associated with shorter OS (double-exposed $p < 0.001$, double-class refractory $p = 0.001$, and triple-class refractory $p < 0.001$) shown in Supplementary Table 4.

Discussion

This real-world study involving patients with heavily pretreated RRMM refractory to PIs, immunomodulatory agents and anti-CD38 mAbs incorporated data from multiple academic and community centers. The cohort of triple-class refractory patients were identified within the database based on laboratory values recorded in EHR which were consistent with the definitions of refractory patients used in clinical trials in triple-class refractory patients [10]. Findings from this study show that overall, bortezomib was the most commonly used PI, and lenalidomide was the most commonly used immunomodulatory agent. Carfilzomib (PI) and pomalidomide (immunomodulatory agent) had elevated rates of use in the index LOT in the double-class refractory and triple-class refractory cohorts. Gaps between successive LOT were short and decreased in

duration as the LOT increased, with disease progression being the most common reason for treatment discontinuation. Patients were retreated with agents despite refractoriness. Triple-class refractory patients had shorter OS, DOT, and TTNT than the double-class refractory or double-exposed patients and these were associated with inferior baseline ECOG-PS and cytogenetic abnormalities.

This study showed that outcomes in the overall population of patients with heavily pretreated RRMM remain poor with median survival of 22 months from index LOT in double-class refractory patients and under 12 months from index LOT in triple-class refractory patients. Outcomes in patients with RRMM refractory to anti-CD38 mAb in the academic multicenter MAMMOTH study [5] were also poor with median OS of 8.6 months after becoming refractory to anti-CD38 mAbs. However, the MAMMOTH study was conducted in academic settings within the US, which may have the capacity to offer patients treatment options that are not widely available or used in the community setting. This could result in a higher rate of positive outcomes for patients treated in academic settings and may render the study result inapplicable to real-world settings [12]. A study analyzing EHR, ranging from 2000 to 2014, of patients refractory to a PI and an immunomodulatory agent [12] reported median OS as 7.9 months compared with a median OS after index LOT of 22.3 months in the double-class refractory cohort of this study [12]. This indicates that OS has increased since the introduction of anti-CD38 therapies. This increase in OS may be explained by Braunlin et al.'s analyses of EHR data in the US using the Flatiron database which incorporated data from academic (12.4%) and community (87.6%) settings with MM diagnoses from 2011 up to 2019 [13]. Treatment pattern evaluation in Braunlin et al. describes the change toward PI, immunomodulatory agent, and dexamethasone triplet frontline therapies for treatment of patients with MM (up to 50.5% of frontline therapies in 2018–2019 and 23.5% of second line therapies in 2018–2019) and the introduction of daratumumab in relapsed settings which may be the driving factor behind the increased survival shown in these studies in comparison with the study by Usmani et al. [12,13]. The recently published prospective LocoMMotion study evaluating efficacy of real-world standard of care (SOC) treatment in patient with triple-class exposed RRMM identified 92 different regimens used across the 248 patients in the study [14]. The LocoMMotion study showed that SOC resulted in 4.6 month PFS and 12.4 months OS for triple-class exposed patients with RRMM which was reduced to 3.9 months PFS and 11.1 month OS for triple-class refractory patients [14], adding to the evidence for novel therapies for this patient population.

Additionally, triple-class refractory patients had shorter median DOT and TTNT compared to double-class refractory and double-exposed cohorts. Multivariate analysis revealed that higher baseline ECOG-PS and high-risk cytogenetic abnormalities were associated with poor outcomes, particularly for double-class refractory and triple-class refractory patients. Similar to our study findings, the MAMMOTH study found that cytogenetic risk was associated with OS. MAMMOTH additionally reported lactate dehydrogenase (LDH) level and renal function to be associated with OS in multivariate analyses [5]. In our overall cohort of double-exposed patients, LDH level was associated with worse prognosis, but insufficient data were available in the double-class refractory and triple-class refractory cohorts for analysis.

Findings from this study showed that patients with heavily pretreated RRMM in the US were treated with a wide range of therapies, indicating that there was no typical treatment for this population. Moreover, the majority of patients discontinued their index LOT, mainly due to disease progression. Retreatment rates with PIs, an immunomodulatory agent, or anti-CD38 mAb were high, even after patients had previously become refractory to these therapies. Guidelines for the treatment of patients with RRMM include eight preferred and a further 21 recommended therapies including doublet and triplet regimens incorporating a range of agents including PIs, and immunomodulatory agents alongside anti-CD38 agents [15]. The range of treatments received in the index and subsequent LOT show that the numerous options within the guidelines produces a variety of treatment patterns that are used in the refractory/relapsed setting. Treatment patterns for patients with heavily pretreated RRMM are varied, as treatment decisions should include consideration of the previous treatments received and the initial responses the patients achieved in addition to other factors [15].

The high rates of retreatment with agents previously used to treat patients with heavily pretreated RRMM reported in this study corroborate the results of previous studies. One previous real-world study showed that retreatment with bortezomib (66.2%) or lenalidomide (53.4%) was common [16]. Other studies have shown that following treatment with the anti-CD38 mAb, daratumumab, retreatment

with a PI or immunomodulatory agent resulted in a high proportion of RRMM patients having clinical benefit from retreatment with an overall response rate (ORR) of 52% for retreatment with immunomodulatory agents and 67% for PIs, although the number of patients retreated with a PI was low and should be interpreted with caution [17]. Madan et al. [18] also reported benefits of retreatment with immunomodulatory agents, with partial response or better in 44% of retreated patients; and Petrucci et al. showed an ORR of 40% for bortezomib retreatment [19]. Treatment of patients refractory to lenalidomide and bortezomib with the triplet therapy including daratumumab, pomalidomide, and dexamethasone resulted in an ORR of 91.7% in daratumumab-naïve patients and 40.9% in patients previously treated with the anti-CD38 mAb [20]. However, the clinical benefit ascribed to subsequent retreatments reportedly decreased over time [16]. The high retreatment rates [16] and the poor outcomes seen in patient treated with SOC [14] are indicative of the need for new therapies for triple-class refractory patients.

Through judicious selection of cohort-defining parameters, real-world studies present an opportunity to compare the outcomes in real-world data to outcomes seen in clinical trials. This effect can be seen in the MAMMOTH study which generated a cohort similar to the STORM trial for comparison of OS [5]. In this real-world study, selection criteria and definitions were established to identify heavily pretreated patients, classified in this study as triple-class refractory. Analyses of real-world data, such as the outcomes seen in the real-world triple-class refractory cohort reported here, can help in the interpretation of the finding of clinical trials of new drugs.

This study included large sample sizes with 41.2% of the 650 double-exposed, 52.0% of 381 double-class refractory and 100% of the 173 triple-class refractory patients being refractory to anti-CD38 mAbs, making the data robust for these analyses. Data collected in both academic (67%) and community centers (33%) were included in this study using a robust definition of refractory status of myeloma that was designed to identify RRMM using IMWG definitions.

Potential limitations identified within this study included the availability and accuracy of the source data and collection procedures. The COTA database draws the majority (67%) of its data from academic centers, while in the US community centers treat over 80% of oncology patients [21]. This may limit the generalizability of the study results despite the inclusion of data from community centers reflecting a more complete picture than has been achieved with previous retrospective studies. EHR notes used to populate COTA data may be subjective for progression or inadequate response, although the data did provide refractoriness at the individual drug level. Additionally, differences may exist between patients identified as double-class refractory or triple-class refractory in COTA compared to clinical studies. The understanding of patients on supportive care (being patients with refractory disease who did not receive subsequent LOT) was limited as these were not identified in the data. Missing baseline values in the data reduced the ability to comprehensively evaluate association between baseline characteristics and outcomes and may bias regression models used in analyses although multiple regression models were used to mitigate this.

Our study confirmed that in the population of patients with heavily pretreated RRMM refractory to a PI, and immunomodulatory agents, and an anti-CD38 mAb, outcomes are poor, and there is currently no standard treatment sequence for patients which results in high retreatment rates despite refractory status to previously used therapies. The unmet needs of this group of patients remain high, substantiating the need for new therapies and effective combinations of therapies.

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Data availability statement

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient/participant-level data, and for clinical studies not listed, please submit an enquiry via the website.

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