Journey of relapsed or refractory multiple myeloma (RRMM) after quadruple-class exposure: poor outcomes and high attrition

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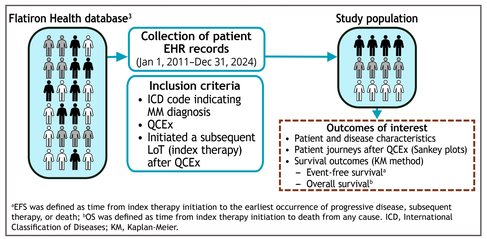
Background

- Patients with multiple myeloma (MM) whose disease has relapsed after or is refractory to treatment with proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 antibodies, and anti-B-cell maturation antigen (BCMA) therapies[1] (quadruple-class exposed [QCEx]) represent a population with aggressive disease biology and cumulative treatment toxicity
- There is no established standard of care post-QCEx, and survival remains poor—underscoring the high unmet medical need
- Here, we characterized treatment journeys across lines of therapy (LoT), documenting clinical outcomes and highlighting critical unmet needs

Methods

- This retrospective study used the Flatiron Health database (from 2011 to 2024), a longitudinal, de-identified patient-level data repository derived from electronic health records (EHRs) in US community oncology practices and cancer centers[2] to identify patients who were QCEx and started a subsequent LoT (**Figure 1**)
- Patient characteristics were summarized using descriptive statistics, and treatment journeys following QCEx were illustrated using Sankey plots
- The index date was the start of the first regimen after meeting QCEx criteria
- Clinical outcomes such as event-free survival (EFS) and overall survival (OS) were estimated using Kaplan-Meier methods
  - EFS was defined as time from index therapy initiation to the earliest occurrence of progressive disease, subsequent therapy, or death
  - OS was defined as time from index therapy initiation to death from any cause

Figure 1. Study design, key eligibility criteria, and outcomes



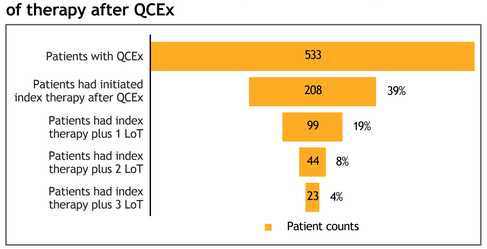
[a]EFS was defined as time from index therapy initiation to the earliest occurrence of progressive disease, subsequent therapy, or death; [b]OS was defined as time from index therapy initiation to death from any cause. ICD, International Classification of Diseases; KM, Kaplan-Meier.

Results

Patient characteristics

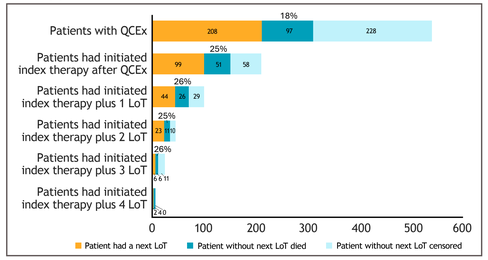
- Among 19,876 patients with MM, a total of N = 533 patients with QCEx RRMM were identified; of these, 39% (n = 208) initiated an index therapy, and 19% (n = 99) proceeded to a subsequent post-index therapy (ie, index therapy plus ≥ 1 LoT; **Figure 2**)

Figure 2. Percentage of RRMM patients initiating next line of therapy after QCEx



- Approximately 18% (n = 97) of patients who were QCEx died before receiving any index therapy, and 25% (n = 51) of patients who received index therapy died before receiving an additional post-index therapy (ie, died before receiving index therapy plus ≥ 1 LoT; **Figure 3**)

Figure 3. Percentage of RRMM patient attrition by line of therapy after QCEx



- At index date, patients had a median age of 67 years (range, 37-85); 56.3% (n = 117) were male, and 69.7% (n = 145) were white (**Table 1**)
  - Patients had received a median of 6 (range, 1-15) prior treatments for MM
  - Nearly all patients (90.9%; n = 189) were refractory to PI, IMiD, and anti-CD38; 50.0% (n = 104) were quadruple-class refractory
- All patients began index therapy between 2020 and 2024 (2020: 1.4% [n = 3]; 2021: 12.5% [n = 26]; 2022: 25.5% [n = 53]; 2023: 30.8% [n = 64]; 2024: 29.8% [n = 62])
- Patients were treated in community (36%; n = 75), academic cancer centers (55%; n = 115), or both settings (9%; n = 18)
- The median duration of follow-up after index therapy initiation was 7.8 (range, 0.2-49.2) months

Table 1. Demographic and clinical characteristics

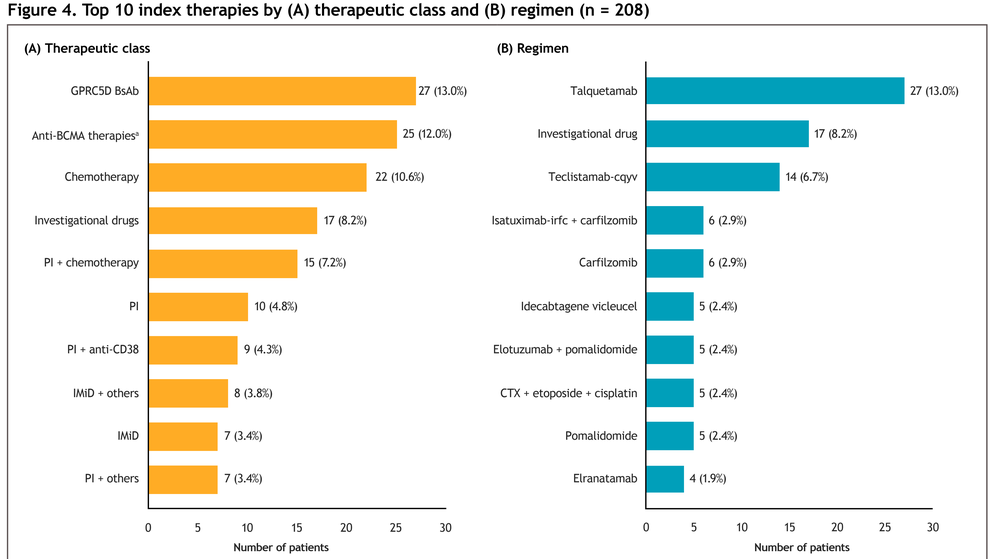
Parameter	QCEx (n = 208)
Age, median (range), y	67 (37-85)
Sex, n (%)	
Male	117 (56.3)
Female	91 (43.8)
Race, n (%)	
White	145 (69.7)
African American	33 (15.9)
Other	30 (14.4)
Disease stage (RISS), n (%)	
I	4 (1.9)
II	191 (91.8)
III	13 (6.3)
High-risk cytogenetics,[a] n (%)	92 (44.2)
ECOG performance status, n (%)	
0	38 (18.3)
1-2	140 (67.3)
3-4	11 (5.3)
Time from initial MM diagnosis, median (range), y	5.9 (0.73-13.6)
Prior stem cell transplant, n (%)	145 (69.7)
No. of prior anti-MM regimens, median (range)	6 (1-15)
Time to progression after last LoT, median (range), mo	9.0 (0.4-39.8)
Treatment-refractory, n (%)	
Double class (PI + IMiD)	200 (96.2)
Triple class (double + anti-CD38)	189 (90.9)
Quad class (triple + anti-BCMA)	104 (50.0)
Penta-drug (2 IMiD + 2 PI + anti-CD38)	119 (57.2)
Penta-drug + BCMA	70 (33.7)
Prior anti-BCMA therapy, n (%)	
CAR T-cell[b]	96 (46.2)
BsAb	36 (17.3)
ADC	76 (36.5)

[a]Presence of t(4;14), t(14;16), del(17p,) amp(1q21); [b]One patient in the CAR T-cell group received both CAR T-cell and ADC treatment. ADC, antibody-drug conjugate; BsAb, bispecific antibody; CAR, chimeric antigen receptor; RISS, Revised International Staging System.

Treatment patterns

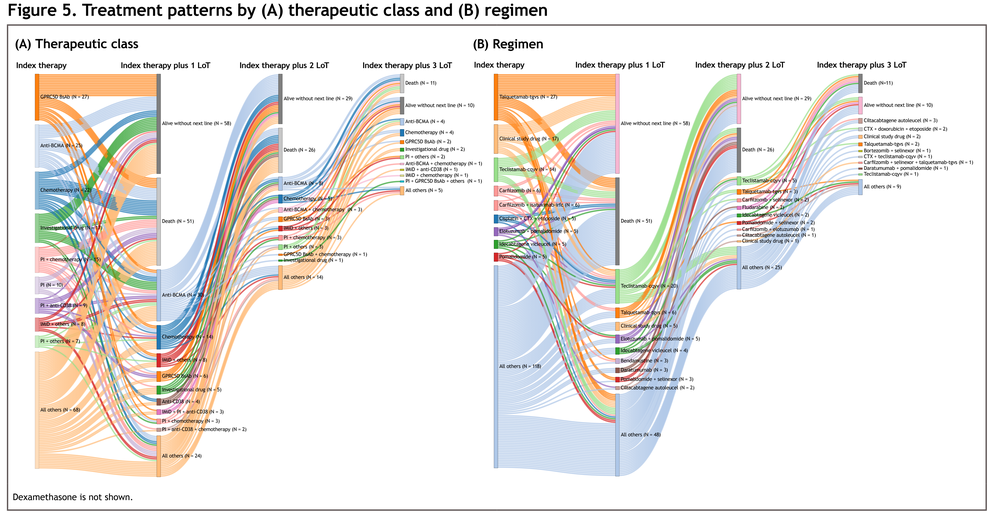
- The most common therapeutic classes for index therapy were G protein-coupled receptor class C group 5 member D (GPRC5D)-directed BsAbs (13.0%; n = 27), anti-BCMA therapies (12.0%; n = 25), and chemotherapy (10.6%; n = 22) (**Figure 4A**), while anti-BCMA therapies were the most frequently used index therapy plus 1 LoT (30.3%; n = 30) (**Figure 5A**)
- The most common index therapy by regimen was talquetamab (13.0%; n = 27) (**Figure 4B**), while teclistamab was the most frequently used index therapy plus 1 LoT (20.2%; n = 20) (**Figure 5B**)

Figure 4. Top 10 index therapies by (A) therapeutic class and (B) regimen (n = 208)



[a]CAR T-cell, BsAb, or ADC.
CTX, cyclophosphamide.

Figure 5. Treatment patterns by (A) therapeutic class and (B) regimen

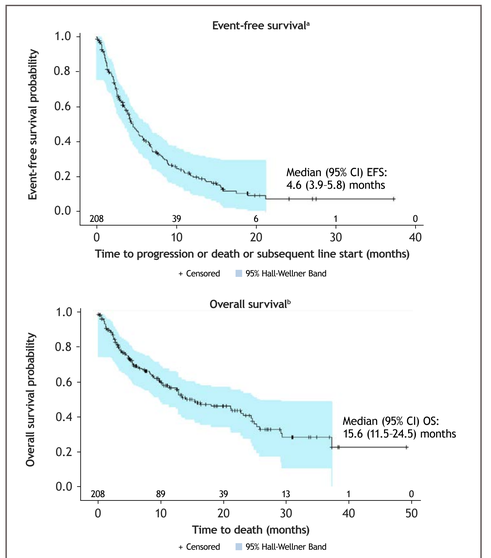


Dexamethasone is not shown.

Survival outcomes

- During follow-up, 76.0% (n = 158) of patients had an event and 47.6% (n = 99) died; the median (95% CI) EFS and OS were 4.6 (3.9-5.8) months and 15.6 (11.5-24.5) months, respectively (**Figure 6**)

Figure 6. Survival outcomes in patients who are QCEx with RRMM (n = 208)



Solid black line with blue shaded area indicates survival probability (95% CI).
[a]EFS was defined as the time from the index date (ie, time of index therapy initiation) to the first occurrence of progressive disease, subsequent therapy, or death; [b]OS was defined as the time from the index date to death from any cause.

Conclusions

- This real-world study underscores the substantial clinical challenges experienced by patients with QCEx
- In this heavily pretreated population, frequently with triple- or quadruple-class refractory disease, almost one-fifth died before initiating any subsequent therapy, and nearly one-quarter died before progressing through each additional LoT
- Clinical outcomes were poor, characterized by rapid disease progression and short survival duration, reflecting the aggressive nature of the disease and the limited efficacy of currently available treatments
- Early intervention with novel and effective therapies is critical to improving outcomes and lowering mortality in patients with QCEx RRMM

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