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Analyses of Real-World Data on Overall Survival in Multiple Myeloma Patients With ≥3 Prior Lines of Therapy Including a PI and an IMiD, or Double Refractory to a PI and an IMiD

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INTRODUCTION

- Over the past decade, the median overall survival (OS) of patients with multiple myeloma (MM) has increased to approximately 6 to 8 years, in part, as a result of novel treatments[1]
- Despite the introduction of the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor (PI) bortezomib, most patients relapse and outcomes are poor in relapsed or refractory patients[2]
  - An International Myeloma Working Group (IMWG) study published in 2012 determined that the median OS of patients refractory to bortezomib and refractory to ≥1 IMiD was 9 months[2]
- Since the IMWG study, other therapies have been approved for relapsed and refractory MM in the United States, including pomalidomide (IMiD) in 2013 and carfilzomib (PI) in 2012
  - In the phase 3 MM-003 study of refractory or relapsed/refractory MM, pomalidomide plus low-dose dexamethasone provided a median OS of 13.1 months[3]
  - Among patients treated with carfilzomib for relapsed/refractory MM treated in the phase 3 FOCUS study, median OS was 10.2 months[4]
- To fully evaluate the potential benefit of novel agents for the treatment of patients with MM who are heavily pretreated and refractory, it is important to understand patient outcomes based on current real-world experience

OBJECTIVES

- To determine the median OS of patients with heavily pretreated or double refractory MM, and to assess the need for new therapies in relapsed disease

METHODS

- Medical records were screened from 2 independent databases; both comprised US patients only
  - The IMS LifeLink: IMS Oncology Electronic Medical Records database (IMS Health Incorporated, Danbury, CT) over the indexing period of 2000 to 2014
  - OPTUM database (OPTUM, Inc., Eden Prairie, MN) over the indexing period of 2007 to 2014
- Inclusion criteria
  - Patients with a diagnosis of MM from 2000 to 2011 in the IMS LifeLink database and from 2007 to 2014 in the OPTUM database were eligible
    - ICD-9 codes for MM were 203X, 203.0X, 203.00X, 203.01X, and 203.02X in the IMS LifeLink and OPTUM databases
  - No other cancer diagnosis prior to diagnosis of MM, with the exception of benign and in situ neoplasms, basal cell carcinoma, and squamous cell carcinoma
  - Patients were required to have received ≥3 prior lines of therapy (LOTs), including a PI and an IMiD, and show disease progression within 60 days of completion of the most recent regimen, *OR* be refractory to both a PI and an IMiD. Refractoriness to a PI or an IMiD was established if any of the definitions contained in **Table 1** were met

Table 1. Definitions of Refractory Status

Definition 1	Duration of therapy of current regimen ≤60 days AND none of the current drugs in next regimen
Definition 2	Time to next regimen ≤60 days AND none of the current drugs in next regimen
Definition 3	Both baseline and follow-up M-protein values available but no >25% decline

- Drugs considered for regimen analysis were the following:
  - Core drugs: thalidomide, bortezomib, lenalidomide, melphalan, pomalidomide, carfilzomib, and cyclophosphamide
  - Steroids: dexamethasone, prednisone, and prednisolone
  - Other MM drugs: vincristine, etoposide, doxorubicin, bendamustine, and vorinostat

Study Endpoints and Analyses

- Median OS from the start of last LOT was assessed using Kaplan-Meier plot estimates with 95% confidence intervals (CIs) for the full cohort, and additionally for cohorts of patients meeting Criteria 1 and 2
  - Criteria 1: Double refractory disease (per **Table 1**) to a PI and an IMiD
    - Further, subgroup analyses were conducted on those who were only double refractory and on those who were triple/quadruple refractory to a PI and an IMiD
  - Criteria 2: Patients treated with ≥3 LOTs, including a PI and an IMiD, and showed disease progression within 60 days of completion of last regimen (but not double refractory)
- OS was defined based on death or lost to follow up >30 days prior to study end date

RESULTS

Patients

- For the IMS LifeLink database, 4,030 patients with MM were screened
  - Approximately 90% of patients were diagnosed with MM in 2006 or later
  - 500 met the criteria for the target population
    - 323 patients met Criteria 1
    - 177 patients only met Criteria 2
- For the OPTUM database, 3,837 patients with MM were screened
  - Approximately 90% of patients were diagnosed after 2009
  - 162 met the criteria for the target population
    - 120 patients met Criteria 1
    - 42 patients only met Criteria 2
- Patient demographics of the target study populations are summarized in **Table 2**

Table 2. Patient Demographics

Characteristic	IMS LifeLink database (N = 500)	OPTUM database (N = 162)
Median (range) age, years		
At diagnosis	66 (31-82)	66 (35-83)
At eligibility	70 (36-85)	67 (39-85)
Male, n (%)	258 (52)	94 (58)
Median (range) prior LOTs	3 (1-25)	3 (1-8)
≥3 prior LOTs, including a PI and an IMiD, but not double refractory, n (%)	177 (35)	42 (26)
Refractory status, n (%)		
Double refractory	253 (51)	97 (60)
Triple refractory	61 (12)	19 (12)
Quadruple refractory	9 (2)	4 (2)
ECOG score at eligibility, n (%)	N = 208*	N = 11*
0	56 (27)	3 (27)
1	98 (47)	5 (45)
2	41 (20)	2 (18)
3	13 (6)	1 (9)

LOT, line of therapy; PI, proteasome inhibitor; IMiD, immunomodulatory drug; ECOG, Eastern Cooperative Oncology Group.
*ECOG scores at eligibility were missing for the majority of patients.

- In both databases, patients received a median of 3 prior LOTs at eligibility, which encompassed a wide variety of treatments, including carfilzomib and pomalidomide (**Table 3**)

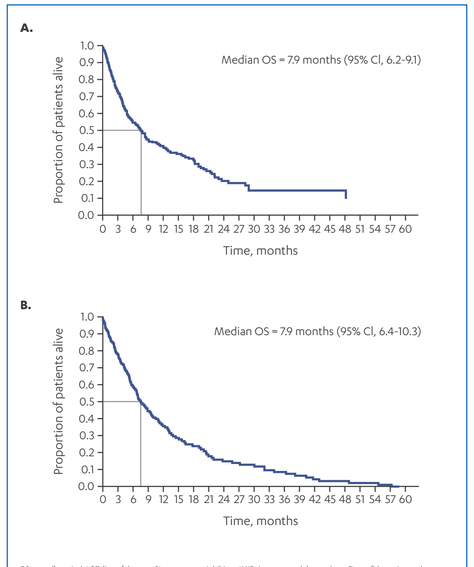
Table 3. Treatment Regimens Received at Eligibility

Regimen	IMS LifeLink patients at identification, % (N = 500)	OPTUM patients at identification, % (N = 162)
Bortezomib only (no IMiDs/cytotoxic agent)	28.8	27.8
Lenalidomide/thalidomide only	24.0	23.5
Bortezomib + lenalidomide/thalidomide (±cytotoxic agent)	21.2	22.2
Bortezomib + cytotoxic agent	6.8	9.2
Any cytotoxic agent	5.2	3.0
Any carfilzomib	5.8	5.5*
Steroid only	4.0	4.3
Any pomalidomide	2.8	3.1*
Lenalidomide/thalidomide + cytotoxic agent	1.0	2.5
Bendamustine	0.4	0

*Two patients (1.2%) received both carfilzomib and pomalidomide.

Overall Survival

- Median OS for all eligible patients was similar between the 2 databases ($P = 0.5358$)
  - 7.9 months in the IMS LifeLink dataset (95% CI, 6.2-9.1; **Figure 1A**)
  - 7.9 months in the OPTUM dataset (95% CI, 6.4-10.3; **Figure 1B**)



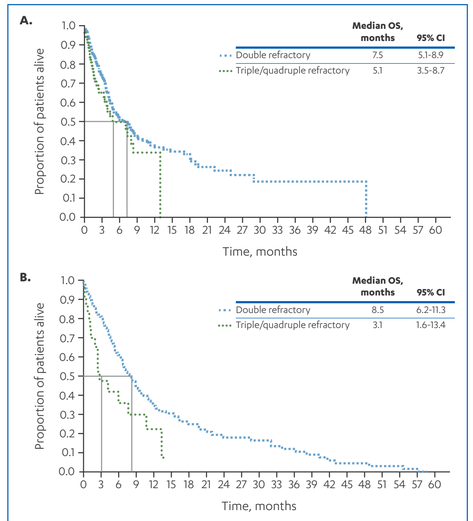
OS, overall survival; LOT, line of therapy; PI, proteasome inhibitor; IMiD, immunomodulatory drug; CI, confidence interval.

Figure 1. OS in patients with ≥3 prior LOTs (including a PI and an IMiD) or double refractory to a PI and an IMiD from (A) the IMS LifeLink and (B) the OPTUM databases.

- Median OS for patients meeting Criteria 1 and Criteria 2
  - 6.7 months and 11.5 months, respectively, in the IMS LifeLink dataset ($P = 0.1196$)
  - 7.3 months and 10.3 months, respectively, in the OPTUM dataset ($P = 0.7113$)

OS and Refractory Status in the IMS LifeLink and OPTUM Datasets

- Median OS by refractory status was not significantly different between the IMS LifeLink and OPTUM datasets (**Figure 2**)
  - Median OS was 7.5 months and 8.5 months among double refractory patients identified in the IMS LifeLink (n = 253) and OPTUM (n = 97) databases, respectively ($P = 0.8052$)
  - Among triple/quadruple refractory patients, median OS was 5.1 months in the IMS LifeLink database (n = 70) and 3.1 months in the OPTUM database (n = 23; $P = 0.6675$)



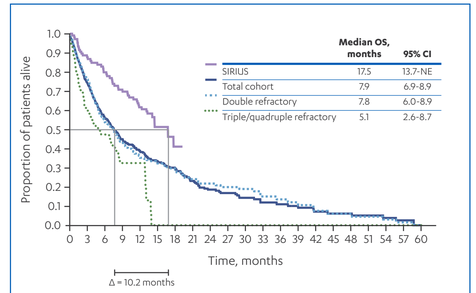
OS, overall survival; CI, confidence interval.

Figure 2. Median OS based on refractory status for patients in the IMS LifeLink(A) and the OPTUM (B) databases.

- Pooled analyses indicated that the median OS was 7.9 months for the eligible population (n = 662), 7.8 months for patients who were only double refractory (n = 350), and 5.1 months for patients who were triple/quadruple refractory (n = 93)

Comparison of Median OS in Combined Datasets With Clinical Study Data

- Daratumumab, a human IgG1 monoclonal antibody, targets CD38, which is expressed at high levels on MM cells, and is in clinical development for MM[5]
- In a first-in-human clinical study (GEN501 [ClinicalTrials.gov Identifier: NCT00574288]), daratumumab monotherapy (16 mg/kg) showed promising antimyeloma activity in patients with relapsed and refractory MM and an overall response rate (ORR) of 36%[6,7]
- In a separate study (SIRIUS [NCT01985126]), ORR was 29% and median OS was 17.5 months (95% CI, 13.7-not estimable) in patients with MM who had received ≥3 prior LOTs, including a PI and an IMiD, or were double refractory to a PI and an IMiD and treated with daratumumab monotherapy (16 mg/kg)[8]
- The eligibility criteria for enrollment in SIRIUS were similar to the cohort of patients identified by the historical analyses presented here
- A naïve comparison of the OS Kaplan-Meier curve from the SIRIUS study (17.5 months) and the pooled analysis of both databases (7.9 months) suggests a survival benefit with daratumumab versus the real-world historical control (difference of 10.2 months; **Figure 3**)
  - A limitation of this naïve comparison is that the first patients were enrolled in SIRIUS in October 2013 and their prior treatment regimens were likely to differ from the historical control population



OS, overall survival; CI, confidence interval; NE, not estimable.

Figure 3. Naïve comparison of OS in the SIRIUS study with pooled database populations by refractory status.

CONCLUSIONS

- **Analyses of real-world data from 2 independent, US patient databases indicated that outcomes remain poor among patients with MM who are heavily pretreated and/or highly refractory, despite the availability and use of newer PIs and IMiDs, such as carfilzomib and pomalidomide**
- **A median OS of approximately 8 months was observed in patients with ≥3 LOTs (including a PI and an IMiD) or those refractory to a PI and an IMiD**
- **These data highlight the critical need for new treatments for patients with advanced MM and provide a point of reference against which novel agents can be evaluated**
- **A comparison of the median OS observed in the IMS LifeLink and OPTUM databases with a study of daratumumab monotherapy suggest a survival benefit in patients with heavily pretreated and/or highly refractory MM**

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