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Duration of Treatment of Multiple Myeloma Regimens in Patients With Relapsed or Refractory Multiple Myeloma: Findings in US Clinical Practice Settings

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Introduction

- Doublet and triplet combinations involving immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and immuno-oncology (I-O) agents have emerged to treat relapsed or refractory multiple myeloma (RRMM)
- RRMM is typically treated until disease progression if treatment is tolerated; therefore, duration of treatment (DoT) and time to next treatment (TTNT) may serve as indications of a regimen's efficacy and safety
  - Prolonged DoT with lenalidomide plus low-dose dexamethasone (Ld) has been associated with improved outcomes[1]
- In clinical trials, combination therapies with the IMiD pomalidomide (pom), the PIs carfilzomib (carf) and ixazomib (ixa), and the I-O agents elotuzumab (elo) and daratumumab (dara) have demonstrated improved survival and acceptable safety[2–7]
  - Median DoT was 12.4 weeks for pom plus dexamethasone, 68 weeks for ixa plus Ld (ILd), and 74 weeks for elo plus Ld (ELd), with continuous treatment until progression[2,4,5]
  - Median DoT for carf plus Ld (CLd) was 88 weeks, but carf was discontinued after 18 cycles (72 weeks) and patients received only Ld from that point onwards[3]
- However, the actual DoT and TTNT of regimens with these key agents and their impact on clinical outcomes in a real-world setting are not known

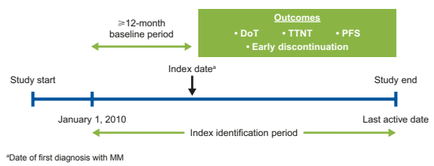
Objective

- To describe the real-world DoT, TTNT, and progression-free survival (PFS) of key agent–based regimens, as indicators of effectiveness and tolerability in RRMM

Methods

- This retrospective, observational study used electronic medical records from the Explorys (IBM Watson Health™) US database
- Patients aged ⩾18 years with ⩾1 diagnosis of MM after January 1, 2010 were followed longitudinally from the index date until the end of available follow-up data (**Figure 1**)
  - Index date was defined as the date of first diagnosis (International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification: ICD-9-CM code 203.0x or ICD-10-CM code C90.0x)
  - A baseline period of ⩾12 months without a diagnosis of MM prior to index date was required

Figure 1. Study design



[a]Date of first diagnosis with MM

- A line of therapy (LoT) was defined as any drug(s) taken within 28 days of treatment initiation, and ended upon either cessation of those drugs or initiation of a salvage regimen
- Patients with RRMM were identified as those with ⩾1 prior LoT
- LoTs containing multiple drugs were included in treatment cohorts identified by the key agent in the LoT; treatment cohorts were not mutually exclusive
- LoTs consisting of ELd, dara plus Ld (DLd), CLd, and ILd were included for analysis if received in 2015 or later, as ELd, CLd, and ILd were approved by the FDA in 2015, and DLd in 2016
- Median DoT, TTNT, and PFS were estimated using Kaplan–Meier (K-M) analyses
- Bootstrapping with 200/500/1000 replicates was conducted as needed, as a sensitivity analysis recognized to address small sample size
  - This method constructs a sampling distribution of a statistic by resampling data with replacement, a process that parallels how the original sample was drawn from the population[8]
- Discontinuation within the first treatment cycle (28 days) was assessed, as early discontinuation can be associated with treatment safety and tolerability

Results

Baseline demographics and clinical characteristics

- At data cut-off (July 5, 2017), 854 patients with RRMM received 1734 LoTs consisting of a key agent (elo, dara, carf, ixa, and pom)–based regimen (**Table 1**)
- Median follow-up was longer for dara-, carf-, and pom-based regimens compared with elo- and ixa-based regimens
- Baseline characteristics were similar across treatment cohorts, but patients who received ixa- and carf-based regimens had higher rates of hypertension and chronic obstructive pulmonary disease (COPD; **Table 1**)

Table 1. Baseline demographics and clinical characteristics at index date

Characteristic	Elo	Dara	Carf	Ixa	Pom	p-value[a]
LoTs, n	65	321	609	172	567	–
Age, years						
Mean (SD)	65 (10)	65 (9)	65 (10)	66 (10)	65 (10)	0.779
Median (range)	64 (41–85)	65 (35–87)	65 (37–87)	65 (41–86)	66 (34–88)	0.649
Male	28 (43)	162 (50)	293 (48)	93 (54)	287 (51)	0.504
Geographic region						0.003
Midwest	38 (58)	233 (73)	368 (60)	112 (65)	385 (68)	
Northeast	3 (5)	10 (3)	20 (3)	7 (4)	22 (4)	
South	11 (17)	47 (15)	112 (18)	34 (20)	106 (19)	
West	13 (20)	31 (10)	105 (17)	18 (10)	53 (9)	
Unknown	0	0	4 (1)	1 (1)	1 (<1)	
Baseline comorbidity						
Hypertension	22 (34)	110 (34)	241 (40)	72 (42)	177 (31)	0.017
Diabetes	10 (15)	45 (14)	110 (18)	27 (16)	73 (13)	0.159
Renal failure	9 (14)	33 (10)	69 (11)	25 (15)	51 (9)	0.257
Cardiac arrhythmia	4 (6)	31 (10)	47 (8)	20 (12)	37 (7)	0.178
COPD	3 (5)	28 (9)	75 (12)	20 (12)	40 (7)	0.015
Congestive HF	3 (5)	9 (3)	17 (3)	7 (4)	15 (3)	0.800
Median prior LoTs (IQR)	3 (2–4)	4 (2–6)	3 (2–4)	3 (2–5)	3 (2–5)	<0.0001
Median follow-up (IQR), months	28 (20–39)	34 (19–54)	35 (23–52)	31 (20–49)	39 (26–57)	0.0001

All values are n (%) except where noted otherwise. Percentages may not total 100 due to rounding
[a]P-values are from a comparison including all treatment cohorts
HF, heart failure

- LoTs using a key triplet regimen with an Ld backbone were ELd (n=22), DLd (n=29), CLd (n=64), and ILd (n=59)
  - Median follow-up was similar among key triplet regimens
  - Baseline characteristics were similar among patients receiving key triplet regimens (data not shown)

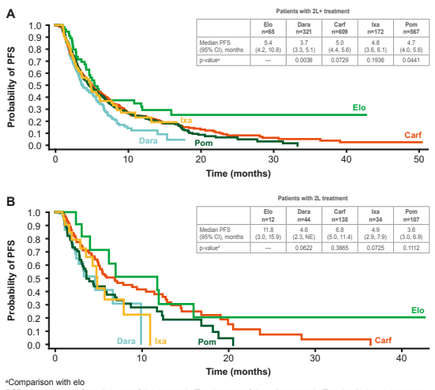
PFS of key agents

- Elo-based regimens had the longest median PFS in patients with second-line (2L) and 2L or more (2L+) treatment (**Figure 2**)
- Of the key triplets with an Ld backbone, ELd, CLd, and ILd showed a trend toward longer median PFS than did DLd in patients with 2L+ and 2L treatment (**Figure 3**)

DoT with key agents

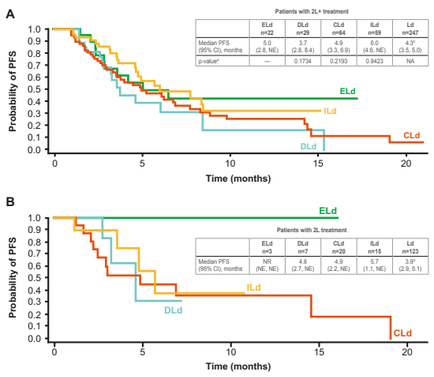
- Median DoT in patients with 2L+ and 2L treatment was significantly longer with elo-based regimens than with dara-, carf-, ixa-, and pom-based regimens (**Table 2**)
- Of the key Ld combinations, ELd and ILd were associated with the longest median DoT for patients with 2L+ treatment (**Table 2**)

Figure 2. K-M curves for PFS with any key agent–based regimen



[a]Comparison with elo
PFS was measured from the start of the current LoT to the start of the subsequent LoT or death due to any cause, whichever occurred first. Patients still alive who did not receive subsequent treatment were censored at last follow-up

Figure 3. K-M curves for PFS with key triplet regimens with Ld backbone



[a]Comparison with ELd. *Refill data were missing for a large percentage of patients who received Ld; therefore, PFS was estimated from a subset of Ld patients with complete data for reference. No statistical comparisons with Ld were made
NA, not applicable; NE, not estimable; NR, not reached

Table 2. K-M estimates of DoT with key agents

Any regimen	Elo	Dara	Carf	Ixa	Pom
2L+ treatment, n	65	321	609	172	567
Median DoT, months (95% CI) p-value	4.6 (2.8, 5.7) –	2.9 (2.4, 3.5) 0.0085	3.1 (2.6, 3.5) 0.0125	2.6 (2.1, 3.3) 0.0150	2.8 (2.5, 3.2) 0.0116
2L treatment, n	12	44	138	34	107
Median DoT, months (95% CI) p-value	6.3 (2.6, 15.5) –	1.9 (1.3, 5.8) 0.0208	3.5 (2.4, 5.1) 0.0125	3.2 (1.1, 3.5) 0.0150	1.8 (1.2, 2.5) 0.0116
Key triplet or Ld	**ELd**	**DLd**	**CLd**	**ILd**	**Ld**
2L+ treatment, n	22	29	64	59	247
Median DoT, months (95% CI) p-value	5.0 (2.6, NE) –	3.7 (2.5, 8.4) 0.2855	3.0 (2.3, 4.4) 0.0543	4.2 (3.1, 5.2) 0.3745	2.9 (2.5, 4.0) NA[a]
2L treatment, n	3	7	20	15	123
Median DoT, months (95% CI) p-value	2.6 (2.6, NE) –	4.6 (1.7, NE) 0.8248	2.4 (0.9, 5.6) 0.1944	3.3 (0.9, NE) 0.5662	3.0 (1.5, 3.9) NA[a]

P-values are for comparison with elo-based regimens
[a]Median DoT for Ld was estimated from a subset of patients who had complete refill data. No statistical comparisons with Ld were made

TTNT with key agents

- Median TTNT in patients with 2L+ treatment was significantly higher with elo-based regimens than with dara-based regimens (**Table 3**)
- ILd and CLd were associated with the highest median TTNT among the key triplet regimens in patients with 2L+ treatment (**Table 3**)

Table 3. K-M estimates of TTNT with key agents

Any regimen	Elo	Dara	Carf	Ixa	Pom
2L+ treatment, n	65	321	609	172	567
Median TTNT, months (95% CI) p-value	5.4 (4.2, 10.8) –	3.8 (3.3, 5.2) 0.0081	5.7 (5.0, 7.1) 0.2759	4.8 (3.6, 6.1) 0.1992	5.1 (4.5, 6.2) 0.1132
2L treatment, n	12	44	138	34	107
Median TTNT, months (95% CI) p-value	11.8 (3.0, 15.9) –	4.6 (2.3, NE) 0.1534	8.9 (5.5, 12.9) 0.6555	4.9 (2.9, 7.9) 0.0725	3.6 (3.0, 7.1) 0.1405
Key triplet or Ld	**ELd**	**DLd**	**CLd**	**ILd**	**Ld**
2L+ treatment, n	22	29	64	59	247
Median TTNT, months (95% CI) p-value	5.0 (2.8, NE) –	3.7 (2.8, 8.4) 0.1734	5.2 (3.5, 8.3) 0.3164	6.0 (4.6, NE) 0.9423	4.7 (4.0, 6.0) NA[a]
2L treatment, n	3	7	20	15	123
Median TTNT, months (95% CI)	NR (NE, NE)	4.6 (0.9, 2.7)	4.9 (1.7, 2.2)	5.7 (1.0, 1.1)	4.5 (3.4, 5.6)

TTNT was defined as the length of time between the start of the current LoT and the start of the subsequent LoT
Patients without a subsequent LoT were censored at last follow-up. P-values are for comparison with elo-based regimens
[a]Median TTNT for Ld was estimated from a subset of patients who had complete refill data. No statistical comparisons with Ld were made

Bootstrap analyses of PFS, DoT, and TTNT

- This analysis was performed to provide small-sample inference from resampled data where sample size allowed, for any regimen (2L) and key triplets (2L+)
- Bootstrap results supported the K-M estimates of median PFS, DoT, and TTNT (**Table 4**)

Table 4. Bootstrap analyses of PFS, DoT, and TTNT with key agents

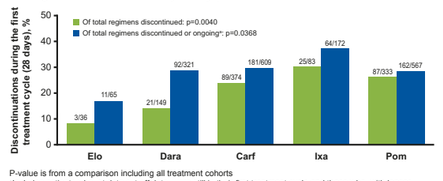
Any regimen	Elo	Dara	Carf	Ixa	Pom
2L replicates, n	6000	22,000	69,000	17,000	53,500
Median PFS, months (95% CI) p-value	11.8 (7.0, 11.8) –	4.6 (4.6, 4.6) <0.0001	6.8 (6.8, 6.8) <0.0001	4.9 (4.8, 4.9) <0.0001	3.6 (3.6, 3.9) <0.0001
Median DoT, months (95% CI) p-value	6.3 (6.3, 6.3) –	1.9 (1.9, 2.5) <0.0001	3.5 (3.5, 3.5) <0.0001	3.2 (3.2, 3.2) <0.0001	1.8 (1.8, 1.8) <0.0001
Median TTNT, months (95% CI) p-value	11.8 (7.0, 11.8) –	4.6 (4.6, 4.6) <0.0001	8.9 (8.9, 8.9) <0.0001	4.9 (4.8, 4.9) <0.0001	3.6 (3.6, 3.6) <0.0001
Key triplet	**ELd**	**DLd**	**CLd**	**ILd**	
2L+ replicates, n	11,000	14,500	32,000	29,500	
Median PFS, months (95% CI) p-value	5.0 (5.0, 5.0) –	3.7 (3.7, 3.7) <0.0001	4.9 (4.9, 4.9) <0.0001	6.0 (6.0, 6.0) 0.3040	
Median DoT, months (95% CI) p-value	5.0 (5.0, 5.0) –	3.7 (3.7, 3.7) <0.0001	3.0 (3.0, 3.0) <0.0001	4.2 (4.0, 4.2) <0.0001	
Median TTNT, months (95% CI) p-value	5.0 (5.0, 6.5) –	3.7 (3.7, 3.7) <0.0001	5.2 (5.2, 5.2) <0.0001	6.0 (6.0, 6.0) 0.3048	

Bootstrapping was performed with 500 replicates. P-values are for comparison with elo-based regimens

Early discontinuations of key agents

- Significantly more patients who received dara-, carf-, ixa-, and pom-based regimens discontinued therapy in the first treatment cycle (28 days) than did those who received elo-based regimens (**Figure 4**)

Figure 4. Treatment discontinuation of key agent–based regimens during the first treatment cycle by patients with 2L+ treatment



P-value is from a comparison including all treatment cohorts
*Includes patients who, at data cut-off date, were still in their first treatment cycle and those who, with longer follow-up, may discontinue within the first 28 days of treatment

Conclusions

- Elotuzumab-based regimens generally had longer median DoT compared with other key agent–based therapies in real-world clinical practice
- Increased DoT may be due to the favorable efficacy and safety profile of elotuzumab, despite longer exposure to treatment
- The following limitations of the study should be considered:
  - Sample sizes were small; however, analyses using the bootstrapping method supported the main findings for all agents
  - TTNT and PFS for oral-based regimens may have been overestimated, although censoring was used to address missing refill data, a common limitation of electronic medical records
- Reasons for agents with short DoT displaying longer TTNT should be explored to determine if this is related to safety and management of treatment-related adverse events prior to starting the next line of therapy

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