Real-world duration of treatment with lenalidomide-dexamethasone (Rd)-based regimens in patients with relapsed/refractory multiple myeloma: Outcomes from the global INSIGHT MM study

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Background

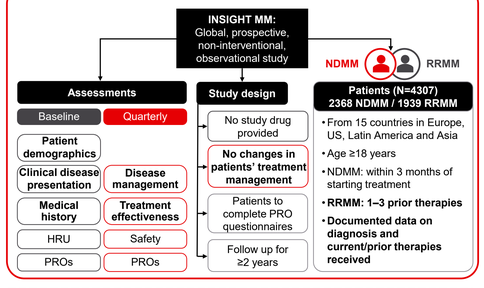
- Rd-based treatment regimens are a standard of care for RRMM.
  - Several therapies are approved for the treatment of RRMM in combination with Rd, including daratumumab (Dara), ixazomib (I), carfilzomib (K), bortezomib (V), and elotuzumab (Elo).
- Longer duration of treatment (DOT) is associated with improved outcomes in MM.[1,2]
  - Median DOTs in clinical trials for RRMM range from 10.1 to 34.3 months.[3–7]
- However, DOTs seen in clinical trials do not always translate to the real-world setting due to multiple patient- and treatment-related factors.[8]
- INSIGHT MM (NCT02761187) is the largest global, prospective, non-interventional, observational MM study to date.[9]
  - The study, which is still ongoing, aims to describe contemporary, real-world patterns of patient characteristics, clinical disease presentation, therapies chosen, clinical outcomes (response, treatment duration, time to next treatment, progression-free and overall survival), safety, healthcare resource utilization, and quality of life.

Objectives

- This analysis uses data from the INSIGHT MM study to estimate real-world DOT with Rd-based regimens in patients with RRMM.

Methods

- The study design and key eligibility criteria for INSIGHT MM are summarized in **Figure 1**.
- Patients were enrolled at 143 study sites in 15 countries worldwide.
- This analysis focuses on a subset of RRMM patients who have received Rd-based treatment with prospective data collection during INSIGHT MM.
- Kaplan-Meier analyses were used to determine DOT for each Rd-based regimen reported, overall, and by line of therapy and by region.
- Best responses to Rd-based treatment regimens were based on IMWG response criteria and physician-reported.
- Exposure to prior therapies and reasons for treatment initiation and discontinuation were also examined.



Results

Patient characteristics

- At data cutoff (July 28, 2020), 822 patients with RRMM from 110 study sites had received 868 lines of Rd-based therapy.
- Baseline characteristics of the analysis population are shown in **Table 1**.

Table 1. Patient demographics and disease characteristics in RRMM patients by Rd-based regimen received*

Patient demographics	Rd (n=226)	Dara-Rd (n=211)	IRd (n=179)	KRd (n=108)	VRd (n=87)	Elo-Rd (n=57)
Median age†, years (range)	70.5 (40–94)	68.0 (33–86)	67.0 (38–86)	63.0 (33–84)	65.0 (39–95)	69.0 (39–88)
Male, n (%)	133 (59)	119 (56)	102 (57)	60 (56)	43 (49)	31 (54)
Female, n (%)	93 (41)	92 (44)	77 (43)	48 (44)	44 (51)	26 (46)
Region, n (%)						
Europe (incl. Israel)	148 (65)	113 (54)	121 (68)	59 (55)	28 (32)	24 (42)
United States	22 (10)	53 (25)	39 (22)	30 (28)	32 (37)	31 (54)
Latin America	7 (3)	40 (19)	3 (2)	14 (13)	10 (11)	2 (4)
Asia	49 (22)	5 (2)	16 (9)	5 (5)	17 (20)	0
Disease characteristics						
Median time since diagnosis, years (range)	2.28 (0.0–30.3)	2.15 (0.1–21.1)	3.23 (0.3–32.3)	1.68 (0.1–17.1)	1.84 (0.0–18.2)	2.51 (0.2–20.3)
ISS stage†, n (%)	*n=168*	*n=176*	*n=129*	*n=95*	*n=76*	*n=45*
I/II	94 (56)	103 (59)	85 (66)	60 (63)	48 (63)	30 (67)
III	74 (44)	73 (41)	44 (34)	35 (37)	28 (37)	15 (33)
ECOG PS score†, n (%)	*n=223*	*n=205*	*n=178*	*n=102*	*n=86*	*n=57*
0/1	193 (87)	181 (88)	164 (92)	84 (82)	76 (88)	50 (88)
≥2	30 (13)	24 (12)	14 (8)	18 (18)	10 (12)	7 (12)

*868 lines of therapy received by 822 patients; patients are included more than once if they received an Rd-based treatment in >1 line of therapy; †At start of line of Rd-based therapy.

QUESTION

What is the real-world DOT with Rd-based regimens in patients with RRMM?

INVESTIGATION

INSIGHT MM: Global, prospective, non-interventional, observational study

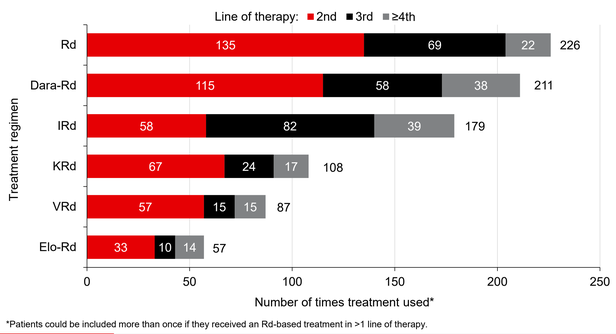
Patients (N=4307)
2368 NDMM / 1939 RRMM

No study drug provided; no changes in treatment/management; follow-up for ≥2 years

Endpoints:
- DOT by line of therapy and region
- Exposure to prior therapies
- Reasons for discontinuation
- Best response to treatment

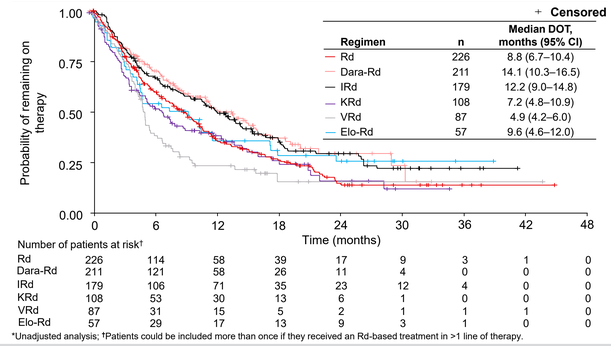
RESULTS

Rd-based regimen usage by line of treatment



*Patients could be included more than once if they received an Rd-based treatment in >1 line of therapy.

DOT by Rd-based regimen in RRMM patients*



*Unadjusted analysis; †Patients could be included more than once if they received an Rd-based treatment in >1 line of therapy.

CONCLUSIONS

Rd-based regimens were most commonly used as 2nd-line therapy, except for IRd, which was most frequently used as 3rd-line therapy. DOT with Rd-based treatment in INSIGHT MM appeared shorter than in clinical trials, with the longest median DOTs reported with Dara-Rd and IRd.

Treatment history

- Almost two-thirds of patients had no exposure to lenalidomide prior to Rd-based treatment during INSIGHT follow-up (**Table 2**).
- The majority of patients had received prior treatment with a PI (**Table 2**).
  - The most common prior PI treatments were V-based and included VCd, VRd, VTd, and Vd, which were used primarily as 1st- and 2nd-line treatments.
- Prior therapies were more diverse in patients receiving Rd-based treatment as ≥4th-line therapy compared with those receiving Rd-based treatment as 2nd- or 3rd-line therapy.

Table 2. Treatment history

Prior treatments	All* (n=868)	Rd (n=226)	Dara-Rd (n=211)	IRd (n=179)	KRd (n=108)	VRd (n=87)	Elo-Rd (n=57)
Prior R exposure, n (%)							
Immediate prior line†‡	216 (24.9)	35 (15)	62 (29)	42 (23)	40 (37)	15 (17)	22 (39)
Before immediate prior line†‡	37 (4.3)	7 (3)	6 (3)	10 (6)	5 (5)	6 (7)	3 (5)
R-refractory#	60 (6.9)	3 (1)	17 (8)	15 (8)	8 (7)	5 (6)	12 (21)
No prior exposure	555 (63.9)	181 (80)	126 (60)	112 (63)	55 (51)	61 (70)	20 (35)
Prior PI exposure, n (%)							
Immediate prior line†‡	449 (51.7)	86 (38)	89 (42)	102 (57)	89 (82)	61 (70)	22 (39)
Before immediate prior line†‡	78 (9.0)	16 (7)	12 (6)	37 (21)	4 (4)	3 (3)	6 (11)
PI-refractory#	269 (31.0)	87 (38)	104 (49)	28 (16)	11 (10)	16 (18)	23 (40)
No prior exposure	72 (8.3)	37 (16)	6 (3)	12 (7)	4 (4)	7 (8)	6 (11)

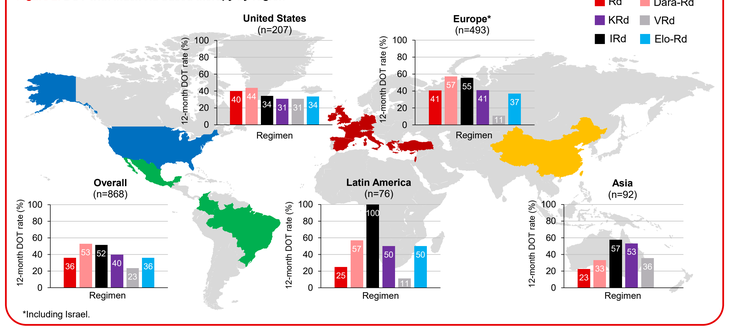
*868 lines of therapy received by 822 patients; patients are included more than once if they received an Rd-based treatment in >1 line of therapy; †Line(s) prior to Rd-based therapy (including lines of treatment received during INSIGHT follow-up); ‡Excluding refractory patients; #Patients who progressed while on R- or PI-based therapy or within 60 days of R- or PI-based regimen discontinuation and/or start of non-R- or PI-based next line of therapy.

- A breakdown of treatments received during INSIGHT MM follow-up, to date, by line of therapy, is shown in the **Summary panel**.
  - Rd-based treatments were most commonly prescribed as 2nd-line therapy (465 / 868 [54%] of all reported lines of treatment), except for IRd, which was most frequently prescribed as 3rd-line therapy.

Duration of treatment

- Overall, median DOT was longest with Dara-Rd (14.1 months) and IRd (12.2 months) (**Summary panel**).
- More than half of patients on Dara-Rd or IRd remained on treatment 12 months after starting that line of treatment (**Figure 2**).
- Analysis by region showed higher 12-month DOT rates in Europe, Latin America and Asia vs US with IRd and KRd, while VRd had a lower 12-month DOT rate in Europe and Latin America (**Figure 2**).

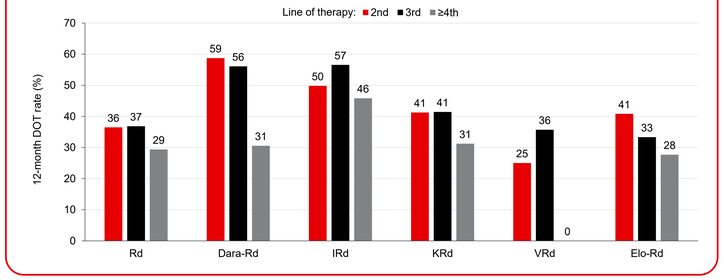
Figure 2. DOT with index Rd-based therapy by region



*Including Israel.

- 12-month DOT rates were relatively consistent when Rd-based regimens were used as 2nd- and 3rd-line treatment, but tended to be lower when regimens were used as ≥4th-line therapy (**Figure 3**).
  - The highest 12-month DOT rates were seen with Dara-Rd and IRd when used as 2nd- or 3rd-lines treatment.

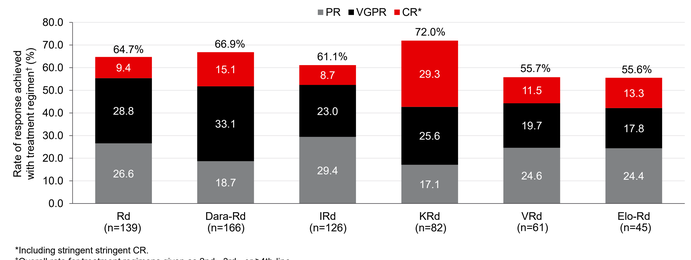
Figure 3. 12-month DOT rate by line of therapy



Best response

- Among patients with available response data, for Rd-based regimens received as any line of treatment (≥2nd-line), ORR ranged from 56% to 72% (**Figure 4**).
  - The highest ORRs and rates of CR or VGPR were seen with Dara-Rd and KRd.

Figure 4. Best responses to Rd-based treatment regimens



*Including stringent stringent CR.
†Overall rate for treatment regimens given as 2nd-, 3rd-, or ≥4th-line.

Treatment initiation and discontinuation

- The most common reasons for initiation of Rd-based treatment regimens were biochemical or clinical progression on previous therapy (**Table 3**).
- At data cut-off, 531 / 868 (61.2%) individual lines of Rd-based therapy had been discontinued during INSIGHT MM follow-up.
  - Reasons for discontinuation are shown in **Table 3**.

Table 3. Reasons for treatment initiation and discontinuation

Reasons for initiation,* n (%)	All† (n=865)	Rd (n=224)	Dara-Rd (n=210)	IRd (n=179)	KRd (n=108)	VRd (n=87)	Elo-Rd (n=57)
Renal failure	39 (5)	11 (5)	10 (5)	7 (4)	1 (1)	6 (7)	4 (7)
Anaemia	102 (12)	26 (12)	26 (12)	26 (15)	6 (6)	12 (14)	6 (11)
Bone involvement	119 (14)	24 (11)	38 (18)	18 (10)	17 (16)	12 (14)	10 (18)
Hypercalcemia	10 (1)	3 (1)	1 (0.5)	3 (2)	1 (1)	0	2 (4)
Biochemical progression	333 (38)	89 (40)	89 (42)	78 (44)	29 (27)	25 (29)	23 (40)
Progressive disease	310 (36)	67 (30)	81 (39)	69 (39)	41 (38)	32 (37)	20 (35)
Resistance to ongoing therapy	72 (8)	12 (5)	16 (8)	16 (9)	12 (11)	11 (13)	5 (9)
Toxicity with previous regimen	31 (4)	12 (5)	6 (3)	2 (1)	2 (2)	5 (6)	4 (7)
Completed course of previous regimen	34 (4)	9 (4)	4 (2)	6 (3)	5 (5)	7 (8)	3 (5)
Other	65 (8)	18 (8)	13 (6)	8 (4)	10 (9)	11 (13)	5 (9)
Reasons for discontinuation,* n (%)	**All (n=531)**	**Rd (n=153)**	**Dara-Rd (n=98)**	**IRd (n=106)**	**KRd (n=73)**	**VRd (n=63)**	**Elo-Rd (n=38)**
Relapse	225 (42)	59 (39)	44 (45)	48 (45)	31 (42)	22 (35)	21 (55)
Adverse events	78 (15)	24 (16)	17 (17)	15 (14)	8 (11)	9 (14)	5 (13)
Death	33 (6)	8 (5)	6 (6)	9 (8)	5 (7)	2 (3)	3 (8)
Other‡	207 (39)	50 (33)	28 (29)	43 (41)	37 (51)	39 (62)	10 (26)
Missing	57 (11)	22 (14)	16 (16)	10 (9)	3 (4)	3 (5)	3 (8)

*Multiple reasons could be given per line of treatment; †Lines of therapy received by 822 patients; reason missing for 1 patient treated with Dara-Rd and 2 patients treated with Rd; ‡Other reasons for discontinuation included financial situation/insurance, lack of response, patient preference, and treatment fatigue.

Conclusions

- Rd-based regimens were most commonly used as 2nd-line treatment for patients with RRMM, except for IRd, which was most frequently used as 3rd-line.
  - 36% of the reported lines of therapy were administered to patients who had received lenalidomide in any prior line, while >90% were initiated after treatment with a PI.
- DOT with Rd-based treatment in the real-world setting of INSIGHT MM generally appeared shorter than in clinical trials.
- The longest median DOTs were seen with Dara-Rd and IRd, with 12-month rates of >50% when used as 2nd- or 3rd-line therapy.
- ORRs >60% were seen with all Rd-based treatment regimens except VRd and Elo-Rd.
  - Despite an ORR of 72% reported with KRd, this regimen had one of the shortest overall median DOTs (7.2 months).
- Biochemical or clinical progression on previous therapy was the most common reason for initiation of new Rd-based treatment regimens and was also the most common reason for discontinuation of the Rd-based treatment lines observed in this analysis.
- Considering the long-term burden of MM, Rd-based regimens associated with longer real-world DOT, such as IRd and Dara-Rd, should be prescribed earlier in the treatment course in order to maximize DOT and potentially thereby prolong progression-free survival.

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Abbreviations

C, cyclophosphamide; CI, confidence interval; CR, complete response; d, dexamethasone; Dara, daratumumab; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; Elo, elotuzumab; HRU, healthcare resource utilization; incl., including; ISS, International Staging System; I, ixazomib; IMWG, International Myeloma Working Group; K, carfilzomib; MM, multiple myeloma; NDMM, newly diagnosed MM; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; PRO, patient-reported outcome; R, lenalidomide; Rd, lenalidomide-dexamethasone; RRMM, relapsed/refractory MM; T, thalidomide; US, United States; V, bortezomib; VGPR, very good partial response.

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