In-Class Transition (*i*CT) from Parenteral Bortezomib to Oral Ixazomib Therapy in Newly Diagnosed Multiple Myeloma Patients from the Community-Based US MM-6 Study: Subgroup Analyses of the Fully Accrued Dataset in Patients Aged <75 and ≥75 Years

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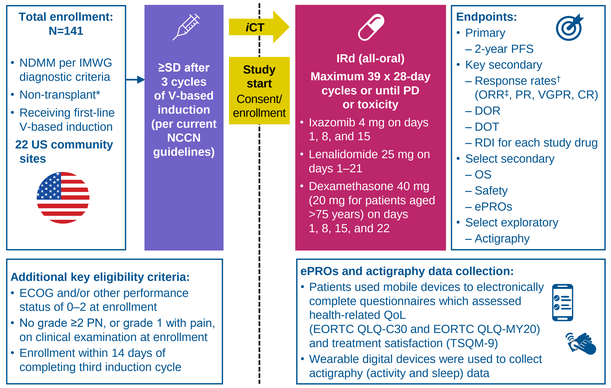
Background

- Long-term proteasome inhibitor (PI)-based treatment can improve outcomes for patients with multiple myeloma (MM)[1,2]
- However, prolonged therapy with parenteral PIs can be difficult to achieve in routine MM practice due to issues relating to poor tolerability/treatment emergent toxicities and the burden of repeated, clinic-based treatment administration, particularly for older patients and those with comorbidities[3]
- Treatment choice is therefore key, especially for older patients and those not eligible for transplant; a tolerable and efficacious option is needed to facilitate long-term treatment to progression in order to maximize clinical benefit[4]
- US MM-6 is a prospective, community-based phase 4 study of *in*-class transition (*i*CT) from parenteral bortezomib (V)-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) therapy in patients with newly diagnosed MM (NDMM) (NCT03173092)[5]
- The objective of US MM-6 is to extend the duration of PI-based therapy and improve clinical outcomes while maintaining patient quality of life (QoL)
  - Overall results for the fully accrued dataset (final enrollment completed in May 2021; N=141) were reported previously[6]
  - Here, we report a subgroup analysis of the fully accrued dataset by patient age

Methods

- Full methods for US MM-6 have been published previously[5]
- The study design for US MM-6 is shown in **Figure 2**
- Key secondary endpoints, including rates of partial, very good partial, and complete response (PR, VGPR, and CR), duration of therapy (DOT), and other endpoints, including safety (secondary), QoL (secondary), and actigraphy (exploratory), were analyzed in the subgroups of patients aged <75 and ≥75 years

Figure 2: US MM-6 Study design



*Transplant-ineligible or transplant delayed by ≥24 months. †One successfully screened patient aged ≥75 years was not treated. ‡Assessed by investigator according to modified IMWG response criteria. Methods have been published previously; IQRR = PR + VGPR + CR + sCR + iCR + mCR; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma module 20 – item 43 measuring peripheral neuropathy; ePRO, electronic patient-reported outcomes; iCR, immunophenotypic complete response; IMWG, International Myeloma Working Group; mCR, molecular complete response; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PN, peripheral neuropathy; RDI, relative dose intensity; sCR, stringent complete response; SD, stable disease; TSQM-9, Treatment Satisfaction Questionnaire for Medication – 9 items.

Results

Patients

- As of February 28, 2022, 140 patients had been enrolled and treated with IRd at 22 sites and were included in the safety and intent-to-treat (ITT) populations
  - Eighty-one patients (57.9%) were aged <75 years and 59 (42.1%) were aged ≥75 years
- Patient demographics and baseline disease characteristics by patient age are shown in **Table 1**

Patient disposition and treatment exposure

- With a median follow-up of 20.0 months at data cut-off, 20.0% of patients were ongoing on study treatment: 22.2% aged <75 years and 16.9% aged ≥75 years
- In patients aged <75 years (n=55) versus those aged ≥75 years (n=47) who had discontinued treatment, reasons for discontinuation were: adverse events (AEs; 29.1% vs 17.0%), PD (20.0% vs 19.1%), patient withdrawal (7.3% vs 10.6%), physician decision (5.5% vs 4.3%), unacceptable toxicity (1.8% vs 2.1%), and 'other reasons' (34.5% vs 38.3%)

Question

Can *in*-class transition (*i*CT) from V-based induction therapy to IRd permit long-term PI-based treatment and thereby improve outcomes for both older and younger community-treated patients with NDMM?

Study design

Patients with non-transplant* NDMM in the US community setting: subgroup analysis by age (<75 years [n=81] and ≥75 years [n=59†])

Parenteral V-based induction (3 cycles) → *i*CT → IRd (all-oral regimen) Maximum 39 x 28-day cycles or until PD or toxicity

Key secondary endpoints included:
- Response rates (ORR, PR, VGPR, CR)
- DOT

Results

Figure 1A: Median duration of IRd therapy from *i*CT by patient age (ITT population; <75 years n=81; ≥75 years n=59)

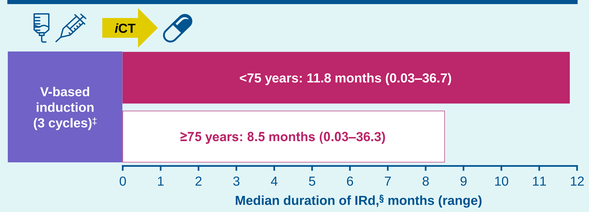
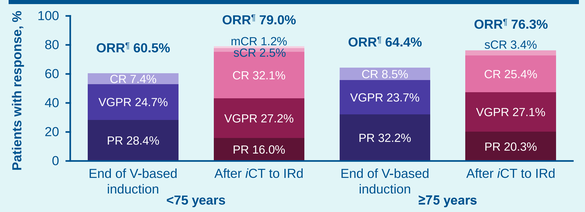


Figure 1B: Response rates at the end of V-based induction and after *i*CT to IRd by patient age (ITT population; <75 years n=81; ≥75 years n=59)



Key take aways

These fully accrued US MM-6 data confirm that *i*CT to IRd permits long-term, tolerable PI-based therapy with improved responses in both older and younger community-treated patients with NDMM

*Transplant-ineligible or transplant delayed by ≥24 months. †One successfully screened patient aged ≥75 years was not treated. ‡V cycle length varied by regimen. §Not Kaplan–Meier estimates; DOT for IRd defined as the time from first administration of IRd to the date of the last administration of any of the 3 study drugs. ¶Investigator-assessed best ORR; ORR = PR + VGPR + CR + sCR + iCR + mCR (percentages may not sum due to rounding).

- In patients aged <75 years versus ≥75 years, median (range) DOT with IRd was 11.8 (0.03–36.7) vs 8.5 (0.03–36.3) months (**Summary Panel**; **Figure 1A**); median (range) duration of total PI-based therapy, including V-based induction, was 14.8 (2.99–39.72) vs 11.1 (2.63–39.33) months
- Patients aged <75 years versus ≥75 years had received a median (range) of 12 (1–39) vs 9 (1–39) cycles of treatment with IRd
  - Sixty-one (75.3%) vs 41 patients (69.5%) had completed 5 or more cycles of IRd

Table 1: Baseline demographic and disease characteristics by patient age

Characteristic	<75 years (n=81)	≥75 years (n=59)*
Median age,† years (range)	69.0 (48–74)	77.0 (75–90)
Male, n (%)	49 (60.5)	32 (54.2)
Race, n (%)		
White	57 (70.4)	44 (74.6)
Black/African American	15 (18.5)	10 (16.9)
Asian	2 (2.5)	1 (1.7)
Native Hawaiian or Other Pacific Islander	1 (1.2)	0
Ethnicity, n (%)		
Hispanic/Latino	9 (11.1)	3 (5.1)
ISS‡ disease stage, n (%)		
I / II / III	21 (25.9) / 35 (43.2) / 24 (29.6)	16 (27.1) / 23 (39.0) / 20 (33.9)
CrCl§ <60 mL/min, n (%)	19 (23.5)	21 (35.6)
Lytic bone disease,‡ n (%)	38 (46.9)	26 (44.1)
≥1 comorbidity at start of IRd therapy, n (%)	74 (91.4)	57 (96.6)
Key comorbidities of clinical importance		
Renal/urinary disorders¶	21 (25.9)	24 (40.7)
Cardiac disorders¶	21 (25.9)	18 (30.5)
Type 2 diabetes mellitus or diabetes mellitus	17 (21.0)	9 (15.3)
PN or sensory PN	18 (22.2)	7 (11.9)
Comorbidities occurring in >25% of patients in either age group		
Hypertension	41 (50.6)	38 (64.4)
Fatigue	30 (37.0)	20 (33.9)
Anemia	25 (30.9)	22 (37.3)
Gastroesophageal reflux disease	24 (29.6)	13 (22.0)
Insomnia	22 (27.2)	17 (28.8)
Back pain	22 (27.2)	12 (20.3)
Constipation	19 (23.5)	15 (25.4)

*One successfully screened patient aged ≥75 years was not treated. †Age and CrCl captured at start of IRd. ‡ISS and lytic bone disease captured at start of V-based induction. §System organ class. CrCl, creatinine clearance; ISS, International Staging System.

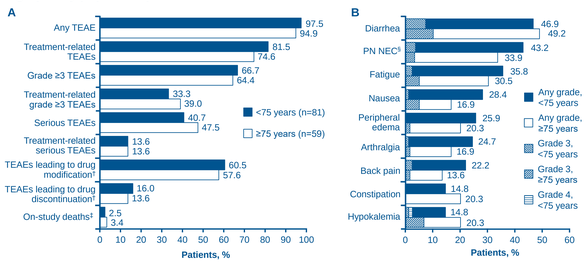
Response rates

- Best ORR increased from 60.5% at the end of 3 cycles of V-based induction to 79.0% after *i*CT to IRd in patients aged <75 years, and from 64.4% to 76.3% in patients aged ≥75 years (**Summary Panel**; **Figure 1B**)

Safety

- The safety profile of IRd by patient age is shown in **Figure 3A**
- The most common any-grade treatment-emergent AEs (TEAEs) in both age groups were (<75 years vs ≥75 years): diarrhea (46.9% vs 49.2%), PN not elsewhere classified (NEC) (43.2% vs 33.9%), and fatigue (35.8% vs 30.5%) (**Figure 3B**)
  - PN NEC was mostly grade 1–2 in both age groups (grade 3: 3.7% vs 3.4%)
  - Any-grade PN NEC was considered treatment-related in 34.6% vs 23.7% of patients
- The most common (occurring in ≥6% of patients) grade 3 TEAEs in patients aged <75 years were diarrhea (7.4%), neutropenia (6.2%), anemia (6.2%), and decreased platelet count (6.2%)
- The most common (occurring in ≥6% of patients) grade 3 TEAEs in patients aged ≥75 years were diarrhea (10.2%), pneumonia (8.5%), and hypokalemia (6.8%)

Figure 3: (A) IRd safety profile overview and (B) most commonly occurring* TEAEs by patient age (safety population)



*In >20% of patients (all grades) in either age group. †Modifications and discontinuations for any of the 3 study drugs. ‡Occurring <30 days after last dose. Deaths were due to: <75 years, unrelated end-stage renal disease and unknown (n=1 each); ≥75 years, treatment-related pneumonia and disease-related complications (n=1 each). §High-level term.

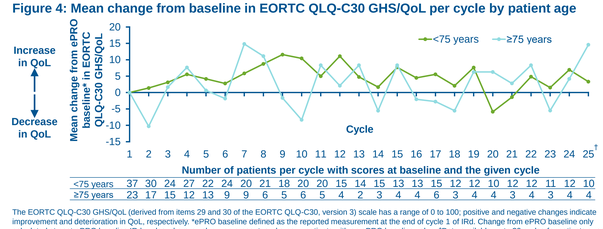
QoL (ePRO)

- Overall (i.e. across both age groups combined), out of a total of 1,775 EORTC QLQ-C30 questionnaires which could have been completed (i.e. all possible assessments across all cycles to date; patients were anticipated to complete a form every cycle during IRd treatment), 945 (53.2%) had been completed
- Patient-reported QoL was maintained during IRd therapy in both age groups, with mean changes from baseline in EORTC QLQ-C30 Global Health Status [GHS]/QoL score generally staying around zero and ranging primarily within -10 to +10 (**Figure 4**)

Actigraphy

- For actigraphy data collection to be compliant, the device had to be worn for ≥12 hours/day for ≥14 days/cycle; the days did not need to be consecutive. Non-compliant data were excluded from analyses
- Any daily actigraphy data were available for 59 patients aged <75 years (a total of 18,842 days) and 34 patients aged ≥75 years (a total of 6,738 days)
  - In patients aged <75 and ≥75 years, a total of 17,077 (90.6%) and 6,164 (91.5%) compliant days were included in the actigraphy analysis, respectively
- Activity and sleep levels were generally maintained during IRd therapy in both age groups (**Figures 5** and **6**), although patient numbers were low in later treatment cycles
- In patients aged <75 years versus ≥75 years:
  - Mean number of steps per day was 3,100 (standard deviation [StDev] 2,394) vs 2,732 (StDev 1,975)
  - Mean daily active time was 0.41 hours (StDev 0.33) vs 0.37 hours (StDev 0.29)
  - Mean daily sleep time was 7.81 hours (StDev 2.81) vs 6.89 hours (StDev 2.44)

Figure 4: Mean change from baseline in EORTC QLQ-C30 GHS/QoL per cycle by patient age



Number of patients per cycle with scores at baseline and the given cycle

<75 years	37	30	24	27	22	24	20	21	18	20	20	15	14	15	13	15	12	12	10	12	12	11	12	10
≥75 years	23	17	15	12	13	9	9	6	5	6	5	4	2	3	4	4	6	3	4	4	3	4	3	4

The EORTC QLQ-C30 GHS/QoL (derived from items 29 and 30 of the EORTC QLQ-C30, version 3) scale has a range of 0 to 100; positive and negative changes indicate improvement and deterioration in QoL, respectively. *ePRO baseline defined as the reported measurement at the end of cycle 1 of IRd. Change from ePRO baseline only calculated at post-ePRO baseline IRd cycles where a value was present, and among patients with an ePRO baseline value. †Data available up to 39 cycles for patients aged <75 years and 38 cycles for patients aged ≥75 years; data not shown beyond cycle 25 due to small patient numbers (n between 1 and 11 within age groups).

Figure 5: Mean daily active time* per cycle by patient age

Number of compliant patients per cycle

<75 years	40	40	34	35	30	26	26	23	22	24	23	21	15	18	13	12	12	11	13	14	15	13	13	12	12
≥75 years	20	17	14	15	13	14	8	8	9	8	10	8	5	4	3	3	3	3	3	3	3	3	3	3	4

*Active time defined as the time for which patients were 'active' or 'highly active'. †Data available up to 39 cycles; data not shown beyond cycle 25 due to small patient numbers (n between 1 and 11 within age groups).

Figure 6: Mean daily sleep time per cycle by patient age

Number of compliant patients per cycle

<75 years	40	40	34	35	30	26	26	23	22	24	23	21	15	18	13	12	12	11	13	14	15	13	13	12	12
≥75 years	20	17	14	15	13	14	8	8	9	8	10	8	5	4	3	3	3	3	3	3	3	3	3	3	4

*Data available up to 39 cycles; data not shown beyond cycle 25 due to small patient numbers (n between 1 and 11 within age groups).

Conclusions

- This analysis of US MM-6 data from the fully accrued study cohort suggests *i*CT to IRd allows long-term, tolerable PI-based treatment in both older and younger community-treated patients with NDMM
- A higher proportion of Black/African American patients were enrolled in US MM-6 (18%) compared with oncology clinical trials (5%)[7]; this may have been a result of the community-based enrollment
- Improved responses were seen in patients aged <75 years and those aged ≥75 years following *i*CT from V-based induction to all-oral IRd
- DOT and response rates in both age groups were comparable to overall results reported previously for the ITT population (median DOT with IRd, 10.0 months; best ORR increased from 62% after V-based induction to 78% after *i*CT to IRd)[6]
- The safety profile of IRd was similar in patients aged <75 years versus ≥75 years
- No adverse impact of IRd on QoL, daily activity, or sleep was observed in either age group
  - The mean number of steps per day in patients aged ≥75 years was consistent with data previously reported for healthy adults aged >65 years (2,000–9,000 steps per day)[8]
  - Sleep durations were in line with National Sleep Foundation recommendations for adults (7–9 hours per night) and those aged ≥65 years (7–8 hours per night)[9]
- *i*CT to the all-oral IRd regimen provides patients with an option to transition off therapy with a parenteral PI, while continuing to receive the benefit of PI-based therapy

References

1. Mateos MV, et al. *Am J Hematol* 2015;90:314–9
2. Jimenez-Zepeda VH, et al. *Ann Hematol* 2017;96:431–9
3. Richardson PG, et al. *Blood Cancer J* 2018;8:109
4. Ailawadhi S, et al. *Cancer Med* 2022; doi: 10.1002/cam4.5239. Online ahead of print
5. Manda S, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:e910–25
6. Yimer HA, et al. *Clin Lymphoma Myeloma Leuk* 2022;22(suppl):S147–8
7. FDA Drug Trials Snapshots Summary Report 2020. Accessed October 2022
8. Tudor-Locke C, et al. *Int J Behav Nutr Phys Act* 2011;8:80
9. Hirshkowitz M, et al. *Sleep Health* 2015;1:40–3

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