Efficacy, Safety, and Quality of Life (QoL) in Patients With Newly Diagnosed Multiple Myeloma (NDMM) After *In*-class Transition (*i*CT) from Parenteral Bortezomib-Based Induction Therapy to All-Oral Ixazomib-Lenalidomide-Dexamethasone (IRd): Data from the Phase 4, Community-Based US MM-6 Study (Fully Accrued Cohort)

MM-253

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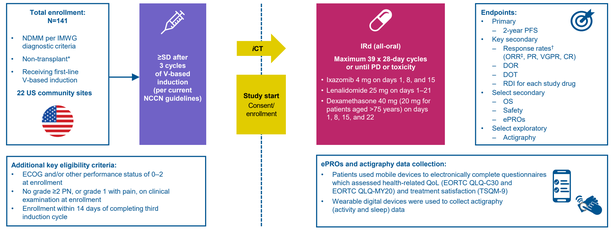
Background

- 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 such as toxicity, comorbidities, the burden of repeated, clinic-based treatment administration, difficulty traveling to treatment centers, and patient preference for treatment outside of a clinic[3]
- 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 IRd therapy in patients with NDMM (NCT03173092)[4]
- The objective of US MM-6 is to increase duration of PI-based therapy and improve outcomes while maintaining QoL
- Results were previously reported for the first 101 patients accrued (median follow-up 18.5 months)[5]
  - Median duration of IRd was 11.7 months and the overall response rate (ORR) after *i*CT to IRd was 78% (complete response [CR] 32%, molecular CR [mCR] 1%, stringent CR [sCR] 3%, very good partial response [VGPR] 25%, and partial response [PR] 17%)
- Here we report data for the fully accrued study cohort (final enrollment completed in May 2021; N=141)

Methods

- Full methods for US MM-6 have been published previously[4]
- The study design for US MM-6 is shown in **Figure 2**

Figure 2: US MM-6 study design



*Transplant-ineligible or transplant delayed by ≥24 months. †Assessed by investigator according to modified IMWG response criteria. Methods have been published previously. ‡ORR = PR + VGPR + CR + sCR + iCR + mCR. 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; DOR, duration of response; DOT, duration of treatment; ePRO, electronic patient-reported outcomes; iCR, immunophenotypic complete response; IMWG, International Myeloma Working Group; NCCN, National Comprehensive Cancer Network; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PN, peripheral neuropathy; RDI, relative dose intensity; 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 at 22 sites (one successfully screened patient was not treated) and were included in the safety and intent-to-treat (ITT) populations
- Patient demographics and baseline disease characteristics for these patients are shown in **Table 1**

Table 1: Baseline demographic and disease characteristics

Characteristic	IRd (N=140)
Median age,* years (range)	72.5 (48–90)
Age* ≥65 years, n (%)	111 (79.3)
Male, n (%)	81 (57.9)
Race, n (%)	
White	101 (72.1)
Black/African American	25 (17.9)
Asian	3 (2.1)
Native Hawaiian or Other Pacific Islander	1 (0.7)
Ethnicity, n (%)	
Hispanic/Latino	12 (8.6)
ISS† disease stage, n (%)	
I / II / III	37 (26.4) / 58 (41.4) / 44 (31.4)
CrCl‡ <60 mL/min, n (%)	40 (28.6)
≥1 comorbidity at start of IRd therapy, n (%)	131 (93.6)
Renal / urinary disorders§	45 (32.1)
Cardiac disorders§	39 (27.9)
Type 2 diabetes mellitus or diabetes mellitus	26 (18.6)
PN or sensory PN	25 (17.9)
Induction regimen, n (%)	
VRd	118 (84.3)
VCd	18 (12.9)
Other (Vd, VR)	4 (2.9)

*Age and CrCl captured at start of IRd. †ISS captured at start of V-based induction. ‡System organ class. CrCl, creatinine clearance; ISS, International Staging System; VCd, bortezomib-cyclophosphamide-dexamethasone; Vd, bortezomib-dexamethasone; VR, bortezomib-lenalidomide; VRd, bortezomib-lenalidomide-dexamethasone

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 community patients with NDMM?

Study design

Patients with non-transplant* NDMM in the US community setting (N=141) → Parenteral V-based induction (3 cycles) → *i*CT → IRd (all-oral regimen) Maximum 39 x 28-day cycles or until PD or toxicity

Primary endpoint: 2-year PFS
Key secondary endpoints included: Response rates (ORR, PR, VGPR, CR)

Results

Figure 1A: Response rates at the end of V-based induction and after *i*CT to IRd (ITT population; N=140†)

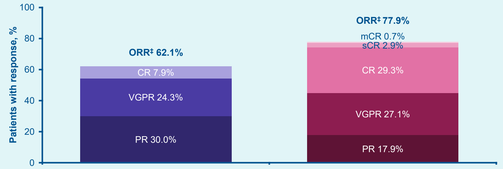
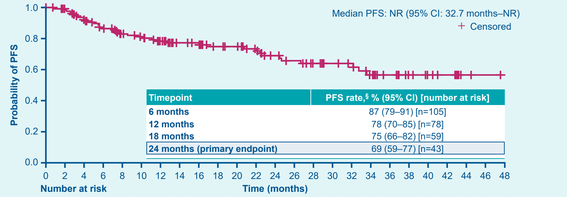


Figure 1B: Investigator-assessed PFS (from start of IRd; ITT population; N=140†)



Timepoint	PFS rate,§ % (95% CI) [number at risk]
6 months	87 (79–91) [n=105]
12 months	78 (70–85) [n=78]
18 months	75 (66–82) [n=59]
24 months (primary endpoint)	69 (59–77) [n=43]

Key take aways

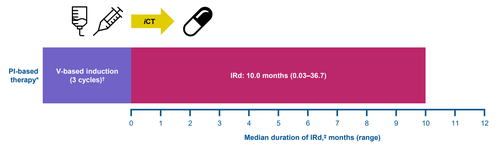
These fully accrued US MM-6 data confirm that *i*CT to IRd permits long-term PI-based therapy and improves responses, with promising PFS and OS seen in these mostly elderly, community-treated patients with NDMM and comorbidities

*Transplant-ineligible or transplant delayed by ≥24 months. †One successfully screened patient was not treated. ‡ORR = PR + VGPR + CR + sCR + iCR + mCR. §Kaplan–Meier estimates; PFS defined as the time from first administration of IRd to the date of the first documentation of PD based on local laboratory results and the investigator's assessment using modified IMWG response criteria, or death due to any cause, whichever occurred first.

Patient disposition and treatment exposure

- With a median follow-up of 20.0 months at data cut-off, 28 out of 140 patients (20%) were ongoing on IRd treatment; 102 (73%) had discontinued study treatment, and 10 (7%) had completed 39 cycles of IRd
- Among all 140 patients, median duration of IRd therapy was 10.0 months (range 0.03–36.7 months; **Figure 3**), with a median of 11 treated cycles (range 1–39 cycles)
  - 102 patients (73%) had completed 5 or more cycles of IRd
- Median duration of ixazomib therapy was 9.9 months (range 0.03–36.7 months)
- Median duration of all PI-based therapy (including V-based induction) was 12.7 months (range 2.6–39.7 months)

Figure 3: Median duration of IRd therapy from *i*CT (ITT population; N=140)



*Time from the date of first administration of the V-based induction regimen to the date of the last administration of ixazomib, lenalidomide, or dexamethasone. †V cycle length varied by regimen. ‡Not Kaplan–Meier estimates.

Response rates, PFS, and OS

- With a median follow-up of 20.0 months at data cut-off:
  - ORR had increased from 62% (CR 8%; VGPR 24%; PR 30%) at the end of V-based induction to 78% after *i*CT to IRd (CR [including sCR and mCR] 33%; VGPR 27%; PR 18%) (**Figure 1A**)
  - The 2-year PFS rate (Kaplan–Meier estimate) from the start of IRd treatment was 69% (95% confidence interval [CI]: 59–77%); median PFS had not been reached (95% CI: 32.7 months–not reached [NR]) (**Figure 1B**)
  - The 2-year OS rate (Kaplan–Meier estimate) from the start of IRd treatment was 85% (95% CI: 76–90%); median OS had not been reached (95% CI: NR–NR)

Safety

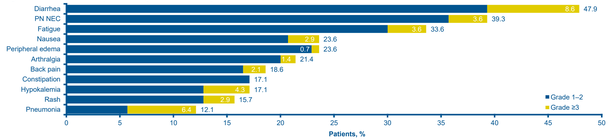
- The adverse event (AE) profile of IRd is shown in **Table 2**
- The most common treatment-emergent AEs (TEAEs) are shown in **Figure 4** and included gastrointestinal disorders and PN

Table 2: Overview of the safety profile of IRd (safety population; N=140)

TEAEs, n (%)	IRd (N=140)
Any TEAE	135 (96.4)
Treatment-related	110 (78.6)
Grade ≥3 TEAEs	92 (65.7)
Treatment-related	50 (35.7)
Serious TEAEs	61 (43.6)
Treatment-related	19 (13.6)
TEAE leading to drug modification*	83 (59.3)
TEAE leading to drug discontinuation*	21 (15.0)
On-study deaths†	4 (2.9)

*Modifications and discontinuations for any of the 3 study drugs. †Occurring <30 days after last dose; deaths were due to unrelated end-stage renal disease, treatment-related pneumonia, disease-related complications, and unknown (n=1 each).

Figure 4: Most commonly occurring TEAEs* (safety population; N=140)

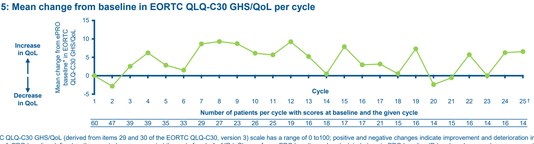


*In >15% of patients at any grade or >5% at ≥grade 3. PN NEC, peripheral neuropathy not elsewhere classified; high-level term.

QoL and treatment satisfaction (ePROs)

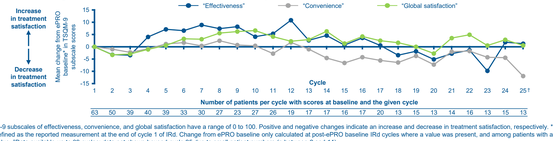
- Out of a total of 1,775 EORTC QLQ-C30, EORTC QLQ-MY20, and TSQM-9 questionnaires which could have been completed (i.e. all possible assessments across all cycles to date; patients were anticipated to complete a form every cycle during IRd treatment), 945 (53.2%), 953 (53.7%), and 953 (53.7%) had been completed, respectively
- Patient-reported QoL (EORTC QLQ-C30 Global Health Status [GHS]/QoL score) and treatment satisfaction (TSQM-9 Global Satisfaction, Effectiveness, and Convenience scores) were maintained during IRd therapy (**Figures 5** and **6**)
- EORTC QLQ-MY20 item 43 ('during the past week have you experienced tingling in your hands or feet?') measures the burden of peripheral neuropathy[6]
  - 1 = Not at all; 2 = A little; 3 = Quite a bit; 4 = Very much
  - Mean change from ePRO baseline (defined as the reported measurement at the end of cycle 1 of IRd) was ≤0.7 through cycle 25 (patient numbers were ≤13 after cycle 25)

Figure 5: Mean change from baseline in EORTC QLQ-C30 GHS/QoL per cycle



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 to100; 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; data not shown beyond cycle 25 due to small patient numbers (n between 1 and 14).

Figure 6: Mean change from baseline in TSQM-9 subscale scores per cycle

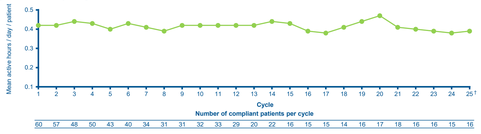


The TSQM-9 subscales of effectiveness, convenience, and global satisfaction have a range of 0 to 100. Positive and negative changes indicate an increase and decrease in treatment satisfaction, respectively. *ePRO baseline defined as the reported measurement at the end of cycle 1 of IRd. Change from ePRO 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; data not shown beyond cycle 25 due to small patient numbers (n between 2 and 14).

Actigraphy

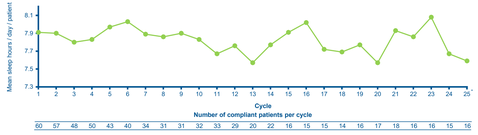
- For actigraphy data collection to be compliant, the device had to be worn for ≥12 hours/day for ≥14 days/cycle; the days did not need to be consecutive. Non-compliant data were excluded from the analysis
- Among 93 patients with any available daily actigraphy data (a total of 25,580 days), a total of 23,241 (91%) compliant days were included in the actigraphy analysis
  - The mean number of steps per day was 2,982 (standard deviation [StDev] 2,258)
  - Mean daily active time was 0.40 hours (StDev 0.31) and is shown by cycle (up to cycle 25) in **Figure 7**
  - Mean daily sleep time was 7.57 hours (StDev 2.75) and is shown by cycle (up to cycle 25) in **Figure 8**

Figure 7: Mean daily active time* per cycle



*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 4 and 14).

Figure 8: Mean daily sleep time per cycle



*Data available up to 39 cycles; data not shown beyond cycle 25 due to small patient numbers (n between 4 and 14).

Conclusions

- These US MM-6 data from the fully accrued study cohort confirm previous findings from this study[5]
- *i*CT to IRd permits long-term PI-based therapy in these mostly elderly, comorbid, community-treated patients with NDMM
- ORR increased from 62% at the end of V-based induction to 78% following *i*CT to IRd
  - This ORR achieved using the *i*CT approach in community-based US MM-6 patients is comparable to the ORR of 82% reported in transplant-ineligible patients with NDMM treated with IRd in the clinical trial setting[7]
- PFS and OS results were promising
- The AE profile of IRd in US MM-6 was similar to previous clinical reports[7,8]
- No adverse impact of *i*CT to IRd on QoL or treatment satisfaction was observed
- Patients receiving IRd achieved activity levels (in terms of steps per day) and sleep durations comparable to previously published data[9,10]

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Disclosures

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Poster presentation at the 10th Society of Hematologic Oncology (SOHO) Annual Meeting, September 28–October 01, 2022, Houston, USA. For questions or comments please contact Dr Sudhir Manda: sudhir.manda@usoncology.com