In-class transition from parenteral bortezomib to oral ixazomib in newly diagnosed multiple myeloma: Updated analysis of US MM-6 overall and by patient subgroups of interest

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Leon Bernal-Mizrachi,[1] Ralph Boccia,[2] Rami Owera,[3] Ramalingam Ratnasabapathy,[4] Kimberly Bogard,[5] Eric Lloyd,[5] Stephen J. Noga,[5] Ruemu Birhiray[6]

[1]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [2]Center for Cancer and Blood Disorders, Bethesda, MD, USA; [3]Woodlands Medical Specialists, Pensacola, FL, USA; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [5]Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, USA; [6]Hematology Oncology of Indiana/American Oncology Network, Indianapolis, IN, USA

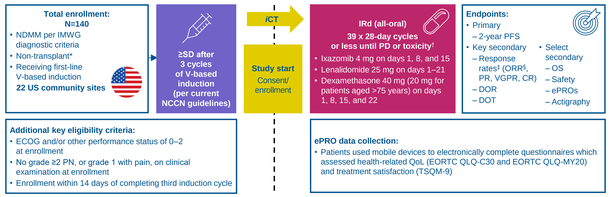
Background

- Although parenteral proteasome inhibitor (PI) therapy can improve survival outcomes in multiple myeloma (MM),[1] prolonged treatment may be difficult to achieve in practice, owing to related toxicity and administration burden, particularly among elderly and frail patients who tend to be transplant-ineligible[2-4]
- Notably, due to strict eligibility criteria, patients enrolled in randomized controlled trials (RCTs) do not wholly reflect the older and frailer patients seen in clinical practice[5]
- 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) in patients with newly diagnosed MM (NDMM; NCT03173092)
  - The key objective was to prolong duration of PI-based therapy and improve outcomes, while maintaining quality of life (QoL) and a tolerable safety profile in a patient population representative of that seen in routine clinical practice[6]
  - Results from the fully accrued study cohort (N=140; median follow-up 26.8 months) showed a 2-year progression-free survival (PFS) rate of 71%, with no notable differences in subgroups defined by patient age, frailty status, or RCT eligibility[6,7]
- We report an updated 3-year PFS analysis of the US MM-6 study

Methods

- Full methods for US MM-6 have been published previously;[8] the study design is shown in **Figure 2**
- In the current analysis, efficacy and safety were assessed in the intent-to-treat (ITT) population and by age (<75 vs ≥75 years), frailty status (non-frail vs frail), and RCT eligibility (eligible vs ineligible)
- Frailty status was determined using a modified Charlson Comorbidity Index score, age, and Eastern Cooperative Oncology Group performance status (ECOG PS)[9]
- RCT eligibility status was based on whether any patient baseline characteristic met common RCT ineligibility criteria including hematologic/organ dysfunction, ECOG PS >2, renal dysfunction, prior malignancies, cardiac dysfunction, and pulmonary disease

Figure 2. Study design



*Transplant-ineligible or transplant delayed by ≥24 months. †Whichever occurs first. ‡Assessed by investigator according to modified IMWG response criteria. §ORR = PR + VGPR + CR + sCR + iCR + mCR.

CR, complete response; DOR, duration of response; DOT, duration of treatment; EORTC, European Organisation for Research and Treatment of Cancer; ePROs, electronic patient-reported outcomes; iCR, immunophenotypic CR; IMWG, International Myeloma Working Group; mCR, molecular CR; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PD, progressive disease; PN, peripheral neuropathy; PR, partial response; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-MY20, Quality of Life Questionnaire Multiple Myeloma module 20 – item 43 measuring PN; SD, stable disease; sCR, stringent CR; TSQM-9, Treatment Satisfaction Questionnaire for Medication – 9 items; VGPR, very good PR.

Results

Baseline demographics and patient disposition

- At time of data abstraction (October 12, 2023), of the 140 patients who had received treatment with IRd, 42% were aged ≥75 years, 61% were classified as frail, and 41% were deemed RCT-ineligible (**Table 1**)
- With a median follow-up of 36.0 months, eight patients (6%) in the ITT population were ongoing on IRd treatment while 79% had discontinued study treatment and 15% had completed IRd treatment; the most common reason for IRd discontinuation was the occurrence of adverse events (**Table 2**)

Table 1. Baseline demographics and disease characteristics

Characteristic	ITT population (N=140)*	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)	RCT-eligible (n=83)	RCT-ineligible (n=57)
Median age, years (range)†	72.5 (48–90)	69 (48–74)	77.0 (75–90)	71.0 (49–78)	75.0 (48–90)	72.0 (49–86)	73.0 (48–90)
Age ≥75 years, %†	42.1	0	100	22.2	54.7	42.2	42.1
Male, %	57.9	60.5	54.2	64.8	53.5	60.2	54.4
Race, %							
White	72.9	70.4	76.3	74.1	72.1	69.9	77.2
Black/African American	17.9	18.5	16.9	14.8	19.8	19.3	15.8
Asian	2.1	2.5	1.7	1.9	2.3	2.4	1.8
Native Hawaiian or Other Pacific Islander	0.7	1.2	0	1.9	0	1.2	0
Ethnicity, %							
Hispanic/Latino	8.6	11.1	5.1	9.3	8.1	10.8	5.3
ISS disease stage, %‡							
I / II / III	26.4 / 41.4 / 31.4	25.9 / 43.2 / 29.6	27.1 / 39.0 / 33.9	25.9 / 42.6 / 31.5	26.7 / 40.7 / 31.4	27.7 / 42.2 / 30.1	24.6 / 40.4 / 33.3
CrCl <60 mL/min, %†	28.6	23.5	35.6	14.8	37.2	26.5	31.6
≥1 comorbidity at start of IRd therapy, %	94.3	92.6	96.6	94.4	94.2	91.6	98.2
Renal/urinary disorders§	32.9	27.2	40.7	16.7	43.0	21.7	49.1
Cardiac disorders§	28.6	27.2	30.5	16.7	36.0	9.6	56.1
T2DM or DM	18.6	20.9	15.3	9.3	24.4	15.7	22.8
PN or sensory PN	20.7	25.9	13.6	24.1	18.6	18.1	24.5
Induction regimen, %							
VRd	84.3	84.0	84.7	87.0	82.6	85.5	82.5
VCd	12.9	13.6	11.9	9.3	15.1	13.3	12.3
Other (Vd, VR)	2.9	2.5	3.4	3.7	2.3	1.2	5.3

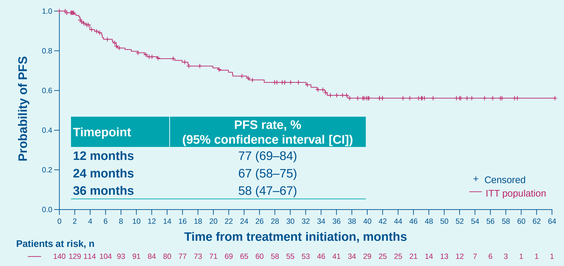
*141 patients were successfully screened, one was not treated. †Age and CrCl captured at start of IRd. ‡ISS captured at start of V-based induction. §System organ class.
CrCl, creatinine clearance; DM, diabetes mellitus; ISS, International Staging System; T2DM, type 2 DM; VCd, bortezomib-cyclophosphamide-dexamethasone; Vd, bortezomib-dexamethasone; VR, bortezomib-lenalidomide; VRd, bortezomib-lenalidomide-dexamethasone.

Question — Does *in*-class transition (*i*CT) from V-based induction regimens to IRd improve outcomes among a community-based cohort of patients with NDMM, while enabling prolonged (3 years) all-oral PI-based therapy?

Study design — Patients with non-transplant* NDMM in the US community setting (N=140) → Parenteral V-based induction (3 cycles) → *i*CT → IRd (all-oral regimen) 39 x 28-day cycles or less until PD or toxicity† → **Primary endpoint:** 2-year PFS; **Key secondary endpoint:** Response rates

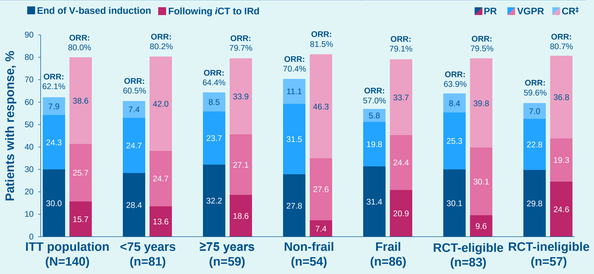
Results

Figure 1A. Investigator-assessed PFS from start of IRd (Kaplan-Meier estimate; N=140)



*Transplant-ineligible or transplant delayed by ≥24 months.

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



†Whichever occurs first. ‡Total CR = CR + sCR + iCR + mCR; totals may not sum due to rounding.

Key conclusion — These data show that *i*CT from V-based induction to IRd permits long-term (3-year), tolerable PI-based therapy translating into improved efficacy in community-treated patients with NDMM who are representative of the wider NDMM population.

Table 2. Patient disposition

	ITT population (N=140)	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)	RCT-eligible (n=83)	RCT-ineligible (n=57)
Median follow-up	36.0	36.0	36.0	34.6	37.7	36.0	37.3
Ongoing IRd, %	5.7	4.9	6.8	5.6	5.8	8.4	1.8
Discontinued IRd,* %	79.3	76.5	83.1	85.2	75.6	77.1	82.5
Adverse event	30.6	29.0	32.7	37.0	26.2	34.4	25.5
Patient withdrawal	26.1	25.8	26.5	26.1	26.2	26.6	25.5
Progressive disease	20.7	21.0	20.4	10.9	27.7	15.6	27.7
Physician decision	18.9	21.0	16.3	23.9	15.4	18.8	19.1
Completed IRd, %	15.0	18.5	10.2	9.3	18.6	14.5	15.8

*Most common reasons occurring in >15% of patients in any subgroup.

Duration of treatment

- Among all 140 patients, median DOT was 14 months with all PI-based therapy, and 11 months with IRd therapy; **Table 3** shows DOT by patient subgroup

Table 3. DOT in the ITT population and by subgroups

	ITT population (N=140)	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)	RCT-eligible (n=83)	RCT-ineligible (n=57)
Median DOT, months							
All PI-based*	14	18	12	15	13	13	17
IRd	11	14	9	12	10	10	12

*Including V-based induction.

Progression-free survival

- In the ITT population, the 3-year PFS rate from the start of IRd treatment was 58% and median PFS was not reached (**Summary Panel; Figure 1A**)
- 3-year PFS rates were higher in patients who were aged <75 vs ≥75 years (65% vs 46%; **Figure 3**), in non-frail vs frail patients (62% vs 55%; **Figure 4**), and in RCT-eligible vs RCT-ineligible patients (62% vs 52%; **Figure 5**); these rates were not meaningfully different

Figure 3. PFS by age

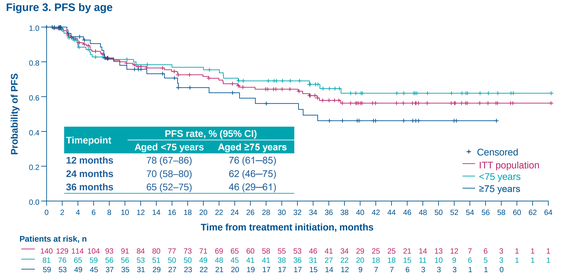


Figure 4. PFS by frailty status

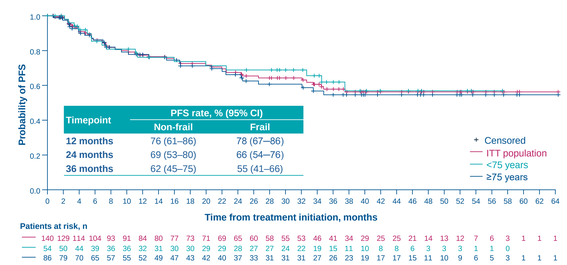
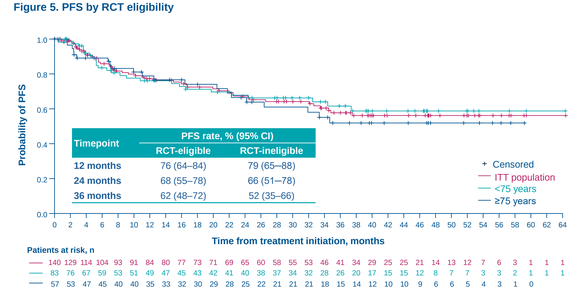


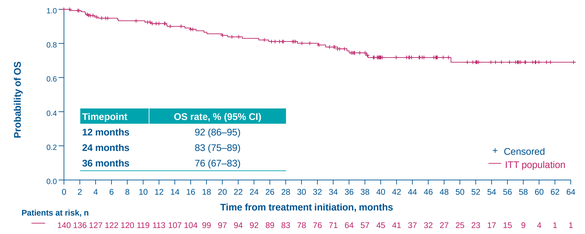
Figure 5. PFS by RCT eligibility



Overall survival

- The 3-year OS rate in the ITT population was 76% and the median was not reached (**Figure 6**)
- 3-year OS rates in the subgroups were:
  - 81% vs 67% in the <75 vs ≥75-year age subgroups
  - 77% vs 75% in the non-frail vs frail subgroups
  - 75% vs 77% in the RCT-eligible vs RCT-ineligible subgroups

Figure 6. 3-year OS rate in the ITT population



Response rates

- Following *i*CT to IRd, in the ITT population, the ORR increased from 62% to 80% and the ≥VGPR rate increased from 32% to 64% (**Summary Panel**; **Figure 1B**)
  - Increases in ORR were also observed for all patient subgroups evaluated (**Summary Panel**; **Figure 1B**)
- At 3 years, DOR rate was 62% in the ITT population; corresponding results in the subgroups were:
  - 71% vs 47% in the <75 vs ≥75-year age subgroups
  - 64% vs 60% in the non-frail vs frail subgroups
  - 66% vs 55% in the RCT-eligible vs RCT-ineligible subgroups

Safety overview

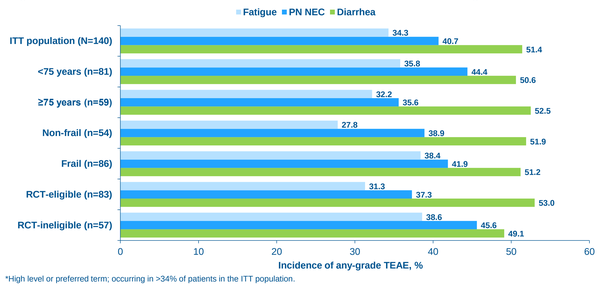
- Of all 140 patients, 99% reported ≥1 treatment-emergent adverse event (TEAE), 70% reported a grade ≥3 TEAE, and 37% reported a grade ≥3 treatment-related TEAE
- Safety outcomes were generally comparable between age subgroups, although treatment-related grade ≥3 TEAEs occurred in a lower proportion of patients aged <75 years (**Table 4**)
  - Grade ≥3 TEAEs that were less common in younger patients included diarrhea (7.4% vs 11.9% in the ≥75-year subgroup) and pneumonia (3.7% vs 8.5% in the ≥75-year subgroup)
    - Grade ≥3 pneumonia was also reported less frequently in non-frail vs frail patients (1.9% vs 8.1%)
- Incidences of grade ≥3 TEAEs, serious TEAEs, and TEAEs leading to dose modification were lower in non-frail vs frail patients; this was also the case for the RCT-eligible vs RCT-ineligible patients, except for the incidence of serious TEAEs, which was similar in the two subgroups (**Table 4**)
- Overall, the most common TEAEs were diarrhea, fatigue, and PN not elsewhere classified (NEC; **Figure 7**)

Table 4. Overview of IRd safety

TEAE, %	ITT population (N=140)	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)	RCT-eligible (n=83)	RCT-ineligible (n=57)
Any grade	98.6	98.8	98.3	98.1	98.8	98.8	98.2
Treatment-related	82.1	85.2	78.0	87.0	79.1	81.9	82.5
Grade ≥3	70.0	70.4	69.5	61.1	75.6	66.3	75.4
Treatment-related	37.1	33.3	42.4	35.2	38.4	36.1	38.6
Serious	44.3	42.0	47.5	38.9	47.7	44.6	43.9
Treatment-related	12.9	12.3	13.6	14.8	11.6	13.3	12.3
Leading to dose modification*	68.6	66.7	71.2	61.1	73.3	66.3	71.9
Leading to discontinuation*	21.4	21.0	22.0	27.8	17.4	21.7	21.1
On-study deaths†	3.6	2.5	5.1	1.9	4.7	1.2	7.0

*Modifications and discontinuations for any of the 3 study drugs. †Occurring <30 days after last dose.

Figure 7. Incidences of the most common* TEAEs in the ITT population and in patient subgroups



*High level or preferred term; occurring in >34% of patients in the ITT population.

Conclusions

- In non-transplant patients with NDMM, *i*CT from V-based induction to all-oral IRd enabled long-term (3-year) PI-based treatment and improved depth of response while maintaining a tolerable safety profile
- The expected decrement in outcomes associated with older, frail, and RCT-ineligible patients was observed; however, these results were not meaningfully different
- Long-term triplet consolidation with IRd may provide an alternative approach to induction/maintenance for community-based NDMM patients who are not eligible for upfront transplantation, including those who are older, frail, and/or have comorbidities

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Disclosures

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