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Long-term proteasome inhibitor-based therapy in multiple myeloma following *in*-class transition (*i*CT) from parenteral bortezomib-based induction to all-oral ixazomib-lenalidomide-dexamethasone: analysis of the community-based US MM-6 study by age

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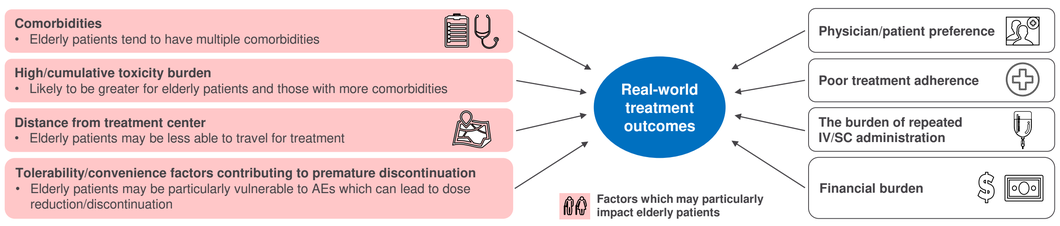
INTRODUCTION AND METHODS

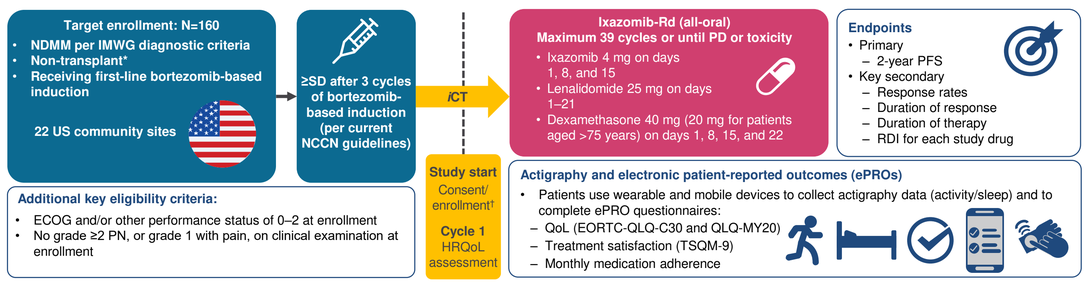
- Long-term treatment is associated with improved outcomes in transplant-ineligible NDMM.[1,2]
- Additionally in this setting, triplet regimens demonstrate prolonged outcomes versus doublets,[3–5] with PI-based triplet therapy associated with prolonged outcomes.[6,7]
- However, long-term treatment with parenteral PI-based therapy can be challenging to achieve in both the clinical trial[4,8] and real-word settings.[9]
- Multiple factors may contribute to reduced treatment duration in routine clinical practice, and to the disparity between efficacy reported in clinical trials and real-world effectiveness (**Figure 1**).[9]

Figure 1. Factors affecting treatment outcomes in real-world settings[9]



- Elderly patients may have more challenges and may be less able to tolerate triplet therapy than younger patients, resulting in poorer outcomes.[10,11]
- Thus, novel, tolerable treatment approaches, particularly for elderly patients, are required, to enable patients to receive prolonged treatment and achieve better outcomes.
- US MM-6 (NCT03173092) is an ongoing, community-based, real-world, open-label, single-arm phase 4 study investigating a novel *i*CT approach in the diverse US community population with the aim of increasing PI-based treatment duration while maintaining QoL and improving outcomes (**Figure 2**).

Figure 2. US MM-6 Study design



*Transplant-ineligible or transplant will be delayed at least 24 months. †Enrollment within 14 days of completing third induction cycle.

RESULTS

- As of November 18, 2019, 84 patients had been enrolled at 19 sites and received ≥1 dose of ixazomib-Rd.
- Fifty-six percent (n=47) and 44% (n=37) of patients were aged <75 and ≥75 years, respectively (**Table 1**).

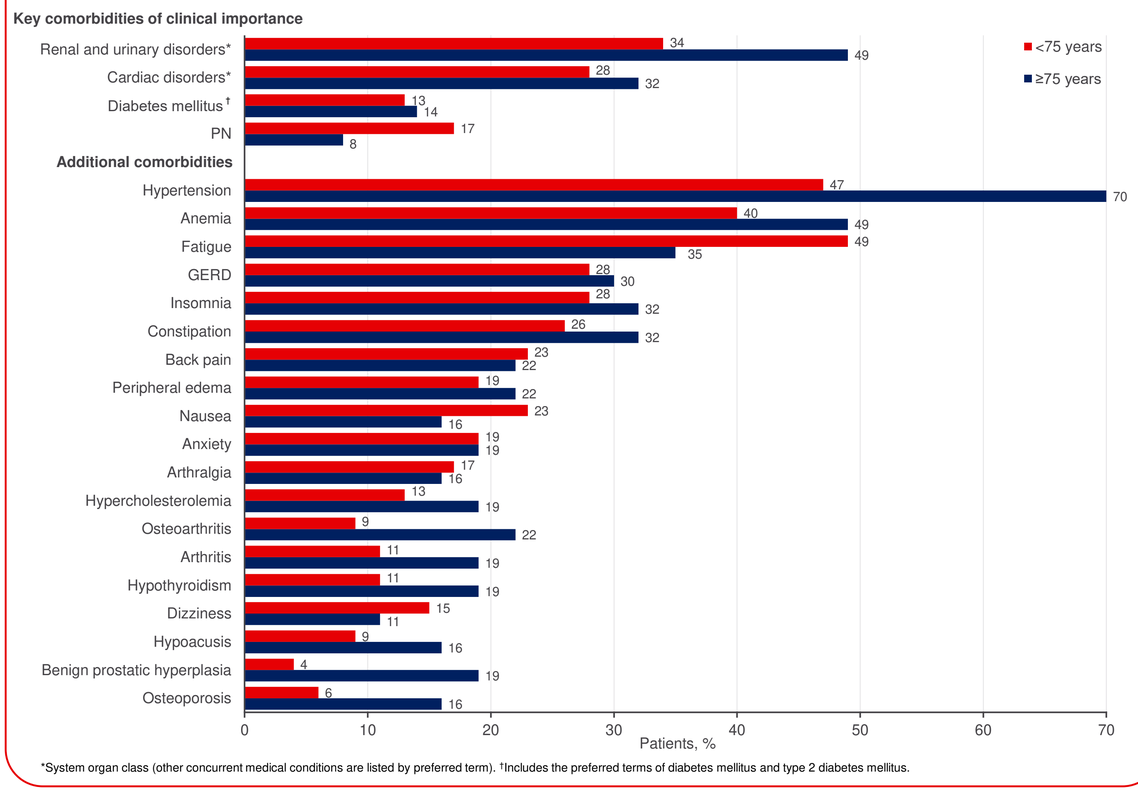
Table 1. Patient demographics and baseline disease characteristics in US MM-6 by patient age

		Ixazomib-Rd	
Characteristic	**Overall (N=84)**	**<75 years (n=47)**	**≥75 years (n=37)**
Median age, years (range)	73 (49–90)	68 (49–74)	78 (75–90)
Male, n (%)	41 (49)	23 (49)	18 (49)
Race, n (%)			
White	61 (73)	37 (79)	24 (65)
Black or African American	13 (15)	6 (13)	7 (19)
Asian	2 (2)	1 (2)	1 (3)
Multiple	1 (1)	0	1 (3)
Missing	7 (8)	3 (6)	4 (11)
Hispanic/Latino ethnicity, n (%)	8 (10)	6 (13)	2 (5)
ISS stage at initial diagnosis, n (%)			
I	22 (26)	14 (30)	8 (22)
II	25 (30)	14 (30)	11 (30)
III	29 (35)	12 (26)	17 (46)
Unknown	8 (10)	7 (15)	1 (3)
Lytic bone disease, n (%)	35 (42)	20 (43)	15 (41)
Extramedullary disease, n (%)	6 (7)	4 (9)	2 (5)
Median creatinine clearance, ml/min (range)*	69 (12–226)	81 (12–226)	63 (19–133)
Creatinine clearance <60 ml/min, n (%)	24 (29)	10 (21)	14 (38)

*Overall: n=76; <75 years: n=42; ≥75 years: n=34.

- Comorbidities of clinical importance were renal and urinary disorders (overall, 40%: <75 vs ≥75 years, 34% vs 49%), cardiac disorders (30%: 28% vs 32%), diabetes mellitus (13%: 13% vs 14%), and PN (13%: 17% vs 8%) (**Figure 3**).

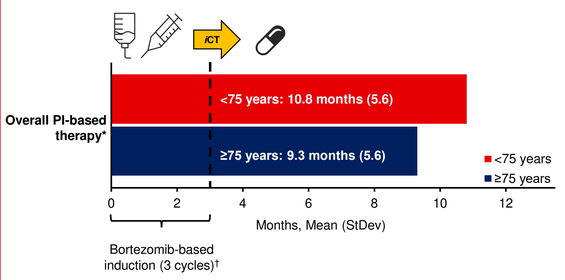
Figure 3. Patient comorbidities: concurrent medical conditions at the time of enrollment (≥15% of patients in either subgroup and specific other comorbidities of clinical importance) by patient age group



*System organ class (other concurrent medical conditions are listed by preferred term). †Includes the preferred terms of diabetes mellitus and type 2 diabetes mellitus.

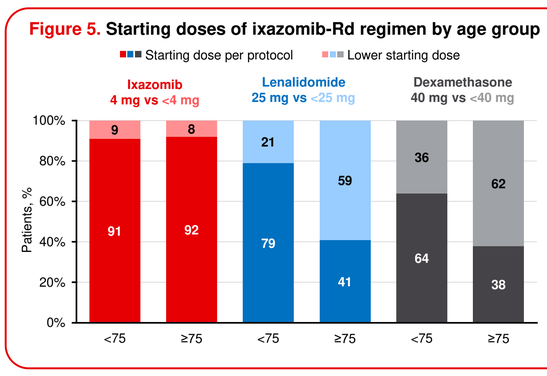
- At data cut-off, 62% of patients remained on therapy overall (<75 vs ≥75 years, 68% vs 54%).
- Treatment was discontinued due to progressive disease (<75 vs ≥75 years, n=3 vs 2), adverse events (n=2 vs 2), and 'other' (n=10 vs 13).
- Overall, mean duration of PI therapy was 10.1 months (StDev 5.6); mean duration by patient age at data cut-off is shown in **Figure 4.**
- Patients aged <75 and ≥75 years have received up to 20 and 23 cycles of therapy with ixazomib-Rd, respectively.
- Starting doses of ixazomib were similar between age groups but starting doses of lenalidomide and dexamethasone were lower in older patients **(Figure 5)**.

Figure 4. Duration of therapy by patient age at data cut-off



*Time from the date of first administration of the bortezomib-based induction regimen to the date of the last administration of ixazomib, lenalidomide, or dexamethasone. †Bortezomib cycle length varied by regimen.

Figure 5. Starting doses of ixazomib-Rd regimen by age group

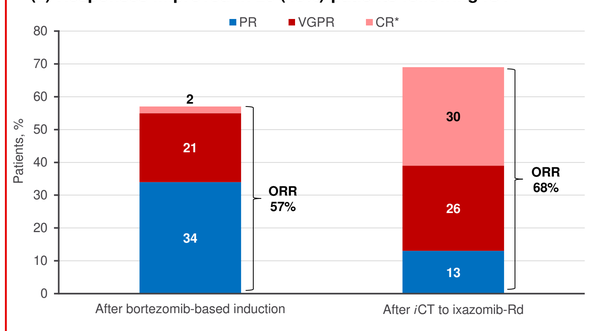


RESULTS (CONTINUED)

- Among all 84 patients, the ORR was 62% (29% ≥VGPR) after bortezomib-based induction and 70% (55% ≥VGPR) following *i*CT to ixazomib-Rd.
- Response rates after bortezomib-based induction and after *i*CT in patients aged <75 and ≥75 years are shown in **Figure 6**.
- Responses improved in 29 patients (35%) overall, including 20 (43%) and 9 (24%) patients aged <75 and ≥75 years, respectively.
- PFS data were immature at the time of this analysis and are not reported.

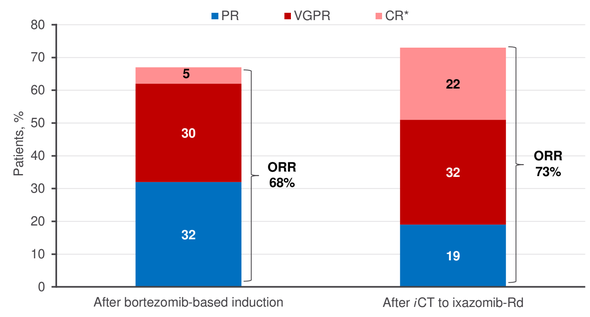
Figure 6. Investigator-assessed best overall responses after bortezomib-based induction and following *i*CT to ixazomib-Rd for patients aged (a) <75 years and (b) ≥75 years

(a) Responses improved in 20 (43%) patients following *i*CT



	<75 years (n=47)	
n (%) [95% CI]	**Bortezomib-based induction**	***i*CT to ixazomib-Rd**
ORR (CR*+ VGPR+PR)	27 (57) [42–72]	32 (68) [52.9–80.9]
≥VGPR	11 (23)	26 (55)
CR*	1 (2) [0.1–11]	14 (30) [17.3–44.9]
VGPR	10 (21) [11–36]	12 (26) [13.9–40.3]
PR	16 (34) [21–49]	6 (13) [4.8–25.7]
MR	0	1 (2)
SD	17 (36)	9 (19)
Not evaluable	3 (6)	5 (11)

(b) Responses improved in 9 (24%) patients following *i*CT



	≥75 years (n=37)	
n (%) [95% CI]	**Bortezomib-based induction**	***i*CT to ixazomib-Rd**
ORR (CR*+ VGPR+PR)	25 (68) [50.2–82.0]	27 (73) [55.9–86.2]
≥VGPR	13 (35)	20 (54)
CR*	2 (5) [0.7–18]	8 (22) [9.8–38.2]
VGPR	11 (30) [16–47]	12 (32) [18.0–49.8]
PR	12 (32) [18–50]	7 (19) [8.0–35.2]
MR	3 (8)	1 (3)
SD	6 (16)	4 (11)
Not evaluable	3 (8)	5 (14)

*CR category will include patients who achieved CR/sCR/Immunophenotypic CR/Molecular CR

- Safety profiles indicate ixazomib-Rd is generally feasible and tolerable in younger and older patients.
- Overall, any-grade TEAEs were reported for 92% of patients and TEAEs led to drug modification and discontinuation in 50% and 7% of patients, respectively; a summary of safety data by patient age is presented in **Figure 7**.
- Any-grade TEAEs occurring in ≥10% of patients in either age group are shown in **Figure 8**.
- Grade 3 TEAEs occurring in ≥5% of patients in either age group are shown in **Figure 9**.

Figure 7. Overview of the safety profile of ixazomib-Rd by patient age

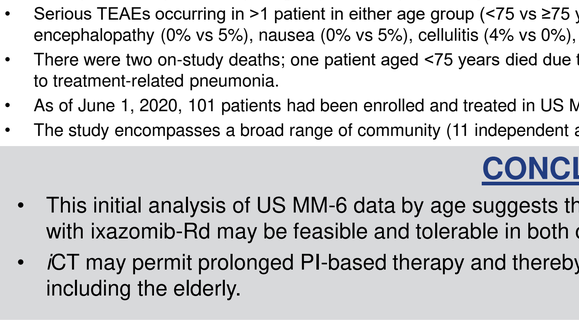
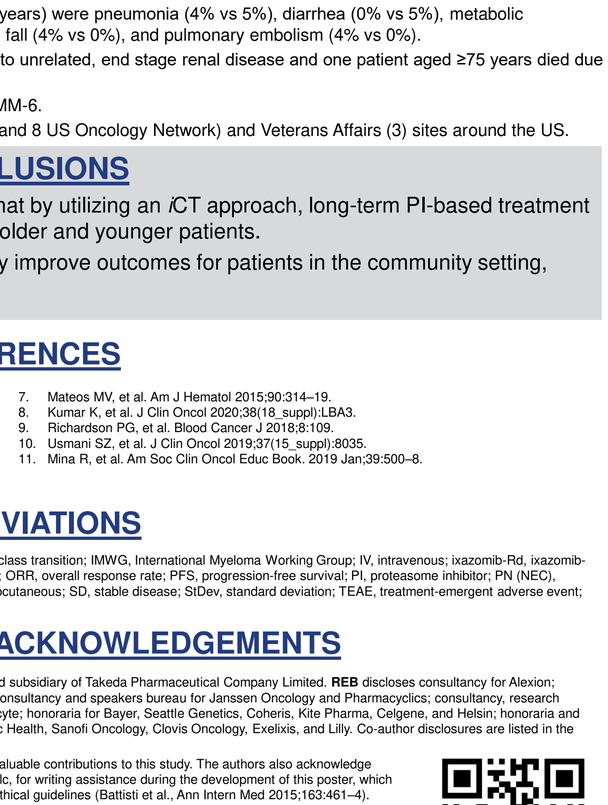
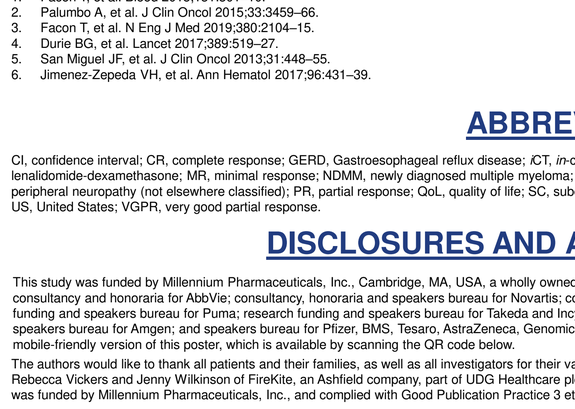


Figure 8. Frequently occurring* any-grade TEAEs by patient age



*Cut-off for inclusion was ≥10% of patients in either age group. †High-level term.

Figure 9. Frequently occurring* grade 3 TEAEs by patient age



*Cut-off for inclusion was ≥5% of patients in either age group.

- Grade 4 TEAEs occurred in 4 and 2 patients aged <75 and ≥75 years, respectively.
  - These were septic shock, neutrophil count decrease, white blood cell count decrease, hypercalcemia and pulmonary embolism in patients aged <75 years and cardiac failure, atrial fibrillation, metabolic acidosis and metabolic encephalopathy in patients aged ≥75 years (patients could have had >1 grade 4 TEAE).
- TEAEs that led to study drug dose modification in patients aged <75 vs ≥75 years included diarrhea (4% vs 14%), PN NEC (11% vs 8%), nausea (4% vs 5%), cellulitis (6% vs 0%), fatigue (6% vs 0%), and dehydration (0% vs 5%).
- Serious TEAEs occurring in >1 patient in either age group (<75 vs ≥75 years) were pneumonia (4% vs 5%), diarrhea (0% vs 5%), metabolic encephalopathy (0% vs 5%), nausea (0% vs 5%), cellulitis (4% vs 0%), fall (4% vs 0%), and pulmonary embolism (4% vs 0%).
- There were two on-study deaths; one patient aged <75 years died due to unrelated, end stage renal disease and one patient aged ≥75 years died due to treatment-related pneumonia.
- As of June 1, 2020, 101 patients had been enrolled and treated in US MM-6.
- The study encompasses a broad range of community (11 independent and 8 US Oncology Network) and Veterans Affairs (3) sites around the US.

CONCLUSIONS

- This initial analysis of US MM-6 data by age suggests that by utilizing an *i*CT approach, long-term PI-based treatment with ixazomib-Rd may be feasible and tolerable in both older and younger patients.
- *i*CT may permit prolonged PI-based therapy and thereby improve outcomes for patients in the community setting, including the elderly.

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ABBREVIATIONS

CI, confidence interval; CR, complete response; GERD, Gastroesophageal reflux disease; *i*CT, *in*-class transition; IMWG, International Myeloma Working Group; IV, intravenous; ixazomib-Rd, ixazomib-lenalidomide-dexamethasone; MR, minimal response; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; PN (NEC), peripheral neuropathy (not elsewhere classified); PR, partial response; QoL, quality of life; SC, subcutaneous; SD, stable disease; StDev, standard deviation; TEAE, treatment-emergent adverse event; US, United States; VGPR, very good partial response.

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