In-class transition from parenteral bortezomib to oral ixazomib in newly diagnosed multiple myeloma: Analysis of US MM-6 by number of treatment cycles received

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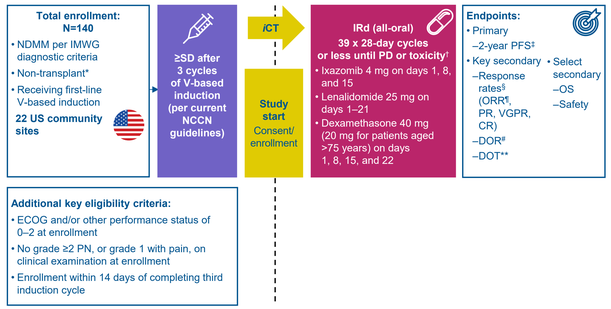
Background

- Results from clinical trials have shown that among patients with newly diagnosed multiple myeloma (NDMM), long-term proteasome inhibitor (PI)-based therapy can improve overall survival and delay disease progression[1–3]
- Achieving this in routine clinical practice, however, is challenging, given that real-life patients tend to be older and frail, and have comorbid conditions[4,5]
- 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 NDMM (NCT03173092)
  - The key objective is to prolong duration of PI-based therapy and improve outcomes, while maintaining quality of life[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 among subgroups classified by patient age or clinical trial eligibility[6,7]
- Here, we report results of the US MM-6 study analyzed according to number of treatment cycles received

Methods

- Full methods for US MM-6 real-world, open-label, single-arm study have been published previously;[8] the study design is shown in **Figure 3**[6,8]
- In the current analysis, efficacy and safety were assessed in subgroups of patients who had received 1−3, 4−9, and >9 cycles of IRd (or 4–6, 7–12, and >12 cycles of overall PI-based therapy, respectively)
- Comorbidities were assessed via a modified Charlson Comorbidity Index (mCCI); a score of 0 indicates no comorbidities, while higher scores indicate higher probability of mortality in patients with comorbidities[9]

Figure 3: Study design



*Transplant-ineligible or transplant delayed by ≥24 months. †Whichever occurs first. ‡Defined as time from date of first administration of IRd to first disease progression. §Proportion of patients achieving a response as assessed by investigator according to modified IMWG response criteria. ¶ORR = PR + VGPR + CR + sCR + iCR + mCR. #Defined as time from first documentation of a PR or better to the date of first documentation of PD. **Defined as time from date of first IRd administration to the date of last administration of any study drug.

CR, complete response; DOR, duration of response; DOT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; 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; SD, stable disease; sCR, stringent CR; V, bortezomib; VGPR, very good PR.

Results

Patient disposition and baseline characteristics

- At data cutoff (October 12, 2023), of the 140 patients who had received treatment with IRd, 27 patients had received 1−3 cycles, 35 had received 4−9 cycles, and 78 had received >9 cycles
- Median follow-up was 3.2, 29.0, and 38.8 months in the 1–3, 4–9, and >9 cycle subgroups, respectively
- All patients in the 1–3 and 4–9 cycle subgroups had discontinued IRd at data cutoff, and 62.8% had discontinued treatment in the >9 cycle subgroup
  - Most common reasons (>25%) for treatment discontinuation were patient withdrawal (40.7%) and adverse events ([AEs] 37%) in the 1−3 cycle subgroup; AEs, progressive disease, or physician decision (25.7% each) in the 4−9 cycle subgroup; and AEs (30.6%) in the >9 cycle subgroup
- In the 1−3, 4−9, and >9 cycle subgroups, respectively, 51.9%, 45.7%, and 37.2% of patients were aged ≥75 years, and the majority had ≥1 comorbidity at baseline (**Table 1**)
  - Overall, 48.1%, 48.6%, and 46.2% of patients had an mCCI score of 0, and 51.9%, 51.4%, and 53.8% of patients had an mCCI score of 1–5

Question

Can *in*-class transition (*i*CT) from parental bortezomib (V)-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) enable prolonged PI-based therapy in patients with NDMM?

Study design

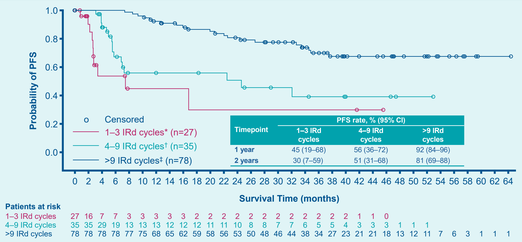
Patients with non-transplant* NDMM in the US community setting (N=140) → Parenteral V-based induction (3 cycles) → *i*CT → IRd (all-oral regimen) 39 x 28-day cycles or less until PD or toxicity†

Primary endpoint: 2-year PFS
Key secondary endpoint: Response rates

*Transplant-ineligible or transplant delayed by ≥24 months. †Whichever occurs first.

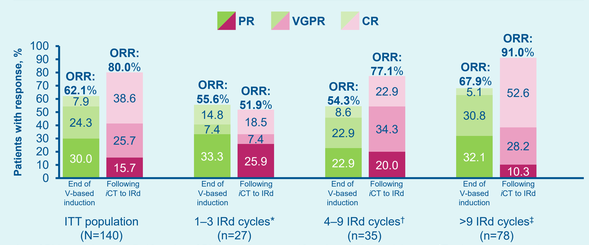
Results

Figure 1: Investigator-assessed PFS from start of IRd by number of treatment cycles



*4–6 cycles of PI-based therapy. †7–12 cycles of PI-based therapy. ‡>12 cycles of PI-based therapy.

Figure 2: Response rates at the end of V-based induction and after *i*CT to IRd by number of treatment cycles (ITT population)§



*4–6 cycles of PI-based therapy. †7–12 cycles of PI-based therapy. ‡>12 cycles of PI-based therapy. §Totals may not sum due to rounding.

Key take aways

Long-term triplet consolidation with IRd may delay progression and provide an alternative and convenient approach to induction/maintenance for community-based NDMM patients who are not eligible for upfront transplantation, including in patients with comorbidities.

Table 1. Baseline demographics and disease characteristics (safety population)

Characteristic	ITT population[6] (N=140)*	Cycles of IRd treatment		
		1–3† (n=27)	4–9‡ (n=35)	>9§ (n=78)
Median age, years (range)¶	72.5 (48–90)	75.0 (60–83)	73.0 (51—90)	71.0 (48–86)
Age ≥75 years, %¶	42.1	51.9	45.7	37.2
Male, %	57.9	59.3	74.3	50.0
Race, %				
White	72.9	74.1	77.1	70.5
Black/African American	17.9	22.2	11.4	19.2
Asian	2.1	3.7	2.9	1.3
Native Hawaiian or Other Pacific Islander	0.7	0	2.9	0
Ethnicity, %				
Hispanic/Latino	8.6	0	11.4	10.3
ISS disease stage, %#				
I / II / III	26.4/41.4/31.4	48.1/25.9/3.7	28.6/51.4/20.0	26.9/34.6/38.5
CrCl <60 mL/min, %¶	28.6	40.7	28.6	24.4
≥1 comorbidity at start of IRd therapy, %	94.3	88.9	91.4	97.4
Renal/urinary disorders**	32.9	40.7	34.3	29.5
Cardiac disorders**	28.6	29.6	20.0	32.1
T2DM/DM	18.6	18.5	11.4	21.8
PN/sensory PN	20.7	29.6	8.6	23.1
Induction regimen, %				
VRd	84.3	88.9	82.9	83.3
VCd	12.9	7.4	17.1	12.8
Other (Vd, VR)	2.9	3.7	0	3.8

*141 patients were successfully screened; one was not treated. †4–6 cycles of PI-based therapy. ‡7–12 cycles of PI-based therapy. §>12 cycles of PI-based therapy. ¶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 stage system; ITT, intent-to-treat; T2DM, type 2 diabetes mellitus; VCd, bortezomib-cyclophosphamide-dexamethasone; Vd, bortezomib-dexamethasone; VR, bortezomib-lenalidomide; VRd, bortezomib-lenalidomide-dexamethasone.

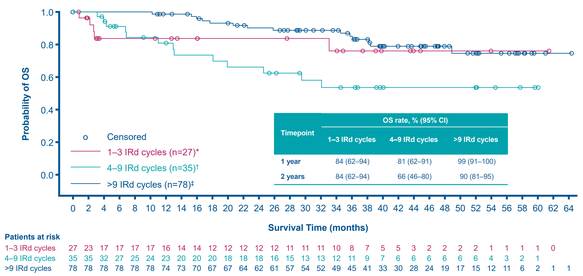
DOT

- Among all 140 patients, median DOT was 13.6 months with all PI-based therapy, and 11 months with IRd therapy[6]
- The median durations of all PI-based therapies and IRd therapy by subgroup were:
  - 4.9 and 1.7 months, respectively, in the 1–3 cycle subgroup
  - 8.6 and 5.4 months, respectively, in the 4–9 cycle subgroup; and
  - 26.7 and 24.4 months, respectively, in the >9 cycle subgroup of IRd

PFS and OS

- In patients who received 1−3, 4−9, and >9 IRd cycles, median PFS was 7.5 months (95% confidence interval [CI] 2.7–not reached [NR]), 24.6 months (5.8–NR), and NR (NR–NR) (**Summary Panel**; **Figure 1**)
- The 2-year PFS rate among patients who received >9 cycles of IRd was 81%
  - In the 1–3 and 4–9 IRd cycle subgroups, 2 -year PFS rates were 30% and 51%, respectively
- Median OS was not reached in any of the three IRd cycle subgroups (**Figure 4**)
  - 2-year OS rates were 84%, 66%, and 90%, respectively, in the 1–3, 4–9, and >9 IRd cycle subgroups

Figure 4: OS by number of IRd cycles (ITT population)



*4–6 cycles of PI-based therapy. †7–12 cycles of PI-based therapy. ‡>12 cycles of PI-based therapy.

Response rates

- Similar to that seen in the overall ITT population, ORRs increased following *i*CT to IRd in the 4–9 cycle subgroup (from 54.3% to 77.1%) and the >9 cycle subgroup (from 67.9% to 91.0%), but remained similar in the 1–3 cycle subgroup (**Summary Panel**; **Figure 2**)
- Median DOR was not reached in the 1–3 cycle and >9 cycle subgroups; in the 4–9 cycle subgroup, median DOR was 31.2 months
  - 2-year DOR rates in the 1–3, 4–9, and >9 cycle subgroups were 50%, 55%, and 77%, respectively

Safety overview

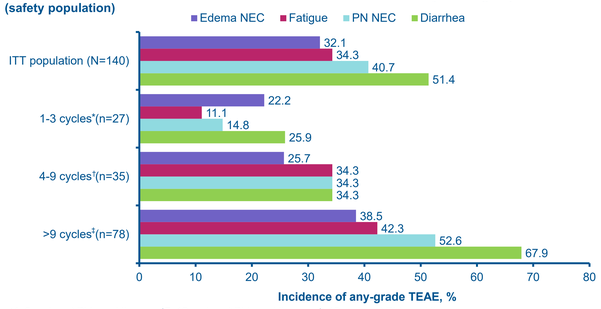
- The overall safety profile according to treatment cycle subgroup is provided in **Table 2**
- In the 1−3 cycle, 4–9 cycle, and >9 cycle subgroups, grade ≥3 TEAEs (treatment emergent adverse events) were reported in 59.3%, 60.0%, and 78.2% of patients, respectively
  - Grade ≥3 TEAEs were treatment-related in 29.6%, 37.1%, and 39.7% of patients, respectively
- Treatment-related serious TEAEs occurred in 18.5% of patients in the 1–3 cycle subgroup, 8.6% of patients in the 4–9 cycle subgroup, and in 12.8% of the >9 cycle subgroup
- More patients in the 1–3 cycle subgroup discontinued treatment due to TEAEs than in the 4–9 and >9 cycle subgroups (33.3%; versus 22.9% and 16.7%)
- The most frequently reported (≥25%) TEAEs of any grade across the three subgroups were diarrhea, PN not elsewhere classified (NEC), fatigue, and edema NEC (**Figure 5**)
  - In the >9 IRd cycle subgroup, additional commonly reported TEAEs were arthralgia (34.6%), nausea (33.3%), and back pain (29.5%)
- The most common grade ≥3 TEAEs in each of the three subgroups were: diarrhea, vomiting, and thrombocytopenia (each 7.4%) in the 1–3 cycle subgroup; diarrhea and syncope (both 8.6%) in the 4–9 cycle subgroup; and diarrhea (10.3%) and pneumonia (9.0%) in the >9 cycle subgroup

Table 2. Overview of IRd safety by number of treatment cycles (safety population)

TEAE, %	ITT population (N=140)	Cycles of IRd treatment		
		1–3* (n=27)	4–9† (n=35)	>9‡ (n=78)
Any grade	98.6	92.6	100	100
Treatment-related	82.1	63.0	77.1	91.0
Grade ≥3	70.0	59.3	60.0	78.2
Treatment-related	37.1	29.6	37.1	39.7
Serious	44.3	48.1	34.3	47.4
Treatment-related	12.9	18.5	8.6	12.8
Leading to dose modification§	68.6	48.1	65.7	76.9
Leading to discontinuation§	21.4	33.3	22.9	16.7
On-study deaths¶	3.6	7.4	2.9	2.6

*4–6 cycles of PI-based therapy. †7–12 cycles of PI-based therapy. ‡>12 cycles of PI-based therapy. §Modifications and discontinuations for any of the 3 study drugs. ¶Occurring <30 days after last dose.

Figure 5: Incidences of the most common TEAEs in the three treatment cycle subgroups (safety population)



*4–6 cycles of PI-based therapy. †7–12 cycles of PI-based therapy. ‡>12 cycles of PI-based therapy.

Conclusions

- In non-transplant patients with NDMM, *i*CT from V-based induction to all-oral IRd permits long-term PI-based treatment while maintaining a tolerable safety profile
- The majority of patients received >9 IRd cycles (or >12 cycles of PI-based therapy) with no new safety concerns reported, despite the high percentage of patients with comorbidities, represented by mCCI scores of ≥1 across all cycle groups analyzed
- As previously reported, longer IRd treatment leads to clinically meaningful benefits in patients with NDMM[10]
- Long-term triplet consolidation with IRd may delay progression and provide an alternative and convenient approach to induction/maintenance for community-based NDMM patients who are not eligible for upfront transplantation, including in patients with comorbidities

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Acknowledgments

This study was funded by Takeda Development Center Americas, Inc. (TDAC), Lexington, MA , USA. Medical writing support for the development of this poster, under the direction of the authors, was provided by Luisa Madeira, PhD, of Ashfield MedComms, an Inizio Company, funded by Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, and complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. *Ann Intern Med*. 2022;175:1298–304).

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Poster presentation at the 66th Annual Meeting of the American Society of Hematology (ASH), December 7–10, 2024, San Diego, California, USA, and online. For questions or comments, please contact Joshua Richter: Joshua.Richter@mountsinai.org.