US MM-6 Subgroup Analysis by Race/Ethnicity, Renal Function, and Area Income of *In*-Class Transition from Parenteral Bortezomib to Oral Ixazomib in Newly Diagnosed Multiple Myeloma

MM-1024

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Question

Does *in*-class transition from parenteral V-based induction regimens to oral IRd improve outcomes, while enabling prolonged all-oral PI-based therapy, among subgroups of patients with NDMM who are often underrepresented in RCTs?

Study design

US MM-6 (NCT03173092):
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†

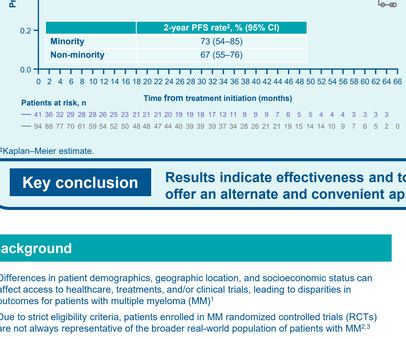
Primary endpoint: 2-year PFS

Subgroups examined in this analysis:
- Patients of racial/ethnic minorities
- Patients with impaired renal function
- Patients from areas of low income

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

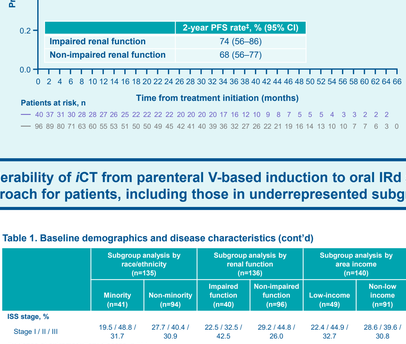
Results

PFS: subgroup analysis by race/ethnicity



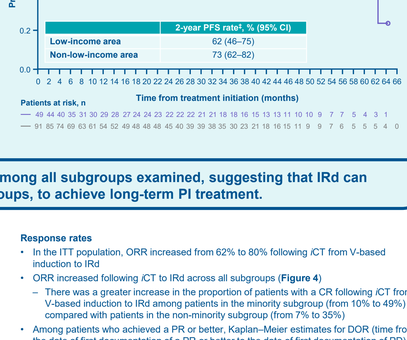
	2-year PFS rate‡, % (95% CI)
Minority	73 (54–85)
Non-minority	67 (55–76)

PFS: subgroup analysis by renal function



	2-year PFS rate‡, % (95% CI)
Impaired renal function	74 (56–86)
Non-impaired renal function	68 (56–77)

PFS: subgroup analysis by area income



	2-year PFS rate‡, % (95% CI)
Low-income area	62 (46–75)
Non-low-income area	73 (62–82)

‡Kaplan–Meier estimate.

Key conclusion

Results indicate effectiveness and tolerability of *i*CT from parenteral V-based induction to oral IRd among all subgroups examined, suggesting that IRd can offer an alternate and convenient approach for patients, including those in underrepresented subgroups, to achieve long-term PI treatment.

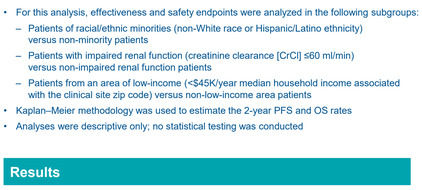
Background

- Differences in patient demographics, geographic location, and socioeconomic status can affect access to healthcare, treatments, and/or clinical trials, leading to disparities in outcomes for patients with multiple myeloma (MM)[1]
- Due to strict eligibility criteria, patients enrolled in MM randomized controlled trials (RCTs) are not always representative of the broader real-world population of patients with MM[2,3]
- Long-term proteasome inhibitor (PI)-based therapy has been shown to improve outcomes in MM,[4–7] but can be difficult to achieve with parenteral administration due to burden of administration[8,9]
- US MM-6 (NCT03173092) is a prospective, community-based, phase 4 study that enrolled a heterogenous cohort of real-world patients with newly diagnosed MM (NDMM), who may not have typically been eligible for an RCT[10,11]
  - The study previously demonstrated that *in*-class transition (*i*CT) from parenteral bortezomib (V)-based induction to all-oral ixazomib, lenalidomide, and dexamethasone (IRd) allows for prolonged PI-based therapy, improving depth of response, whilst maintaining quality of life (QoL) and a tolerable safety profile[11,12]
- Using data from US MM-6, we report outcomes among key patient subgroups who may be underrepresented in traditional RCTs, including patients of racial/ethnic minorities, patients with impaired renal function, and patients from areas of low income

Methods

- Full US MM-6 methods have been published previously;[10] the study design is shown in **Figure 1**

Figure 1. US MM-6 study design



*Transplant-ineligible or transplant delayed by ≥24 months. †Whichever occured first. ‡Assessed by investigator according to modified IMWG response criteria. §ORR = PR + VGPR + CR + sCR + iCR + mCR. ¶Not all sites chose to participate in the wearables that included QoL and actigraphy activities.

CR, complete response; DOR, duration of response; DOT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; 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; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; 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; sCR, stringent CR; SD, stable disease; TSQM-9, Treatment Satisfaction Questionnaire for Medication – 9 items; VGPR, very good PR.

- For this analysis, effectiveness and safety endpoints were analyzed in the following subgroups:
  - Patients of racial/ethnic minorities (non-White race or Hispanic/Latino ethnicity) versus non-minority patients
  - Patients with impaired renal function (creatinine clearance [CrCl] ≤60 ml/min) versus non-impaired renal function patients
  - Patients from an area of low-income (<$45K/year median household income associated with the clinical site zip code) versus non-low-income area patients
- Kaplan–Meier methodology was used to estimate the 2-year PFS and OS rates
- Analyses were descriptive only; no statistical testing was conducted

Results

Baseline demographics and patient disposition

- At the time of data abstraction (October 2024), of 140 patients from US MM-6 who were treated with IRd (**Table 1**):
  - 135 patients had available race and/or ethnicity data; of these, 41 patients (30%) were in the minority subgroup
  - 136 patients had available renal function data; of these, 40 patients (29%) had impaired renal function
  - 49 patients (35%) were from an area of low income (based on the location of the clinical site at screening)

Table 1. Baseline demographics and disease characteristics

	Subgroup analysis by race/ethnicity (n=135)		Subgroup analysis by renal function (n=136)		Subgroup analysis by area income (n=140)	
	Minority (n=41)	Non-minority (n=94)	Impaired function (n=40)	Non-impaired function (n=96)	Low-income (n=49)	Non-low income (n=91)
Median (range) age, years	71.0 (48–83)	73.0 (49–90)	75.0 (49–90)	71.0 (48–86)	71.0 (55–83)	73.0 (48–90)
Age category, n (%)						
<65 years	13 (31.7)	16 (17.0)	5 (12.5)	24 (25.0)	16 (32.7)	13 (14.3)
65–<75 years	13 (31.7)	36 (38.3)	14 (35.0)	38 (39.6)	15 (30.6)	37 (40.7)
≥75 years	15 (36.6)	42 (44.7)	21 (52.5)	34 (35.4)	18 (36.7)	41 (45.1)
Male, n (%)	24 (58.5)	56 (59.6)	19 (47.5)	59 (61.5)	37 (75.5)	44 (48.4)
Race, n (%)						
Asian	3 (7.3)	0	2 (5.0)	1 (1.0)	0	3 (3.3)
Black/African American	25 (61.0)	0	7 (17.5)	15 (15.6)	10 (20.4)	15 (16.5)
Native Hawaiian or other Pacific Islander	1 (2.4)	0	0	1 (1.0)	1 (2.0)	0
White	8 (19.5)	94 (100)	29 (72.5)	72 (75.0)	38 (77.6)	64 (70.3)
Multiple	1 (2.4)	0	1 (2.5)	0	0	1 (1.1)
Not reported	3 (7.3)	0	1 (2.5)	7 (7.3)	0	8 (8.8)
Ethnicity, n (%)						
Hispanic or Latino	12 (29.3)	0	2 (5.0)	9 (9.4)	4 (8.2)	8 (8.8)
Non-Hispanic or Latino	26 (63.4)	94 (100)	37 (92.5)	85 (88.5)	45 (91.8)	79 (86.8)
Not reported	3 (7.3)	0	1 (2.5)	1 (1.0)	0	3 (3.3)
Unknown	0	0	0	1 (1.0)	0	1 (1.1)
Evidence of lytic bone disease, n (%)						
Yes	22 (53.7)	39 (41.5)	9 (22.5)	53 (55.2)	24 (49.0)	40 (44.0)
No	17 (41.5)	45 (47.9)	26 (65.0)	36 (37.5)	19 (38.8)	45 (49.5)
Unknown	2 (4.9)	10 (10.6)	5 (12.5)	7 (7.3)	6 (12.2)	6 (6.6)

Table 1. Baseline demographics and disease characteristics (cont'd)

	Subgroup analysis by race/ethnicity (n=135)		Subgroup analysis by renal function (n=136)		Subgroup analysis by area income (n=140)	
	Minority (n=41)	Non-minority (n=94)	Impaired function (n=40)	Non-impaired function (n=96)	Low-income (n=49)	Non-low income (n=91)
ISS stage, %						
Stage I / II / III	19.5 / 48.8 / 31.7	27.7 / 40.4 / 30.9	22.5 / 32.5 / 42.5	29.2 / 44.8 / 26.0	22.4 / 44.9 / 32.7	28.6 / 39.6 / 30.8
Evidence of extramedullary disease, n (%)						
Yes	3 (7.3)	7 (7.4)	1 (2.5)	9 (9.4)	4 (8.2)	6 (6.6)
No	31 (75.6)	69 (73.4)	30 (75.0)	71 (74.0)	32 (65.3)	73 (80.2)
Unknown	7 (17.1)	18 (19.1)	9 (22.5)	16 (16.7)	13 (26.5)	12 (13.2)
≥1 comorbidity at start of IRd therapy, n (%)	40 (97.6)	87 (92.6)	37 (92.5)	91 (94.8)	43 (87.8)	89 (97.8)
Calculated CrCl category (ml/min), n (%)						
<30	1 (2.4)	4 (4.3)	5 (12.5)	0	3 (6.1)	2 (2.2)
30 to <60	11 (26.8)	24 (25.5)	35 (87.5)	0	11 (22.4)	24 (26.4)
60 to <90	12 (29.3)	41 (43.6)	0	57 (59.4)	17 (34.7)	40 (44.0)
≥90	13 (31.7)	25 (26.6)	0	39 (40.6)	18 (36.7)	21 (23.1)
Missing	4 (9.8)	0	0	0	0	4 (4.4)

ISS, International Staging System.

- At a median of 37.4 months follow-up, no patients were ongoing on IRd treatment (**Table 2**)

Loss to follow-up

- A lower proportion of minority versus non-minority patients discontinued the study due to being lost to follow-up (7% vs 18%)
- A higher proportion of patients from low- versus non-low-income areas were lost to follow-up (29% vs 8%)

Withdrawal from study

- A higher proportion of minority versus non-minority patients withdrew from the study (86% vs 71%)
- A lower proportion of patients from low- vs non-low-income areas withdrew from the study (43% vs 88%)

Table 2. Patient disposition

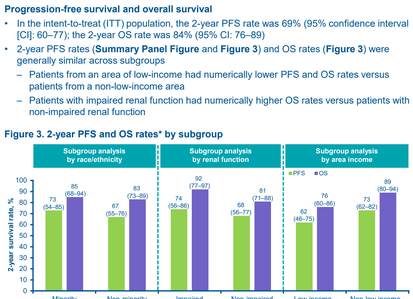
	Subgroup analysis by race/ethnicity (n=135)		Subgroup analysis by renal function (n=136)		Subgroup analysis by area income (n=140)	
	Minority (n=41)	Non-minority (n=94)	Impaired function (n=40)	Non-impaired function (n=96)	Low-income (n=49)	Non-low income (n=91)
Median follow-up, months	34	40	37	40	42	37
Ongoing IRd†, %	0	0	0	0	0	0
Discontinued IRd†, %	76	81	80	79	76	82
Reason for discontinuation of IRd†, %						
Adverse event	29	33	22	36	30	32
Loss to follow-up	0	1	3	0	0	1
Withdrawal by patient	32	24	38	20	27	25
PD	26	18	16	24	30	16
Physician decision	10	21	22	17	8	24
Other	3	3	0	4	5	1
Completed IRd†, %	24	19	20	21	24	18
Discontinued study‡, %	34	18	23	21	14	27
Reason for discontinuation of study‡, %						
Loss to follow-up	7	18	11	15	29	8
Withdrawal by patient	86	71	89	75	43	88
Other	7	12	0	10	29	4
Completed study‡, %	44	54	53	54	53	52

*Percentages are based on the number of patients in the safety population. †Percentages are based on the number of patients who discontinued study drug. ‡Percentages are based on the number of patients who discontinued the study.

Duration of treatment

- Median duration of IRd treatment ranged from 8 to 15 months across subgroups (**Figure 2**)

Figure 2. Duration of treatment

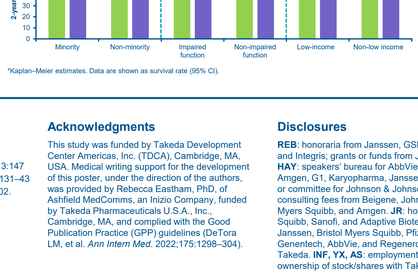


*Duration of PI therapy is defined as the time from the date of first administration of the V-based regimen to the date of the last administration of ixazomib. †Duration of IRd is defined as the time from the date of the first administration of IRd to the date of the last administration of any of the three study drugs in the regimen. ‡Duration of ixazomib therapy is defined as the time from the date of first administration of ixazomib therapy to the date of the last administration of ixazomib therapy.

Progression-free survival and overall survival

- In the intent-to-treat (ITT) population, the 2-year PFS rate was 69% (95% confidence interval [CI]: 60–77); the 2-year OS rate was 84% (95% CI: 76–89)
- 2-year PFS rates (**Summary Panel Figure** and **Figure 3**) and OS rates (**Figure 3**) were generally similar across subgroups
  - Patients from an area of low-income had numerically lower PFS and OS rates versus patients from a non-low-income area
  - Patients with impaired renal function had numerically higher OS rates versus patients with non-impaired renal function

Figure 3. 2-year PFS and OS rates* by subgroup

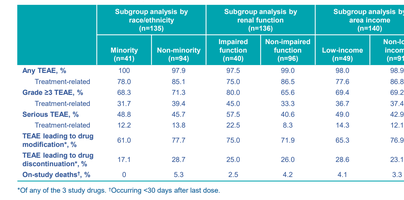


*Kaplan–Meier estimates. Data are shown as survival rate (95% CI).

Response rates

- In the ITT population, ORR increased from 62% to 80% following *i*CT from V-based induction to IRd
- ORR increased following *i*CT to IRd across all subgroups (**Figure 4**)
  - There was a greater increase in the proportion of patients with a CR following *i*CT from V-based induction to IRd among patients in the minority subgroup (from 10% to 49%) compared with patients in the non-minority subgroup (from 7% to 35%)
- Among patients who achieved a PR or better, Kaplan–Meier estimates for DOR (time from the date of first documentation of a PR or better to the date of first documentation of PD) at 2 years were:
  - 77% versus 68% in the minority versus non-minority subgroups
  - 85% versus 68% in the renally impaired versus non-renally impaired subgroups
  - 75% versus 71% in the low- versus non-low-income subgroups

Figure 4. Best ORR* at the end of V-based induction and after *i*CT to IRd



*ORR: CR (CR + sCR + iCR + mCR) + VGPR + PR.

Safety

- The proportion of patients with any-grade treatment-emergent adverse events (TEAEs), grade ≥3 TEAEs, or serious TEAEs was similar between minority and non-minority subgroups (**Table 3**)
  - A lower proportion of patients in the minority subgroup versus non-minority subgroup had a TEAE leading to drug modification (61.0% vs 77.7%) or drug discontinuation (17.1% vs 28.7%)
- The proportion of patients with any-grade TEAEs was similar between patients with impaired renal function and those with non-impaired renal function
  - A higher proportion of patients in the impaired renal function subgroup versus non-impaired renal function subgroup had grade ≥3 TEAEs (80.0% vs 65.6%) or serious TEAEs (57.5% vs 40.6%)
- The proportion of patients with any-grade TEAEs, grade ≥3 TEAEs, or serious TEAEs was similar between patients from areas of low income and those from non-low-income areas
  - A lower proportion of patients in the low-income subgroup versus non-low-income subgroup had a TEAE leading to drug modification (65.3% vs 76.9%)

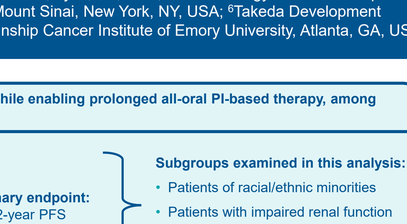
Table 3. Overview of safety profile

	Subgroup analysis by race/ethnicity (n=135)		Subgroup analysis by renal function (n=136)		Subgroup analysis by area income (n=140)	
	Minority (n=41)	Non-minority (n=94)	Impaired function (n=40)	Non-impaired function (n=96)	Low-income (n=49)	Non-low income (n=91)
Any TEAE, %	100	97.9	97.5	99.0	98.0	98.9
Treatment-related	78.0	85.1	75.0	86.5	77.6	86.8
Grade ≥3 TEAE, %	68.3	71.3	80.0	65.6	69.4	69.2
Treatment-related	31.7	39.4	45.0	33.3	36.7	37.4
Serious TEAE, %	48.8	45.7	57.5	40.6	49.0	42.9
Treatment-related	12.2	13.8	22.5	8.3	14.3	12.1
TEAE leading to drug modification*, %	61.0	77.7	75.0	71.9	65.3	76.9
TEAE leading to drug discontinuation*, %	17.1	28.7	25.0	26.0	28.6	23.1
On-study deaths†, %	0	5.3	2.5	4.2	4.1	3.3

*Of any of the 3 study drugs. †Occurring <30 days after last dose.

- The most common TEAE across all subgroups was diarrhea (**Figure 5**)

Figure 5. Most commonly occurring TEAEs (≥30% of patients in any subgroup)



PN NEC, PN not elsewhere classified.

Quality of life

- In most subgroups, changes from baseline in EORTC QLQ-C30 global health status were less than 10 (which is the minimal important difference),[13] indicating overall maintenance of QoL during IRd treatment

Conclusions

- This analysis of US MM-6 indicates the effectiveness and tolerability of *i*CT from parenteral V-based induction to oral IRd in patient subgroups that are often underrepresented in RCTs, including patients of racial/ethnic minorities, patients with impaired renal function, and patients from areas of low income
- Promising PFS and OS rates as well as elevated ORRs following *i*CT were observed across all subgroups
- Patients of racial/ethnic minorities remained on treatment for longer and a lower proportion of these patients were lost to follow-up versus non-minority patients
- In line with the results seen in the ITT population,[11] *i*CT to IRd enabled long-term PI-based treatment and improved depth of response while maintaining a tolerable safety profile, thus providing an alternate and convenient approach for transplant-ineligible patients with NDMM (including those in underrepresented subgroups) to achieve long-term PI-based treatment
- Further research in key subgroups of patients with NDMM, while accounting for treatment cohort imbalances, is needed to support these findings

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