

In-class transition from parenteral bortezomib to oral ixazomib in newly diagnosed multiple myeloma: subgroup analysis of US MM-6 by race/ethnicity, renal function, and area income

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Ruemu E. Birhiray,¹ Habte A. Yimer,² Richy Agajanian,³ Saulius Girnius,⁴ Joshua Richter,⁵ Stephen J. Noga,⁶ **Isabel Nascimento-Ferreira,**⁷ Yunlong Xie,⁶ Dasha Cherepanov,⁶ Alexandra Savell,⁶ Leon Bernal-Mizrachi⁸

¹Hematology Oncology of Indiana/American Oncology Network, Indianapolis, IN, USA; ²Texas Oncology/US Oncology Research, Tyler, TX, USA; ³The Oncology Institute of Hope and Innovation, Cerritos, CA, USA; ⁴Trihealth Cancer and Blood Institute, Cincinnati, OH, USA; ⁵Icahn School of Medicine at Mount Sinai, New York, NY, USA; ⁶Takeda Development Center Americas, Inc. (TDCA), Cambridge, MA, USA; ⁷Takeda Pharmaceuticals International AG, Zurich, Switzerland; ⁸Winship Cancer Institute of Emory University, Atlanta, GA, USA

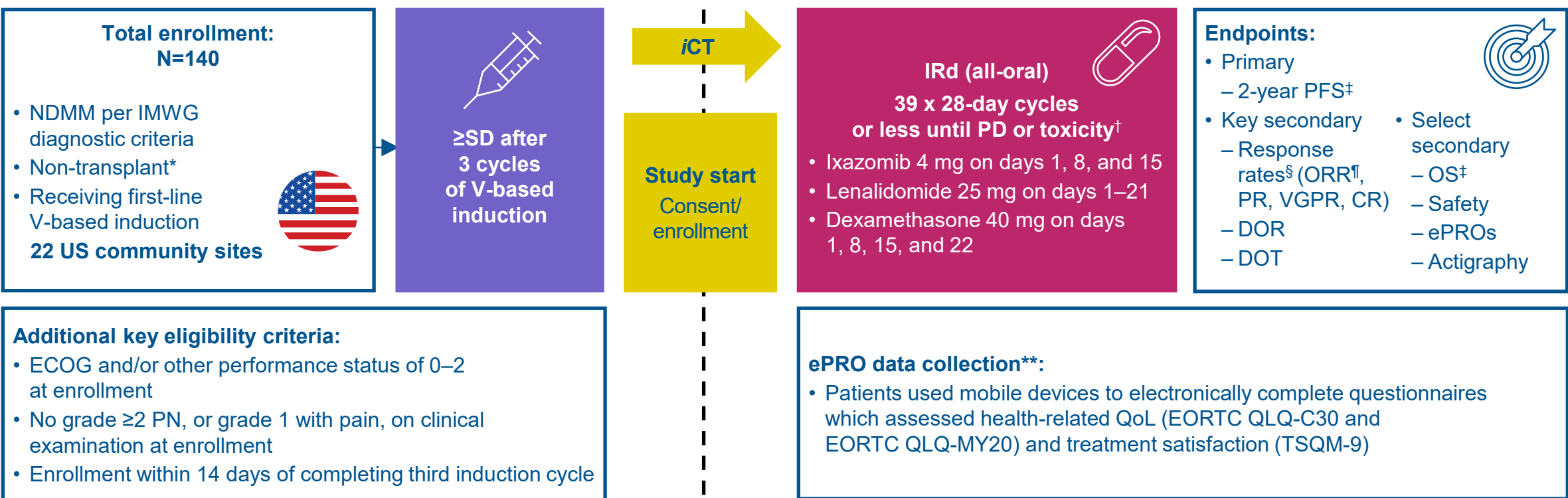
Background

- Differences in patient demographics, as well as 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 real-world population of patients with MM^{2,3}
- Long-term proteasome inhibitor (PI)-based therapy has been demonstrated 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 heterogeneous 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 (iCT) 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;⁸ the study design is shown in **Figure 2**

Figure 2. US MM-6 study design



*Transplant-ineligible or transplant delayed by ≥24 months. *Whichever occurs first. *Maximum of 30 months follow-up. *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; 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; PN, 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.

- 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) vs non-minority patients
 - Patients with impaired renal function (creatinine clearance [CrCl] ≤60 mL/min) vs non-impaired renal function patients
 - Patients from an area of low-income (<\$45K/year median household income associated with the clinical site zip code) vs 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)	15 (30.6)	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	1 (1.1)	0
Not reported	3 (7.3)	0	0	0	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)	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)
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

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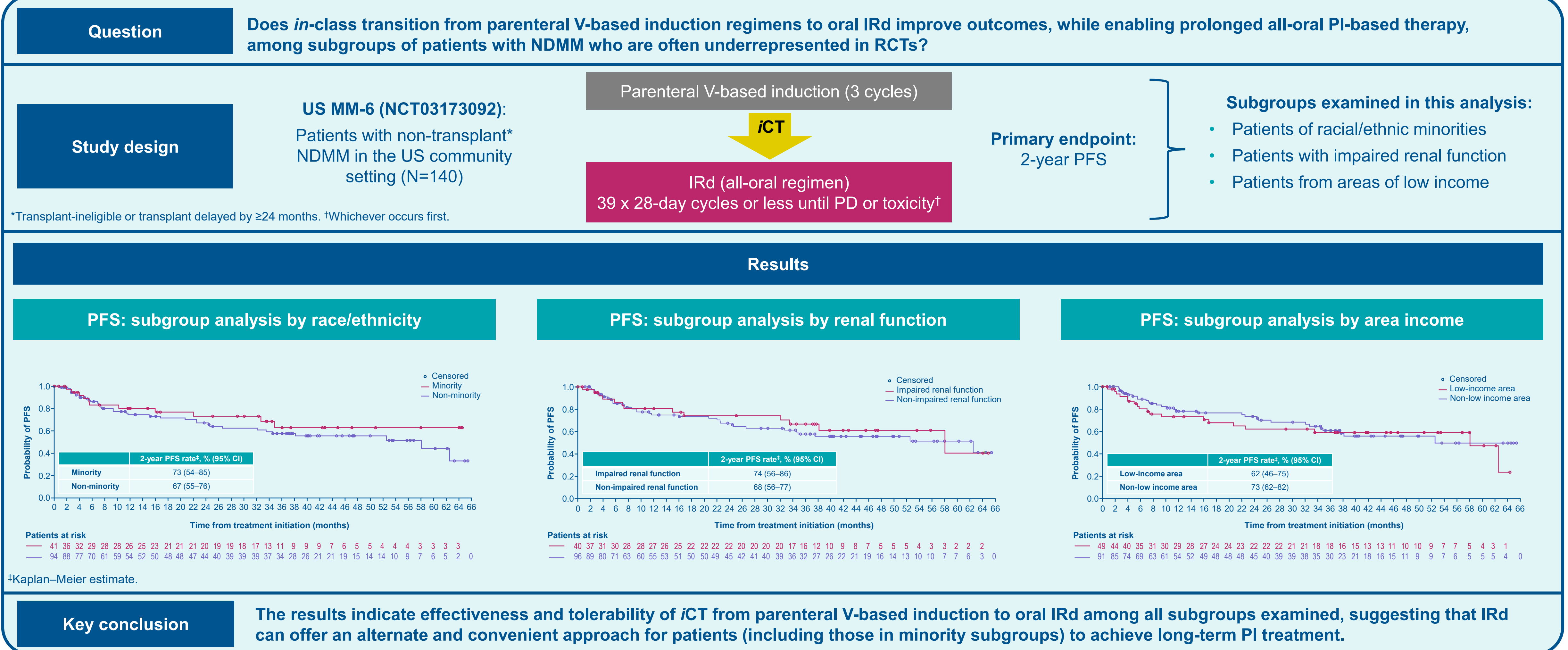


Table 1. Baseline demographics and disease characteristics (cont'd)

	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)
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)	16 (19.1)	9 (22.5)	16 (16.7)	12 (24.5)	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 vs non-minority patients discontinued the study due to being lost to follow-up (7% vs 18%)
 - A higher proportion of patients from low- vs non-low income areas were lost to follow-up (29% vs 8%)
- Withdrawal from study
 - A higher proportion of minority vs 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
Progressive disease†	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.

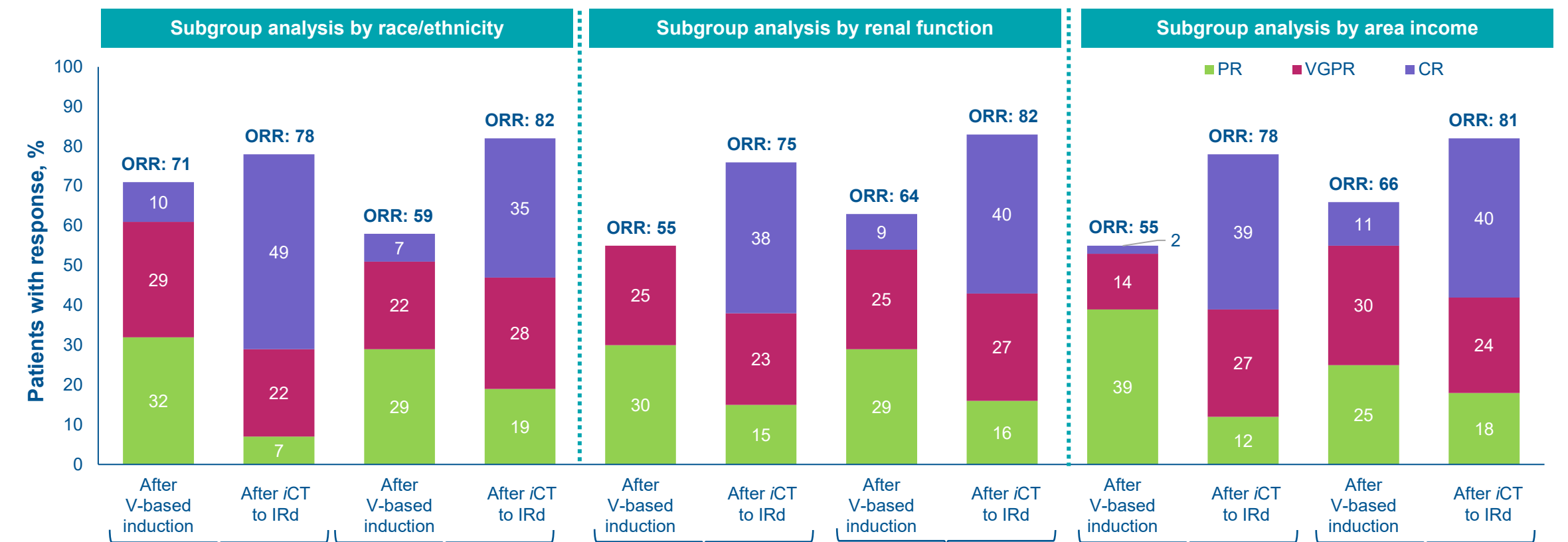
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Disclosures

REB: honoraria from Janssen, GSK, Pfizer, Prothena, Genesis Pharma, and Integris; grants or funds from Janssen, GSK, Pfizer, and Takeda. **HAY:** speakers' bureau for AbbVie, Genmab, AstraZeneca, Pfizer, Amgen, G1, Karyopharma, Janssen, and Beigene. **SG:** advisory council or committee for Johnson & Johnson, Bristol Myers Squibb, and Sanofi; consulting fees from Beigene, Johnson & Johnson, Takeda, Bristol Myers Squibb, and Amgen. **JR:** honoraria from Janssen, Bristol Myers Squibb, Sanofi, and Adaptive Biotechnologies; consulting fees from Janssen, Bristol Myers Squibb, Pfizer, Karyopharma, Sanofi, Takeda, Genentech, AbbVie, and Regeneron. **SJN:** previous employment with Takeda. **INF, YX, AS:** employment with Takeda. **DC:** employment and ownership of stock/shares with Takeda. **RA, LBM:** none.

Figure 5. Best ORR* at the end of V-based induction and after iCT to IRd



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

Safety

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

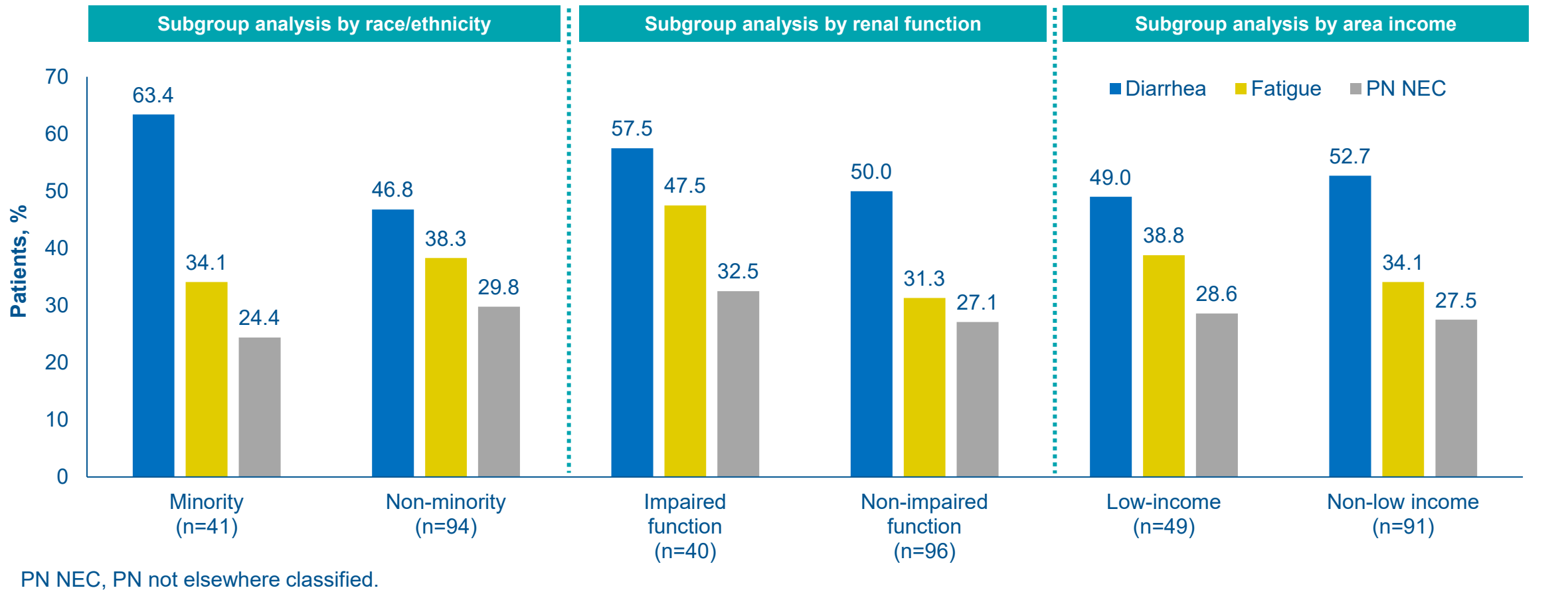
Table 3. Overview of safety profile

TEAE, %	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

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

- The most common TEAEs across all subgroups were diarrhea and fatigue (**Figure 6**)

Figure 6. 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), indicating overall maintenance of QoL

Conclusions

- This analysis of US MM-6 indicates the effectiveness and tolerability of iCT from parenteral V-based induction to oral IRd in patient subgroups that are often underrepresented in clinical trials 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 iCT were observed across all subgroups
- Patients of racial/ethnic minorities remained on treatment for longer and fewer of these patients were lost to follow-up vs non-minority patients
- In line with the results seen in the ITT population, iCT 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 minority subgroups) to achieve long-term PI 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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