In-Class Transition (*i*CT) from Parenteral Bortezomib-based Induction to All-oral Ixazomib-lenalidomide-dexamethasone in Transplant-ineligible Patients with Newly Diagnosed Multiple Myeloma: Updated Subgroup Analysis from the Community-based US MM-6 Study

MM-465

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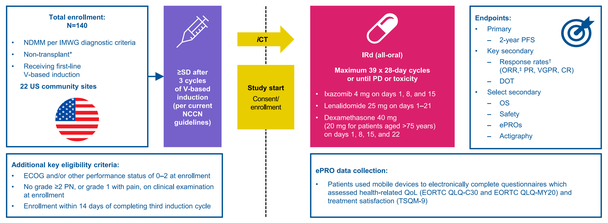
Background and aims

- Prolonged therapy with parenteral proteasome inhibitors (PIs) can improve multiple myeloma (MM) outcomes,[1] but is often challenging in routine practice due to PI-related toxicity and treatment burden, particularly among elderly and frail patients who are often transplant-ineligible[2,3]
- Due to strict eligibility criteria, randomized controlled trials (RCTs) include patients who are generally younger and healthier vs real-world patient populations[4]
- US MM-6 was designed to investigate *in*-class transition (*i*CT) from parenteral bortezomib (V)-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) in community-based patients with newly diagnosed MM (NDMM; NCT03173092)
  - The objective was to increase duration of PI-based therapy and improve outcomes, while maintaining a tolerable safety profile and patient quality of life (QoL)
  - Results were previously reported for the fully accrued study cohort (N=141; median follow-up 20.0 months)[5]
    - Median duration of IRd was 10.0 months and the overall response rate (ORR) after *i*CT to IRd was 78% (complete response [CR] 29%, molecular CR [mCR] 1%, stringent CR [sCR] 3%, very good partial response [VGPR] 27%, and partial response [PR] 18%)
- Here we report updated results for the fully accrued study cohort, including analysis by age (<75 vs ≥75 years) and frailty status (non-frail vs frail)

Methods

- Full methods for US MM-6 have been published previously; the study design is shown in **Figure 2**
- The primary endpoint was 2-year progression-free survival (PFS), and secondary endpoints included response, duration of treatment (DOT), overall survival (OS), safety, electronic patient-reported outcomes (ePROs), and actigraphy outcomes

Figure 2: US MM-6 study design[6]



*Transplant-ineligible or transplant delayed by ≥24 months, †Assessed by investigator according to modified IMWG response criteria, Methods have been published previously, ‡ORR = PR + VGPR + CR + sCR + ICR + mCR,
ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma module 20 – item 43 measuring peripheral neuropathy; ICR, immunophenotypic CR; IMWG, International Myeloma Working Group; NCCN, National Comprehensive Cancer Network; PD, progressive disease; PN, peripheral neuropathy; SD, stable disease; TSQM-9, Treatment Satisfaction Questionnaire for Medication – 9 items

Results

Patients

- At the time of data abstraction (October 17, 2022), 140 patients had been enrolled and treated at 22 sites, and were included in the safety and intent-to-treat (ITT) populations
- In total, 42% were aged ≥75 years, and 61% were defined as frail (**Table 1**)

Table 1: Baseline demographics and disease characteristics

Characteristic	Overall (N=140)*	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)
Median age, years (range)†	72.5 (48–90)	69.0 (48–74)	77.0 (75–90)	71.0 (49–78)	75.0 (48–90)
Age ≥75 years, %‡	42.1	0	100	22.2	54.7
Male, %	57.9	60.5	54.2	64.8	53.5
Race, %					
White	72.9	70.4	76.3	74.1	72.1
Black/African American	17.9	18.5	16.9	14.8	19.8
Asian	2.1	2.5	1.7	1.9	2.3
Native Hawaiian or Other Pacific Islander	0.7	1.2	0	1.9	0
Ethnicity, %					
Hispanic/Latino	8.6	11.1	5.1	9.3	8.1
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
CrCl <60 mL/min, %‡	28.6	23.5	35.6	14.8	37.2
≥1 comorbidity at start of IRd therapy, %	93.6	91.4	96.6	92.6	94.2
Renal/urinary disorders‡	32.9	27.2	40.7	16.7	43.0
Cardiac disorders‡	28.6	27.2	30.5	16.7	36.0
Type 2 diabetes mellitus or diabetes mellitus	18.6	21.0	15.3	9.3	24.4
PN or sensory PN	18.6	23.5	11.9	22.2	16.3
Induction regimen, %					
VRd	84.3	84.0	84.7	87.0	82.6
VCd	12.9	13.6	11.9	9.3	15.1
Other (Vd, VR)	2.9	2.5	3.4	3.7	2.3

*141 patients were successfully screened, one was not treated, †Age and CrCl captured at start of IRd, ‡BSA captured at start of V-based induction, §System organ class,
CrCl, creatinine clearance; ISS, international stage system; 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 all-oral PI-based therapy?

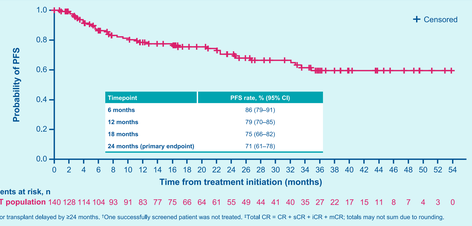
Study design

Patients with non-transplant* NDMM in the US community setting (N=141) → Parenteral V-based induction (3 cycles) → ***i*CT** → IRd (all-oral regimen) Maximum 39 x 28-day cycles or until PD or toxicity

Primary endpoint: 2-year PFS
Key secondary endpoints included: Response rates (ORR, PR, VGPR, CR)

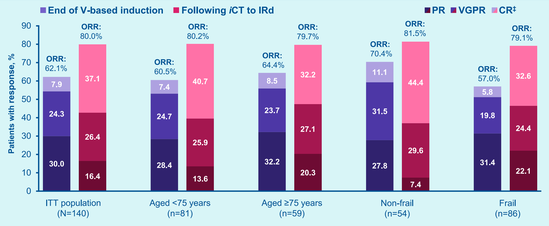
Results

Figure 1A: Investigator-assessed PFS from start of IRd (KM estimate; ITT population; N=140)†



*Transplant-ineligible or transplant delayed by ≥24 months, †One successfully screened patient was not treated, ‡Total CR = CR + sCR + ICR + mCR; totals may not sum due to rounding.

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



Key conclusions

In non-transplant community-based patients with NDMM, *i*CT from V-based induction to IRd permits long-term PI-based treatment and improves depth of response, with a tolerable safety profile, in elderly/frail subgroups

Patient disposition and treatment exposure

- With a median follow-up of 27 months at the time of data accrual, 10% of patients in the overall cohort were ongoing on IRd treatment; 79% had discontinued study treatment, and 11% had completed IRd treatment (**Table 2**)

Table 2: Disposition and treatment exposure

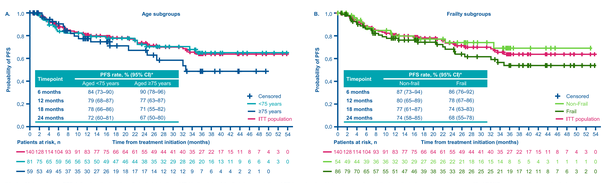
	Overall (N=140)*	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)
Median follow-up, months	26.8	29.2	24.3	27.5	26.7
Ongoing on IRd, %	10.0	12.3	6.8	13.0	8.1
Discontinued IRd, %	79.3	74.1	86.4	83.3	76.7
Completed IRd, %	10.7	13.6	6.8	3.7	15.1
Median duration of IRd, months (range)†	11.0 (0.7–38.0)	13.8 (0.7–37.8)	9.2 (0.7–38.0)	11.9 (0.7–36.6)	10.3 (0.7–38.0)

*141 patients were successfully screened, one was not treated, †Median durations were 'simple', not calculated using the Kaplan-Meier method.

PFS, OS, and response rates

- Among the overall cohort, the 2-year PFS rate from the start of IRd treatment was 71% (**Summary Panel; Figure 1A**)
- In patients who were aged <75 vs ≥75 years, the 2-year PFS rates were 72% vs 67% (**Figure 3A**)
- In non-frail and frail patients, the 2-year PFS rates were 74% vs 68% (**Figure 3B**)

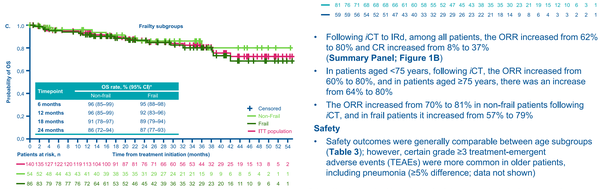
Figure 3: PFS by age and frailty status



*Kaplan-Meier estimate; PFS defined as the time from first administration of IRd to the date of the first documentation of PD based on local laboratory results and the investigator's assessment using modified IMWG response criteria, or death due to any cause, whichever occurred first, CI, confidence interval

- At data accrual, median OS had not been reached in the overall population; the overall 2-year OS rate from the start of IRd treatment was 86% (**Figure 4A**)
- In patients aged <75 vs ≥75 years, the 2-year OS rate was 86% vs 87% (**Figure 4B**)
- In the non-frail vs frail patient subgroups, the 2-year OS rate was 86% vs 87% (**Figure 4C**)

Figure 4: (A) OS in the ITT population, (B) and (C) OS by age and frailty status



*Kaplan-Meier estimate; OS defined as the time from the date of the first administration of IRd to the date of death from any cause. Patients without documentation of death at the time of analysis were censored at the date last known to be alive.

- Following *i*CT to IRd, among all patients, the ORR increased from 62% to 80% and CR increased from 8% to 37% (**Summary Panel; Figure 1B**)
- In patients aged <75 years, following *i*CT, the ORR increased from 60% to 80%, and in patients aged ≥75 years, there was an increase from 64% to 80%
- The ORR increased from 70% to 81% in non-frail patients following *i*CT, and in frail patients it increased from 57% to 79%

Safety

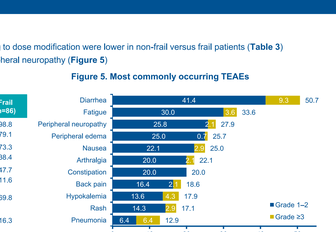
- Safety outcomes were generally comparable between age subgroups (**Table 3**); however, certain grade ≥3 treatment-emergent adverse events (TEAEs) were more common in older patients, including pneumonia (≥5% difference; data not shown)
- Incidences of grade ≥3 TEAEs, serious TEAEs, and TEAEs leading to dose modification were lower in non-frail versus frail patients (**Table 3**)
- Overall, the most common TEAEs were diarrhea, fatigue, and peripheral neuropathy (**Figure 5**)

Table 3: IRd safety profile overview

TEAEs, %	Overall (N=140)	<75 years (n=81)	≥75 years (n=59)	Non-frail (n=54)	Frail (n=86)
Any grade	97.9	97.5	98.3	96.3	98.8
Treatment-related	82.1	85.2	78.0	87.0	79.1
Grade ≥3	68.6	69.1	67.8	61.1	73.3
Treatment-related	37.1	33.3	42.4	35.2	38.4
Serious	44.3	42.0	47.5	38.9	47.7
Treatment-related	12.9	12.3	13.6	14.8	11.6
Leading to dose modification*	66.4	66.7	66.1	61.1	69.8
Leading to discontinuation*	20.0	19.8	20.3	25.9	16.3
On-study deaths†	2.9	2.5	3.4	1.9	3.5

*Modifications and discontinuations for any of the 3 study drugs, †Occurring <30 days after last dose; deaths were due to unrelated end-stage renal disease, treatment-related pneumonia, disease-related complications, and unknown (n=1 each),

Figure 5. Most commonly occurring TEAEs

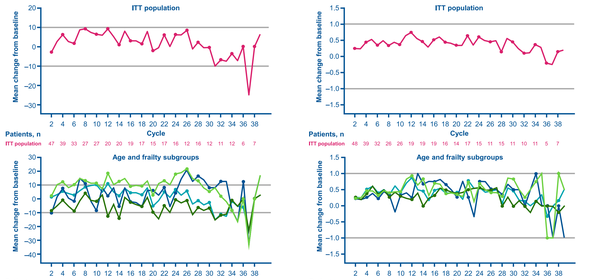


*N=140; most commonly occurring TEAEs in >15% of patients at any grade or >5% at grade ≥3; totals may not sum due to rounding.

QoL and treatment satisfaction

- Patient-reported QoL scores were maintained during IRd therapy overall, and in age and frailty subgroups (**Figure 6A**)
- **Figure 6B** shows progression of peripheral neuropathy symptoms. An overall mean change from baseline score of ≤0.7 was observed

Figure 6: Mean change from baseline in EORTC QLQ-C30 GHS/QoL and EORTC QLQ-MY20 scores per cycle



GHS, global health status

Actigraphy

- Among 94 patients with available daily actigraphy data (a total of 26,665 days), 24,283 (91.1%) compliant days were included in the analysis
- Activity and sleep levels were generally maintained during IRd therapy overall and in all subgroups, although patient numbers were low in later treatment cycles (**Table 4**)

Table 4: Actigraphy outcomes

	Overall	<75 years	≥75 years	Non-frail	Frail
Mean number of steps per day (StDev)*	3,107 (2,360)	3,256 (2,533)	2,798 (2,006)	3,356 (2,422)	2,858 (2,251)
Mean daily active time,† hours (StDev)*	0.42 (0.33)	0.43 (0.34)	0.39 (0.29)	0.45 (0.33)	0.38 (0.32)
Mean daily sleep time,‡ hours (StDev)*	7.55 (2.71)	7.79 (2.78)	6.89 (2.41)	7.54 (2.48)	7.56 (2.91)

*Outliers more than 4 standard deviations from the mean have been excluded from each mean (StDev) calculation, †Active time defined as the time for which patients were 'active' or 'highly active', ‡Sleep time includes deep sleep; light sleep; "awake" time that is reported as part of the sleep record, StDev, standard deviation

Conclusions

- In non-transplant NDMM patients, *i*CT from V-based induction to IRd permits long-term PI-based treatment and improves depth of response, with a tolerable safety profile
- Overall 2-year PFS and OS rates (71% and 86%) appeared similar to those observed in the SWOG S0777 RCT (~65% and ~90%);[7] however compared with US MM-6, SWOG S0777 included generally younger and healthier patients, including patients who went on to receive transplant
- PFS, OS, and safety data were comparable between patients aged ≥75 years and frail patients vs the ITT population, and the expected decrement in outcomes associated with older age/frailty was not observed
- ePRO and actigraphy results suggest no adverse impact or decline in activity or QoL with continued IRd treatment
- Long-term triplet consolidation with IRd may provide an alternative approach to induction/maintenance in the community for patients with comorbidities and/or frailty who are not eligible for upfront transplantation

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