Comparative Effectiveness of Oral Ixazomib-lenalidomide-dexamethasone (IRd) After Initial Bortezomib (V)-based Induction versus Parenteral V-based Therapy in Newly Diagnosed Multiple Myeloma (NDMM)

Robert M. Rifkin,[1] Caitlin L. Costello,[2] Ruemu E. Birhiray,[3] Suman Kambhampati,[4] Joshua Richter,[5] Rafat Abonour,[6] Hans C. Lee,[7] Yong Jin Kim,[8] Kaili Ren,[9] Dawn Marie Stull,[10] Dasha Cherepanov,[9] Kimberly Bogard,[10] Stephen J. Noga,[10] Saulius Girnius[11]

[1]Rocky Mountain Cancer Centers/US Oncology Research, Denver, CO, USA; [2]Department of Medicine, Division of Blood and Marrow Transplantation, Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [3]Hematology Oncology of Indiana/American Oncology Network, Indianapolis, IN, USA; [4]Kansas City Veterans Affairs Medical Center, Kansas City, MO, USA; [5]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]Indiana University School of Medicine, Indianapolis, IN, USA; [7]M.D. Anderson Cancer Center, Houston, TX, USA; [8]Evidera, Data Analytics, St-Laurent, Quebec, Canada; [9]Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA; [10]Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, USA; [11]TriHealth Cancer Institute, Cincinnati, OH, USA

Background

- Long-term proteasome inhibitor (PI)-based treatment can improve outcomes for patients with MM[1,2]
- However, prolonged parenteral PI therapy (e.g., with V) can be challenging to achieve in routine clinical practice, and outcomes for patients are often poorer in this setting compared with clinical trials[3]
  - This discrepancy could be due in part to the fact that up to 72% of real-world patients with relapsed/refractory MM (RRMM) would not meet the eligibility criteria for randomized clinical trials[4]
  - Real-world studies with less stringent eligibility criteria may permit inclusion of a more diverse patient population and better inform on the effectiveness of therapies as used in routine clinical practice
  - Various physical, geographical, and/or socioeconomic barriers to prolonged therapy with parenteral PIs are encountered in community practice,[3] including:
    - Burden of repeated intravenous/subcutaneous administration
    - Difficulty traveling to treatment centers
    - Patient preference for treatment outside of a clinic
    - Comorbidities
    - Toxicities
- The phase 4, community-based, single-arm US MM-6 study (NCT03173092) is assessing *in*-class transition (*i*CT) from V-based induction to all-oral ixazomib-lenalidomide-dexamethasone (IRd) in transplant ineligible newly-diagnosed MM (NDMM) patients treated in routine clinical practice, with the objective of increasing the duration of PI-based treatment while maintaining quality of life[5]
- The US MM-6 study provided the patients for the IRd cohort
- INSIGHT MM is the largest global, prospective, observational study (NCT02761187) of MM patients (>4200),[6] and provided a subset of patients on V-based therapy as the comparator cohort
- This enabled assessment of *i*CT versus V-based therapy in NDMM patients in community oncology practices in the US

Aims

- To examine the comparative effectiveness of IRd following initial V-based induction (3 cycles; US MM-6 patients; 'IRd' cohort) versus patients who continued to receive V-based therapy (INSIGHT MM patients; 'V-based' cohort) until progression in patients with NDMM

Methods

Patients

- A secondary analysis of transplant ineligible US NDMM patients with ≥stable disease (SD) after 3 cycles of V-based induction and baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1 or 2 from the US MM-6 and INSIGHT MM studies was performed[5,6]

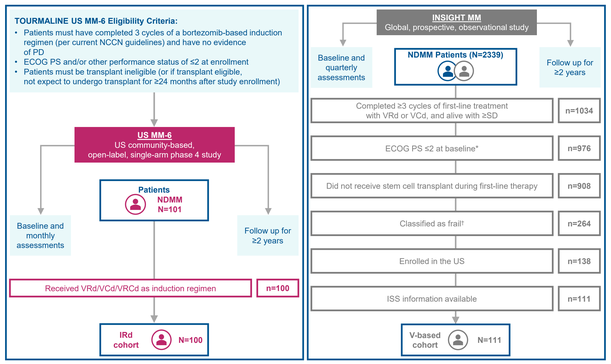
Endpoints

- Study outcomes included first-line duration of treatment (DOT), overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and reasons for treatment discontinuation

Statistical Analyses

- All analyses were weighted using the IPTW approach to reduce the imbalance of potential confounding factors between the two cohorts (**Figure 2**)
- The Kaplan–Meier method was used to examine DOT, PFS, OS, and associated 95% confidence intervals (CIs); the log-rank test was used to compare distribution of time to events
  - The Clopper-Pearson method was applied to estimate 95% CIs for ORR
  - Statistical significance was evaluated at alpha=0.05

Figure 2: Populations for the IRd and V-based cohorts Selected from US MM-6 and INSIGHT MM



*ECOG PS was only measured at baseline and then on a yearly basis in INSIGHT MM. †Frailty status was assessed based on the Simplified Frailty Score Score estimated using age, CCI and ECOG PS.[7] CCI, Charlson Comorbidity Index; ISS, International System Staging; NCCN, National Comprehensive Cancer Network; PD, progressive disease; VCd, bortezomib-cyclophosphamide-dexamethasone; VRCd, bortezomib-lenalidomide-cyclophosphamide-dexamethasone; VRd, bortezomib-lenalidomide-dexamethasone

Question

In transplant ineligible patients with NDMM, does IRd following 3 initial cycles of V-based induction (US MM-6 patients; 'IRd cohort') have comparable effectiveness with patients who continued to receive V-based therapy (INSIGHT MM patient; V-based cohort)?

Study design

Results

Figure 1A: Adjusted* ORR† in the IRd and V-based cohorts

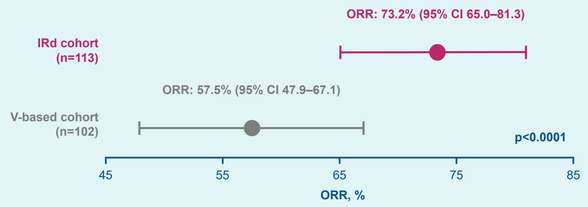
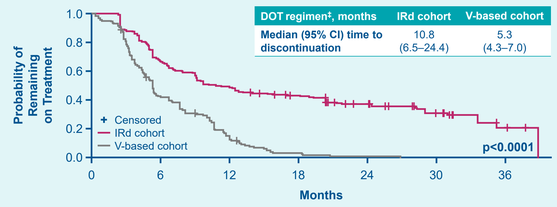


Figure 1B: Adjusted* DOT regimen‡ in the IRd and V-based cohorts



Patients at risk, n							
IRd cohort	113	75	55	43	25	15	5
V-based cohort	102	42	15	3	1	0	

*IPTW-weighted cohorts. †Defined as the proportion of patients with partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR) during initial treatment regimen and prior to disease progression. ‡Time from the index date (date that patients began V-based therapy) to the date of the last administration of any of the three study drugs in the IRd regimen or first-line V-based regimen for comparators (event), death (due to any cause, event), or end of follow-up (censored).

Key take aways

US MM-6 NDMM patients who transitioned to IRd after 3 initial cycles of V-based induction had a significantly higher ORR and longer DOT compared with patients who continued to receive V-based therapy in INSIGHT MM.
The results suggest that *i*CT from parenteral V-based therapy to all-oral IRd may improve outcomes in patients treated at community oncology practices.

Results

Patients

- 100 patients from the IRd cohort (US MM-6) and 111 patients from the V-based cohort (INSIGHT MM) were included in the analysis
- In the IPTW-weighted cohorts, 113 patients from MM-6 and 102 patients from INSIGHT MM contributed to the analyses
- In the weighted IRd versus V-based cohorts: median age was 75.0 versus 74.8 years; 57 versus 51% of patients were male; 37 versus 29% had an ECOG PS of ≥2; 49 versus 41% had ISS stage III at initial diagnosis, and 79/18/3 versus 77/20/3% patients had received VRd/VCd/VRCd as initial induction therapy (**Table 1**)

Efficacy

- Adjusted ORRs in the IRd versus V-based cohorts were 73.2% (95% CI 65.0–81.3) versus 57.5% (95% CI 47.9–67.1; p<0.0001; **Figure 1A**)
- After a median follow-up of 20.3 and 15.8 months in the IRd and V-based cohorts, respectively, median DOT was 10.8 months (95% CI 6.5–24.4) versus 5.3 months (95% CI 4.3–7.0; p<0.0001) (**Figure 1B**)
- Median PFS and OS were not estimable (NE) in either cohort (**Figures 3 & 4**)
  - PFS rates (95% CI) for the IRd vs V-based cohorts were:
    - 6-month: 96.0% (81.2–99.2) versus 95.3% (87.1–98.4)
    - 12-month: 86.9% (69.6–94.7) versus 87.5% (76.9–93.5)
    - 18-month: 85.7% (68.1–94.0) versus 80.1% (67.8–88.1)
    - 24-month: 85.7% (68.1–94.0) versus 76.5% (62.6–85.8)
  - OS rates (95% CI) for the IRd vs V-based cohorts were:
    - 6-month: 100% (100–100) versus 98.0% (90.5–99.6)
    - 12-month: 99.3% (61.0–100) versus 96.6% (88.2–99.1)
    - 18-month: 96.9% (80.9–99.5) versus 90.4% (79.7–95.6)
    - 24-month: 94.0% (77.7–98.5) versus 84.9% (70.6–92.6)

Reasons for Treatment Discontinuation

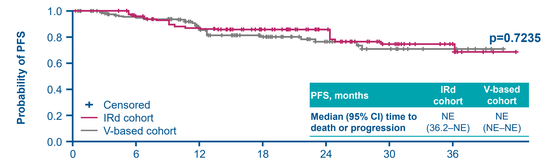
- In the IRd and V-based cohorts, 18 and 24% of patients discontinued IRd and V, respectively, due to an adverse event (AE; **Table 2**)

Table 1: Patient Baseline and Disease Characteristics after IPTW

Characteristic	IRd cohort (N=113*)	V-based cohort (N=102*)	P value
Median follow-up period, months (range)	20.3 (4.3–41.9)	15.8 (0.3–40.8)	0.0027
Median age, years (range)	75.0 (47.0–90.0)	74.8 (44.3–88.0)	0.1874
Age category, years, n (%)			
<55	4 (3.4)	7 (6.4)	0.4419
55–64	15 (12.9)	17 (17.0)	
65–74	28 (24.5)	28 (27.2)	
≥75 years	67 (59.2)	50 (49.3)	
Male, n (%)	64 (56.7)	52 (51.3)	0.4328
ECOG PS, n (%)			
0	16 (14.2)	13 (12.8)	0.3493
1	55 (48.4)	59 (58.1)	
2	42 (37.4)	30 (29.1)	
ISS disease stage (at initial diagnosis), n (%)			
I	19 (17.1)	21 (20.7)	0.5404
II	39 (34.1)	39 (37.9)	
III	55 (48.8)	42 (41.4)	
Induction regimen, n (%)			
VRd	90 (79.5)	79 (77.3)	0.9309
VCd	20 (17.7)	20 (19.5)	
VRCd	3 (2.8)	3 (3.1)	
CCI score, n (%)			
0	36 (31.4)	39 (37.7)	0.6268
1	17 (14.9)	13 (13.0)	
2	20 (17.6)	21 (20.2)	
3+	41 (36.0)	30 (29.0)	
Race, n (%)			
White	78 (69.0)	73 (71.4)	0.0364
Black	23 (20.6)	16 (16.0)	
Asian	2 (1.8)	1 (0.6)	
Other	9 (8.1)	4 (4.0)	
Missing/Unknown	1 (0.5)	8 (8.0)	
Renal impairment†, n (%)			
Yes	25 (21.8)	20 (19.9)	0.1400
No	88 (78.2)	78 (76.7)	
Missing	0	3 (3.4)	

*IPTW-weighted cohorts, percentages may not sum due to rounding. †Defined as estimated glomerular filtration rate <40 mL/min/1.73m^2 calculated from creatinine levels using the Modification of Diet in Renal Disease study equation.[8,9]

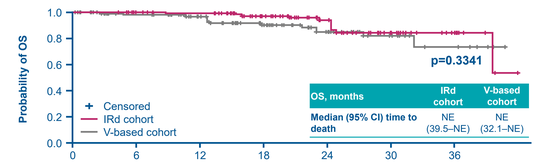
Figure 3. Adjusted PFS in the IRd and V-based cohorts



Patients at risk, n*							
IRd cohort	113	104	88	61	37	21	9
V-based cohort	102	87	59	42	25	9	5

*IPTW-weighted cohorts.

Figure 4. Adjusted OS in the IRd and V-based cohorts



Patients at risk, n*							
IRd cohort	113	106	99	68	40	22	9
V-based cohort	102	88	66	47	29	10	5

*IPTW-weighted cohorts.

Table 2: Reasons for Discontinuation of IRd or V

	IRd cohort (N=113*)	V-based cohort (N=102*)
Discontinued medication, n (%)	**72 (63.3)**	**73 (71.9)**
Reason for discontinuation, n (%)		
PD	16 (22.6)	9 (12.8)
AE	13 (17.6)	18 (24.4)
Patient request	34 (48.0)	1 (0.8)
Planned therapy completed	–	33 (44.6)
Inadequate response	–	1 (1.8)
Other	9 (11.9)	11 (15.5)

*IPTW-weighted cohorts, percentages may not sum due to rounding.

Limitations

- This study has limitations, of which some are inherent to analyses of observational data
- INSIGHT-MM (V-based cohort) was an observational study where outcomes were assessed on a quarterly basis, whereas outcomes for the US MM-6 single arm clinical trial (IRd cohort) were assessed at the end of each 28-day treatment cycle
  - This difference in timing of the assessments may have introduced bias, as patients in the IRd cohort were being followed-up more frequently
- Across treatment cohorts there were differences in geography (INSIGHT-MM was a global study, whereas US MM-6 was restricted to the US) and type of treatment centers (most treatment centers in INSIGHT were academic, whereas US MM-6 centers were from community settings)
  - To account for the differences in geography, only INSIGHT-MM patients residing in the US were included in this analysis. This ensured more balanced cohorts, however resulted in a reduced sample size for this analysis
- Propensity score values used in the IPTW were based on a vector of observed covariates, and thus any confounding due to unobserved covariates (e.g., residual confounding) could not be accounted for

Conclusions

- US MM-6 NDMM patients who transitioned to IRd after 3 initial cycles of V-based induction had a significantly higher ORR and longer DOT compared with patients who continued to receive V-based therapy in INSIGHT MM
- *i*CT from V-based therapy to all-oral IRd therapy resulted in a lower treatment discontinuation rate due to AEs compared with patients who continued to receive V-based therapy
- The results suggest that *i*CT from V-based therapy to all-oral IRd may improve outcomes in patients treated at community oncology clinics
- In addition to offering a viable treatment option, the ability to transition from a parenteral to an oral treatment regimen could prevent disruption to patients' treatment course
- All-oral IRd may be most beneficial to patients with restricted mobility (e.g. elderly patients), those who may prefer to remain outside of a hospital/clinic setting for treatments, or those with work commitments/ family obligations

References

1. Mateos MV, et al. *Am J Hematol* 2015;90:314–9
2. Jimenez-Zepeda VH, et al. *Ann Hematol* 2017;96:431–9
3. Richardson PG, et al. *Blood Cancer J* 2018;8:109
4. Chari A, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:8–17
5. Manda S, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:e910–25
6. Costello C, et al. *Future Oncol* 2019;15:1411–28
7. Facon T, et al. *Leukemia* 2020;34:224–33
8. Nakaya A, et al. *Hematol Rep* 2017;9:6887
9. Thomas C & Thomas L. *Dtsch Arztebl Int.* 2009;106:849–54

Acknowledgments

These studies were funded by Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA. The authors would like to thank all patients and their families, as well as investigators at all clinical sites for their participation in the study. Medical writing support for the development of this poster, under the direction of the authors, was provided by Laura Webb, PhD, of Ashfield MedComms, an Ashfield Health company, funded by Takeda Pharmaceuticals U.S.A., Inc., and complied with the Good Publication Practice-3 (GPP3) guidelines (Battisti WP, et al. Ann Intern Med 2015; 163:461–4). We also thank Michael Stokes, of Evidera, Data Analytics, for his contribution towards study design and data analysis.

Disclosures

RMR: Employment with McKesson; Ownership of stock/shares with McKesson; Member of advisory council/committees for Amgen, BMS, Coherus, Fresenius, and Takeda; **CLC**: Member of advisory council/committees for BMS, Janssen, Takeda, and Pfizer; **REB**: Member of advisory council/committees for Array Biopharma Inc., Lilly Oncology, Janssen Scientific Affairs Llc, Epizyme, Tg Therapeutics, and Regeneron; Other financial relationship with Janssen Biotech Inc., Amgen Inc., Puma Biotechnology Inc., Lilly USA Llc, Incyte Corporation, Pharmacyclics Llc (an Abbvie company), Genzyme Corporation, Dova/Sobi Pharmaceuticals, Exelixis Inc., E.R. Squibb & Sons Llc, Abbvie Inc., Astrazeneca Pharmaceuticals Lp, Sanofi, Daichi Sancho, Morphosys, Regeneron, Glaxo Oncology, and Seagen; **SK**: none; **JR**: Consulting fees from Takeda, and BMS/Celgene; **RA**: Member of advisory council/committees for Takeda, BMS, and Jensen; Honoraria from Takeda, BMS, Jensen, and GSK; Consulting fees from Takeda, BMS, Jensen, and GSK; Grants or funds from Takeda, BMS, Jensen, and GSK; **HCL**: Consulting fees from BMS/Celgene, Genentech, Janssen, Karyopharm, Legend Biotech, GSK, Sanofi, Pfizer, Monte Rosa Therapeutics, Immunitas Therapeutics, Oncopeptides, and Takeda Pharmaceuticals; Grants or funds from Amgen, Janssen, GSK, Regeneron, and Takeda Pharmaceuticals; **YJK**: Employment with Takeda Pharmaceutical Company Limited; Consulting fees from Takeda; **KR**: Employment with Takeda Development Center Americas, Inc. (TDCA); **DMS**: Employment with Takeda Pharmaceuticals; Ownership of stock/shares with Takeda Pharmaceuticals; **DC**: Employment with Takeda; Ownership of stock/shares with Takeda; **KB**: Employment with Takeda Oncology; **SJN**: Employment with Takeda Pharmaceuticals; **SG**: Member of advisory council/committees for Takeda, BMS, Janssen, and GSK; Honoraria from Takeda, BMS, Beigene, GSK, and Adaptive.

Poster presentation at the 2022 European Hematology Association (EHA2022) Hybrid Congress, June 9–12, 2022, Vienna, Austria. For questions or comments please contact Dr Robert M. Rifkin: robert.rifkin@usoncology.com