The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

TREATING RELAPSED/REFRACTORY MULTIPLE MYELOMA OUTSIDE OF CLINICAL TRIALS VIA AN EARLY ACCESS PROGRAM: SECOND INTERIM ANALYSIS OF EFFECTIVENESS/SAFETY IN THE 'USE VIA EARLY ACCESS TO IXAZOMIB' (UVEA-IXA) STUDY

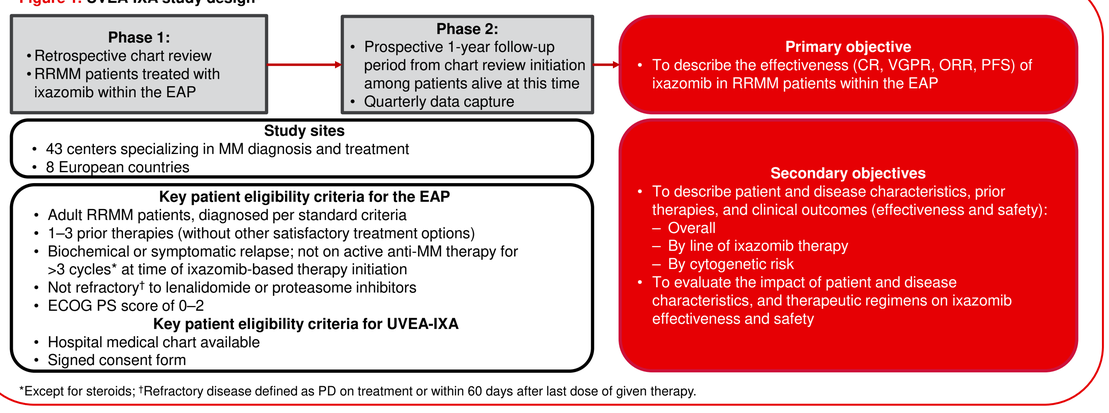
Bhuvan Kishore,[1] Heinz Ludwig,[2] Evangelos Terpos,[3] María-Victoria Mateos,[4] Mario Boccadoro,[5] Karthik Ramasamy,[6] Sylvie Fernandez,[7] Fabio Ferri,[8] Nawal Bent-Ennakhil,[9] Athanasios Zomas,[9] François Gavini,[9] Roman Hájek[10]

[1]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [2]Wilhelminen Cancer Research Institute, c/o Department of Medicine I, Center for Oncology, Hematology, and Palliative Care, Clinic Ottakring, Vienna, Austria; [3]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [4]Departamento de Hematología, Hospital Universitario de Salamanca (HUSAL), IBSAL, IBMCC (USAL-CSIC), CIBERONC, Salamanca, Spain; [5]Division of Hematology, University of Torino, Torino, Italy; [6]Department of Haematology, Oxford University Hospital, NHS Trust, Oxford, United Kingdom; [7]MediNeos Observational Research, Modena, Italy; [8]Data Management and Statistics Unit, MediNeos Observational Research, Modena, Italy; [9]Medical Affairs, Europe & Canada, Takeda Pharmaceuticals International AG, Zurich, Switzerland; [10]University Hospital Ostrava, Ostrava, Czech Republic.

INTRODUCTION AND METHODS

- It is becoming increasingly important in the treatment of MM to improve our understanding of routine clinical practice and of the effectiveness of new agents and regimens outside the clinical trial setting.[1]
- UVEA-IXA is a European, multicenter, observational, longitudinal cohort study of RRMM patients who received therapy with ixazomib via an Early Access Program (EAP) before its approval in the EU (Nov 2016).[2,3] Study design is shown in **Figure 1**.
  - Ixazomib was available in Europe via the EAP from Nov 2015, when it was initially approved in the US in combination with lenalidomide and dexamethasone for the treatment of MM patients who have received ≥1 prior therapy.[4]
    - Approval was based on the results of the phase 3 TOURMALINE-MM1 study.[5]
  - UVEA-IXA included patients receiving treatment via the EAP at MM specialist centers in the Czech Republic, Greece, Hungary, Italy, Slovakia, Slovenia, Spain, and Great Britain.[3]

Figure 1. UVEA-IXA study design[3]



*Except for steroids; †Refractory disease defined as PD on treatment or within 60 days after last dose of given therapy.

OBJECTIVE

- The study aims to improve our understanding of routine clinical practice and outcomes of ixazomib-based therapy outside of clinical trials.
  - We report data from the second interim analysis (data cutoff May 22, 2020) of 302 patients enrolled in the UVEA-IXA study.

RESULTS

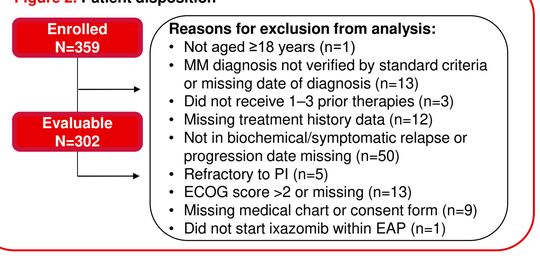
PATIENT DISPOSITION AND OBSERVATION PERIOD

- At the data cutoff of May 22, 2020, 359 patients had been enrolled.
  - A total of 302 patients from eight countries were evaluable for the current analyses (**Table 1**); patient disposition is shown in **Figure 2**.
- 134 patients from the full analysis set had died or were untraceable at enrollment.
- The median observation period was 24.9 months (range, 0.2–49.3)
  - For seven deceased/untraceable patients, the observation period duration cannot not be estimated because the date of the end of observation has not been recorded yet.

Table 1. Evaluable patients by country of enrollment

Country, n (%)	N=302
Great Britain	97 (32.1)
Czech Republic	80 (26.5)
Hungary	44 (14.6)
Spain	22 (7.3)
Greece	21 (7.0)
Slovakia	18 (6.0)
Italy	16 (5.3)
Slovenia	4 (1.3)

Figure 2. Patient disposition



PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS AT MM DIAGNOSIS

- Median age at MM diagnosis was 64 years, and most patients had secretory MM, an ECOG PS score of 0–1, and standard-risk cytogenetics (**Table 2**).

Table 2. Patient demographics and disease characteristics at MM diagnosis

Characteristic	Data available	Data unknown
N (%) Median age, years (25th–75th percentile)	302 (100) 64 (57–69)	0
N (%) Type of MM Light chain only Secretory Non-secretory	284 (94) 72 (25) 203 (71) 9 (3)	18 (6)
N (%) ECOG PS score 0–1 ≥2	236 (78) 196 (83) 40 (17)	66 (22)
N (%) Cytogenetic risk Standard-risk High-risk	206 (68) 183 (89) 23 (11)	96 (32)

PATIENT DEMOGRAPHICS AT ENROLLMENT AND DISEASE CHARACTERISTICS AT START OF IXAZOMIB-BASED THERAPY

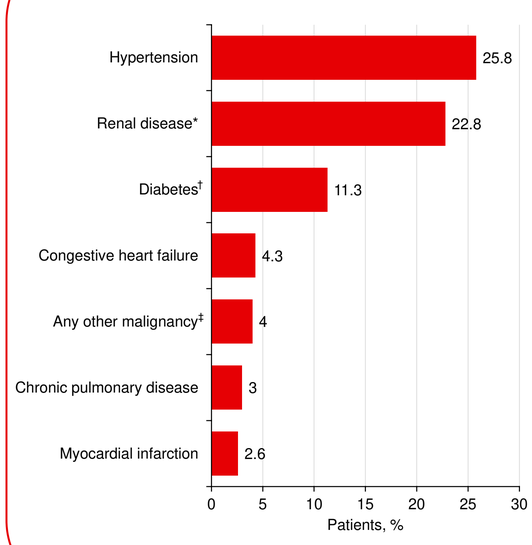
- All patients received ixazomib-based therapy; the majority of the 302 patients who received ixazomib did so in combination with Rd.
  - Eight patients did not receive lenalidomide and 13 patients did not receive dexamethasone.
- Median age at enrollment was 68 years (**Table 3**).
- Of the 117 patients with ISS disease stage data available, 36 (31%) had ISS stage III disease at the start of ixazomib-based therapy.
- 20% of patients had ECOG PS 2 at the start of ixazomib-based therapy.
  - In TOURMALINE-MM1, the median age was 66 years, 12% of patients had ISS stage III and 5% had ECOG PS 2 in the ixazomib-Rd arm.[5]
- A total of 182 patients (60%) had ≥1 comorbidity before or at ixazomib-based therapy initiation; **Figure 3** shows comorbidities of clinical importance reported in >2% of patients.

Table 3. Patient demographics at enrollment and disease characteristics at start of ixazomib-based therapy

Patient demographics at enrollment		N=302
Median age, years (25th–75th percentile)		68 (61–73)
Age <60 / 60–69 / 70–79 / ≥80 years, %		20 / 40 / 32 / 8
Male, %		55
Race, % White/Caucasian / Other* (n=285, 6% unknown)		98 / 2
Disease characteristics at start of ixazomib-based therapy	**Data available**	**Data unknown**
N (%) ISS stage I / II / III, %	117 (39) 36 / 33 / 31	185 (61)
N (%) ECOG PS score 0 / 1 / 2, %	301 (>99) 23 / 56 / 20	1 (<1)
N (%) eGFR (mL/min/1.73 m²), ≥60 / 30 to <60 / <30, %	271 (90) 72 / 23 / 5	31 (10)
N (%) High LDH, No / Yes, %	206 (68) 88 / 12	96 (32)
N (%) Standard-risk / High-risk cytogenetics, %	47 (16) 70 / 30	255 (84)
N (%) ≥1 comorbidity,† %	302 (100) 60	0
N (%) Median time from MM diagnosis, months (range)	302 (100) 37 (5–232)	0

*Includes Black/African, Asian or Pacific Islander, and Other; †The most common comorbidities were hypertension (26%), renal disease (23%) and diabetes (10%).

Figure 3. Patient comorbidities of clinical importance before/at ixazomib-based therapy initiation (>2% of patients)

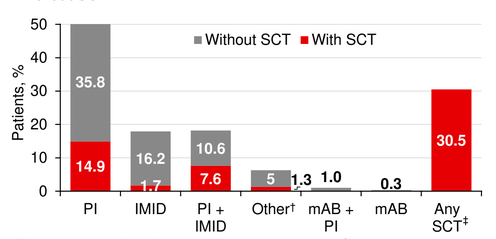


*Per reported comorbidities; †Includes diabetes with chronic complications; ‡Includes lymphoma and leukemia.

PRIOR THERAPIES

- A total of 39% of patients had received 1 prior therapy, and 61% of patients had 2–3 prior therapies (43% with 2 prior therapies, and 18% with 3 prior therapies).
  - In the TOURMALINE-MM1 trial, 38% of patients in the ixazomib-Rd arm had 2–3 prior therapies.[5]
- The median duration of prior therapies was 10.8 months (range, 0.5–105.7) overall, and:
  - 6.5 months (range, 0.3–95.0) for first prior therapy
  - 5.2 months (range, 0.2–74.0) for second prior therapy
  - 8.0 months (range, 0.4–60.3) for third prior therapy.
- **Figure 4** summarizes data for the most recent prior line of therapy received before ixazomib-based therapy (N=302).

Figure 4. Most recent prior line of therapy received with or without SCT*



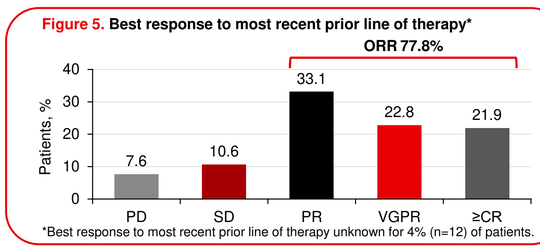
*Most recent prior line of therapy unknown for 2 patients; †Includes other chemotherapy drugs, steroids and bisphosphonates that are not PIs or IMIDs; ‡Includes all patients with SCT recorded as part of their most recent prior line.

RESULTS (CONTINUED)

TTP AND BEST RESPONSE TO MOST RECENT PRIOR LINE OF THERAPY

- The median TTP was 19.6 months (range, 1.5–192.3), 10.1 months (range, 0.3–110.7), and 10.8 months (range, 1.0–59.0) for first-, second-, and third-line therapies, respectively.
- Data on best response to most recent prior line of therapy received before ixazomib-based therapy for all evaluable patients (N=302) are shown in **Figure 5**; the ORR was 77.8%.
- The median TTP on most recent prior line of therapy was 13.2 months (range, 0.3–134.6).

Figure 5. Best response to most recent prior line of therapy*



*Best response to most recent prior line of therapy unknown for 4% (n=12) of patients.

DURATION OF THERAPY AND BEST RESPONSE TO IXAZOMIB-BASED THERAPY

- At data cutoff, the median duration of ixazomib-based therapy (N=302) was 12.1 months (range, 0.2–49.3) and the median number of cycles received was 9 (range, 1.0–46.0).
  - Median duration of treatment by individual agent during ixazomib-based therapy is shown in **Figure 6**.
- Of the 302 patients who received ixazomib-based therapy, 12 (4%) also underwent transplant as part of the same line of therapy.
- Data on best response to ixazomib-based therapy are shown in **Figure 7**; overall, in 275 evaluable patients, the ORR was 60%.
  - In TOURMALINE-MM1, ORR was 78% in the ixazomib-Rd arm.[5]

Figure 6. Median duration of individual agents of ixazomib, lenalidomide and dexamethasone therapy during ixazomib-based therapy

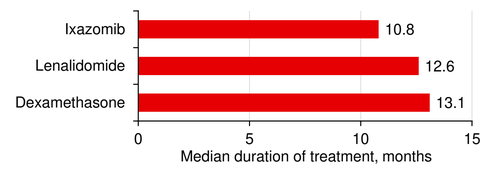
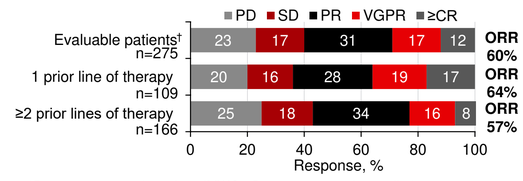


Figure 7. Best response* to ixazomib-based therapy: overall and by number of prior lines of therapy

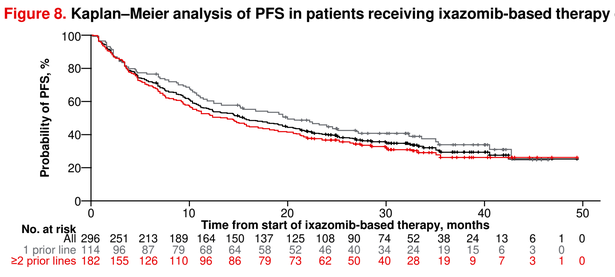


*Response was evaluated per IMWG; †Best response to ixazomib therapy not available for 27 patients at cutoff; data collection ongoing.

PFS IN PATIENTS RECEIVING IXAZOMIB-BASED THERAPY

- PFS was evaluated in 296/302 patients, overall and by number of prior lines of therapy.
- Median PFS was 15.6 months overall, 20.0 months in patients with 1 prior line, and 13.6 months in patients with ≥2 prior lines (**Figure 8**).
  - In TOURMALINE-MM1, median PFS was 20.6 months in patients with 1 prior line of therapy, 17.5 months in patients with 2 prior lines and NE in patients with 3 prior lines.[5]

Figure 8. Kaplan–Meier analysis of PFS in patients receiving ixazomib-based therapy overall and by number of prior lines of therapy



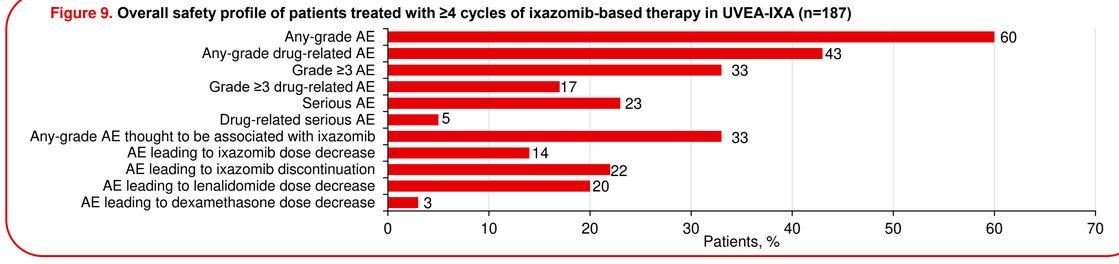
Group	n	Events, n	Median PFS (95% CI), months
All	296*	199	15.6 (11.8–20.0)
1 prior line	114	72	20.0 (12.5–27.2)
≥2 prior lines	182	127	13.6 (10.0–18.1)

*Observations with invalid time or censoring values were deleted for 6 patients since the last observation date for these patients was not available.

SAFETY

- The overall safety profile for patients treated with at least 4 cycles of ixazomib-based therapy in UVEA-IXA is shown in **Figure 9**.

Figure 9. Overall safety profile of patients treated with ≥4 cycles of ixazomib-based therapy in UVEA-IXA (n=187)



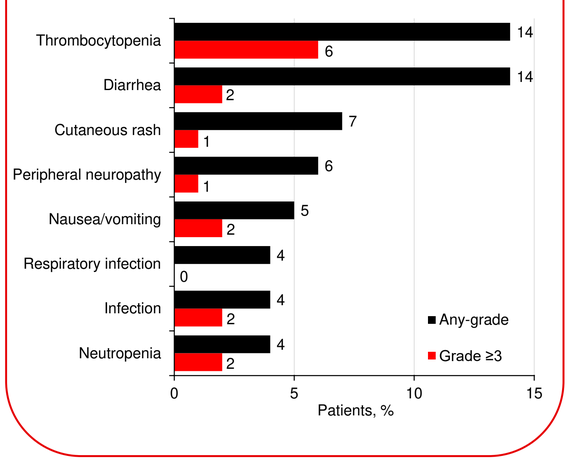
- Dose reductions and treatment discontinuations are summarized in **Table 3**.
  - Ixazomib dose reductions were required in 19% of patients, mostly due to AEs (14%).
  - 73% of patients discontinued ixazomib; 32%/16%/10% discontinued due to progression/AEs/lack of response.
- The most common AEs reported in UVEA-IXA were hematologic and gastrointestinal (**Figure 10**).
  - Common AEs were in line with those reported in the ixazomib-Rd arm of the TOURMALINE-MM1 trial.[5]

Table 3. Dose reductions and treatment discontinuations

n (%)	Ixazomib (N=302)	Lenalidomide (n=294)	Dexamethasone (n=289)
Dose reduction*	57/302 (19)	103/294 (35)	NA
Reasons for dose reduction			
Toxicities / AEs	42 (14)	69 (23)	NA
Other	13 (4)	25 (9)	NA
Unknown	3 (1)	13 (4)	NA
Treatment discontinuation†	219/302 (73)	190/294 (65)	180/289 (62)
Reasons for discontinuation			
Disease progression	96 (32)	93 (32)	0
Toxicities / AEs	49 (16)	33 (11)	25 (9)
Loss/lack of response	31 (10)	28 (10)	64 (22)
Achievement of CR	14 (5)	12 (4)	0
Patient preference	10 (3)	8 (3)	14 (5)
Other	28 (9)	23 (8)	56 (19)
Unknown	6 (2)	7 (2)	26 (9)

*Patients with ≥1 ixazomib/lenalidomide/dexamethasone dose reduction. Dose reduction and discontinuation data were not recorded for n=11 receiving ixazomib and n=9 receiving lenalidomide; †Treatment discontinuation data were not recorded for n=7 receiving dexamethasone; a patient could have had more than one reason for discontinuing treatment.

Figure 10. AEs occurring in ≥3% of patients at any grade and/or in ≥2% of patients at grade ≥3, among patients treated with ≥4 cycles of ixazomib-based therapy (n=187)



CONCLUSION

- Ixazomib-based therapy is an effective and tolerable treatment option outside the clinical trial setting.
- Data from the second interim analysis of UVEA-IXA demonstrate that ixazomib-based therapy is effective outside the clinical trial setting, with an ORR of 60% and a median PFS of 15.6 months.
  - This is in line with other smaller registry studies of ixazomib-based combinations (mainly ixazomib-Rd) in RRMM patients (ORRs: range, 66–88%; PFS: range of medians, 11.4–27.6 months).[6–11]
- Compared with TOURMALINE-MM1 patients (ixazomib arm; ORR 78%, median PFS 20.6 months), UVEA-IXA patients have higher rates of ECOG PS 2 (20% vs 5%) and ISS stage III MM (31% vs 12%), and had received more prior therapies (61% vs 38% had ≥2 prior therapies).[3,5]
- The most common AEs were gastrointestinal and hematologic AEs, in line with the well-characterized and manageable safety profile of ixazomib.[5]
  - Data are not directly comparable with clinical trial safety data due to the retrospective/infrequent prospective collection schedule.

REFERENCES

1. Richardson PG, et al. Blood Cancer J 2018;8:109.
2. Takeda Pharma A/S. NINLARO: European Product Assessment Report (EPAR) - Product Information. Annex I - Summary of Product Characteristics; 2017 (accessed Sept 25, 2020).
3. Ludwig H, et al. EHA 2020 [poster #EP976].
4. Millennium Pharmaceuticals Inc. NINLARO® (ixazomib) capsules, for oral use. United States Prescribing Information; 2016 (accessed Sept 25, 2020).
5. Moreau P, et al. N Engl J Med 2016;374:1621–34.
6. Cohen YC, et al. Ann Hematol 2020;99:1273–81.
7. Ziff M, et al. Haematologica 2017;102:786–87.
8. Minarik J, et al. Blood 2018;132:1959.
9. Terpos E, et al. Blood 2017;130:3087.
10. Terpos E, et al. Haematologica 2017;102:511–12.
11. Varga G, et al. Pathol Oncol Res 2019;25:1615–20.

ABBREVIATIONS

AE, adverse event; CI, confidence interval; CR, complete response; EAP, Early Access Program; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; EU, European Union; IMID, immunomodulatory imide drug; IMWG, International Myeloma Working Group; ISS, International Staging System; LDH, lactate dehydrogenase; mAB, monoclonal antibody; MM, multiple myeloma; NE, not estimable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; Rd, lenalidomide-dexamethasone; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplant; SD, stable disease; TTP, time to progression; US, United States; UVEA-IXA, Use Via Early Access to Ixazomib; VGPR, very good partial response.

DISCLOSURES AND ACKNOWLEDGEMENTS

This study was funded by Takeda Pharmaceuticals International AG.
Dr Kishore discloses conference support from Takeda, Celgene, and Janssen. COI disclosures from the co-authors are available upon request.
The authors would like to thank all patients and their families, as well as all investigators for their valuable contributions to this study.
Medical writing support for the development of this poster presentation, under the direction of the authors, was provided by Laura Webb, PhD, of Ashfield MedComms, an Ashfield Health company, funded by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and complied with the Good Publication Practice-3 (GPP3) guidelines (Battisti WP, et al. Ann Intern Med 2015;163:461–4).

Electronic poster presentation at the 7th World Congress on Controversies in Multiple Myeloma (COMy) Virtual Meeting, May 7–9, 2021.
For questions or comments please contact Dr Kishore:bhuvan.kishore@nhs.net.

https://comylive.cme-congresses.com/