Effectiveness and safety of ixazomib-based therapy in relapsed/refractory multiple myeloma outside of a clinical trial: Final analysis of the 'Use Via Early Access to Ixazomib' (UVEA-IXA) study

EP994

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Background

- The oral proteasome inhibitor ixazomib was initially approved in the US in November 2015, in combination with lenalidomide and dexamethasone, for the treatment of MM patients who have received ≥1 prior therapy.[1]
  - Approval was based on the phase 3 TOURMALINE-MM1 study, in which ixazomib-Rd demonstrated superior PFS (median 20.6 vs 14.7 months, HR 0.74, p=0.01) and ORR (78.3% vs 71.5%, p=0.04) vs placebo-Rd, with limited additional toxicity.[2]
- Ixazomib was made available to RRMM patients in Europe via an EAP from the time of US approval through to its subsequent EU approval in November 2016.[3,4]

Objectives

UVEA-IXA

- For physicians involved in the treatment of patients with MM, it is increasingly important to improve our understanding of routine clinical practice and the effectiveness of new agents outside of clinical trials.[5]
- UVEA-IXA is a European, multicenter, observational, longitudinal cohort study of RRMM patients who received therapy with ixazomib via the EAP at MM specialist centers in the Czech Republic, Greece, Hungary, Italy, Slovakia, Slovenia, Spain, and the UK.[3,4]
- Here, we report data from the final analysis of UVEA-IXA.

Methods

- The UVEA-IXA study design is summarized in **Figure 1**, and key eligibility criteria are listed in **Table 1**.

Figure 1. UVEA-IXA study design

Study sites
- 43 centers specializing in MM diagnosis and treatment
- 8 European countries: Czech Republic, Greece, Hungary, Italy, Slovakia, Slovenia, Spain, and the UK

Phase 1:
- Retrospective chart review
- RRMM patients treated with ixazomib within the EAP

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Phase 2:
- Prospective 1-year follow-up period from chart review initiation among patients alive at this time
- Quarterly data capture

Primary objective
- To describe the effectiveness (CR, VGPR, ORR, PFS) of ixazomib in RRMM patients within the EAP

Secondary objectives
- To describe patient and disease characteristics, prior therapies, and clinical outcomes (effectiveness and safety):
  - Overall
  - By line of ixazomib therapy
  - By cytogenetic risk

Table 1. Eligibility criteria

Key patient eligibility criteria for the EAP	
• Adult RRMM patients, diagnosed per standard criteria	• 1–3 prior therapies (without other satisfactory treatment options)
• ECOG PS score of 0–2	• Biochemical or symptomatic relapse
• Not on active anti-MM therapy for >3 cycles* at time of ixazomib-based therapy initiation	• Not refractory† to lenalidomide or proteasome inhibitors
Key patient eligibility criteria for UVEA-IXA	
• Hospital medical chart available	• Signed consent form

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

Results

Patients and disposition

- Enrollment for this final analysis at data cutoff of October 26, 2020, is summarized in **Table 2**.
  - Median observation period was 25.5 months (range 0.8–54.1).*

*For n=3 deceased/untraceable patients, the observation period duration cannot be estimated because the date of the end of observation wasn't recorded.

Table 2. Enrollment to UVEA-IXA

Country	Patients enrolled, n (%)	Evaluable patients, n (%)	Patients excluded, N=48 (applies to all enrolled patients)
All	357 (100)	309 (100)	Reasons for exclusion:
UK	119 (33)	100 (32)	• MM diagnosis not verified by standard criteria or missing date of diagnosis (n=11)
Czech Republic	95 (27)	80 (26)	• Did not receive 1–3 prior therapies (n=8)
Hungary	46 (13)	44 (14)	• Missing treatment history data (n=9)
Spain	30 (8)	29 (9)	• Not in biochemical/symptomatic relapse or progression date missing (n=40)
Greece	21 (6)	21 (7)	• Refractory to lenalidomide or PI (n=5)
Italy	20 (6)	16 (5)	• ECOG score missing (n=11)
Slovakia	18 (5)	16 (5)	• Missing medical chart or consent form (n=2)
Slovenia	8 (2)	3 (1)	• Did not start ixazomib within EAP (n=1)

- Patient demographics and disease characteristics at diagnosis are summarized in **Table 3**.

Table 3. Patient demographics and disease characteristics at MM diagnosis

Characteristic	N=309
Median age at diagnosis, years (range)	64 (32–88)
Type of MM, n (%)	
Light chain only	74 (24)
Secretory	208 (67)
Non-secretory	9 (3)
Unknown	18 (6)
ECOG PS score, n (%)	
0–1	200 (65)
≥2	40 (13)
Unknown	69 (22)
Cytogenetic risk, n (%)	
High-risk*	26 (8)
No- or standard-risk	183 (59)
Unknown	100 (32)

*Patients with del(17p), t(4;14) or t(14;16) were classified as high-risk.

QUESTION

How effective is ixazomib-based therapy outside of the clinical trial setting in patients with RRMM?

INVESTIGATION

Study sites: 43 centers across 8 European countries

Phase 1:
- Retrospective chart review
- RRMM patients treated with ixazomib within the EAP

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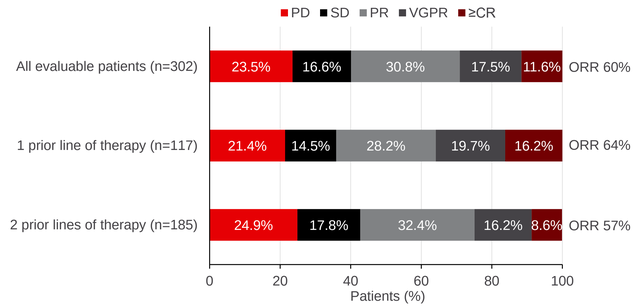
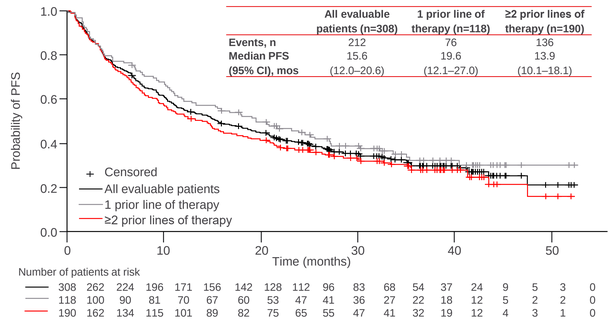
Phase 2:
- Prospective 1-year follow-up period from chart review initiation
- Quarterly data capture

RESULTS

Primary endpoint: ORR



Primary endpoint: PFS



	All evaluable patients (n=308)	1 prior line of therapy (n=118)	≥2 prior lines of therapy (n=190)
Events, n	212	76	136
Median PFS (95% CI), mos	15.6 (12.0–20.6)	19.6 (12.1–27.0)	13.9 (10.1–18.1)

Number of patients at risk

All evaluable patients	308	262	224	196	171	156	142	128	112	96	83	68	54	37	24	9	5	3	0
1 prior line of therapy	118	100	90	81	70	67	60	53	47	41	36	27	22	18	12	5	2	2	0
≥2 prior lines of therapy	190	162	134	115	101	89	82	75	65	55	47	41	32	19	12	4	3	1	0

CONCLUSIONS

Results of the final analysis of the UVEA-IXA study support ixazomib-based therapy as an effective treatment option outside the clinical trial setting.

- Demographics at enrollment and disease characteristics at the start of ixazomib-based therapy are summarized in **Table 4**.

Table 4. Patient demographics at enrollment and disease characteristics at start of ixazomib-based therapy

Patient demographics at enrollment	N=309
Median age, years (range)	68 (36–92)
Age <60 / 60–69 / 70–79 / ≥80 years, %	21 / 39 / 32 / 8
Male, %	54
Race: White / Other* (n=292, 6% unknown)	98 / 2

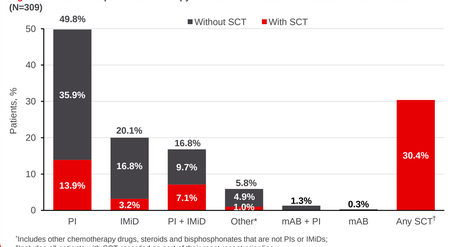
Disease characteristics at start of ixazomib-based therapy	Data available	Data unknown
N (%) ISS stage I / II / III, %	123 (40) 35 / 35 / 30	186 (60)
N (%) ECOG PS score 0 / 1 / 2, %	308 (>99) 24 / 56 / 20	1 (<1)
N (%) eGFR (mL/min/1.73 m²), ≥60 / 30 to <60 / <30, %	279 (90) 72 / 23 / 5	30 (10)
N (%) High LDH, No / Yes, %	212 (69) 88 / 12	97 (31)
N (%) High-risk / No- risk or standard-risk, %	47 (15) 30 / 70	262 (89)
N (%) Median duration of MM, months (range)	309 (100) 37 (5–233)	0
N (%) Patients with ≥1 comorbidity, % Hypertension Renal disease Diabetes	309 (100) 61 26 23 9	0

*Includes Black/African, Asian or Pacific Islander, and Other.

Prior therapy

- 39%, 43%, and 18% of patients had received 1, 2, and 3 prior therapies, respectively.
- Median duration of prior therapies was 11.2 (range 0.5–105.7) months, overall, and:
  - 6.5 (range 0.3–95.0) months for first prior line of therapy
  - 5.4 (range 0.2–74.0) months for second prior line of therapy
  - 7.2 (range 0.2–60.3) months for third prior line of therapy.
- Most recent prior line of therapy received before ixazomib is summarized in **Figure 2**.

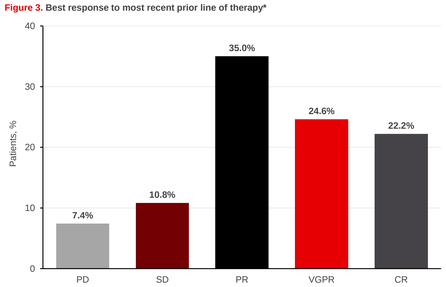
Figure 2. Most recent prior line of therapy received before ixazomib treatment with or without SCT (N=309)



‡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.

- Before initiating ixazomib-based therapy, best response to most recent prior line of therapy was available for 297 patients (**Figure 3**).
- Median TTP was 19.8 months (range 1.5–192.3), 10.1 months (range 0.3–110.7), and 11.5 months (range 1.0–59.0) for first, second, and third prior lines of therapy, respectively.
- Median TTP on most recent prior line of therapy was 13.4 months (range 0.3–134.6).

Figure 3. Best response to most recent prior line of therapy*



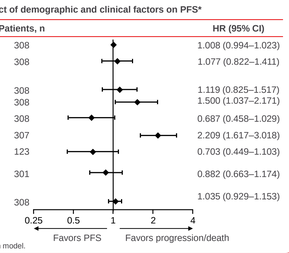
*Response was evaluated per IMWG criteria.

Effectiveness

- At data cutoff, median duration of therapy of the individual agents as part of ixazomib-based treatment was as follows:
  - Ixazomib (n=309): 10.5 (range 0.2–52.3) months
  - lenalidomide (n=303): 11.8 (range 0.2–52.7) months
  - dexamethasone (n=300): 11.9 (range 0.5–52.7) months.
- Best response to ixazomib-based therapy was available for 302 patients (**Summary panel**).
- PFS was evaluated in 308 patients (response was evaluated per IMWG criteria), overall and by number of prior lines of therapy (1, ≥2) (**Summary panel**).
- Median PFS was 15.6 months overall, and 19.6 and 13.9 months in patients with 1 and ≥2 prior lines, respectively.
- Risk of progression/death was greater in patients with ECOG PS 2 vs 0–1: 87% vs 64% had PFS events (p=0.0004).
- The impact of demographic and clinical factors on PFS is summarized in **Figure 4**.
- Overall, median time to next line of therapy (from start of ixazomib-based therapy) was 21.4 months (95% CI 17.3–25.2).

Figure 4. Forest plot showing impact of demographic and clinical factors on PFS*

Demographic/clinical factor	Patients, n	HR (95% CI)
Age at enrollment (continuous)	308	1.008 (0.994–1.023)
Gender, female vs male	308	1.077 (0.822–1.411)
Number of prior lines of therapy		
2 vs 1	308	1.119 (0.825–1.517)
3 vs 1	308	1.500 (1.037–2.171)
Ixazomib initial dose	308	0.687 (0.458–1.029)
ECOG PS ≥2 vs <2	307	2.209 (1.617–3.018)
ISS stage: I–II vs III	123	0.703 (0.449–1.103)
Comorbidity status, no comorbidity vs any comorbidity	301	0.882 (0.663–1.174)
Charlson Comorbidity Index score (continuous)	308	1.035 (0.929–1.153)

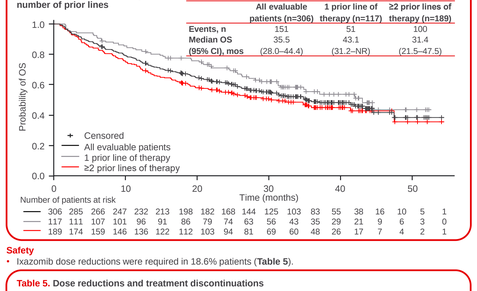


*Evaluated using a univariate Cox regression model.

- OS was evaluated in 306 patients,* overall and by number of prior lines of therapy (1, ≥2) (**Figure 5**).
- After a median observation period of 25.5 months, median OS was 35.5 months (95% CI 28.0–44.4) overall, and 43.1 and 31.4 months in patients with 1 and ≥2 prior lines, respectively.

*Three observations with invalid time, censoring, or strata values were deleted.

Figure 5. Kaplan–Meier analysis of OS with ixazomib-based therapy for all evaluable patients and by number of prior lines



	All evaluable patients (n=306)	1 prior line of therapy (n=117)	≥2 prior lines of therapy (n=189)
Events, n	151	51	100
Median OS (95% CI), mos	35.5 (28.0–44.4)	43.1 (31.2–NR)	31.4 (21.5–47.5)

Number of patients at risk

All evaluable patients	306	285	266	247	232	213	198	182	168	144	125	103	83	55	38	16	10	5	1
1 prior line of therapy	117	111	107	101	96	91	86	79	74	63	56	43	35	29	21	9	6	3	0
≥2 prior lines of therapy	189	174	159	146	136	122	112	103	94	81	69	60	48	26	17	7	4	2	1

Safety

- Ixazomib dose reductions were required in 18.6% patients (**Table 5**).

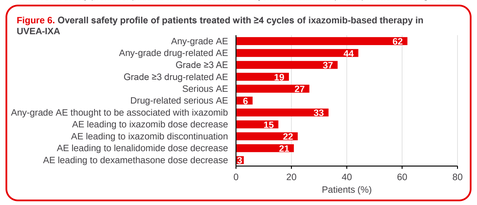
Table 5. Dose reductions and treatment discontinuations

Dose reductions and treatment discontinuations	Ixazomib (n=309)	Lenalidomide (n=303)	Dexamethasone (n=300)
Dose reduction,* n (%)	57 / 307 (19)	102 / 303 (34)	NA
Reasons for dose reduction, n (%)			
Toxicities / AEs	51 (17)	76 (25)	NA
Other	4 (1)	16 (5)	NA
Unknown	2 (<1)	12 (4)	NA
Treatment discontinuation, n (%)	246 / 309 (80)	223 / 303 (74)	208 / 300 (69)
Reasons for discontinuation†			
Disease progression	113 (37)	113 (37)	0 (0)
Toxicities / AEs	58 (19)	40 (13)	32 (11)
Loss/lack of response	32 (10)	30 (10)	76 (25)
Achievement of CR	12 (4)	9 (3)	0 (0)
Patient preference	11 (4)	9 (3)	15 (5)
Other	27 (9)	29 (10)	63 (21)
Unknown	9 (3)	10 (3)	28 (9)

*Patients with ≥1 ixazomib/lenalidomide/dexamethasone dose reduction. Dose reduction data were not recorded for n=2 receiving ixazomib; †A patient could have more than one reason to discontinue agents.

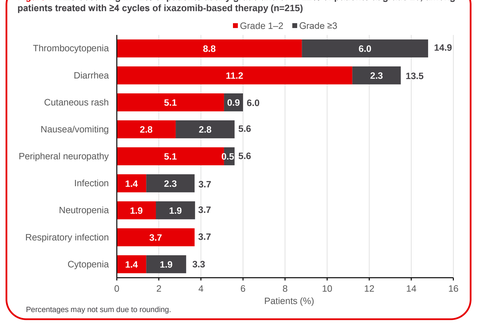
- The overall safety profile for patients who had received ≥4 cycles of treatment (n=215) is shown in **Figure 6**.

Figure 6. Overall safety profile of patients treated with ≥4 cycles of ixazomib-based therapy in UVEA-IXA



- Most common (>2%) any-grade and grade ≥3 AEs in patients who have received ≥4 cycles of treatment (n=215) are shown in **Figure 7.**

Figure 7. AEs occurring in >2% 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=215)



Percentages may not sum due to rounding.

- Diarrhea, thrombocytopenia, and peripheral neuropathy (n=7 each) were the most common AEs recorded as resulting in ixazomib discontinuation.
- The reported AEs are manageable and tolerable, and remain consistent with the known safety profile of ixazomib.

Conclusions

- Results of the final analysis of the UVEA-IXA study support ixazomib-based therapy as an effective and tolerable treatment option outside the clinical trial setting, with an ORR of 60%, median PFS of 15.6 months, and median OS of 35.5 months.
  - Outcomes from TOURMALINE-MM1 (ixazomib arm; ORR 78%, median PFS 20.6 months) differ from UVEA-IXA likely due to favorable disease characteristics, as summarized in the table below.[2]

	UVEA-IXA	TOURMALINE-MM1[2]
ECOG PS 2	20%	5%
ISS stage III MM	30%	12%
eGFR <30 mL/min	5%	1%
≥2 prior lines of therapy	61%	38%
ORR	60%	78%
Median PFS	15.6 months	20.6 months

- Outcomes were favorable in patients with 1 vs ≥2 prior lines of therapy and ECOG PS 0–1 vs 2.
- The effectiveness of ixazomib in this analysis 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]
- The UVEA-IXA study showed that ixazomib-based regimens and ixazomib specifically is well tolerated with a safety profile that is consistent with previous reports.[2] No new safety signal were identified.
- The UVEA-IXA data are derived from retrospective chart review/infrequent prospective data capture and so are not directly comparable with clinical trial data.

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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; HR, hazard ratio; IMiD, immunomodulatory imide drugs; IMWG, International Myeloma Working Group; ISS, International Staging System; LDH, lactate dehydrogenase; mAB, monoclonal antibody; MM, multiple myeloma; Mos, months; NA, not available; ORR, overall response rate; OS, overall survival; PD, progressive disease; PI, protease inhibitor; PR, partial response; PFS, progression-free survival; Rd, lenalidomide-dexamethasone; RRMM relapsed/refractory MM; SCT, stem cell transplant; SD, stable disease; TTP, time to progression; US, United States; UK, United Kingdom; UVEA-IXA, Use Via Early Access to Ixazomib; VGPR, very good partial response.

Acknowledgments

The authors would like to thank all patients and their families, and 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, Wager E, Baltzer L, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461–4).

Disclosures

The study was funded by Takeda Pharmaceuticals International AG.

HL: research grants from Amgen, Takeda, Sanofi; speaker's bureau for Amgen, BMS, Celgene, Janssen, Takeda, Sanofi; data monitoring committee for Janssen; advisory boards for Sanofi, Oncopeptides, BMS, Janssen, Seattle Genetics, Amgen. **ET:** honoraria and research funding from Takeda, Amgen, Janssen, Genesis, Sanofi; honoraria from Celgene, Sanofi, BMS, Novartis. **MVM:** honoraria from GSK; honoraria and membership on an entity's Board of Directors or advisory committees for Janssen, Celgene, Amgen, Takeda, AbbVie, Adaptive, Regeneron, Roche, Sanofi, Oncopeptides, Seattle Genetics, Pfizer. **MB:** research funding from Mundipharma; honoraria and research funding from Sanofi, Celgene, Amgen, Novartis, BMS; honoraria from AbbVie; membership on an entity's Board of Directors or advisory committees for GSK; honoraria, research funding and membership on an entity's Board of Directors or advisory committees for Janssen. **BK:** conference support from Takeda, Celgene and Janssen. **KR:** Consultancy/advisory board for Takeda, Janssen, Celgene/BMS, Amgen, Adaptive Biotech, Karyopharm, AbbVie, GSK, Sanofi, Oncopeptides, Pfizer; Grant/research support from Takeda, Janssen, Celgene/BMS, Amgen; speaker's bureau for Takeda, Celgene/BMS; Travel expenses from Celgene/BMS, Takeda, Janssen. **PK:** Consulting fee from Takeda, Celgene. **MS:** Consulting fee from Takeda, Celgene, Sanofi, Eusa. **VG:** Consultancy for AbbVie, Takeda, Janssen, Celgene. **ML:** Advisory council or committee for Janssen, Takeda, Amgen; Consultancy for Janssen, Takeda, Celgene, Teva, Sandoz, Glenmark; Conference support from Takeda, Celgene, Janssen, Glenmark and Servier. **SF and LS:** Employment with MediNeos Observational Research. **NBE, AZ and FG:** Employment with Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. **RH:** Consultancy, honoraria and research funding from Janssen, Celgene, BMS; consultancy and honoraria from AbbVie. Pharma MAR; consultancy and research funding from Novartis; consultancy, honoraria, research funding and membership on an entity's Board of Directors or advisory committees for Takeda, Amgen.

Electronic poster presentation at the virtual 2021 Congress of the European Hematology Association (EHA), June 9–17, 2021; for questions or comments please contact Professor Heinz Ludwig: heinz.ludwig@extern.gesundheitsverbund.at