






# Ixazomib-lenalidomide-dexamethasone in routine clinical practice: effectiveness in relapsed/refractory multiple myeloma

Roman Hájek<sup>\*1</sup> , Jiří Minařík<sup>2</sup>, Jan Straub<sup>3</sup>, Luděk Pour<sup>4</sup>, Alexandra Jungova<sup>5</sup>, Jesus G Berdeja<sup>6</sup>, Mario Boccardo<sup>7</sup> , Lucie Brozova<sup>8</sup>, Andrew Spencer<sup>9</sup>, Frits van Rhee<sup>10</sup>, Jorge Vela-Ojeda<sup>11</sup>, Michael A Thompson<sup>12</sup>, Rafat Abonour<sup>13</sup>, Ajai Chari<sup>14</sup>, Gordon Cook<sup>15</sup>, Caitlin L Costello<sup>16</sup> , Faith E Davies<sup>17</sup>, Vania TM Hungria<sup>18</sup>, Hans C Lee<sup>19</sup>, Xavier Leleu<sup>20</sup>, Noemi Puig<sup>21</sup> , Robert M Rifkin<sup>22</sup>, Evangelos Terpos<sup>23</sup> , Saad Z Usmani<sup>24</sup>, Katja C Weisel<sup>25</sup>, Jeffrey A Zonder<sup>26</sup>, Magda Bařinová<sup>8</sup>, Matyáš Kuhn<sup>8</sup>, Jiří Šilar<sup>8</sup>, Lenka Čápková<sup>8</sup>, Kenny Galvez<sup>27</sup>, Jin Lu<sup>28</sup>, Jennifer Elliott<sup>29</sup>, Dawn Marie Stull<sup>29</sup>, Kaili Ren<sup>29</sup> & Vladimír Maisnar<sup>‡,30</sup>

<sup>1</sup>University Hospital Ostrava & Faculty of Medicine, University of Ostrava, Ostrava, 703 00, Czech Republic

<sup>2</sup>Palacky University & University Hospital Olomouc, Olomouc, 771 47, Czech Republic

<sup>3</sup>General Teaching Hospital, Prague, 128 08, Czech Republic

<sup>4</sup>University Hospital, Brno, 625 00, Czech Republic

<sup>5</sup>Faculty Hospital Pilsen, Pilsen, 301 00, Czech Republic

<sup>6</sup>Sarah Cannon Research Institute, Nashville, TN 37203, USA

<sup>7</sup>University of Torino, Torino, 10124, Italy

<sup>8</sup>Institute of Biostatistics & Analyses, Ltd, Brno, 602 00, Czech Republic

<sup>9</sup>Alfred Health-Monash University, Melbourne, 3004, Australia

<sup>10</sup>University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

<sup>11</sup>UMAE Especialidades Centro Medico La Raza IMSS, Ciudad de México, 02990, Mexico

<sup>12</sup>Advocate Aurora Research Institute, Advocate Aurora Health, Milwaukee, WI 53227, USA

<sup>13</sup>Indiana University School of Medicine, Indianapolis, IN 46202, USA

<sup>14</sup>Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

<sup>15</sup>Leeds Teaching Hospital, Leeds, LS1 3EX, UK

<sup>16</sup>Moore's Cancer Center, University of California San Diego, La Jolla, CA 92037, USA

<sup>17</sup>Perlmutter Cancer Center, NYU Langone, New York, NY 10016, USA

<sup>18</sup>Clinica São Germano & Santa Casa Medical School, São Paulo, 04537-081, Brazil

<sup>19</sup>M.D. Anderson Cancer Center, Houston, TX 77030, USA

<sup>20</sup>Pôle Régional de Cancérologie, CHU de Poitiers, Poitiers, 86000, France

<sup>21</sup>Department of Hematology, Hospital Universitario de Salamanca (HUSAL), IBSAL, IBMCC (USAL-CSIC), CIBERON (CB16/12/00233), Salamanca, 37007, Spain

<sup>22</sup>Rocky Mountain Cancer Centers US Oncology Research, Denver, CO 80218, USA

<sup>23</sup>National & Kapodistrian University of Athens, School of Medicine, Athens, 115 27, Greece

<sup>24</sup>Levine Cancer Institute, Charlotte, NC 115 27, USA

<sup>25</sup>University Medical Center Hamburg-Eppendorf, Hamburg, 20251, Germany

<sup>26</sup>Barbara Ann Karmanos Cancer Institute / Wayne State University School of Medicine, Detroit, MI 48201, USA

<sup>27</sup>Hospital Pablo Tobón Uribe, Medellín, 11001, Colombia

<sup>28</sup>Peking University People's Hospital, National Clinical Research Center for Hematologic Disease, Beijing, 100044, China

<sup>29</sup>Millennium Pharmaceuticals, Inc., Cambridge, MA 02139, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

<sup>30</sup>Charles University Hospital & Faculty of Medicine, Hradec Králové, 121 08, Czech Republic

\*Author for correspondence: Tel.: +420 597 372 091; [roman.hajek@fno.cz](mailto:roman.hajek@fno.cz)

‡Senior author on the paper

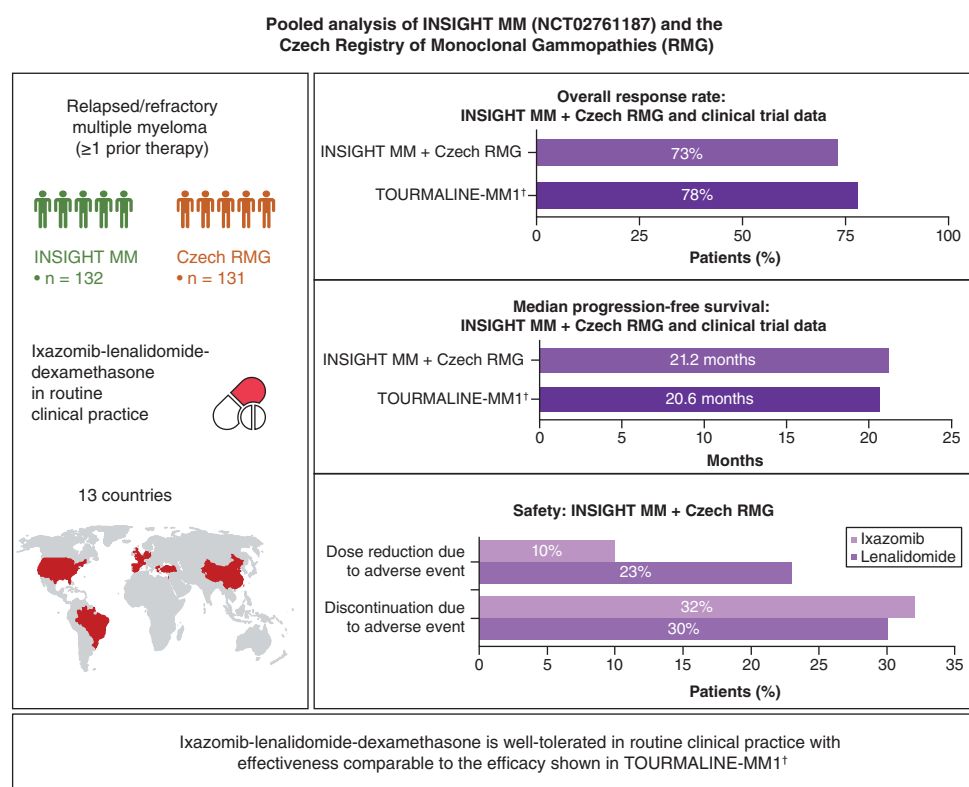
**Aim:** To evaluate the effectiveness and safety of ixazomib-lenalidomide-dexamethasone (IRd) in relapsed/refractory multiple myeloma in routine clinical practice. **Patients & methods:** Patient-level data from the global, observational INSIGHT MM and the Czech Registry of Monoclonal Gammopathies were integrated and analyzed. **Results:** At data cut-off, 263 patients from 13 countries were included. Median time from diagnosis to start of IRd was 35.8 months; median duration of follow-up was 14.8 months. Overall response rate was 73%, median progression-free survival, 21.2 months and time-to-next therapy,

33.0 months. Ixazomib/lenalidomide dose reductions were required in 17%/36% of patients; 32%/30% of patients discontinued ixazomib/lenalidomide due to adverse events. **Conclusion:** The effectiveness and safety of IRd in routine clinical practice are comparable to those reported in TOURMALINE-MM1.

**Clinical trial registration:** NCT02761187 (ClinicalTrials.gov)

**Lay abstract:** Proteasome inhibitors are drugs used in multiple myeloma (MM), a blood cancer that develops from cells in the bone marrow. Ixazomib is the first oral proteasome inhibitor to be approved for use in MM, when given in combination with two other oral drugs, lenalidomide and dexamethasone, to adult patients who have received one prior therapy. Our study, which was conducted in routine clinical practice, found that the effectiveness and safety of ixazomib + lenalidomide + dexamethasone in previously treated MM patients were similar to those seen in the Phase III clinical trial on which approval was based. These findings are important because they suggest that MM patients in everyday practice can achieve the same benefits from this treatment as patients in clinical trials, despite often being in poorer health.

**Graphical abstract:**



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**Keywords:** effectiveness • ixazomib • multiple myeloma • proteasome inhibitor • relapsed/refractory • routine clinical practice

Outcomes in routine clinical practice (effectiveness) often differ from data reported in clinical trials (efficacy) for multiple myeloma (MM) therapies, with poorer long-term outcomes reported for real-world patients [1,2]. Differences in patient characteristics and the strict eligibility criteria used to select patients for enrollment in clinical trials are among the factors that may contribute to this gap. It has been reported that 40% of patients enrolled in the CONNECT-MM registry (ClinicalTrials.gov: NCT01081028) do not meet standard eligibility criteria for randomized trials [3]. Similarly, an analysis of over 3000 patients enrolled in the INSIGHT MM global, prospective, observational study (NCT02761187) showed that 39% of MM patients treated in routine clinical practice would be ineligible for trials [4]. Furthermore, a retrospective analysis of a US electronic health record

database demonstrated that 47.9 to 72.3% of real-world patients with relapsed/refractory MM (RRMM) did not meet the eligibility criteria for clinical trials [5]. Observational studies may therefore provide important information on the effectiveness and safety of new therapies in routine clinical practice, as they have less stringent inclusion criteria and consequently include a more diverse patient population that is often under-represented in clinical trials (e.g., elderly and frail patients, patients with comorbidities and/or advanced disease and specific ethnic or racial minorities) [3,6,7].

Differences in outcomes between real-world and clinical trial settings may also arise from variations in the duration of therapy (DOT). Factors that can limit treatment duration in routine practice include, but are not limited to, treatment-center effects, with academic and community centers having different levels of experience in utilizing new regimens and managing adverse effects, and differences in patient/physician preferences for treatment-to-progression approaches. Additionally, a greater comorbidity burden compared with that in clinical trials may affect the real-world tolerability, convenience and practicality of therapy, leading to premature discontinuation of treatment [1]. Results from observational studies may therefore better inform the true therapeutic benefit that can be achieved and help to guide treatment decisions in everyday practice [8].

Ixazomib, the first oral proteasome inhibitor [9], is approved in over 70 countries, in combination with lenalidomide and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy [10]. Approvals were based on the results of the Phase III, double-blind TOURMALINE-MM1 study (NCT01564537), which compared ixazomib-lenalidomide-dexamethasone (IRd) versus placebo-lenalidomide-dexamethasone (placebo-Rd) in adults with RRMM, who had received one to three prior therapies (Supplementary Table 1) [11]. The study demonstrated a significantly longer progression-free survival (PFS) for IRd versus placebo-Rd (median PFS: 20.6 vs 14.7 months; hazard ratio [HR]: 0.74; 95% [CI]: 0.587–0.939;  $p = 0.01$ ), as well as significantly improved response rates (overall response rate [ORR]: 78 vs 72%; rate of very good partial response or better [ $\geq$ VGPR]: 48 vs 39%; Supplementary Table 1) [11]. Limited additional toxicity was observed in the IRd arm compared with the placebo-Rd arm [11].

Emerging evidence from observational studies of MM patients treated with ixazomib suggests that outcomes in routine practice may be broadly comparable to those observed in TOURMALINE-MM1 [12–17]. However, global, long-term data in a large, varied and unselected patient population are lacking. Therefore, we performed a pooled analysis of the INSIGHT MM observational study (NCT02761187) and the Czech Registry of Monoclonal Gammopathies (RMG), referred to as ‘INSIGHT-RMG’ going forward, to evaluate the effectiveness and safety of IRd in patients with RRMM in routine clinical practice.

## Methods

### Included studies & patients

This was a pooled analysis of data for RRMM patients who received IRd from INSIGHT MM (NCT02761187) [8] and the Czech RMG [18]. INSIGHT MM is the largest global, prospective, observational study in MM to date, which has enrolled 4311 adult patients with newly diagnosed MM or RRMM who have received one to three prior therapies, from 15 countries worldwide. Longitudinal follow-up of patients is planned for an extended period of time in an effort to track patterns of disease presentation, patient characteristics, treatment patterns, clinical outcomes and safety, as well as the impact of the disease and its management on the patient’s quality of life and healthcare resource utilization [8]. The Czech RMG includes clinical data on diagnosis, treatment, treatment outcomes and survival for >7000 patients with MM. Data were analyzed for the study period from 1 July 2016 to September 2019 for INSIGHT MM and from 1 May 2007 to 5 February 2020 for the Czech RMG.

For this analysis, adult patients with RRMM, with  $\geq 1$  prior therapy, who had been treated with IRd, were identified. INSIGHT MM patients could have received IRd at any line of therapy after study entry. Patients from the two registries who received a regimen with an ixazomib-lenalidomide backbone therapy as index regimen were included in the analysis. INSIGHT MM patients required prospectively collected data on IRd therapy; patients who signed the study informed consent from more than 3 months after starting IRd were excluded from the analysis. RMG patients from 11 Czech centers who received IRd were included; patients who had incomplete or missing data were excluded. Treatment within the context of a clinical trial was permitted for Czech RMG patients.

### Data extraction & end points

Individual patient-level data on demographics, disease characteristics, treatment history (including therapies received before and after IRd), effectiveness and safety for RRMM patients who had received IRd from INSIGHT-RMG

were integrated and analyzed. Treatment effectiveness was evaluated by best response to therapy (defined as the best response recorded at any timepoint), and through assessment of DOT, time-to-next treatment (TTNT), PFS and overall survival (OS). DOT was defined as time from IRd initiation to discontinuation of therapy or death from any cause. TTNT was defined as the interval from initiation of IRd to 1 day prior to the start of a new line of therapy. PFS was defined as the time from IRd initiation to disease progression or death from any cause, whichever came first; OS was defined as the time from IRd initiation to death from any cause. Response and PFS were defined based on International Myeloma Working Group criteria, per the assessment of the treating physician or local investigator [19]. Time to response was defined slightly differently in the INSIGHT MM study and the Czech RMG database analysis, per individual protocols: in INSIGHT MM, it was defined as the time interval from initiation of IRd therapy to initial achievement of best response; in the analysis of the Czech RMG, it was defined as the time from initiation of IRd to first documented response of partial response (PR) or better (i.e. even if the response improved during the IRd treatment, time to response was captured as the time to first response of PR or better only). Safety was assessed by recording dose reductions and discontinuations of ixazomib or lenalidomide, and the reasons for these events during the study period.

### Statistical analysis

The time-to-event end points of DOT, PFS and OS were estimated using Kaplan–Meier methodology. TTNT was estimated using a cumulative incidence (competing risk) method. Death was considered a competing risk in TTNT analyses and was not censored.

Overall, analyses were primarily descriptive and no statistical comparisons between groups were made. Responses were evaluated for each data set (INSIGHT MM and Czech RMG). Patient baseline characteristics and outcomes (DOT, TTNT, PFS and OS) were analyzed for all patients and by line of IRd therapy in which IRd was received (second, third, fourth and >fourth line). Analyses of PFS for patients who received IRd in second line versus >second line and for patients who received IRd in second and third lines versus >third line, were also conducted.

Aggregated safety data per patient are reported. If treatment was modified or interrupted more than once, all reasons for all actions were considered; therefore, patients could have more than one documented reason for taking an action on a drug.

For all effectiveness and safety analyses, missing data were not included in the denominators for percentages. The analyses were conducted using SAS<sup>®</sup> v9.4. Data analysis was performed by Matyáš Kuhn, Jiří Šilar and Lenka Čápková (Institute of Biostatistics and Analyses, Ltd, Brno, Czech Republic), as well as the sponsor, and all authors had access to the primary clinical trial data.

## Results

### Patients

At data cut-off, 263 patients from 13 countries who had received IRd had been included in the analyses, with 132 patients from INSIGHT MM and 131 from the Czech RMG (Supplementary Table 2). Countries from which >20 patients were included were the Czech Republic (n = 131), the UK (n = 50) and the USA (n = 25). Patients had received a median of two prior lines of treatment (range: 1 to 9). Overall, 44% (n = 115) of patients received IRd in second line (INSIGHT MM, 35%, n = 46; Czech RMG, 53%, n = 69), 35% (n = 93) in third line (INSIGHT MM, 44%, n = 58; Czech RMG, 27%, n = 35), 11% (n = 29) in fourth line (INSIGHT MM, 14%, n = 19; Czech RMG, 8%, n = 10) and 10% (n = 26) in >fourth line (INSIGHT MM, 7%, n = 9; Czech RMG, 13%, n = 17).

Patient baseline characteristics and disease characteristics are summarized in Table 1. Median age of patients at start of IRd therapy was 68 years (range: 40 to 87), with 15% of patients aged more than 75 years, and 56% were male. Patients were almost equally distributed across International Staging System (ISS) stages at diagnosis. Most patients received IRd at an academic or university facility (86%), 14% of patients were treated in community hospital or clinic and 4% (n = 5) of patients overall received IRd in the context of a clinical trial (INSIGHT MM, n = 3; Czech RMG, n = 2). At the start of IRd therapy, the most common M-protein type was immunoglobulin G (69%) and 21% of patients had extramedullary disease (extramedullary mass not related to bone, bone-related extramedullary tumor mass, or both). All patients with extramedullary disease also had CRAB criteria (hypercalcemia, renal insufficiency, anemia and bone lesions) present. A clinical relapse (defined as the presence of extramedullary disease and/or CRAB criteria) occurred in 59% of patients and a biochemical relapse in 41% of patients. Overall, 7% of patients had high-risk cytogenetics recorded at any time before IRd treatment, 24%

**Table 1. Patient demographics and disease characteristics, overall and by line of ixazomib-lenalidomide-dexamethasone therapy.**

Characteristic	All (N = 263)	Second line (n = 115)	Third line (n = 93)	Fourth line (n = 29)	>Fourth line (n = 26)
Male, n (%)	146 (56)	59 (51)	48 (52)	23 (79)	16 (62)
Median age at start of IRd, years (range)	68 (40–87)	70 (41–84)	67 (40–87)	67 (45–79)	67 (52–81)
Age at start of IRd, n (%), years					
– <50	18 (7)	9 (8)	7 (8)	2 (7)	0
– 50–65	90 (34)	32 (28)	35 (38)	11 (38)	12 (46)
– 66–75	115 (44)	52 (45)	36 (39)	15 (52)	12 (46)
– >75	40 (15)	22 (19)	15 (16)	1 (3)	2 (8)
ISS stage at diagnosis, n (%)					
– I	n = 216 73 (34)	n = 105 32 (30)	n = 65 24 (37)	n = 21 6 (29)	n = 25 11 (44)
– II	67 (31)	40 (38)	19 (29)	3 (14)	5 (20)
– III	76 (35)	33 (31)	22 (34)	12 (57)	9 (36)
Median time from initial diagnosis, months (range)					
	n = 260 35.8 (3.0–387.4)	n = 115 28.3 (3.0–196.6)	n = 90 43.4 (5.2–234.8)	n = 29 53.7 (8.6–387.4)	n = 26 83.8 (26.9–378.8)
IRd treatment facility, n (%) <sup>†</sup>					
– Academic/university	225 (86)	102 (89)	79 (85)	23 (79)	21 (81)
– Community hospital/clinic	38 (14)	13 (11)	14 (15)	6 (21)	5 (19)
Patients receiving IRd on a clinical trial, n (%)					
	n = 134 5 (4)	n = 72 3 (4)	n = 35 2 (6)	n = 10 0 (0)	n = 17 0 (0)
ECOG performance status at start of IRd, n (%)					
– 0	n = 216 63 (29)	n = 105 24 (23)	n = 71 26 (37)	n = 21 9 (43)	n = 19 4 (21)
– 1	123 (57)	60 (57)	39 (55)	11 (52)	13 (68)
– 2	27 (13)	18 (17)	6 (8)	1 (5)	2 (11)
– 3	3 (1)	3 (3)	0	0	0
M-protein type at start of IRd, n (%)					
– IgG	n = 218 150 (69)	n = 101 62 (61)	n = 68 49 (72)	n = 23 17 (74)	n = 26 22 (85)
– IgA	43 (20)	26 (26)	12 (18)	3 (13)	2 (8)
– Light chain	19 (9)	11 (11)	4 (6)	2 (9)	2 (8)
– Other	6 (3)	2 (2)	3 (4)	1 (4)	0
Cytogenetic features prior to/at start of IRd, n (%) <sup>‡</sup>					
– High-risk cytogenetics abnormalities	19 (7)	11 (10)	4 (4)	1 (3)	3 (12)
– Standard-risk cytogenetics abnormalities	63 (24)	32 (28)	20 (22)	6 (21)	5 (19)
– Data not available	181 (69)	72 (63)	69 (74)	22 (76)	18 (69)
Type of relapse, n (%) <sup>§</sup>					
– Clinical relapse	154 (59)	77 (67)	48 (52)	11 (38)	18 (69)
– Biochemical relapse	109 (41)	38 (33)	45 (48)	18 (62)	8 (31)
Extramedullary disease at start of IRd, n (%) <sup>¶</sup>					
	n = 212 45 (21)	n = 94 18 (19)	n = 72 18 (25)	n = 23 0	n = 23 9 (39)

<sup>†</sup> 71% and 100% of INSIGHT MM and Czech RMG patients, respectively, were treated at academic/university facilities; 29% and 0% of INSIGHT MM and RMG patients, respectively, were treated at community hospital/clinic facilities.

<sup>‡</sup> Extramedullary disease was considered any of the following options: extramedullary mass not related to bone, bone-related extramedullary tumor mass or both.

<sup>§</sup> Clinical relapse was recorded for patients with CRAB criteria, extramedullary disease, or both, at the time of starting IRd therapy; biochemical relapse was recorded for patients with none of these parameters.

<sup>¶</sup> High-risk cytogenetic abnormalities were detected by fluorescence *in situ* hybridization and were defined as del(17p), t(4;14), t(14;16) detected any time before the start of IRd treatment. For INSIGHT MM, cytogenetic results were assessed at relapse whereas, for RMG, they could be evaluated at any time.

<sup>¶</sup> Refractory was defined as progression while on or within 60 days of discontinuing a PI (bortezomib or carfilzomib)-containing or lenalidomide-containing regimen.

CRAB: Hypercalcemia, renal insufficiency, anemia, bone lesions; ECOG: Eastern Cooperative Oncology Group; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IRd: Ixazomib-lenalidomide-dexamethasone; ISS: International Staging System; PI: Proteasome inhibitor; RMG: Registry of Monoclonal Gammopathies.

Table 1. Patient demographics and disease characteristics, overall and by line of ixazomib-lenalidomide-dexamethasone therapy (cont.).

Characteristic	All (N = 263)	Second line (n = 115)	Third line (n = 93)	Fourth line (n = 29)	>Fourth line (n = 26)
Therapies received in any previous line before IRd, n (%)					
– Bortezomib	238 (90)	100 (87)	86 (92)	27 (93)	25 (96)
– Stem-cell transplantation	145 (55)	47 (41)	56 (60)	20 (69)	22 (85)
– Allogeneic stem-cell transplantation	2 (<1)	0 (0)	1 (1)	0 (0)	1 (4)
– Thalidomide	121 (46)	25 (22)	57 (61)	20 (69)	19 (73)
– Lenalidomide	71 (27)	14 (12)	21 (23)	17 (59)	19 (73)
– Carfilzomib	24 (9)	6 (5)	8 (9)	3 (10)	7 (27)
– Daratumumab	22 (8)	4 (3)	5 (5)	5 (17)	8 (31)
– Pomalidomide	5 (2)	0 (0)	0 (0)	0 (0)	5 (19)
Refractory to prior therapy, n (%) <sup>#</sup>					
– PI	27 (10)	8 (7)	9 (10)	3 (10)	7 (27)
– Lenalidomide	19 (7)	2 (2)	5 (5)	6 (21)	6 (23)

<sup>†</sup>71% and 100% of INSIGHT MM and Czech RMG patients, respectively, were treated at academic/university facilities; 29% and 0% of INSIGHT MM and RMG patients, respectively, were treated at community hospital/clinic facilities.

<sup>‡</sup>Extramedullary disease was considered any of the following options: extramedullary mass not related to bone, bone-related extramedullary tumor mass or both.

<sup>§</sup>Clinical relapse was recorded for patients with CRAB criteria, extramedullary disease, or both, at the time of starting IRd therapy; biochemical relapse was recorded for patients with none of these parameters.

<sup>¶</sup>High-risk cytogenetic abnormalities were detected by fluorescence *in situ* hybridization and were defined as del(17p), t(4;14), t(14;16) detected any time before the start of IRd treatment. For INSIGHT MM, cytogenetic results were assessed at relapse whereas, for RMG, they could be evaluated at any time.

<sup>#</sup>Refractory was defined as progression while on or within 60 days of discontinuing a PI (bortezomib or carfilzomib)-containing or lenalidomide-containing regimen.

CRAB: Hypercalcemia, renal insufficiency, anemia, bone lesions; ECOG: Eastern Cooperative Oncology Group; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IRd: ixazomib-lenalidomide-dexamethasone; ISS: International Staging System; PI: Proteasome inhibitor; RMG: Registry of Monoclonal Gammopathies.

had standard-risk cytogenetics and data were missing for the remaining 69%. Median time from initial diagnosis to start of IRd was 35.8 (range: 3.0–387.4) months.

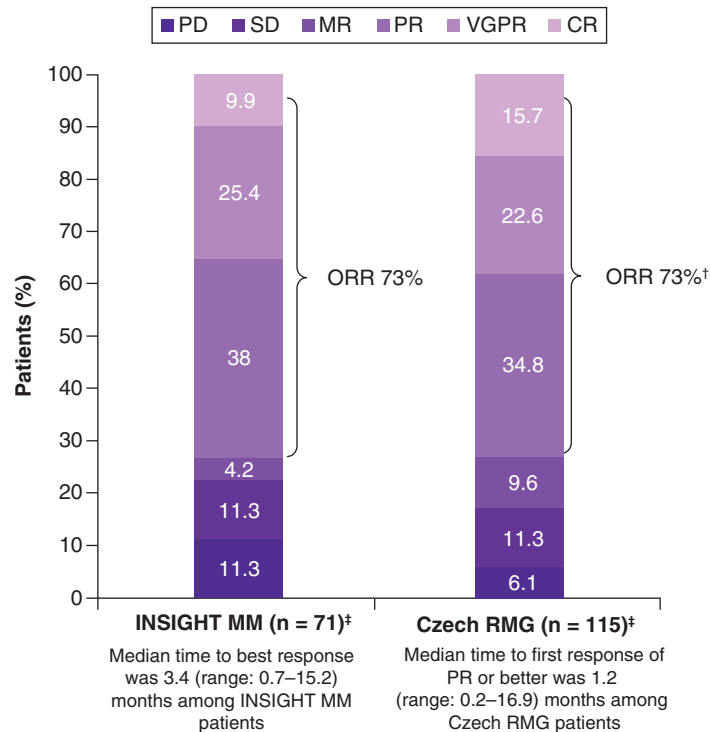
Among all patients, 86% (n = 226) reported relapse or progression as the reason for initiation of IRd therapy (85% [n = 98] in second line, 83% [n = 77] in third line, 90% [n = 26] in fourth line and 96% [n = 25] in >fourth line); 10% (n = 25) of patients reported insufficient response as a reason for starting IRd and 3% (n = 9) provided another reason (Supplementary Figure 1). Clinical symptoms (CRAB criteria) reported at relapse prior to IRd initiation are presented in Supplementary Figure 2: 40% (n = 106) of patients reported bone lesions, 17% (n = 45) reported anemia, 3% (n = 8) reported renal insufficiency and 2% (n = 6) reported hypercalcemia.

Treatments received before IRd in any previous line included bortezomib (90%), stem cell transplantation (55%; <1% allogeneic), thalidomide (46%), lenalidomide (27%), carfilzomib (9%), daratumumab (8%) and pomalidomide (2%) (Table 1). 10% of patients were refractory to prior proteasome inhibitor-containing therapy (bortezomib or carfilzomib) and 7% were refractory to prior lenalidomide-based regimens.

### Response & outcomes with IRd

Data on best response to IRd were available for 186 patients (INSIGHT MM, n = 71; Czech RMG, n = 115). For all patients, the combined ORR was 73% (INSIGHT MM, 73%, n = 52; Czech RMG, 73%, n = 84), including 37% of patients who achieved  $\geq$ VGPR (INSIGHT MM, 35%, n = 25; Czech RMG, 38%, n = 44) (Figure 1). Median time to best response was 3.4 months (range: 0.7–15.2) among INSIGHT MM patients. For Czech RMG patients, median time to first response of PR or better was 1.2 months (range: 0.2–16.9).

Median duration of follow-up for all patients was 14.8 months. At data cut-off, 159 patients (61%) had discontinued IRd; reasons for discontinuation were relapse/progression (43%, n = 68), completed regimen/treatment response (14%, n = 22), resistance/insufficient response (12%, n = 19), death (11%, n = 17), AE (7%, n = 11), patient preference (3%, n = 4), other (6%, n = 9) and unknown (6%, n = 9). Median DOT was 11.8 months (Figure 2A) and was longer in patients receiving IRd in second or third line (12.8, 13.0 months) versus fourth or >fourth line (8.5, 5.2 months) of therapy (Supplementary Figure 3A). Among all patients, median TTNT was 33.0 months (Figure 2B) and was longer for patients receiving IRd in earlier lines (35.2 and 27.7 months in second and third line, respectively) versus later lines of therapy (23.3 months and not reached in fourth and >fourth line, respectively) (Supplementary Figure 3B). The treatment-free interval according to reason for discontinuation of IRd is presented in Supplementary Table 3. A total of 119 (45%) patients had experienced PFS events and 75 (29%)



**Figure 1. Best response (INSIGHT multiple myeloma and Czech registry of monoclonal gammopathies) and time to best (INSIGHT multiple myeloma) or first (Czech registry of monoclonal gammopathies) response to ixazomib-lenalidomide-dexamethasone.**

<sup>†</sup>For RMG data, due to rounding, PR, VGPR and CR do not sum to the exact ORR.

<sup>‡</sup>Response data were missing for 61 INSIGHT MM patients and 16 Czech RMG patients.

CR: Complete response; MM: Multiple myeloma; MR: Minimal response; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; RMG: Registry of Monoclonal Gammopathies; SD: Stable disease; VGPR: Very good PR.

had had OS events. Overall median PFS was 21.2 months (Figure 2C); and 26.0, 23.8, 13.6 and 6.7 months in patients receiving IRd in second third, fourth and >fourth line, respectively (Supplementary Figure 3C). Median PFS was significantly longer in second versus >second line (HR: 0.66; 95% CI: 0.45–0.95;  $p = 0.026$ ) and also for patients who received IRd in second and third lines versus >third line (HR: 0.44; 95% CI: 0.29–0.66;  $p < 0.001$ ). Median OS, for all patients and for those receiving IRd in second, third and fourth line, was not reached; median OS in >fourth line was 9.8 months (Figure 2D & Supplementary Figure 3D).

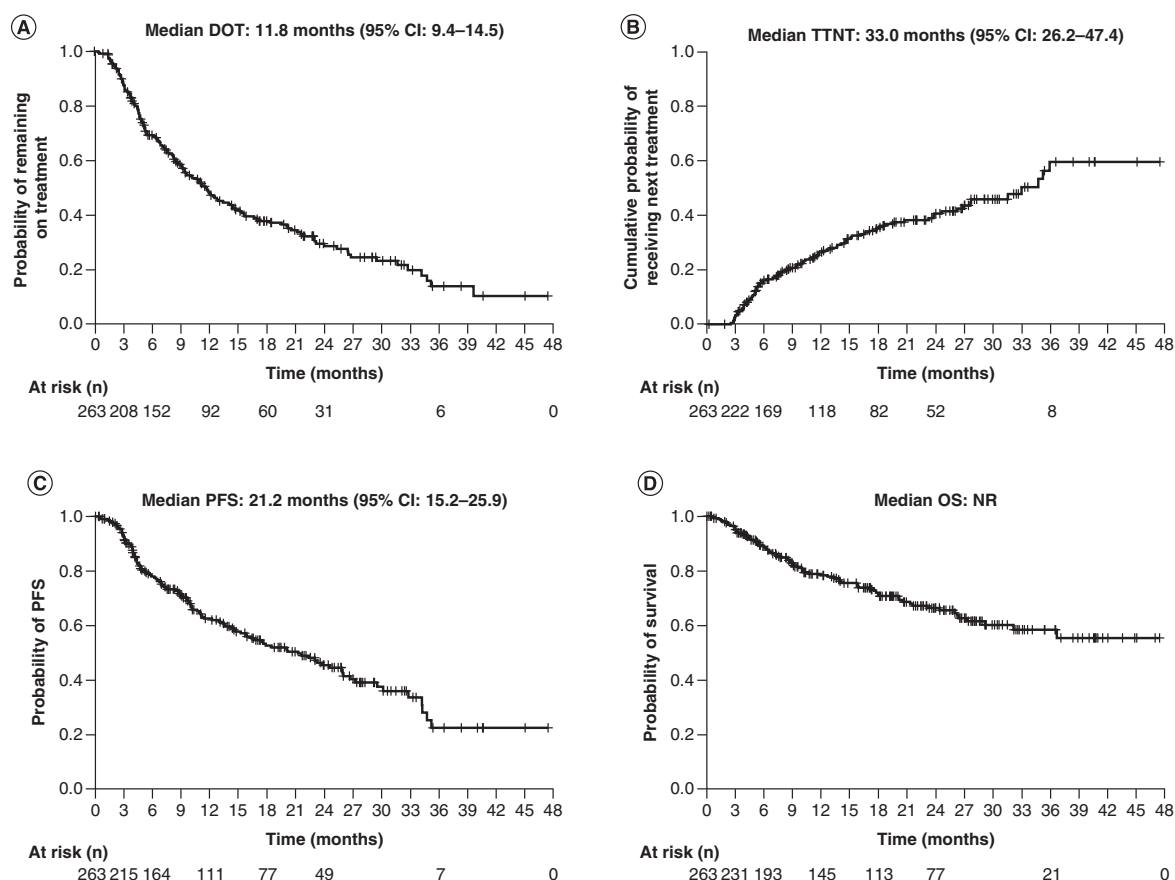
### Subsequent treatment

Ninety-one patients had complete records of subsequent treatment immediately after IRd therapy. Among these patients, 26% ( $n = 24$ ) received subsequent daratumumab, 24% ( $n = 22$ ) received pomalidomide, 20% ( $n = 18$ ) received bortezomib, 19% ( $n = 17$ ) received lenalidomide, 14% ( $n = 13$ ) received carfilzomib, 9% ( $n = 8$ ) received thalidomide, 3% ( $n = 3$ ) underwent stem cell transplantation and 12% ( $n = 11$ ) received other therapies.

### Safety

Ixazomib and lenalidomide dose reductions were required in 17% ( $n = 44$ ) and 36% ( $n = 95$ ) of patients treated with IRd, respectively; 10% ( $n = 27$ ) of patients required ixazomib dose reductions due to documented adverse events (AEs), with the most common AEs leading to these events being diarrhea, neutropenia, thrombocytopenia and neuropathy (2% each) (Supplementary Table 4). Lenalidomide dose reductions due to documented AEs were required for 23% ( $n = 60$ ) of patients; the most common AEs leading to these events were neutropenia (7%), thrombocytopenia (5%), fatigue and diarrhea (3% each) (Supplementary Table 4). Ixazomib and lenalidomide discontinuations, including temporary interruptions and dose delays, were reported in 50% of patients ( $n = 131$  and 130, respectively); 32% ( $n = 83$ ) required discontinuation of ixazomib due to documented AEs, most frequently due to infection (19%), neutropenia or thrombocytopenia (6% each) (Supplementary Table 4). Lenalidomide discontinuations due to documented AEs were required for 30% ( $n = 78$ ) of patients and the most frequent AEs leading to this action were infection (20%), neutropenia (6%) and thrombocytopenia (5%) (Supplementary Table 4). Patients may have had multiple reasons for discontinuation documented and those with a dose reduction may have also subsequently discontinued treatment.

+ Censored



**Figure 2. Time-to-event end points with ixazomib-lenalidomide-dexamethasone for the overall patient population (N = 263). (A) Duration of therapy, (B) time-to-next treatment, (C) progression-free survival and (D) overall survival. DOT, PFS and OS were analyzed using Kaplan–Meier methodology. TTNT was determined by cumulative incidence analysis. DOT: Duration of therapy; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; TTNT: Time-to-next treatment.**

## Discussion

Observational studies are important for establishing the real-world effectiveness of medications and are particularly relevant in MM, where treatment outcomes in routine clinical practice often fail to match those reported in Phase III trials [1]. This pooled analysis of INSIGHT-RMG demonstrated that the effectiveness of IRd treatment in routine clinical practice (ORR: 73%; median PFS: 21.2 months) was similar to that reported in the registrational TOURMALINE-MM1 trial (ORR: 78%; median PFS: 20.6 months) [11], as shown in [Supplementary Table 1](#). This comparable level of effectiveness was observed despite the pooled INSIGHT-RMG population having more advanced disease (ISS stage II/III: INSIGHT-RMG, 31%/35%; TOURMALINE-MM1, 25%/12%), a worse performance status (Eastern Cooperative Oncology Group performance status 2/3: INSIGHT-RMG, 13%/1%; TOURMALINE-MM1, 5%/0%), a greater number of prior lines of therapies (1/2/3/≥4 prior therapies: INSIGHT-RMG, 44%/35%/11%/10%; TOURMALINE-MM1, 62%/27%/11%/0%) and greater prior exposure to proteasome inhibitors and immunomodulatory drugs (including lenalidomide) than patients receiving IRd in the TOURMALINE-MM1 study ([Supplementary Table 1](#)) [11]. In addition, patients with comorbidities were not excluded from the INSIGHT MM and Czech RMG registries, whereas in TOURMALINE-MM1, patients were excluded if investigators deemed them inappropriate for study entry based on the presence of a comorbid systemic illness or other severe concurrent disease [11]. Patients who were refractory to prior bortezomib or lenalidomide therapy were also excluded from TOURMALINE-MM1, whereas in INSIGHT-RMG, 10 and



7% of patients were refractory to bortezomib and lenalidomide, respectively. Age, sex, time since diagnosis and rates of prior transplantation were, however, similar between the two populations (Supplementary Table 1).

Our data support growing evidence that outcomes in RRMM patients treated with IRd in routine clinical practice are in line with those reported in TOURMALINE-MM1 [11]. This seemingly narrow gap between efficacy and effectiveness is encouraging, particularly in the context of results from a network meta-analysis of treatment outcomes in RRMM, in which IRd was ranked as one of the most effective treatment options evaluated [20]. Other smaller registry studies and analyses in the nonclinical trial setting of ixazomib in RRMM patients have reported generally similar ORRs (range: 66–88%) and PFS outcomes (range of medians: 11.4–27.6 months) to those reported here and in TOURMALINE-MM1 [11–17]. Analyses of electronic medical records (EMR)/claims-based data showed median PFS values of 11.1 and 13.5 months for ixazomib-based regimens [2,21]. Comparative retrospective analyses of real-world outcomes in US RRMM patients receiving ixazomib-, carfilzomib-, or bortezomib-based therapy, using the Optum EMR database, indicated a gap between clinical trial efficacy and real-world effectiveness for all three proteasome inhibitor (PI)-Rd combinations, this being most pronounced for carfilzomib-Rd (KRd) [2]. Prolonged PI-based treatment appeared feasible with ixazomib (median DOT of 12.3 months) compared with the parenteral PIs (median DOT of 10.0 months with bortezomib-Rd [VRd], 7.2 months with KRd) [2]. After adjusting for covariates, TTNT was similar with IRd, VRd and KRd in the overall patient populations, but was significantly shorter with KRd versus IRd or VRd in intermediate or frail patients, who are typically underrepresented in clinical trials and was numerically longer with KRd among fit patients [2]. In another similar study, while unadjusted median TTNT was longer for ixazomib-based triplet regimens (11.1 months) compared with bortezomib-based triplets (9.8 months), the difference was not significant after adjustment for patient and disease characteristics [21]. Collectively, these data indicate real-world effectiveness with PI-Rd triplet regimens in the patient populations for which they are selected. Similarly to ixazomib, recent registry/observational studies as well as EMR/claims-based analyses of patients treated in the non-clinical trial setting also suggest similar median PFS/TTNT values with bortezomib-based [2,21–27] and carfilzomib-based [2,21,24,25,27–32] regimens to those seen in Phase III studies [33–35].

Clinically meaningful activity was demonstrated for IRd treatment across all lines of therapy, and median PFS was significantly longer in patients who received IRd in earlier lines of therapy compared with those who received the regimen in later lines. However, it should be noted that for all time-to-event analyses the number of patients receiving IRd in fourth and >fourth line was small. Real-world data reports of IRd in RRMM [14–17,36,37], also support the trend seen in the present study for prolonged PFS in patients who received IRd earlier in their treatment course. This observation is expected, and is consistent with previous studies showing that PFS, duration of response and OS for RRMM patients decrease with successive lines of treatment [25,36–38]. This is in contrast with results from TOURMALINE-MM1, showing that PFS benefit with IRd versus Rd appeared to be more pronounced in patients with two or three prior lines of therapy as compared with those with just one prior therapy [39]. This highlights the fact that outcomes observed in routine clinical practice may not always match those observed in clinical trials, underscoring the importance of real-world data to improve our understanding of the true therapeutic benefit of anti-myeloma regimens in routine clinical practice. Further analysis of these specific patient populations is warranted, to account for any bias in the selection of treatment regimens across lines of therapy.

Our INSIGHT-RMG analysis suggests that IRd is well tolerated by patients in routine clinical practice, with no new safety signals observed during the study period. Notably, rates of dose reductions due to AEs for ixazomib and lenalidomide were low (10 and 23%, respectively), while rates of drug discontinuations due to AEs were similar for the two drugs (32 and 30%, respectively). The most common AEs leading to dose reductions or discontinuations were hematologic and gastrointestinal events, infections and fatigue, which is in line with the safety profile reported in the IRd arm of the TOURMALINE-MM1 study [11]. Safety findings from this pooled analysis are also comparable to those reported in other real-world studies of ixazomib-based therapy [12–17]. In addition to offering a tolerable treatment option, the all-oral IRd regimen could also represent a convenient treatment approach for patients who may find it difficult to access infusion centers or who do not want to travel to a hospital or clinical setting to receive treatment, which is critically important during the current COVID-19 pandemic. Therefore, IRd therapy offers the potential for improved medication adherence compared with regimens which include a parenteral component. Additionally, the administration of an all-oral treatment regimen has been associated with increased patient-reported satisfaction with treatment convenience [40].

As with all real-world, observational studies, there are limitations associated with the conclusions drawn from the data. While providing an important indication of effectiveness and safety, the outcomes reported in this study should be interpreted with caution due to the limited maturity of the data, particularly in later lines where the

patient numbers are small. Secondly, there was a high number of patients with missing response data, which is likely a consequence of several factors: the quarterly data collection procedures employed in INSIGHT MM, which can result in a long period of time between the relevant laboratory analysis and the point at which results are recorded in the case report forms; the fact that documentation of depth of response within patients' progress notes is not routine; the lack of a standard process for the documentation of the interpretation of response assessments in patients' progress notes, which makes it difficult for the study coordinators to accurately interpret and record this information; and the continuous enrolment/registration of new patients, meaning that many patients will not yet have sufficient follow-up for a response to be documented. Thirdly, it should be emphasized that many patients included in this analysis (including all patients in the Czech RMG) were treated at academic centers, as these were often the only sites where IRd was available; therefore, the results may not be representative of the community practice setting. It is possible that inclusion of more patients from community settings, who may be older and more frail, and fewer patients from academic centers, akin to those centers used in clinical trials, may impact the real-world outcomes seen with IRd therapy; this will require further investigation. Fourthly, missing or inconclusive cytogenetic data prohibited an analysis of the effectiveness of IRd according to cytogenetic features. A subgroup analysis of the TOURMALINE-MM1 study has previously shown that IRd improves the prognosis for patients with high-risk cytogenetics, with PFS similar to that in patients with standard-risk cytogenetics [11]. Lastly, as in most observational studies, potential bias may be present in the data due to unobserved treatment selection biases associated with any non-randomized study design.

In summary, the findings from this pooled analysis of global observational data from INSIGHT MM and the Czech RMG suggest that the effectiveness of IRd in routine clinical practice may be comparable to the efficacy reported in the registrational, Phase III TOURMALINE-MM1 trial [11]. These real-world data suggest that IRd provides a greater benefit to patients with RRMM when given in earlier (second or third) versus later lines of therapy. The data also suggest that IRd is well tolerated by patients when used in routine clinical practice, including older patients and those with advanced disease and/or multiple comorbidities, with no new safety signals.

### Future perspective

MM is a highly heterogeneous disease; growing evidence suggests that individualized treatment provides the best chance for prolonged remission. In addition to the ongoing study of current agents, the development of therapeutics for MM with novel mechanisms of action continues at a rapid pace and new treatment combinations with existing agents are continuously being explored. New therapies focus on improving the ability of the immune system to fight cancer and are broadly referred to as immunotherapy or cellular therapies. How best to combine or sequence these agents with existing effective therapies such as proteasome inhibitors will be explored. In addition, all-oral treatment combinations will continue to be important, potentially offering improved medication adherence compared with parenterally administered therapies. This is particularly relevant for elderly and frail patients, and for those who are unable to, or are unwilling to make frequent trips to receive medication.

Collection of real-world data with the use of well-managed registries is integral to our understanding of how approved regimens perform outside of randomized controlled trials. The prospective collection of real-world data for these new therapeutic modalities and combinations, alongside pivotal randomized trial data, will lead to a more complete picture of effectiveness and help to develop confidence in the use of these treatments, which in turn should lead to better outcomes for patients with MM.

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/fon-2020-1225](http://www.futuremedicine.com/doi/suppl/10.2217/fon-2020-1225)

### Author contributions

All authors were responsible for study conception and design. R Hájek, J Minařík, J Straub, L Pour, A Jungova, V Maisnar, X Leleu, K Weisel, E Terpos, N Puig, G Cook, JG Berdeja, RM Rifkin, HC Lee and R Abonour collected the data. All authors analyzed and interpreted the data. R Hájek, J Minařík, J Straub, L Pour, A Jungova, V Maisnar, X Leleu, K Weisel, E Terpos, N Puig, G Cook, JG Berdeja, RM Rifkin, HC Lee and R Abonour provided study materials or patients. All authors contributed to manuscript preparation and revised the manuscript critically; all authors gave their approval to submit the final version of the manuscript for publication.

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#### Ethical conduct of research statement

INSIGHT MM is being conducted in accordance with the Declaration of Helsinki, The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines, Good Pharmacoepidemiology Practice guidelines, European directives on protection of human patients in research, and local relevant guidelines, laws or regulations. The research is approved by local or central independent review boards or independent ethics committees at each site. The Czech RMG complies with all local relevant guidelines, laws or regulations. All patients gave written informed consent.

#### Statement of prior presentation

Results from an earlier data cut were presented as posters at the 61st Annual Meeting of the American Society of Hematology (ASH), Orlando, FL, USA, December 7–10, 2019 (abstract #1845), and at the 16th Annual Meeting of the Hematology/Oncology Pharmacy Association (HOPA), Tampa, FL, USA, March 11–14, 2020 (abstract # CT11; encore presentation).

#### Data sharing statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. The statistical analysis plan for this pooled analysis is included as a data supplement available with the online version of this article.

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#### Summary points

- Clinical outcomes in multiple myeloma often differ in routine clinical practice compared with clinical trial data.
- We performed a pooled analysis of the global, prospective, observational INSIGHT MM study and the Czech Registry of Monoclonal Gammopathies (RMG) to evaluate the effectiveness and safety of ixazomib-lenalidomide-dexamethasone (IRd) in relapsed/refractory MM in routine clinical practice.
- Patient-level data on demographics, disease characteristics, treatment history, effectiveness and safety from both registries were integrated and analyzed.
- At data cut-off, 263 patients (132 INSIGHT MM, 131 Czech RMG) from 13 countries were included.
- Median time from diagnosis to start of IRd was 35.8 months; median duration of follow-up was 14.8 months.
- Among 186 patients with best response data available, overall response rate (ORR) was 73%; median progression-free survival (PFS) and time-to-next therapy were 21.2 (95% CI: 15.2–25.9) and 33.0 (95% CI: 26.2–47.4) months, respectively.
- Ixazomib and lenalidomide dose reductions were required in 17 and 36% of patients, respectively (10 and 23% due to adverse events [AEs], most commonly hematologic and gastrointestinal AEs, and fatigue).
- A total of 32 and 30% of patients discontinued ixazomib and lenalidomide, respectively, due to AEs, most frequently, infection and hematologic events.
- The effectiveness of IRd in routine clinical practice is comparable to the efficacy of IRd reported in the Phase III TOURMALINE-MM1 trial (ORR: 78%; median PFS: 20.6 months).
- IRd is well tolerated, with no new safety signals, and rates of dose reductions and discontinuations due to AEs similar to those reported in TOURMALINE-MM1.

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