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Impact of prior lenalidomide or proteasome inhibitor exposure on the effectiveness of ixazomib–lenalidomide–dexamethasone for relapsed/refractory multiple myeloma: A pooled analysis from the INSURE study

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Abstract

Objectives: To characterize the impact of prior exposure and refractoriness to lenalidomide or proteasome inhibitors (PIs) on the effectiveness and safety of ixazomib–lenalidomide–dexamethasone (IRd) in relapsed/refractory multiple myeloma (RRMM).

Methods: INSURE is a pooled analysis of adult RRMM patients who had received IRd in ≥2 line of therapy from three studies: INSIGHT MM, UVEA-IXA, and REMIX.

Results: Overall, 391/100/68 were lenalidomide-naïve/−exposed/−refractory and 37/411/110 were PI-naïve/−exposed/−refractory. Median duration of therapy (DOT) was 15.3/15.6/4.7 months and median progression-free survival (PFS) was 21.6/25.8/5.6 months in lenalidomide-naïve/exposed/refractory patients. Median DOT and PFS in PI-naïve/exposed/refractory patients were 20.4/15.2/6.9 months and not reached/19.8/11.4 months, respectively. The proportion of lenalidomide-naïve/exposed/refractory patients in INSIGHT and UVEA-IXA who discontinued a

study drug due to adverse events (AEs) was ixazomib, 31.6/28.2/28.0% and 18.6/6.7/10.5%; lenalidomide, 21.9/28.2/16.0% and 16.1/6.7/10.5%; dexamethasone, 18.4/20.5/16.0% and 10.6/0/10.5%, respectively. The proportion of PI-naïve/exposed/refractory patients in INSIGHT and UVEA-IXA who discontinued a study drug due to AEs was: ixazomib, 44.4/28.8/27.8% and 22.2/16.7/15.7%; lenalidomide, 33.3/22.0/19.4% and 16.7/15.9/11.8%; dexamethasone, 33.3/17.4/16.7% and 16.7/9.5/7.8%, respectively. REMIX AE discontinuation rates were unavailable.

Conclusion: IRd appeared to be effective in RRMM patients in routine clinical practice regardless of prior lenalidomide or PI exposure, with better outcomes seen in lenalidomide- and/or PI-nonrefractory versus refractory patients.

KEYWORDS

effectiveness, ixazomib, lenalidomide, multiple myeloma, prior treatment exposure, proteasome inhibitor, relapsed/refractory

Novelty Statement

What is the new aspect of your work?

INSURE is the first global, pooled, real-world evidence analysis among patients with relapsed/refractory multiple myeloma (RRMM) administered ixazomib–lenalidomide–dexamethasone (IRd), designed to characterize the impact of prior exposure and refractoriness to lenalidomide/proteasome inhibitors (PIs) on the effectiveness and safety of IRd.

What is the central finding of your work?

IRd appeared to be effective in patients with RRMM, regardless of prior lenalidomide or PI exposure (but not refractoriness).

What is (or could be) the specific clinical relevance of your work?

When treating patients with RRMM in routine clinical practice, prior exposure to lenalidomide or a PI should not preclude the use of IRd in subsequent lines of therapy.

1 | INTRODUCTION

The all-oral regimen of ixazomib combined with lenalidomide and dexamethasone (IRd) has been approved for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy, based on the results of the TOURMALINE-MM1 randomized controlled trial (RCT).[1,2] In this phase 3 study of patients with relapsed/refractory MM (RRMM), IRd improved both progression-free survival (PFS) in comparison with placebo plus lenalidomide and dexamethasone (Rd), (median, 20.6 vs.14.7 months, respectively; hazard ratio 0.74; 95% confidence interval [CI]: 0.59–0.94; $p = .01$) and objective response rates (overall response rate [ORR], 78 vs. 72%, $p = .04$; ≥very good partial response rate, 48 vs. 39%, respectively, $p = .01$) with only minor additional increases in toxicity.[3] Multiple subsequent studies have investigated IRd among patients with MM in routine clinical practice; for example, INSIGHT MM is a prospective, global study of 4307 patients with MM from 15 countries[4]; UVEA-IXA is a multicenter, longitudinal, retrospective cohort study of 309 patients with RRMM receiving ixazomib-based therapy via an early access program in Europe[5]; and REMIX is a retrospective/prospective study of 197 patients with RRMM treated with IRd via a compassionate-use program in France.[6] The present study, INSURE, is a pooled global analysis of outcomes from INSIGHT MM, UVEA-IXA, and REMIX, designed to provide a broad, overview of how patients with MM are impacted by IRd in routine clinical practice; analyses have already shown that the effectiveness of IRd used to treat patients with RRMM in routine clinical practice is comparable to its efficacy seen in the TOURMALINE-MM1 RCT.[7] Median PFS in INSURE was 19.9 months and no new safety concerns were reported.[7] Furthermore, these findings are consistent with those reported in other real-world observational studies of IRd in patients with RRMM.[6,8–13]

Lenalidomide-containing regimens and proteasome inhibitors (PIs) are used commonly across lines of therapy (LoTs) for the treatment of patients with MM.[14] Although data on effectiveness outcomes following retreatment with agents used in earlier LoTs are limited, there is some evidence to suggest that patients may derive benefit from retreatment with an agent they have been previously exposed to (but are not refractory to).[14] For example, in the phase 3 POLLUX study in patients with RRMM, PFS benefit with daratumumab-Rd versus Rd

alone was observed in patients with prior lenalidomide exposure but who were not refractory.[15] While RCTs are the gold standard for establishing the efficacy and safety of therapies and informing treatment guidelines, these data may have limited generalizability to patients in a real-world setting and routine care practices due to strict eligibility criteria and conditions imposed by clinical trial designs.[16–18] This highlights the need for supplemental treatment effectiveness data from real-world observational studies in patient populations not well represented in clinical trials, such as those being retreated with the same agent across multiple LoTs. Considering the guideline-recommended use of lenalidomide and/or PIs in early LoTs,[14] it is important to understand the effectiveness and feasibility of retreatment with these agents in later lines.

With these considerations in mind, the objective of the current analysis, using data from the INSURE study, was to characterize the impact of prior exposure and refractoriness to lenalidomide or PIs on the effectiveness and safety of IRd in patients with RRMM in routine clinical practice.

2 | METHODS

2.1 | Study design

The full methodology for the INSURE study has been published previously.[7] In brief, INSURE was an analysis of a global dataset pooled from three observational studies: INSIGHT MM, UVEA-IXA, and REMIX ($N = 564$). INSIGHT MM is a prospective study of 4307 patients with MM from 15 countries across Europe, Asia, the US, and Latin America, with a planned follow-up of ≥2 years[4] (data cut-off for this analysis: March 1, 2021). UVEA-IXA is a multicenter, longitudinal cohort study (comprising a retrospective chart review and prospective 12-month follow-up) of 309 patients with RRMM receiving ixazomib-based regimens via an early access program in eight European countries[5] (data cut-off for this analysis: September 30, 2019). REMIX is a retrospective/prospective study of 197 patients with RRMM treated with IRd through a compassionate use program in France,[6] with a planned follow-up of between 2 and 4 years (data cut-off for this analysis: June 4, 2020). Each source study was conducted according to the Declaration of Helsinki and applicable local regulations. Patients provided written informed consent for inclusion in each study, while study documentation (including protocols) was approved by local independent review boards or independent ethics committees at each investigational site.

2.2 | Patients

The INSURE study included patients aged ≥18 years with RRMM, with initiation of at least a second (≥2nd) LoT for MM after the diagnosis date; patients were required to have received IRd as ≥2nd LoT in routine practice. LoT assignment was assessed by the physician. Patients were excluded under the following circumstances: if they had received IRd during any prior LoT (including as maintenance or consolidation); if their IRd treatment commenced >90 days prior to providing informed consent (INSIGHT MM only); if they were enrolled in a clinical trial when receiving IRd; if they had received a stem cell transplant and IRd in the same LoT; or if there was >2 months (≥60 days) difference in the start dates for ixazomib or lenalidomide. Patients who were enrolled in >1 study were only counted once and only for the first LoT of IRd received. All patients were followed until the end of each study, loss to follow-up, or death, whichever occurred first.

2.3 | Outcomes and assessments

Outcomes in the INSURE intent-to-treat (ITT) population have been reported previously.[7] For this analysis, effectiveness outcomes of interest were duration of therapy (DOT), time to next therapy (TTNT), PFS, overall survival (OS), and ORR by prior lenalidomide and PI exposure. Definitions used for the effectiveness-related clinical outcome measures are provided in Table S1. For time-to-event outcomes, the index date and start of follow-up was defined as the date of initiation of IRd treatment in the ≥2nd LoT. Safety outcomes included in this analysis were adverse events (AEs) and discontinuations/dose reductions due to AEs. Safety data for REMIX were recorded differently compared with INSIGHT MM and UVEA-IXA, with a focus on certain AEs in the case report form. Thus, for REMIX, the most common AEs leading to ixazomib dose reduction are not reported. Consequently, in this analysis, AEs and discontinuations/dose reductions due to AEs are presented separately for each study.

2.4 | Statistical analysis

As statistical hypotheses were not tested in the INSURE study, sample size calculations were not performed; all evaluable patients with available data were included. In this analysis, all treatment outcomes were stratified by prior lenalidomide or prior PI exposure (not mutually exclusive), and categorized as naïve, exposed, or refractory (mutually exclusive). Refractory was defined as having progressed on treatment or within 60 days of discontinuing treatment, or where the treatment-free interval between discontinuation and next index regimen (not containing lenalidomide or a PI) was ≤60 days. Patients were considered exposed (but not refractory) to a treatment following discontinuation for reasons other than disease progression; patients were considered naïve to a treatment if no prior exposure to that treatment was observed. Time-to-event outcomes were analyzed by Kaplan–Meier methods and univariable and multivariable Cox proportional hazards models, with effect of the study as a random effect.

3 | RESULTS

3.1 | Patients

In total, 562 patients were included in this analysis (data were missing for two patients from the 564 patients in the ITT population). Of the 562 patients included, data were missing for three patients in

TABLE 1 Baseline and disease characteristics for patients treated with IRd by prior lenalidomide and proteasome inhibitor exposure.

Characteristic	Lenalidomide ($N = 559$)[a]			PI ($N = 558$)[a]		
	Naïve ($n = 391$)	Exposed ($n = 100$)	Refractory ($n = 68$)	Naïve ($n = 37$)	Exposed ($n = 411$)	Refractory ($n = 110$)
LoT[b] (%)	**$n = 391$**	**$n = 100$**	**$n = 68$**	**$n = 37$**	**$n = 411$**	**$n = 110$**
Second LoT	50.9	23.0	10.3	45.9	47.7	14.5
Third LoT	39.4	41.0	27.9	37.8	36.3	44.5
≥Fourth line	9.7	36.0	61.8	16.2	16.1	40.9
Male (%)	51.9	53.0	47.1	48.6	50.6	56.4
White/Caucasian race[c] (%)	**$n = 197$**	**$n = 29$**	**$n = 27$**	**$n = 22$**	**$n = 169$**	**$n = 62$**
	93.9	79.3	85.2	95.5	91.1	91.9
Country[d] (%)	**$n = 391$**	**$n = 100$**	**$n = 68$**	**$n = 37$**	**$n = 411$**	**$n = 110$**
Belgium	0.8	0	0	0	0.5	1.8
Brazil	1.0	0	0	0	0.7	0.9
China	0.5	1.0	0	0	0.2	1.8
Czech Republic	5.1	2.0	7.4	10.8	4.1	5.5
France	32.7	49.0	35.3	27.0	40.6	22.7
Germany	0.3	1.0	8.8	2.7	1.0	2.7
Greece	5.1	4.0	5.9	5.4	5.4	3.6
Hungary	6.4	2.0	8.8	13.5	3.2	13.6
Israel	1.0	2.0	1.5	0	1.2	1.8
Italy	2.8	1.0	2.9	0	1.2	8.2
Slovakia	3.6	0	1.5	8.1	2.7	0.9
Slovenia	0.8	1.0	0	0	1.0	0
Spain	2.8	3.0	2.9	0	3.4	1.8
Taiwan	2.0	6.0	1.5	0	2.4	3.6
Turkey	0.3	3.0	0	2.7	0.7	0
UK	34.0	8.0	4.4	10.8	26.5	25.5
USA	0.8	17.0	19.1	18.9	5.1	5.5
At diagnosis						
M-protein type (%)	**$n = 265$**	**$n = 67$**	**$n = 50$**	**$n = 28$**	**$n = 278$**	**$n = 75$**
IgG/IgA/Light chain only[e]	54.0/21.1/20.0	73.1/9.0/16.4	36.0/22.0/30.6	50.0/21.4/25.0	57.9/20.5/16.6	46.7/13.3/33.3
Cytogenetic risk[f] (%)	**$n = 180$**	**$n = 33$**	**$n = 29$**	**$n = 22$**	**$n = 170$**	**$n = 50$**
High/standard	14.4/85.6	24.2/75.8	10.3/89.7	9.1/90.9	16.5/83.5	14.0/86.0
At the start of IRd						
Age	**$n = 384$**	**$n = 99$**	**$n = 65$**	**$n = 37$**	**$n = 403$**	**$n = 108$**
Median, years (range)	69.0 (36.0–91.0)	68.0 (36.0–87.0)	68.0 (39.0–92.0)	71.0 (40.0–86.0)	68.0 (36.0–92.0)	68.5 (36.0–91.0)
Aged ≤65 years (%)	35.9	38.4	38.5	24.3	37.2	38.9
Aged 66–75 years (%)	40.1	47.5	43.1	37.8	41.2	45.4
Aged >75 years (%)	24.0	14.1	18.5	37.8	21.6	15.7
ECOG PS[g] (%)	**$n = 348$**	**$n = 80$**	**$n = 61$**	**$n = 34$**	**$n = 355$**	**$n = 99$**
0/1/≥2	32.8/49.4/17.8	38.8/48.8/12.5	21.3/55.7/23.0	20.6/73.5/5.9	36.1/48.5/15.5	23.2/47.5 /29.3
Charlson comorbidity index[g] (%)	**$n = 308$**	**$n = 81$**	**$n = 54$**	**$n = 30$**	**$n = 322$**	**$n = 90$**
0/1/≥2	66.9/11.0/22.1	63.0/14.8/22.2	53.7/13.0/33.3	53.3/20.0/26.7	66.5/10.9/22.7	62.2/13.3/24.4
Frailty score (%)	**$n = 289$**	**$n = 67$**	**$n = 48$**	**$n = 30$**	**$n = 293$**	**$n = 80$**
0–1/≥2	58.8/41.2	70.1/29.9	47.9/52.1	60.0/40.0	61.8/38.2	51.3/48.8
eGFR[h] (%)	**$n = 365$**	**$n = 89$**	**$n = 62$**	**$n = 35$**	**$n = 382$**	**$n = 99$**
≥60/30–60/<30 mL/min/1.73m^2	68.8/24.1/7.1	71.9/16.9/11.2	74.2/21.0/4.8	77.1/22.9/0	69.1/22.3/8.6	71.7/21.2/7.1

TABLE 1 (Continued)

Characteristic	Lenalidomide ($N = 559$)[a]			PI ($N = 558$)[a]		
	Naïve ($n = 391$)	Exposed ($n = 100$)	Refractory ($n = 68$)	Naïve ($n = 37$)	Exposed ($n = 411$)	Refractory ($n = 110$)
Biochemical progression prior to IRd (%)	**$n = 350$**	**$n = 77$**	**$n = 57$**	**$n = 33$**	**$n = 352$**	**$n = 100$**
	57.1	53.2	54.4	66.7	56.5	53.0
Symptomatic progression prior to IRd (%)	42.9	46.8	45.6	33.3	43.5	47.0
Follow-up time from IRd onset (months)	**$n = 391$**	**$n = 100$**	**$n = 68$**	**$n = 37$**	**$n = 411$**	**$n = 110$**
Median	19.4	18.8	10.4	20.7	19.6	11.4

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; Ig, immunoglobulin; IRd, ixazomib-lenalidomide-dexamethasone; ITT, intent-to-treat; LoT, line of therapy; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.
[a]Data were missing for two patients from the 564 patients in the ITT population. Of the 562 patients included, data were missing for three patients in the prior lenalidomide exposure cohort and four patients in the prior PI exposure cohort.
[b]Denominator for LoT percentages is the total number of patients who were naïve, exposed, or refractory and is not based on the total number of patients receiving 2, 3, or ≥4 prior LoTs, as in the INSURE ITT publication.[7]
[c]Race not collected for REMIX study.
[d]France for REMIX only.
[e]$n = 49$ (lenalidomide-refractory), $n = 277$ (PI-exposed), for light chain assessment. Patients with IgD, IgM, or IgA + IgG + IgM, those with no M-protein detected, any other M-protein classification are not listed, thus percentages may not sum to 100%.
[f]Defined as the presence of del[17p], t[4;14], and/or t[14;16]; a high percentage of patients were not assessed for all abnormalities in this RRMM population and were classified as missing.
[g]From 1 year prior to until ≤90 days after the start of IRd therapy for INSIGHT MM and REMIX patients; date of assessment not available for UVEA-IXA patients.
[h]As recorded for UVEA-IXA; for INSIGHT MM and REMIX, the values were estimated according to serum creatinine, age, and race.

the prior lenalidomide exposure cohort and four patients in the prior PI exposure cohort. Overall, 391/100/68 patients were lenalidomide-naïve/exposed/refractory ($n = 559$) and 37/411/110 were PI-naïve/exposed/refractory ($n = 558$; Table 1); 81 patients were both lenalidomide- and PI-exposed. Lenalidomide-naïve/exposed/refractory patients had received a median of one/two/three LoTs prior to IRd while PI-naïve/exposed/refractory patients had received a median of two LoTs prior to IRd, in all three subgroups. Notably, there were imbalances in baseline characteristics among the patient subgroups, particularly with respect to M-protein type, cytogenetic risk status, and Eastern Cooperative Oncology Group performance status (Table 1).

3.2 | Effectiveness outcomes

The median duration of follow-up from the start of IRd was 19.4/18.8/10.4 months for lenalidomide-naïve/exposed/refractory patients, and 20.7/19.6/11.4 months for PI-naïve/exposed/refractory patients (Table 1). The median DOT with IRd was 15.3/15.6/4.7 months in lenalidomide-naïve/exposed/refractory patients (Figure 1A), and 20.4/15.2/6.9 months in PI-naïve/exposed/refractory patients (Figure 1B). The median DOT for the individual agents of the IRd regimen is shown in Table S2. Among lenalidomide-naïve/exposed/refractory patients, the median TTNT was 19.8/19.6/5.2 months, respectively (Figure 1C); for PI-naïve/exposed/refractory patients, the median TTNT was 24.0/18.9/9.3 months, respectively (Figure 1D). Lenalidomide-naïve/exposed/refractory patients had median PFS of 21.6/25.8/5.6 months, respectively (Figure 1E), while PI-naïve/exposed/refractory patients had median PFS that was not reached (NR)/19.8/11.4 months, respectively (Figure 1F). Multivariable analyses of DOT, TTNT, and PFS were conducted to adjust for potential confounders (Table S3). At the time of this data accrual, OS data were not mature (32.6% of patients had died overall; $n = 184$). Median OS had not been reached in lenalidomide- or PI-naïve/exposed patients and was 20.7 months (95% CI: 11.0–not estimable [NE]) in lenalidomide-refractory patients and 17.8 months (95% CI: 11.6–NE) in PI-refractory patients. These data, as well as median DOT, TTNT, and PFS, are summarized by lenalidomide- and PI-refractory status in Table 2. Time-to-event outcomes were numerically lower in the lenalidomide-refractory and PI-nonrefractory subgroup and the lenalidomide- and PI-refractory subgroup versus the lenalidomide-nonrefractory and PI-refractory subgroup and the lenalidomide- and PI-nonrefractory subgroup (Table 2). Best response to IRd therapy among response-evaluable patients ($n = 404$, overall) is shown by prior lenalidomide and PI exposure in Figure 2. Among lenalidomide-naïve/exposed/refractory patients, ORR was 67.5/61.8/50.0%, respectively, and median time to best response was 4.4/4.6/3.3 months, respectively. For PI-naïve/exposed/refractory patients, ORR was 70.8/67.0/50.8%, with a median time to best response of 2.9/4.4/3.5 months, respectively.

3.3 | Safety outcomes

The proportion of lenalidomide-naïve/exposed/refractory patients in INSIGHT MM and UVEA-IXA who discontinued a study drug due to AEs was: ixazomib, 31.6/28.2/28.0% and 18.6/6.7/10.5%; lenalidomide,

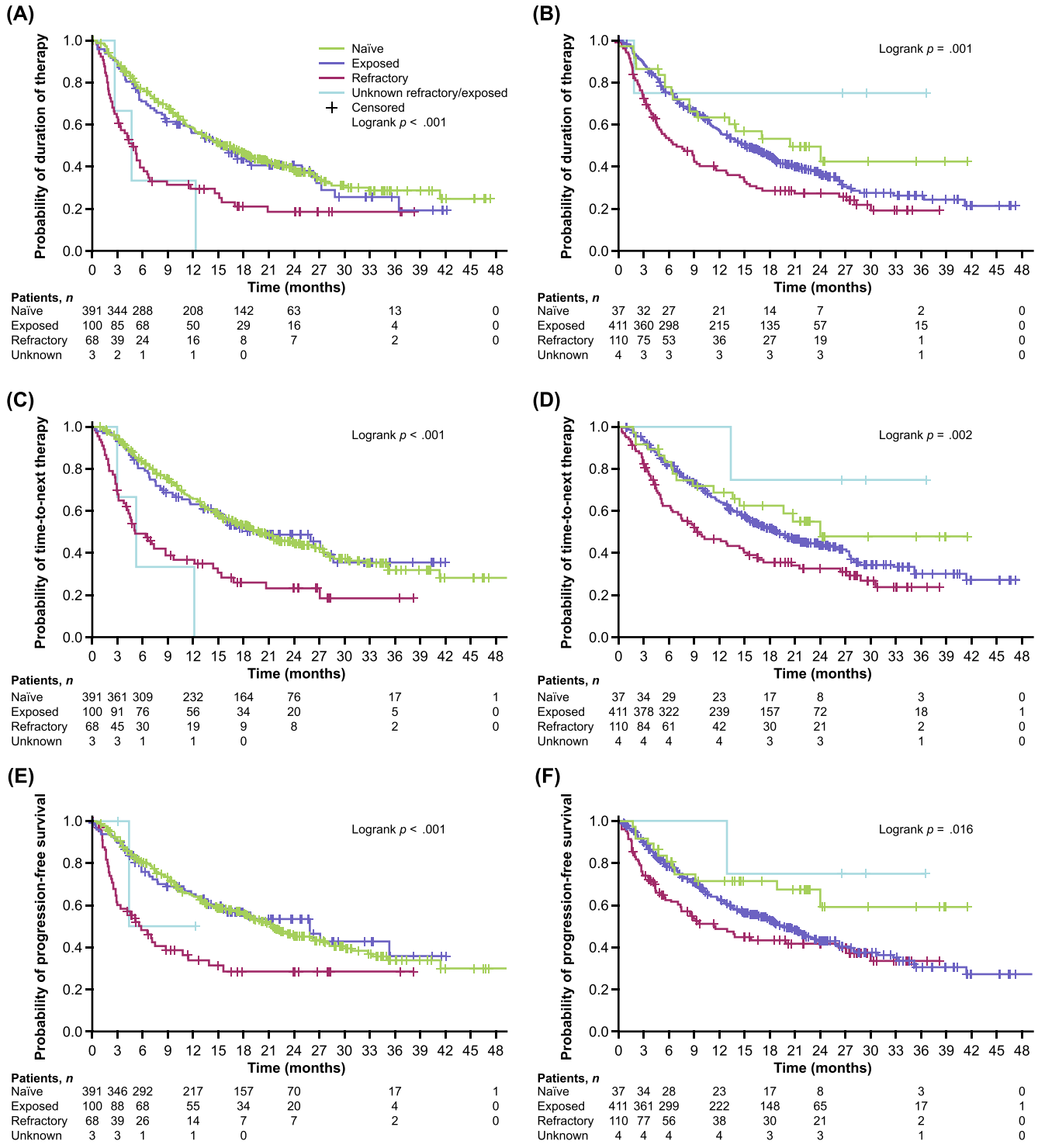

FIGURE 1 Kaplan–Meier analyses of time-to-event outcomes with IRd: duration of therapy by prior (A) lenalidomide and (B) proteasome inhibitor (PI) exposure; time-to-next therapy by prior (C) lenalidomide and (D) PI exposure; and progression-free survival by prior (E) lenalidomide and (F) PI exposure.

21.9/28.2/16.0% and 16.1/6.7/10.5%; and dexamethasone, 18.4/20.5/16.0% and 10.6/0/10.5%, respectively (Table 3). The proportion of PI-naïve/exposed/refractory patients in INSIGHT MM and UVEA-IXA who discontinued a study drug due to AEs was: ixazomib, 44.4/28.8/27.8% and 22.2/16.7/15.7%; lenalidomide, 33.3/22.0/19.4% and 16.7/15.9/11.8%; and dexamethasone, 33.3/17.4/16.7% and 16.7/9.5/7.8%, respectively (Table 3). AE discontinuation rates were unavailable for REMIX. However, rates of AEs, serious AEs, and the most common AEs reported in REMIX are shown by prior lenalidomide and PI exposure in Table 4.

TABLE 2 Duration of therapy, time-to-next therapy, progression-free survival, and overall survival by lenalidomide- and proteasome inhibitor-refractory status.

	Lenalidomide- and PI-nonrefractory ($n = 417$)	Lenalidomide-nonrefractory and PI-refractory ($n = 71$)	Lenalidomide-refractory and PI-nonrefractory ($n = 29$)	Lenalidomide- and PI-refractory ($n = 38$)
Median DOT, months (95% CI)	16.9 (13.9–18.8)	9.0 (6.3–16.4)	5.2 (3.2–6.7)	3.3 (1.8–6.0)
Median TTNT, months (95% CI)	20.7 (17.4–26.1)	14.9 (9.0–26.4)	6.7 (4.0–16.8)	4.6 (2.9–12.2)
Median PFS, months (95% CI)	21.6 (18.5–25.8)	19.9 (9.2–NE)	7.0 (3.4–15.6)	3.0 (1.9–11.4)
Median OS, months (95% CI)	Not reached	27.1 (13.6–NE)	21.4 (16.0–27.1)	12.1 (4.6–NE)

Note: Data are based on Kaplan–Meier estimates.
Abbreviations: DOT, duration of therapy; NE, not estimable; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; TTNT, time-to-next therapy.

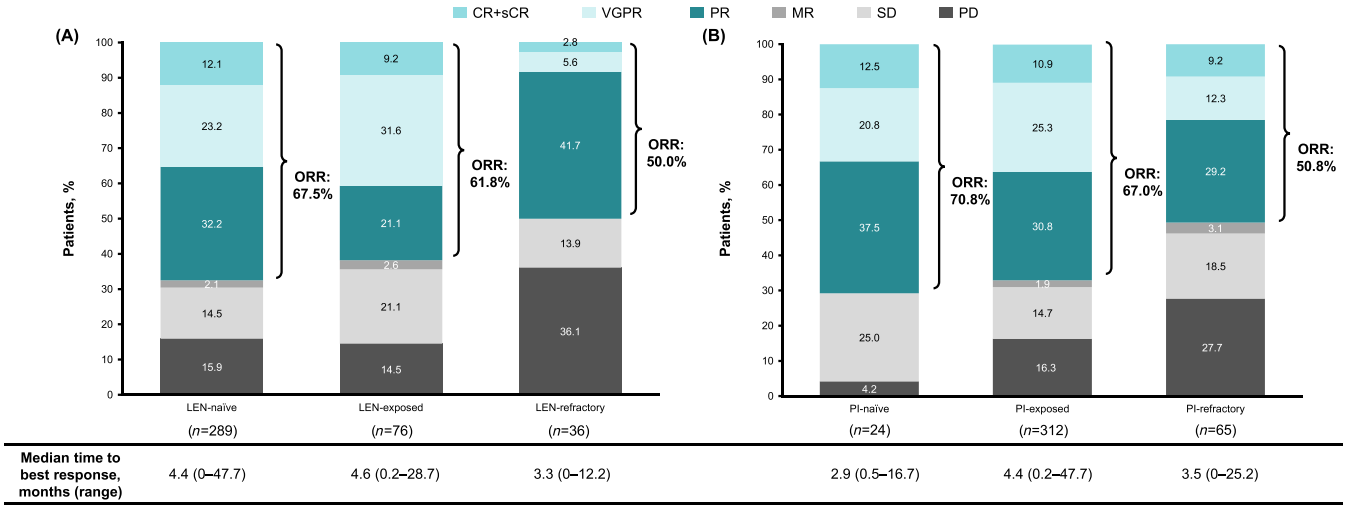

FIGURE 2 Best response* to IRd therapy by prior (A) lenalidomide and (B) PI exposure. *Best response recorded after IRd onset and before, or at the end of, IRd therapy. Response data missing for 102/24/32 lenalidomide-naïve/exposed/refractory patients and 13/99/45 PI-naïve/exposed/refractory patients. Percentages may not sum owing to rounding. ORR = PR + VGPR + CR + sCR. CR, complete response; IRd, ixazomib-lenalidomide-dexamethasone; LEN, lenalidomide; MR, minimal response; ORR, overall response rate; PD, progressive disease; PI, proteasome inhibitor; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

4 | DISCUSSION

In this analysis of the INSURE global pooled dataset, we present indicative data which suggest that prior lenalidomide exposure may have little impact on IRd effectiveness in lenalidomide-nonrefractory patients with RRMM treated in routine clinical practice, while prior PI exposure might affect outcomes with IRd in PI-nonrefractory patients to a limited degree, although clinical benefit can still be achieved with treatment. These data are consistent with the phase 3 POLLUX study in patients with RRMM, where a PFS benefit with daratumumab-Rd versus Rd alone was observed with prior lenalidomide exposure,[15] thus supporting the use of different lenalidomide-containing regimens for RRMM in second and later LoTs even in patients who have previously received lenalidomide. Our results are also congruent with a subanalysis of the TOURMALINE-MM1 trial demonstrating the clinical efficacy of IRd, in terms of PFS, regardless of prior treatment with immunomodulatory drugs, including lenalidomide[19]; the subanalysis also indicated that the efficacy of IRd was unaffected by prior PI exposure. The disparity with our results may be explained by the longer treatment history and slightly higher proportion of PI-exposed patients in INSURE.[7] Even considering the small, observed impact of prior PI exposure on IRd effectiveness in the current study, median PFS outcomes in the lenalidomide- and PI-naïve/exposed cohorts (21.6/25.8 months and NR/19.8 months, respectively) were numerically comparable to that reported in TOURMALINE-MM1 for patients administered IRd (20.6 months),[3] thus confirming the benefits of IRd in a more heavily pretreated, real-world population with less favorable baseline characteristics. Unsurprisingly, and in accordance with previous real-world data,[13,20] patients who were lenalidomide- and PI-refractory achieved poorer PFS outcomes with IRd than those who were

TABLE 3 Dose reductions and discontinuations owing to adverse events in INSIGHT MM and UVEA-IXA by prior lenalidomide and proteasome inhibitor exposure.

		Lenalidomide			PI		
		Naïve	Exposed	Refractory	Naïve	Exposed	Refractory
Dose reductions (%)	**INSIGHT MM**	***n* = 114**	***n* = 39**	***n* = 25**	***n* = 9**	***n* = 132**	***n* = 36**
	Ixazomib	18.4	10.3	0	0	16.7	8.3
	Lenalidomide	22.8	17.9	8.0	33.3	21.2	11.1
	Dexamethasone	15.8	2.6	8.0	0	13.6	5.6
	UVEA-IXA	***n* = 161**	***n* = 15**	***n* = 19**	***n* = 18**	***n* = 126**	***n* = 51**
	Ixazomib	11.2	0	0	11.1	11.1	3.9
	Lenalidomide	9.9	6.7	5.3	11.1	9.5	7.8
	Dexamethasone	1.2	0	0	5.6	0	2.0
Discontinuations (%)	**INSIGHT MM**	***n* = 114**	***n* = 39**	***n* = 25**	***n* = 9**	***n* = 132**	***n* = 36**
	Ixazomib	31.6	28.2	28.0	44.4	28.8	27.8
	Lenalidomide	21.9	28.2	16.0	33.3	22.0	19.4
	Dexamethasone	18.4	20.5	16.0	33.3	17.4	16.7
	UVEA-IXA	***n* = 161**	***n* = 15**	***n* = 19**	***n* = 18**	***n* = 126**	***n* = 51**
	Ixazomib	18.6	6.7	10.5	22.2	16.7	15.7
	Lenalidomide	16.1	6.7	10.5	16.7	15.9	11.8
	Dexamethasone	10.6	0	10.5	16.7	9.5	7.8

Abbreviations: MM, multiple myeloma; PI, proteasome inhibitor.

TABLE 4 REMIX safety summary (for ixazomib only) by prior lenalidomide and proteasome inhibitor exposure.

	Lenalidomide (*n* = 186)			PI (*n* = 186)		
	Naïve (*n* = 116)	Exposed (*n* = 46)	Refractory (*n* = 24)	Naïve (*n* = 10)	Exposed (*n* = 153)	Refractory (*n* = 23)
AEs (%)	69.0	58.7	62.5	60.0	64.7	73.9
Serious AEs (%)	35.3	39.1	50.0	30.0	35.9	56.5
Most common[a] AEs (%)						
Diarrhea	16.4	13.0	12.5	20.0	15.0	13.0
Thrombocytopenia	15.5	10.9	16.7	10.0	14.4	17.4
Asthenia	8.6	10.9	8.3	20.0	9.2	4.3
Nausea	5.2	10.9	12.5	10.0	5.9	17.4
Most common[a] serious AEs (%)						
Thrombocytopenia	4.3	4.3	12.5	10.0	4.6	8.7

Abbreviations: AE, adverse event; PI, proteasome inhibitor.
[a]Occurring in >15% of patients for AEs and >10% for serious AEs in at least one subgroup.

lenalidomide- or PI-nonrefractory; for example, in lenalidomide- and PI-refractory patients, median PFS was 5.6 and 11.4 months, respectively. These results possibly reflect prior treatment burden since the majority (85%–90%) of patients who were PI- and IMiD-refractory received IRd as their third or ≥4th LoT; in the INSURE ITT population, IRd benefit was associated with earlier versus later LoT.[7] Additionally, these data were potentially driven by depth of response; ORR comprised a greater proportion of patients with partial response in the lenalidomide- and PI-refractory versus lenalidomide- and PI-nonrefractory subgroups, although patient numbers were small in some subgroups. The current analysis also revealed relatively poor outcomes in patients who were both lenalidomide-refractory and PI-nonrefractory (median PFS, 7.0 months), a subgroup of patients with RRMM that is becoming increasingly common as MM treatment paradigms continue to evolve.[21] However, it should be noted that the number of patients in this subgroup was relatively small (*n* = 29); thus, further investigation with a larger cohort of patients would be needed to confirm these findings. Published analyses suggest that such patients may benefit from regimens that do not contain lenalidomide.[22] In our analysis, a higher proportion of patients receiving IRd

enrolled in INSIGHT MM discontinued ixazomib treatment due to AEs (lenalidomide naïve/exposed/refractory: 31.6/28.2/28.0%; PI naïve/exposed/refractory: 44.4/28.8/27.8%) compared with IRd discontinuation in the TOURMALINE-MM1 RCT (25.2%).[23] This dissimilarity is likely due to the notably different follow-up durations for each analysis (INSIGHT MM vs. TOURMALINE-MM1, planned ≥24 vs. 85 months),[23] as well as divergent treatment patterns among real-world and RCT populations, where patients may be less likely to discontinue therapy than to undergo dose reduction in RCTs. Overall, the safety profile of IRd was manageable with no new, additional safety concerns compared with those reported in the published literature.[3–9] AEs frequently reported with IRd include diarrhea, thrombocytopenia, and neutropenia, which can be managed with dose holds and/or dose modifications as needed to either ixazomib and/or lenalidomide as per their respective product labels.[1,2]

As reported in our previously published analysis of the overall INSURE population, the present study may be impacted by limitations inherent to real-world studies, including selection and confounding biases, missing data, and inconsistent data reporting across study sites.[7] The small number of patients in some subgroups also prohibits meaningful conclusions. This was particularly evident for the safety data, where low patient numbers made interpretation very difficult; however, no new safety signals were apparent. The treatment landscape for early RRMM continues to evolve, and since INSIGHT MM, UVEA-IXA, and REMIX were conducted, new therapies and combinations have been approved and widely adopted in this space. These include newer anti-CD38 monoclonal antibody combinations such as daratumumab and isatuximab in combination with carfilzomib and dexamethasone,[24,25] now approved and widely used for patients with >1 line of prior therapy. Moreover, the use of PIs and IMiDs as part of frontline therapy with triplet or quadruplet induction regimens will lead to fewer non-PI and non-IMiD refractory patients at the time of 2nd line therapy and beyond.[26,27] Furthermore, several T-cell redirecting therapies, such as bispecific antibodies teclistamab, elranatamab, and talquetamab, and chimeric antigen receptor T cell products idecabtagene vicleucel and ciltacabtagene autoleucel, have now been approved as ≥4th line following prior treatment with PIs, IMiDs, and an anti-CD38 monoclonal antibody. However, access remains limited to these agents and their toxicity profile with risk of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome may preclude use in frail and elderly patient populations.[28–30] Despite these everchanging treatment paradigms, current guidelines and the data from this analysis support the use of IRd as an all-oral regimen for the treatment of RRMM in certain patient populations.[14,22]

4.1 | Conclusions

This analysis of the INSURE pooled global dataset suggests prior lenalidomide exposure (without refractoriness) appeared to have no impact on IRd effectiveness in patients with RRMM in routine clinical practice, while prior PI exposure or PI-refractory status may have impacted outcomes seen with IRd, although clinical benefit may still be achieved without refractoriness to lenalidomide or a PI. Patients who were lenalidomide- or PI-refractory did not achieve the same outcomes with IRd as those who were lenalidomide- or PI-nonrefractory. While responses were seen in half of such patients suggesting some clinical benefit, the depth and duration of response was inferior to nonlenalidomide- or non-PI-refractory patients and therefore alternative treatment approaches should likely be considered. Nevertheless, prior exposure, but not refractoriness, to lenalidomide or a PI should not preclude use of the IRd regimen in subsequent LoTs for patients with RRMM.

AUTHOR CONTRIBUTIONS

Hans C. Lee, Faith E. Davies, Dasha Cherepanov, and Xavier Leleu conceived and designed the study. Hans C. Lee, Karthik Ramasamy, Margaret Macro, Faith E. Davies, Rafat Abonour, Frits van Rhee, Vania T. M. Hungria, Noemi Puig, Kaili Ren, Jiri Silar, Victoria Enwemadu, Dasha Cherepanov, and Xavier Leleu contributed to the acquisition, analysis and/or interpretation of data for the work. All authors drafted the work or revised it critically. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DATA AVAILABILITY 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 3 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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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