

INSURE: a global pooled analysis of patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with ixazomib-lenalidomide-dexamethasone (IRd) in routine clinical practice

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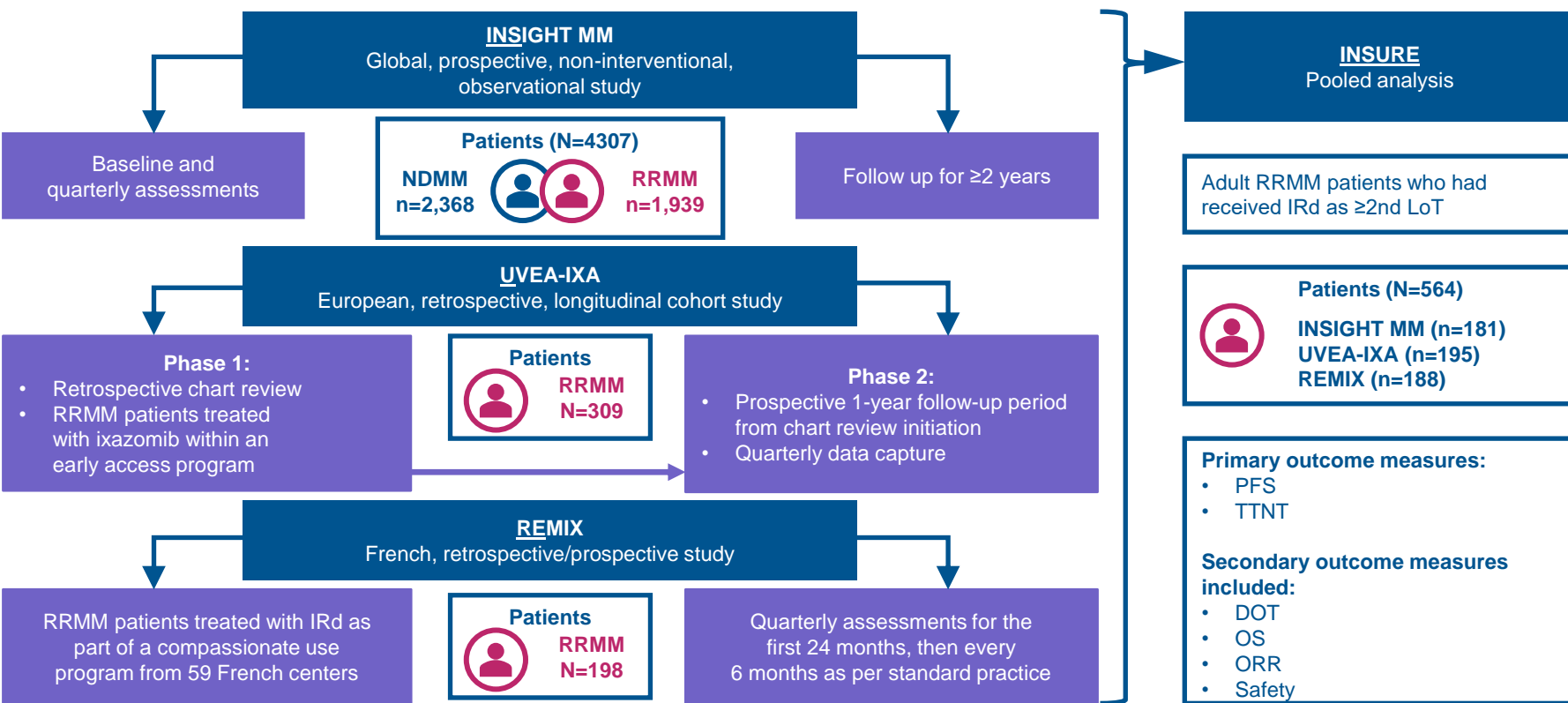
Background

- IRd has been approved for the treatment of RRMM based on the results of the TOURMALINE-MM1 phase 3 study:¹
 - IRd demonstrated superior progression-free survival (PFS; median 20.6 vs 14.7 months; hazard ratio 0.74) and improved response rates (overall response rate [ORR] 78 vs 72%; ≥ very good partial response [VGPR] rate 48 vs 39%) versus placebo-Rd, with limited added toxicity²
- However, outcomes in routine clinical practice often differ from data reported in clinical trials for multiple myeloma (MM) therapies, being poorer for real-world versus clinical trial patients³
 - This discrepancy could be due in part to the fact that up to 72% of real-world patients with RRMM would not meet the eligibility criteria for randomized clinical trials⁴
 - Real-world studies with less stringent eligibility criteria may permit inclusion of a more diverse patient population and better inform on the effectiveness of therapies as used in routine clinical practice
- Several retrospective and prospective observational studies have now shown comparable effectiveness of IRd in ≥2nd line of therapy (LoT) in the real-world setting to the efficacy observed in TOURMALINE-MM1, with median PFS ranging from 11 to 43 months⁵⁻¹¹
- The objective of the current analysis of a large, global dataset pooled from three observational studies is to investigate the effectiveness of IRd in the overall RRMM population, by LoT, and in subpopulations of patients defined by frailty status

Methods

- Figure 2** summarizes the design of each observational study included in the INSURE pooled analysis:
 - INSIGHT MM is a large, prospective study which has enrolled 4,307 MM patients from 15 countries in Europe, Asia, the US, and Latin America, with a planned follow-up of ≥2 years¹²
 - UVEA-IXA is a multicenter, longitudinal, retrospective cohort study of 309 RRMM patients receiving ixazomib-based treatment via an early access program in 8 countries in Europe¹³
 - REMIX is a retrospective/prospective study of 198 RRMM patients receiving IRd via a compassionate use program in France¹¹
- The **INSURE** pooled analysis included adult patients with ≥2 prior MM therapy lines and who had received IRd as ≥2nd LoT (**Figure 2**)
 - Time-to-event endpoints were analyzed in the overall analysis population, by LoT, and in subpopulations of patients defined by a simplified International Myeloma Working Group (IMWG)¹⁴ frailty score (based on age, Charlson comorbidity index, and Eastern Cooperative Oncology Group performance status [ECOG PS]; 0–1 [non-frail] vs ≥2 [frail])¹⁵ assessed at the start of IRd
 - Duration of treatment (DOT), time to next treatment (TTNT), PFS, and overall survival (OS) were analyzed using Kaplan-Meier methodology
 - Due to differences in how safety data were captured in each study, adverse events (AEs) and discontinuations/dose reductions due to AEs were reported separately for each study
 - Patients who were enrolled in >1 study were only counted once and only for the first LoT of IRd therapy received

Figure 2: INSURE pooled analysis: Summary of studies included



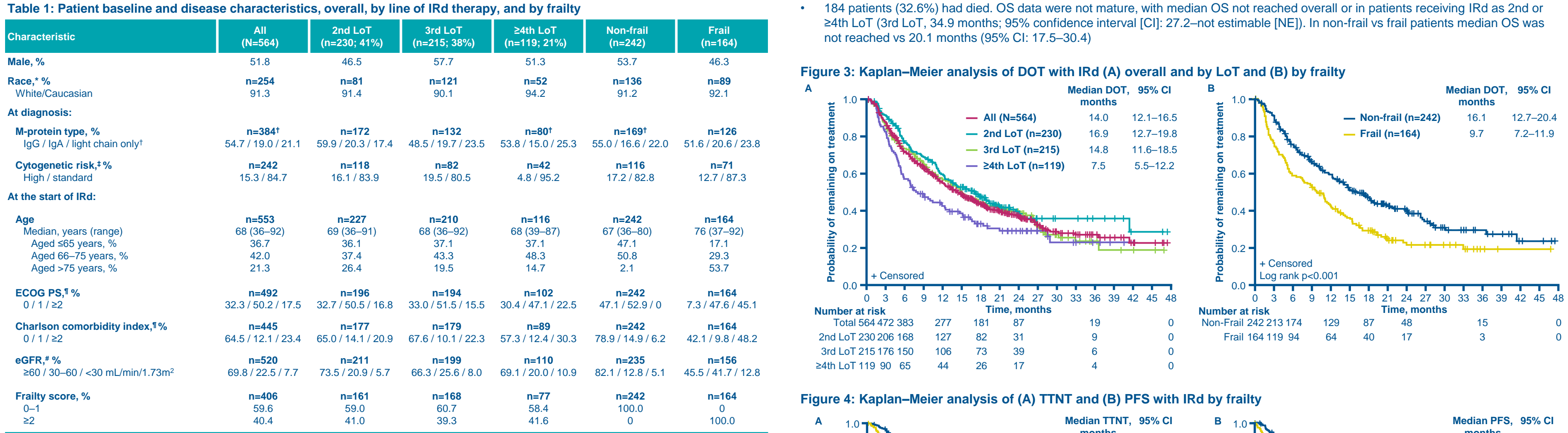
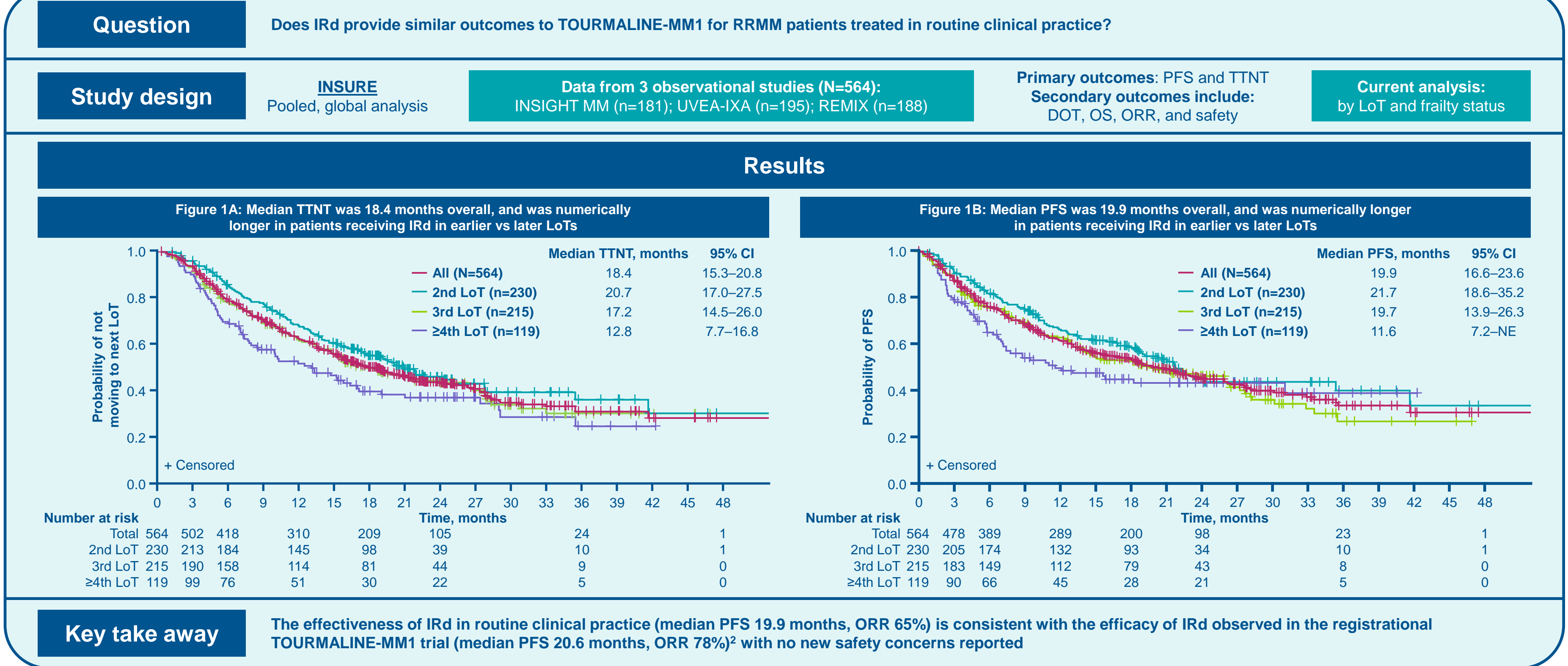
Results

Patient demographics, disease characteristics, and treatment history

- In total, 564 patients enrolled in 17 countries were included in INSURE; most patients were enrolled in France (n=204, 36.2%) and the United Kingdom (n=144, 25.5%)
- Patients had received a median of 2 prior LoT (range: 1–12), with approximately 80% receiving IRd in either 2nd (40.8%) or 3rd (38.1%) LoT
- Patient baseline characteristics and disease characteristics at the start of IRd therapy overall and by line of IRd therapy are summarized in **Table 1**
 - Of the 406 patients with frailty scores recorded, 164 (40%) were defined as frail, with similar percentages (39–42%) of frail patients across all LoT
- Median time from MM diagnosis to start of IRd therapy was 39.3 months overall, and 29.7, 43.4, and 71.1 months for patients who received IRd as 2nd, 3rd, and ≥4th LoT, respectively
- Overall (n=562; data missing for 2 patients), the percentages of patients exposed to refractory (progressed on treatment or within 60 days of discontinuing treatment, or treatment-free interval between discontinuation and next index regimen of ≤60 days; up to 4% of the lenalidomide-refractory and 6% of the proteasome inhibitor [PI]-refractory cohorts may have discontinued therapy and started a new therapy in less than 60 days for reasons other than progression) to PIs or immunomodulatory drugs (IMiDs) in any prior line were: PIs (bortezomib, carfilzomib, or ixazomib), 93%; lenalidomide, 30%; IMiDs (lenalidomide or pomalidomide), 31%
 - In 2nd / 3rd / ≥4th LoT, 93 / 93 / 95%, 13 / 28 / 68%, and 14 / 29 / 70% of patients were exposed or refractory in any prior line to a PI, to lenalidomide, or to an IMiD, respectively

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[†]Race not collected for REMIX study, n=383 (overall), 79 (≥4th LoT) and 168 (non-frail) for light chain only assessment. [‡]Defined as the presence of del(17p), t(4;14), t(14;16); patients for whom an abnormality was not detected but were not assessed for all abnormalities were classified as missing. [§]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. [¶]AS recorded for UVEA-IXA; for INSIGHT MM and REMIX, the values were estimated according to serum creatinine, age, and race. eGFR, estimated glomerular filtration rate; Ig, immunoglobulin.

Outcomes

- Median duration of follow-up from start of IRd for all patients was 18.5 months
- Median DOT was 14.0 months overall, and was numerically longer in patients receiving IRd as 2nd or 3rd (16.9 and 14.8 months) vs ≥4th LoT (7.5 months) and in non-frail (16.1 months) vs frail (9.7 months) patients (**Figure 3**)
- Median TTNT was 18.4 months overall, and was numerically longer in patients receiving IRd in earlier vs later LoTs (**Figure 1A**) and in non-frail vs frail patients (**Figure 4A**)
- 280 patients (49.6%) had progressed or died; median PFS was 19.9 months overall, and numerically longer in patients receiving IRd in earlier vs later LoTs (**Figure 1B**) and in non-frail vs frail patients (**Figure 4B**)

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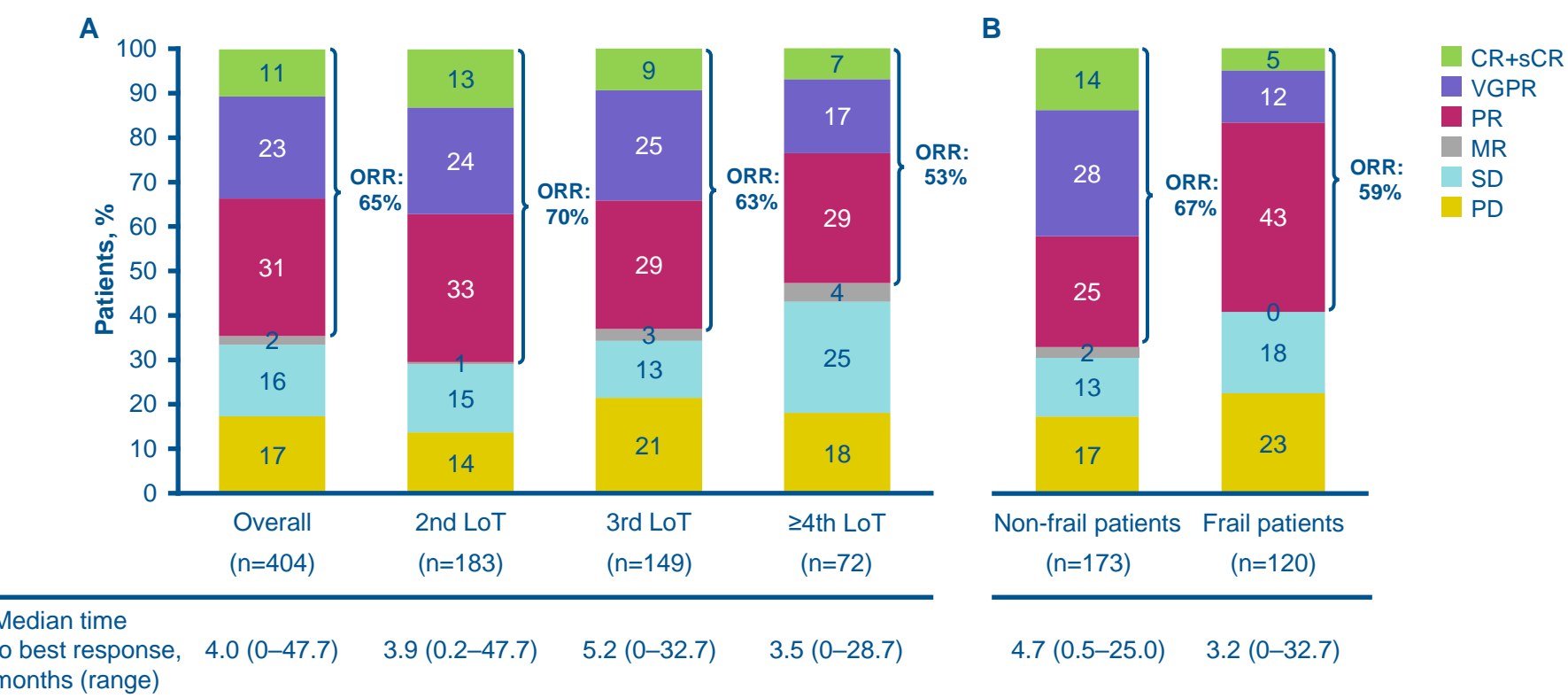
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- Best response to IRd therapy among the 404 response-evaluable patients is shown overall, by LoT and by frailty status in **Figure 5**
 - ORR was 70%, 63%, and 53% among patients receiving IRd as 2nd, 3rd, and ≥4th LoT, with a median time to best response of 3.9, 5.2, and 3.5 months, respectively
 - There was a higher proportion of non-frail (42%) vs frail (17%) patients with ≥VGPR

Figure 5: Best response* to IRd therapy (A) overall and by LoT and (B) by frailty



*Best response recorded after IRd onset and before, or at the end of, IRd therapy. Response data missing for 160 patients overall; 47, 66, and 47 for patients receiving IRd as 2nd, 3rd, and 4th LoT, respectively; 69 non-frail and 44 frail patients. Percentages may not sum due to rounding. ORR = PR + VGPR + CR + sCR. CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease

Safety

- Dose reductions and discontinuations and the most common AEs leading to ixazomib dose reduction and discontinuation in INSIGHT MM and UVEA-IXA are shown in **Table 2**
- Rates of AEs and serious AEs and most common AEs reported in REMIX are shown in **Table 3**

Table 2: Dose reductions and discontinuations due to AEs in INSIGHT MM and UVEA-IXA		INSIGHT MM (n=181)	UVEA-IXA (n=195)
Dose reductions, %	Ixazomib	13.8	9.2
	Lenalidomide	19.3	9.2
	Dexamethasone	11.6	1.0
	Ixazomib	29.8	16.9
Discontinuations, %	Lenalidomide	22.7	14.9
	Dexamethasone	18.2	9.7
	Ixazomib	29.8	16.9
	Lenalidomide	22.7	14.9
Most common* AEs leading to ixazomib dose reduction, %	n=25		
	Diarrhea	20.0	38.9
	Peripheral neuropathy	24.0	24.0
	Thrombocytopenia	20.0	11.1
Most common* AEs leading to ixazomib discontinuation, %	n=54		
	Thrombocytopenia	18.5	24.2
	Diarrhea	9.3	18.2
	Infections and infestations	14.8	6.1 [†]
Most common [‡] serious AEs, %	n=33		
	Peripheral neuropathy	7.4	12.1
	Fatigue	11.1	0
	Fatigue	11.1	0

*Occurring in >10% of patients with dose reduction or discontinuation in at least one study. [†]Nausea only. [‡]Infection only

Table 3: REMIX safety summary*		REMIX (n=188)
AEs, %		64.9
Serious AEs, %		37.8
Most common [†] AEs, %		
Diarrhea		14.9
Thrombocytopenia		14.4
Most common [‡] serious AEs, %		
Plasma cell myeloma		5.3
Thrombocytopenia		5.3

*Safety data for ixazomib only. [†]Occurring in >10% of patients for AEs and >5% for serious AEs

Conclusions

- These findings from INSURE, an analysis of a large, global, pooled dataset of 564 patients, show that the effectiveness of IRd in routine clinical practice (median PFS 19.9 months, ORR 65%) is consistent with the efficacy of IRd observed in the registrational TOURMALINE-MM1 trial (median PFS 20.6 months, ORR 78%)² with no new safety concerns
- Our results suggest a greater benefit of treatment with IRd in earlier versus later lines, consistent with reports from previous, smaller real-world studies of IRd in RRMM patients^{8,9}
- Assessment of TTNT (a real-world proxy for PFS) and PFS was feasible in INSURE with similar median values overall and similar trends by LoT; this supports the robustness of the observed effectiveness of IRd
- In addition, this analysis provides important insights on the effectiveness of IRd in frail patients, helping to increase the understanding of achievable outcomes in this subpopulation; future analyses should focus on further evaluation of the effectiveness of therapies in frail and non-frail MM patients in the real world
- This study may be impacted by typical limitations inherent to real-world studies, including selection and confounding biases, missing data, and inconsistent data reporting across study sites