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

REAL-WORLD EFFICACY AND TOLERABILITY OF IXAZOMIB IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA: INTERIM ANALYSIS OF THE REMIX STUDY

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INTRODUCTION

- Ixazomib is the first oral proteasome inhibitor.[1]
- It was approved in Europe in November 2016 for the treatment of adult patients with MM who have received at least one prior therapy, based on significant positive results of the pivotal, phase III, TOURMALINE-MM1 clinical trial in favor of ixazomib in combination with lenalidomide and dexamethasone (IRd) versus placebo-Rd.[2,3]
- Ixazomib became available in France from **May 2017 via a compassionate use program (CUP) and from October 2018 via classical market access (non-CUP).**
- In addition to pivotal clinical trials, real-world evidence is required to evaluate effectiveness and safety of MM treatment in routine clinical practice, as results can differ mainly because of patient selection.
- Here, we present the first interim analysis of the REMIX study **describing effectiveness and safety of patients enrolled in the study during the CUP.**

METHODS

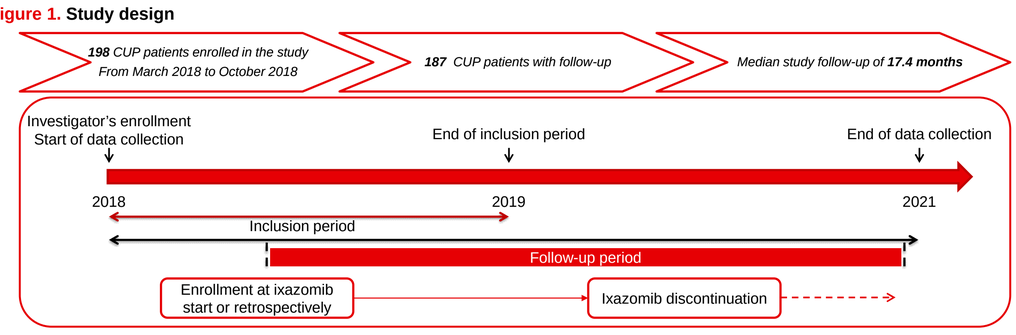
Objectives

- REMIX aims to assess:
  - Primary endpoint – **IRd effectiveness (median PFS)**
  - Secondary endpoints – **12/24-month OS rate and safety** in patients with RRMM initiating ixazomib concomitantly to Rd.

Design

- The study design is shown in **Figure 1.**
- REMIX is a non-interventional, multicenter, prospective study conducted in 59 French sites (public or private practitioners) in patients with RRMM, initiating IRd in second or later line of treatment (patients who started lenalidomide more than 6 weeks before ixazomib were excluded).
- After inclusion, patients were assessed every 3 months for the first 24 months and then every 6 months thereafter, as per standard practice.
- This interim analysis was conducted in patients receiving ixazomib concomitantly to Rd via the CUP.
  - Median PFS, OS rates and tolerability of IRd were assessed in the overall CUP cohort and by age, frailty (as defined by Facon, T et al.[4]) and line of treatment.

Figure 1. Study design



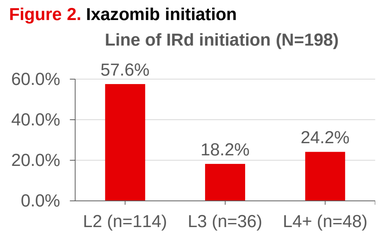
RESULTS

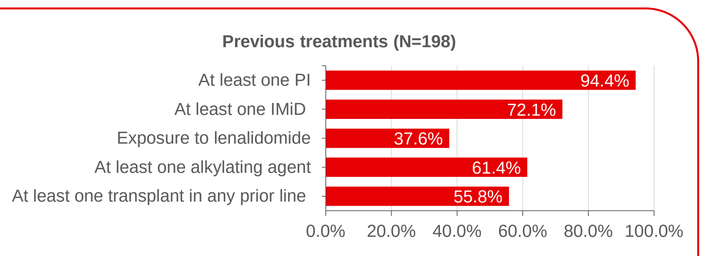
Table 1. Baseline CUP patients' demographics and characteristics

		CUP patients N	CUP patients n (%) unless stated
Age	Median, years (range)	198	69 (36–91)
	≥75		52 (26.3)
Sex	Male	198	92 (46.5)
ECOG PS assessment	0	98	29 (32.6)
	1		42 (47.2)
	≥2		18 (20.2)
Frailty*	Yes	142	64 (45.1)
	No		78 (54.9)
Renal failure	CrCl ≤30 mL/min	157	11 (7.0)
Comorbidities†	≥1	198	127 (64.1)
Time since initial diagnosis‡	Median, years (range)	196	4 (0–33)
High cytogenetics risk	Yes	198	26 (13.1)
	No		90 (45.5)
	Unavailable		82 (41.4)

*Frailty as defined by Facon T et al.[4]
†Corresponds to all comorbidities listed in the Charlson index plus an item for 'other' comorbidities.
‡Duration between date of initial MM diagnosis and date of patients' enrollment.

Figure 2. Ixazomib initiation





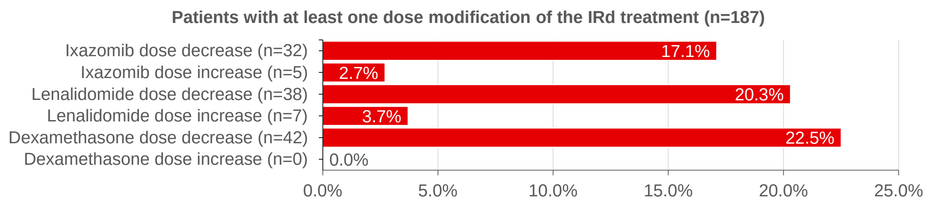
Reasons* for IRd initiation:
- Biochemical relapse† (37.4%)
- Clinical ± biochemical relapse† (44.9%)
- Other (17.7%)

Lenalidomide exposure prior to IRd initiation:
- Mainly in L3 or L4+ patients (78.3%, 65/84) versus L2 patients (7.9%, 9/114)
- Median washout period‡ between prior lenalidomide discontinuation and IRd start: **18 months** (95%CI 17.6–29.6)

*Multiple responses were possible.
†According to investigator judgement.
‡Washout period: period without lenalidomide, from date of prior lenalidomide end to date of IRd start.

- A median of **14 IRd cycles** were received.
- Ixazomib was initiated at a dose **of 4 mg in 90.7% patients**.
- Ixazomib was administered with lenalidomide 25 mg (65.4%), 15 mg (16.2%), 10 mg (9.4%) or other (8.9%).

Figure 3. Ixazomib treatment



- Median PFS for IRd was **19.2 months (95%CI 13.3–21.9)** in the 187 followed-up CUP patients (**Figure 4**).
- Median PFS for IRd in TOURMALINE-MM1 was **20.6 months**.[3]

Figure 4. PFS for IRd in CUP patients

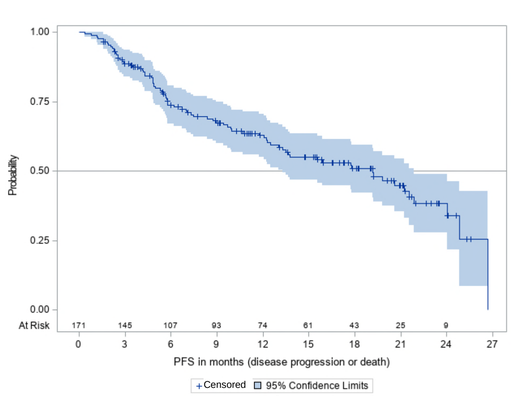
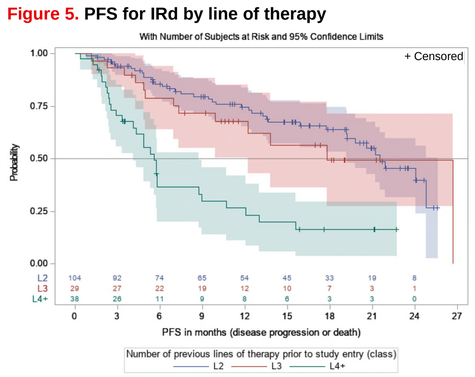


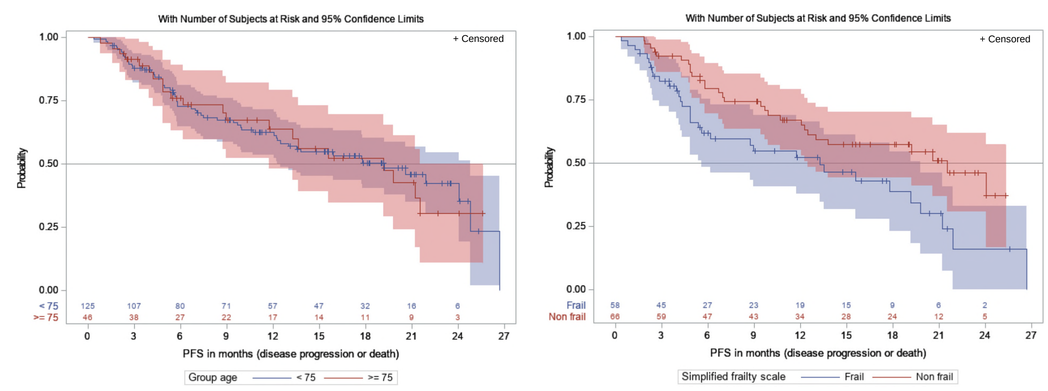
Figure 5. PFS for IRd by line of therapy



		n	IRd median PFS months (95% CI)
Line of treatment	L2	104	21.5 (19.–not reached)
	L3	29	17.8 (12.2–26.7)
	L4+	38	5.6 (4.1–8.8)

RESULTS (CONTINUED)

Figure 6. PFS for IRd by age and frailty



		n	Median PFS months (95% CI)
Age	<75 years	125	19.2 (12.3–24.8)
	≥75 years	46	19.2 (11.7–21.5)
Frailty	Yes	58	13.3 (5.6–19.8)
	No	66	21.5 (12.5–not reached)

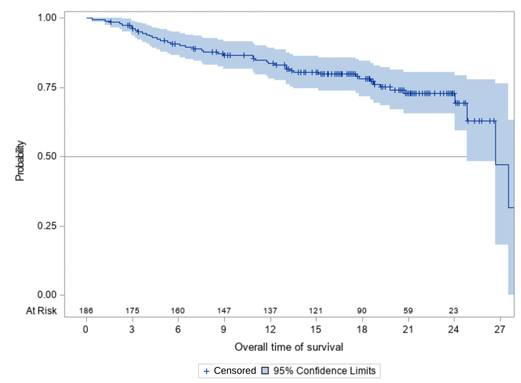
- 166 patients had at least one response assessment (**Table 2**).
  - The ORR was 66.4% in patients aged <75 years and 70.5% in patients aged ≥75 years.
- The median OS has not been reached (**Figure 7**).
  - 12-month OS rate was 83.6% (95%CI 78–89).
  - 24-month OS rate was 72.9% (95%CI 65–80).
- Death due to any cause was reported in **47/198** patients during the study.
- Death occurred after ixazomib discontinuation in 36 cases with a median time of **95 days** between discontinuation and death.

Table 2. Response rate

Best response to treatment, n (%)	All patients (n=166)*
ORR	112 (67.5%)
≥VGPR	67 (40.4%)
CR	17 (10.2%)
VGPR	58 (34.9%)
PR	58 (34.9%)

*Physicians could check more than one response category on the electronic case report form for an individual patient. The numbers of the individual response categories may not therefore sum to the ORR or rate of ≥VGPR.

Figure 7. Overall survival for IRd CUP patients



- Overall, **49.2% of the 187 CUP patients with at least one follow up had discontinued ixazomib** (n=92), with 12.8% of patients discontinuing due to AEs (n=24).
  - The median age of patients discontinuing was 70 years.
- SAEs were reported in 34.8% of patients (n=69), including 14 (7.1%) of them with SAEs considered to be related to ixazomib.
- Most frequent AEs (>10%) were diarrhea (34.0%), thrombocytopenia (27.8%), asthenia (17.5%), nausea (15.5%), anemia (14.3%), neutropenia (13.4), and vomiting (12.4%).

Table 3. Safety

	N	CUP patients, n (%)
At least one AE	198	122 (61.6)
At least one SAE	198	69 (34.8)
At least one ixazomib-related* AE	198	64 (32.3)
At least one ixazomib-related* SAE	198	14 (7.1)

*A causal relationship between AE and ixazomib was reported by investigator, whether ixazomib was discontinued or not.

CONCLUSION

- Few real-world evidence data have been published for IRd use in Europe.
- In France under the CUP program, IRd was prescribed to elderly patients primarily as second- or third-line therapy using the standard ixazomib dose of 4 mg.
- Estimation of median PFS in this first interim analysis was consistent with TOURMALINE-MM1[3] (19.2 vs 20.6 months) although CUP patients in REMIX were overall older, more frail and more frequently treated in advanced lines (24% of L4+ in REMIX vs 11% of L4 in TOURMALINE-MM1).
- A high proportion of patients were previously treated with lenalidomide prior to initiating IRd (38%), especially those patients who had received 2+ lines of treatment (78%), compared to 12% in TOURMALINE-MM1.
- Reported adverse events were consistent with the established ixazomib safety profile.

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ABBREVIATIONS

AEs, adverse events; CI, confidence interval; CR, complete response, CrCl, creatinine clearance; CUP, Compassionate Use Program; ECOG, Eastern Clinical Oncology Group Performance Status; IMiD, immunomodulatory agent; IRd, ixazomib-lenalidomide-dexamethasone; L, line of therapy; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; Rd, lenalidomide-dexamethasone; SAEs, serious AEs; VGPR, very good partial response.

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