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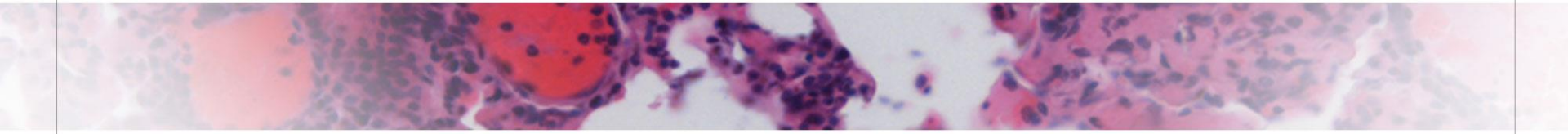

The Phase 3 TOURMALINE-MM2 Trial: Oral Ixazomib, Lenalidomide, and Dexamethasone vs Placebo-Rd for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

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Introduction

- The transplant-ineligible NDMM patient population is diverse, ranging from fit 70-year-olds to elderly/frail patients with poor performance status, so treatment must be adapted to individual patient settings.

- Use of PIs in a continuous fashion or to higher cumulative doses leads to improved long-term outcomes;[1-3] however, long-term administration of injectable PIs may be challenging due to limitations in terms of tolerability and treatment burden.

- An all-oral PI-Rd triplet may be useful for patients who prefer not to or cannot travel to clinic frequently.

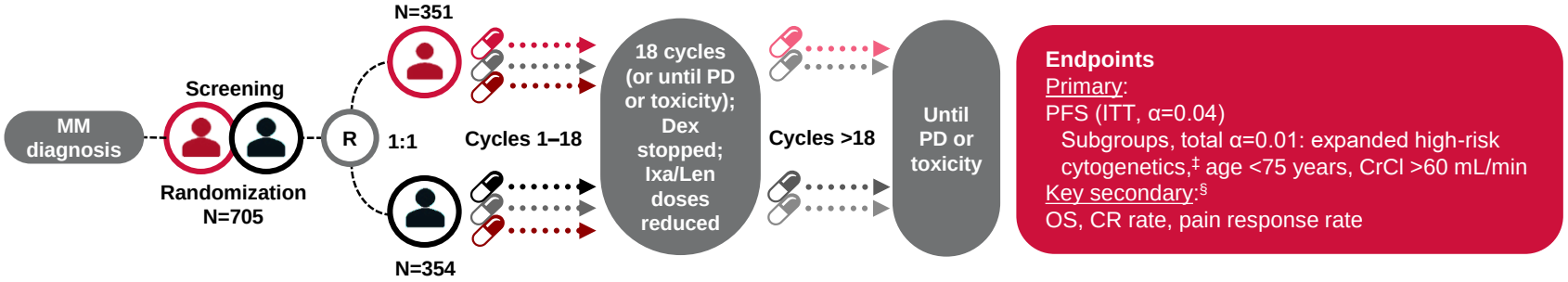
- Ixazomib, the first oral PI, is suitable for continuous dosing, with predictable, manageable toxicities.[4]

NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; Rd, lenalidomide-dexamethasone.

1. Jimenez-Zepeda VH, et al. Ann Hematol 2017;96:431–9.
2. Mateos MV, et al. Am J Hematol 2015;90:314–9.
3. Palumbo A, et al. J Clin Oncol 2015;33:3459–66.
4. Moreau P, et al. N Engl J Med 2016;374:1621–34.

TOURMALINE-MM2: international, randomized, double-blind, multicenter, phase 3 study of ixazomib-Rd vs placebo-Rd in transplant-ineligible NDMM patients

Inclusion criteria	Exclusion criteria
Adult NDMM patients with measurable disease diagnosed per IMWG criteria	Prior treatment for MM
Eligible for Rd treatment and ineligible for ASCT	Current uncontrolled cardiovascular conditions
ECOG PS of 0–2	Inability or unwillingness to receive thromboembolism prophylaxis
Adequate hematologic and hepatic function	Localized radiotherapy, major surgery, or serious infection within 14 days prior to randomization
Calculated CrCl ≥30 mL/min	Peripheral neuropathy of grade ≥2 or grade 1 with pain



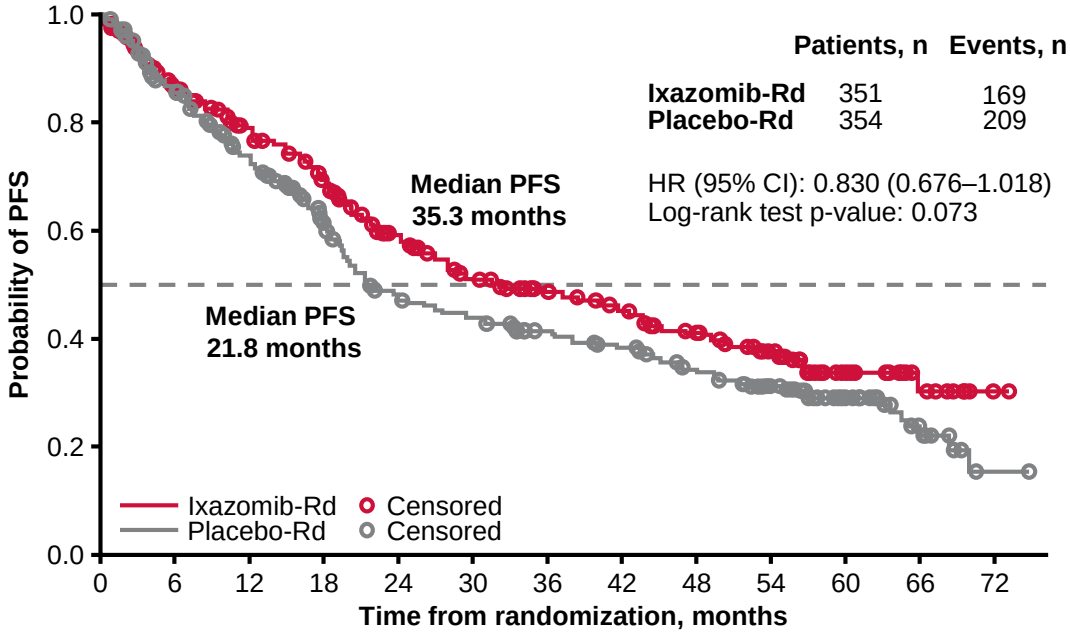
*Patients with renal impairment; †Patients aged >75 years; ‡Includes t(4;14), t(14;16), del(17p), amp(1q21); §Additional secondary endpoints included TTP and safety.
ASCT, autologous stem cell transplant; BPI-SF, Brief Pain Inventory-Short Form; CR, complete response; CrCl, creatinine clearance; Dex, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; ISS, International Staging System; ITT, intent-to-treat; Ixa, ixazomib; Len, lenalidomide; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomization; TTP, time to progression.

Patient demographics and disease characteristics were well balanced between arms

Characteristic*	Ixazomib-Rd (N=351)	Placebo-Rd (N=354)
Median age (range), years	73 (48–90)	74 (48–88)
Age <75 / ≥75 years, %	57 / 43	56 / 44
Male, %	49	51
Race, White / Asian / Other,† %	83 / 13 / 5	81 / 15 / 5
ECOG PS, 0 / 1 / 2, %	31 / 52 / 17	30 / 56 / 14
ISS stage at study entry, I / II / III, %	49 / 35 / 16	43 / 40 / 17
BPI-SF worst pain score <4 / ≥4 at screening, %	46 / 54	46 / 54
Expanded high-risk cytogenetics, % [t(4;14), t(14;16), del(17p), amp(1q21)]	38	41
CrCl >60 mL/min, %	58	58
Elevated LDH, %	12	9
Extramedullary disease at study entry, %	3	3

*Totals may not sum to 100% due to rounding; †Other includes Black or African American, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, and Other.
LDH, lactate dehydrogenase.

Clinically meaningful PFS benefit with ixazomib-Rd vs placebo-Rd



Patients at risk, n

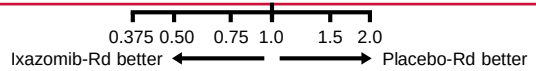
Ixazomib-Rd	351	261	220	187	147	120	107	96	81	64	28	10	1
Placebo-Rd	354	273	225	174	132	121	106	98	82	63	35	16	1

Data cut-off: December 2, 2019.
CI, confidence interval; DOT, duration of treatment; HR, hazard ratio.

- Median follow-up for PFS: 53.3 vs 55.8 months in ixazomib-Rd and placebo-Rd arms, respectively.
- A 13.5-month PFS benefit was seen with ixazomib-Rd vs placebo-Rd, although it was not statistically significant.
- Median DOT: 20 cycles in each arm.
  - 54% of patients in the ixazomib-Rd arm and 54% in the placebo-Rd arm entered cycle 19.
  - Relative dose intensity for all agents was similar between arms.

PFS benefit observed in pre-specified subgroups, particularly patients aged <75 years, with ISS stage III MM, and with CrCI ≤60 mL/min

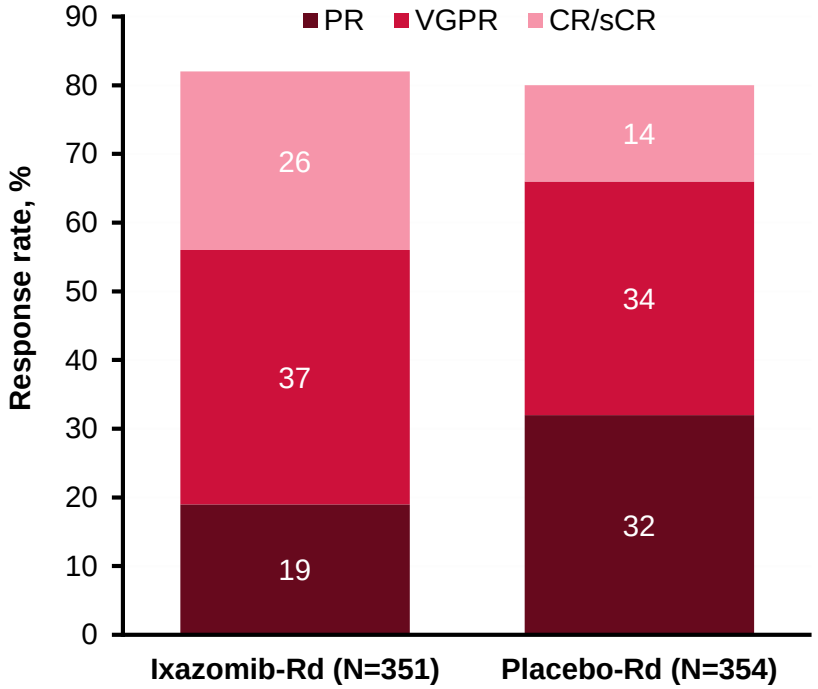
Subgroup	Events, n/N		Median PFS, months		HR	95% CI
	Ixazomib-Rd	Placebo-Rd	Ixazomib-Rd	Placebo-Rd		
All (N=705)	169/351	209/354	35.3	21.8	0.830	0.676–1.018
Age						
<75 years (n=397)	94/198	117/199	41.4	26.2	0.799	0.608–1.049
≥75 years (n=308)	75/153	92/155	27.9	20.5	0.871	0.640–1.186
ISS stage at screening						
I or II (n=582)	136/292	162/290	40.9	27.5	0.855	0.680–1.075
III (n=123)	33/59	47/64	27.9	16.1	0.736	0.466–1.163
BPI-SF worst pain score						
<4 (n=326)	73/162	86/164	41.4	30.9	0.829	0.605–1.136
≥4 (n=379)	96/189	123/190	25.8	19.4	0.830	0.634–1.086
ISS stage at study entry						
I (n=324)	78/171	77/153	43.5	37.9	0.904	0.658–1.242
II (n=265)	62/123	88/142	27.9	19.8	0.825	0.592–1.149
III (n=115)	29/56	44/59	27.9	17.8	0.786	0.485–1.276
Cytogenetics risk group*						
Expanded high risk (n=280)	80/134	104/146	23.8	18.0	0.690	0.506–0.941
Corresponding std risk (n=294)	59/155	69/139	56.3	46.8	0.821	0.577–1.168
Unclassifiable (n=131)	30/62	36/69	27.9	33.1	1.165	0.686–1.978
Baseline CrCI						
≤60 mL/min (n=298)	65/148	100/150	40.0	19.4	0.625	0.450–0.869
>60 mL/min (n=407)	104/203	109/204	31.8	30.8	0.992	0.754–1.305



*Corresponding std risk category includes normal results and all abnormalities other than expanded high risk; unclassifiable is defined as patients who cannot be categorized to expanded high risk or corresponding std risk group because of missing, unknown or indeterminate cytogenetic results.
std, standard.

- Clinically meaningful, obvious positive trend for patients with expanded high-risk cytogenetic abnormalities receiving ixazomib-Rd vs placebo-Rd (p=0.019).

Higher ≥VGPR and CR rates with ixazomib-Rd vs placebo-Rd, and improved TTR and DOR

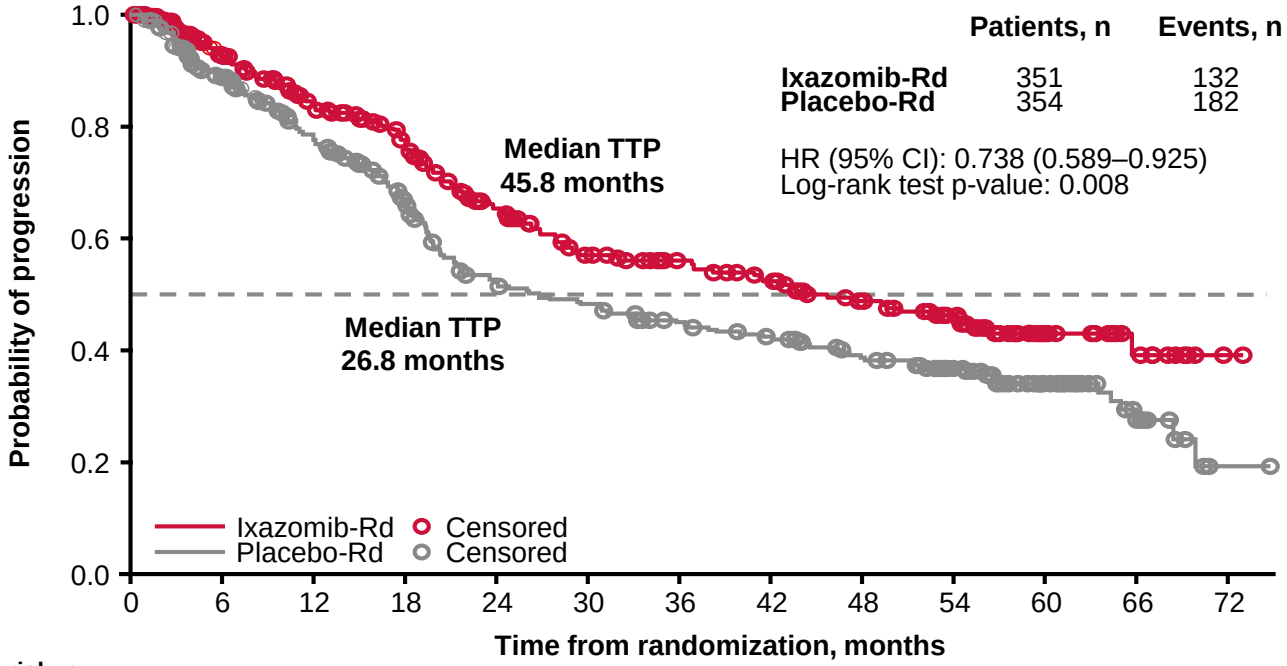


	Ixazomib-Rd (N=351)	Placebo-Rd (N=354)	OR (95% CI)	p-value
ORR	82.1%	79.7%	1.16 (0.79–1.70)	0.436
CR/sCR rate	25.6%	14.1%	2.10 (1.43–3.09)	<0.001
≥VGPR rate	63.0%	47.7%	1.87 (1.38–2.53)	<0.001

	Ixazomib-Rd	Placebo-Rd
TTR	N=351	N=354
Median, months (95% CI)	1.0 (0.99–1.08)	1.9 (1.15–1.87)
	HR 1.402 (95% CI, 1.185–1.659), p<0.001	
DOR	n=287	n=281
Median, months (95% CI)	50.6 (39.98–NE)	37.5 (25.69–50.27)
Events (relapse/progression/death), n (%)	112 (39.0)	141 (50.2)

DOR, duration of response; NE, not estimable; OR, odds ratio; ORR, overall response rate; sCR, stringent complete response; TTR, time to response; VGPR, very good partial response.

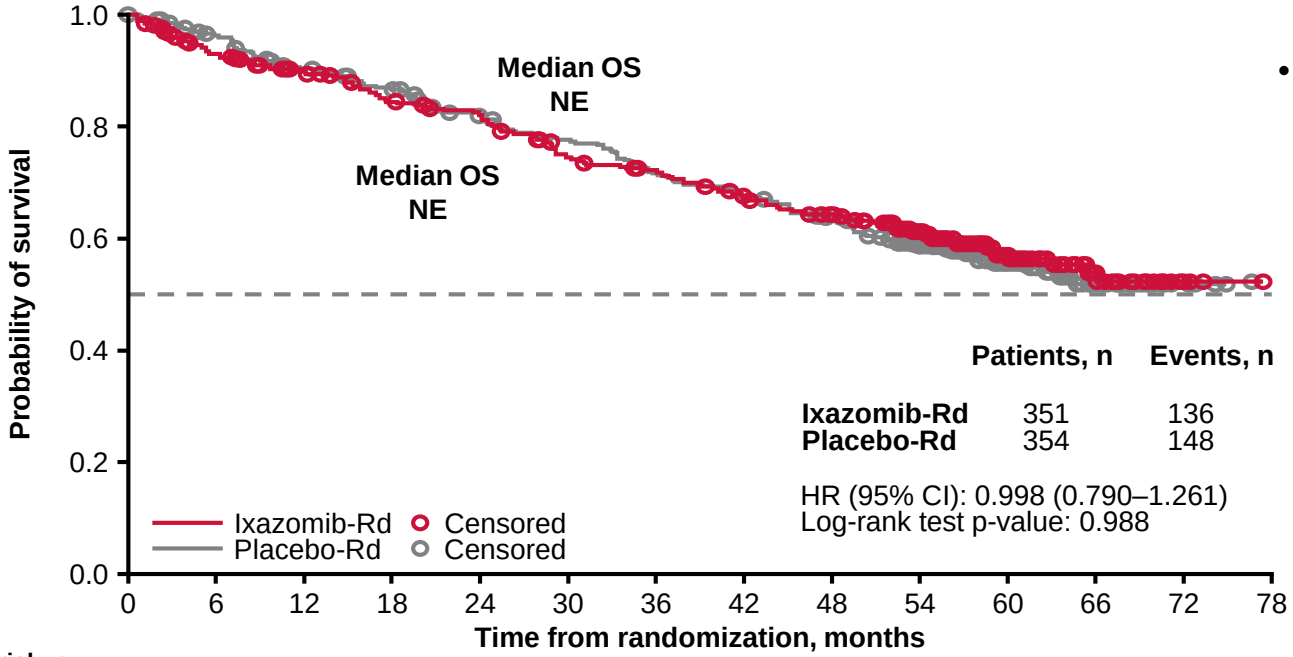
Longer TTP with ixazomib-Rd vs placebo-Rd



Patients at risk, n

Ixazomib-Rd	351	260	218	187	147	119	107	96	80	64	28	10	1
Placebo-Rd	354	272	224	174	132	121	106	97	82	63	35	16	1

Median OS not reached in either arm

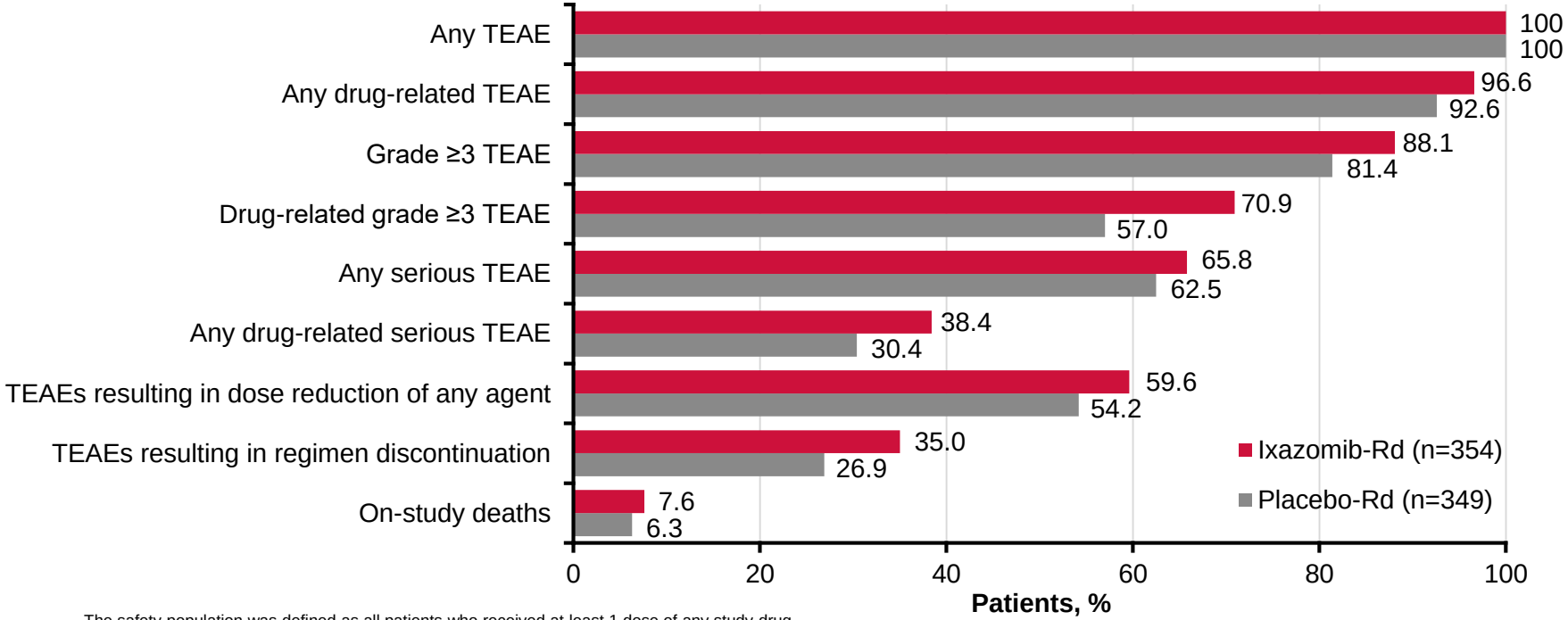


Patients at risk, n

Ixazomib-Rd	351	316	296	274	262	235	225	208	194	151	79	36	4
Placebo-Rd	354	334	310	294	271	256	236	222	204	158	83	43	7

- Median follow-up for OS: ~58 months.

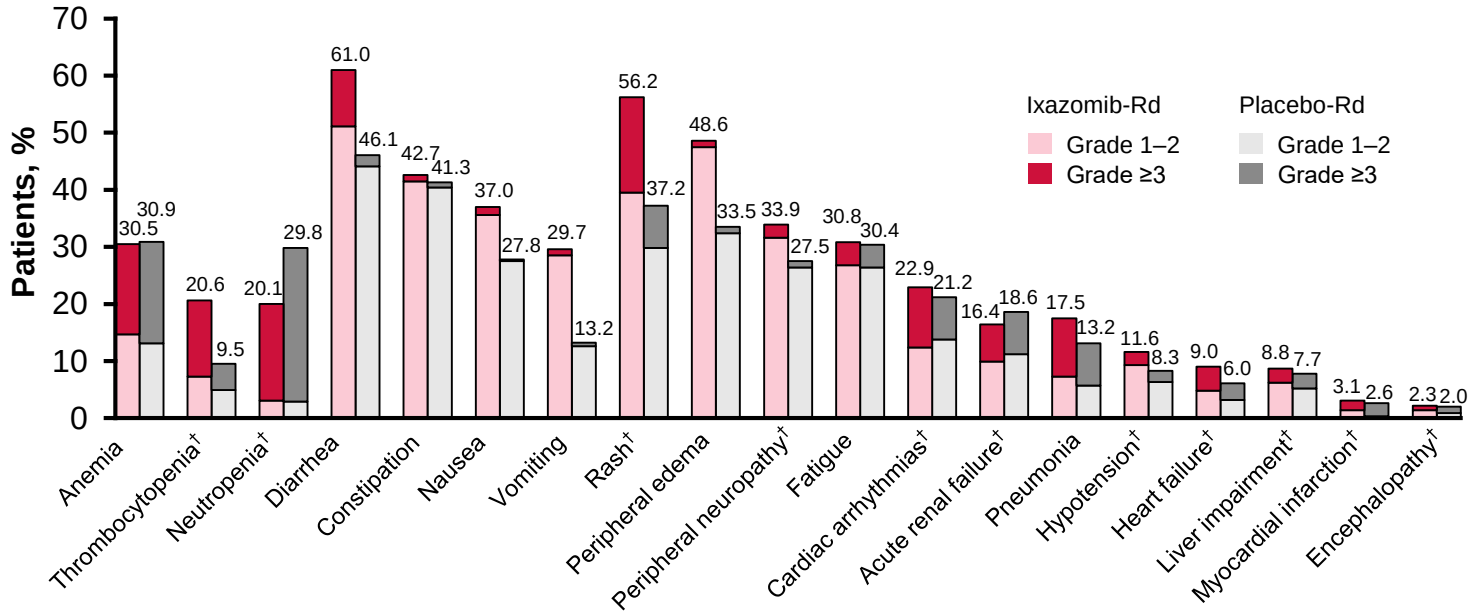
Safety profile: TEAEs were mostly grade 1/2



The safety population was defined as all patients who received at least 1 dose of any study drug.
Patients were analyzed according to the treatment actually received.
TEAE, treatment-emergent adverse event.

Common TEAEs were consistent with the toxicity profile of ixazomib/ixazomib-Rd

- The most common TEAEs* and TEAEs of clinical importance in the ixazomib-Rd arm were diarrhea, rash, peripheral edema, constipation, and nausea.



*Any grade reported in ≥30% and grade ≥3 reported in ≥10% of patients on the ixazomib-Rd arm;
†TEAEs based on composite/high-level terms incorporating multiple preferred terms.

Conclusions

- Addition of ixazomib to Rd in patients with NDMM led to a clinically meaningful PFS benefit, with a 13.5-month improvement in the median in this elderly, transplant-ineligible patient population, although this did not reach statistical significance.
- A clinically meaningful benefit was also observed in TTP and in CR rate, with deeper responses in the ixazomib-Rd arm vs the placebo-Rd arm.
- Consistent with results from the TOURMALINE-MM1 trial,[1,2] the all-oral ixazomib-Rd triplet improved the poor PFS associated with expanded high-risk cytogenetics vs placebo-Rd.
- Safety findings were generally consistent with the well-characterized, tolerable, and manageable toxicity profile of ixazomib/ixazomib-Rd.[1,3,4]
- Ixazomib-Rd is a feasible treatment option for certain transplant-ineligible patients with NDMM who could benefit from an all-oral triplet combination.

1. Moreau P, et al. N Engl J Med 2016;374:1621–34.
2. Avet-Loiseau H, et al. Blood 2017;130:2610–18.
3. Dimopoulos MA, et al. Lancet 2019;393:253–64.
4. Kumar S, et al. Br J Haematol 2017;178:571–82.

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Off-label disclosure:

- This presentation contains information about off-label use of ixazomib

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