Takeda | ONCOLOGY

REAL-WORLD EFFECTIVENESS AND TOLERABILITY OF NINLARO® (ixazomib) + Rd IN RRMM: REMIX MULTICENTER STUDY

Rd, lenalidomide + dexamethasone; RRMM, relapsed/refractory multiple myeloma.

INDICATION AND USAGE

Indication: NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Limitations of Use: NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia,** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14–21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

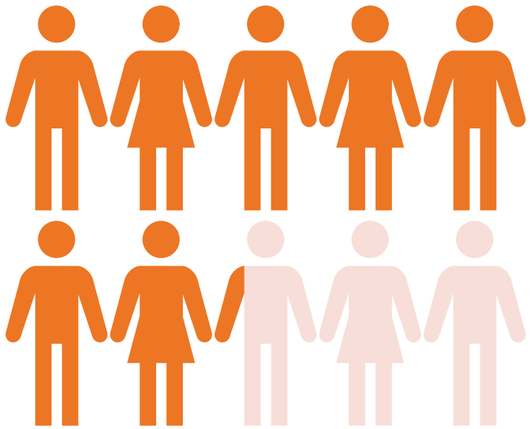
RCTs PROVIDE ROBUST EVIDENCE OF THE SAFETY PROFILE AND EFFICACY OF THERAPEUTIC AGENTS[1]

RCTs REMAIN THE GOLD STANDARD FOR THERAPEUTIC EVALUATION AND REGULATORY DECISION-MAKING[1,2]

VALUE OF RCTs

By utilizing randomization and strict patient inclusion and exclusion criteria, investigators can minimize bias and the influence of confounding variables to gather robust evidence of the safety and efficacy of medical interventions.[1]

LIMITATIONS OF RCTs



UP TO 72%

OF REAL-WORLD PATIENTS WITH RRMM DO NOT MEET THE ELIGIBILITY CRITERIA FOR CLINICAL TRIALS*[3]

Due to the stringent eligibility criteria, certain MM patient populations commonly seen in clinical practice are typically under-represented in clinical trials, including:[4,5]

- Patients with comorbidities[6] or advanced disease[6,7]
- Ethnic or racial minorities[6–9]
- Elderly, frail patients[6,7]

*Range: 47.9%-72.3%. Based on US EHR data from > 140,00 providers, 600 hospitals and 6,500 clinics. RRMM patients included received Rd (N=788) or Vd (N=447) in LOT 2–4. [control arm for the RCTs evaluated]. Patients not meeting the eligibility criteria of >=1 of the 6 hallmark RCTs identified were considered to be ineligible (>50% of patients did not meet the eligibility criteria for ≥4 of the 6 hallmark RCTs).
EHR, electronic health record; LOT, line of treatment; MM, multiple myeloma; RCT, randomized controlled trial; Rd, lenalidomide + dexamthasone; RRMM, relapsed/refractory MM; Vd, bortezomib + dexamethasone.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Gastrointestinal Toxicities,** including diarrhea, constipation, nausea and vomiting were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

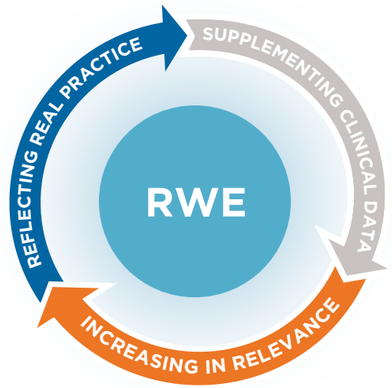
UNDERSTANDING EVOLVING TREATMENT PRACTICES AND THERAPEUTIC OUTCOMES IN THE REAL-WORLD SETTING[10]

RWE IS CLINICAL EVIDENCE REGARDING THE USE AND POTENTIAL BENEFITS OR RISKS OF A MEDICAL PRODUCT, DERIVED FROM ANALYSIS OF RWD[11–14]

VALUE OF RWE

Real-world studies have become increasingly important in providing essential information that informs payers, clinicians and patients on the effectiveness and safety of drugs in large heterogenous populations in real-world practice settings.[1]

By collecting data on patient populations typically under-represented in RCTs, RWE can provide additional insights into a wide range of health outcomes for people living with MM.[1,15]



LIMITATIONS OF RWE

Real-world analyses are often non-randomized, observational, retrospective or prospective studies that may have unobserved confounding and treatment selection biases as well as other limitations that should be considered, when interpreting the data and when comparing results with clinical trials.[1]

Observational, retrospective and prospective analyses are not intended for direct comparison with clinical trials. Outcomes should be interpreted with caution because of small sample size, limited follow-up and limited maturity of data.

In addition, each real-world study should be examined individually to understand any study-specific limitations[1]

RWE CAN BE USED TO COMPLEMENT RCT DATA BY PROVIDING INSIGHTS INTO PATIENT CHARACTERISTICS, TREATMENT PRACTICE AND PRACTICAL CONSIDERATIONS IN THE REAL-WORLD SETTING[1,10,16,17]

MM, multiple myeloma; RCT, randomized controlled trial; RWD, real-world data; RWE, real-world evidence.

IMPORTANT SAFETY INFORMATION (cont'd)

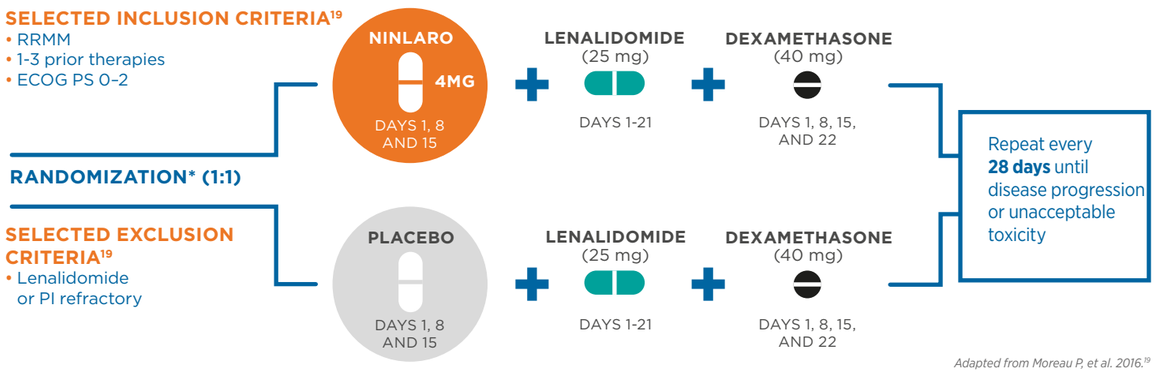
WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Neuropathy** was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.

NINLARO + Rd PROLONGED PFS VS PLACEBO + Rd[18,19]

STUDY DESIGN[18,19]

TOURMALINE-MM1 was a global, Phase 3, randomized (1:1), double-blind, placebo-controlled trial that evaluated the safety and efficacy of NINLARO + Rd vs placebo + Rd until disease progression or unacceptable toxicity in 722 patients with RRMM.[18,19]



Adapted from Moreau P, et al. 2016.[19]

PRIMARY ENDPOINT[18,19]
- PFS according to 2011 IMWG criteria
- Assessed every 4 weeks until disease progression by a blinded irc (based on central laboratory results)

KEY SECONDARY ENDPOINTS[19]
- OS
- OS in del(17p)

OTHER SECONDARY ENDPOINTS[19]
- ORR
- PFS in patients with high-risk cytogenics*
- Change in global health status
- CR and VGPR rate
- DOR
- Safety

*Defined as patients with del(17p), t(4;14), and/or t(14;16).[19]

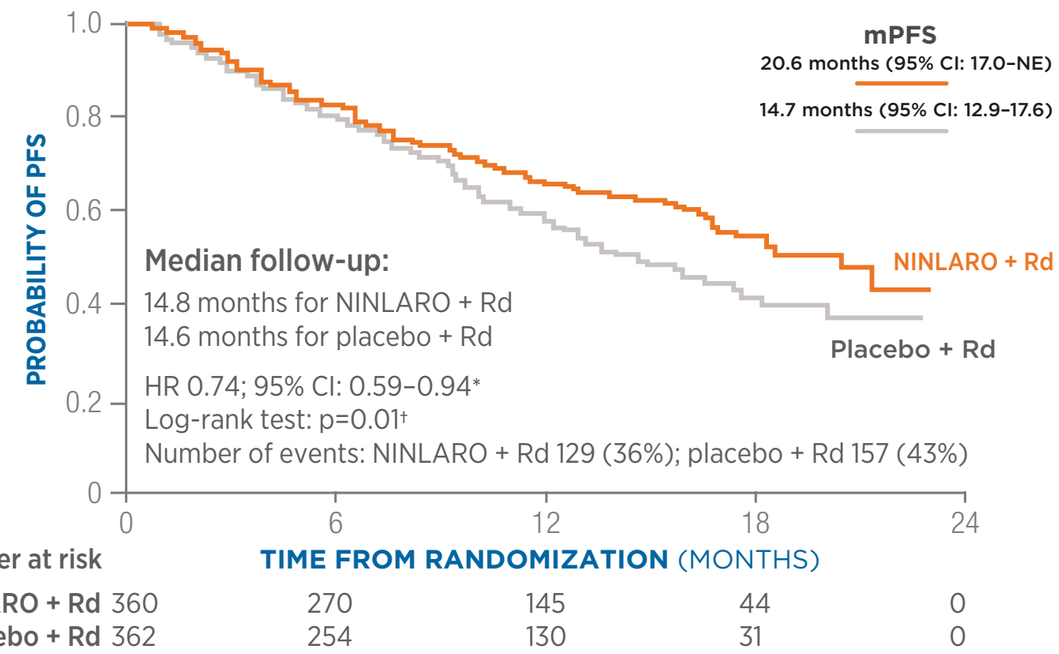
CR, complete response; DOR, duration of response; IMWG, International Myeloma Working Group; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Edema** was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.

PRIMARY PFS ANALYSIS[18,19]



Adapted from Moreau P, et al. 2016.[19]

FINAL OS ANALYSIS[18]

With a median relative follow-up of ~85 months, median OS in the ITT population was 53.6 months for patients treated with NINLARO + Rd and 51.6 months for patients treated with placebo + Rd (HR=0.94 [95% CI: 0.78–1.13])[18]

*Based on the stratified Cox's proportional hazard regression model.[18]
†Based on the stratified log-rank test.[18]
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median PFS; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone.

IMPORTANT SAFETY INFORMATION (cont'd)

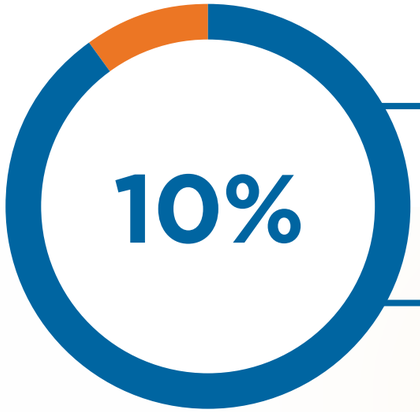
WARNINGS AND PRECAUTIONS (cont'd)

- **Cutaneous Reactions.** Stevens-Johnson syndrome and toxic epidermal necrolysis, including fatal cases, have been reported with NINLARO. If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, discontinue NINLARO and manage as clinically indicated. Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

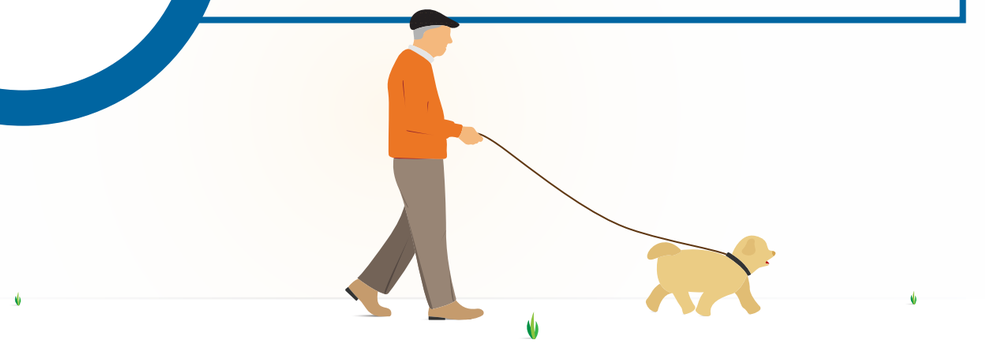
NINLARO + Rd DEMONSTRATED A SAFETY PROFILE APPROPRIATE FOR LONG-TERM* TREATMENT [18,20–23]

FINAL SAFETY ANALYSIS†[18]

THE MAJORITY OF PATIENTS DID NOT EXPERIENCE PERMANENT DISCONTINUATION OF NINLARO DUE TO ARs[18]



After a median follow-up of ~85 months, permanent discontinuation of NINLARO due to an AR occurred in 10% of patients[18,20]



*Used herein to refer to treatment until disease progression or unacceptable toxicity.[18]

†Data cut-off for the final analysis: 28 September 2020.[20]

AR, adverse reaction; Rd, lenalidomide + dexamethasone.

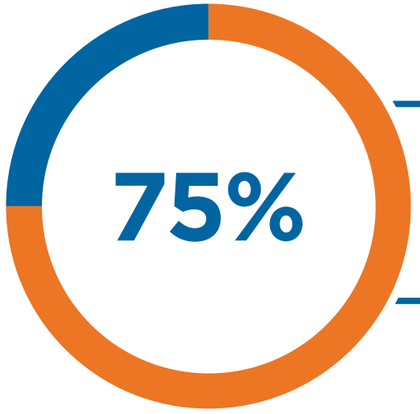
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Thrombotic Microangiopathy** has been reported with NINLARO. Fatal cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

THE MAJORITY OF PATIENTS CONTINUED AT THE STARTING DOSE OF NINLARO WITHOUT DOSE REDUCTION[21]

- The median relative dose intensity for NINLARO + Rd and placebo + Rd was high and similar between both arms: 97.8% and 100%, respectively[22]
- Relative dose intensity was calculated as: 100 x (total amount of dose taken) ÷ (total prescribed dose of treated cycles)*[22]



of patients (n=269/361) receiving NINLARO + Rd in TOURMALINE-MM1 continued on their starting NINLARO dose†[21]

SAFETY IN HIGH-RISK‡ PATIENT POPULATION

- The overall safety profiles in the high-risk and standard-risk cytogenetics patients in each group are consistent with data reported for the overall population[23]
- As seen in the overall population, in both high-risk and standard-risk cytogenetics patients, common AEs were primarily of Grade 1 or 2 severity and included diarrhea, constipation, neutropenia, and anemia[2]

*Total prescribed dose equals (dose prescribed at enrollment × number of prescribed doses per cycle × the number of treated cycles).[22]

†Median duration of exposure to NINLARO was 457 days (range: 1–2768 days).[24]

‡Defined as patients with del(17p), t(4;14), and/or t(14;16).[19]

AE, adverse event; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

NINLARO + Rd DEMONSTRATED A SAFETY PROFILE COMPARABLE WITH PLACEBO + Rd[18]

NON-HEMATOLOGIC ARs OCCURRING IN ≥5% OF PATIENTS WITH A ≥5% DIFFERENCE BETWEEN NINLARO + Rd AND PLACEBO + Rd IN TOURMALINE-MM1[18]

AR	NINLARO + Rd (n=361)			Placebo + Rd (n=359)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Diarrhea	52%	10%	0	43%	3%	0
Constipation	35%	<1%	0	28%	<1%	0
Peripheral neuropathies*	32%	2%	0	24%	2%	0
Nausea	32%	2%	0	23%	0	0
Peripheral edema	27%	2%	0	21%	1%	0
Back pain†	27%	<1%	0	24%	3%	0
Rash*	27%	3%	0	16%	2%	0
Upper respiratory tract infection†	27%	1%	0	23%	1%	0
Vomiting	26%	1%	0	13%	<1%	0
Bronchitis	22%	2%	0	17%	2%	<1%

Adapted from NINLARO (ixazomib). Prescribing Information. 2024.[18]

*Represents a pooling of preferred terms.[18]
†At the time of the final analysis, these ARs no longer met the criterion for a ≥5% difference between NINLARO + Rd and placebo + Rd.[18]
AR, adverse reaction; Rd, lenalidomide + dexamethasone.

Serious ARs reported in ≥2% of patients treated with NINLARO + Rd included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%)[18]

Incidence of thrombocytopenia in patients treated with NINLARO + Rd and placebo + Rd, respectively: Any grade, 85% vs 67%; Grades 3–4, 30% vs 14%[18]

Incidence of neutropenia in patients treated with NINLARO + Rd and placebo + Rd, respectively: Any grade, 74% vs 70%; Grades 3–4, 34% vs 37%[18]

NINLARO + Rd MAY OFFER EXTENDED* EFFICACY WITH SAFETY THAT IS SIMILAR TO A DOUBLET FOR PATIENTS WITH RRMM[18,19]

*Extended refers to NINLARO + Rd vs placebo + Rd.
AR, adverse reaction; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; RRMM, relapsed/refractory multiple myeloma.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

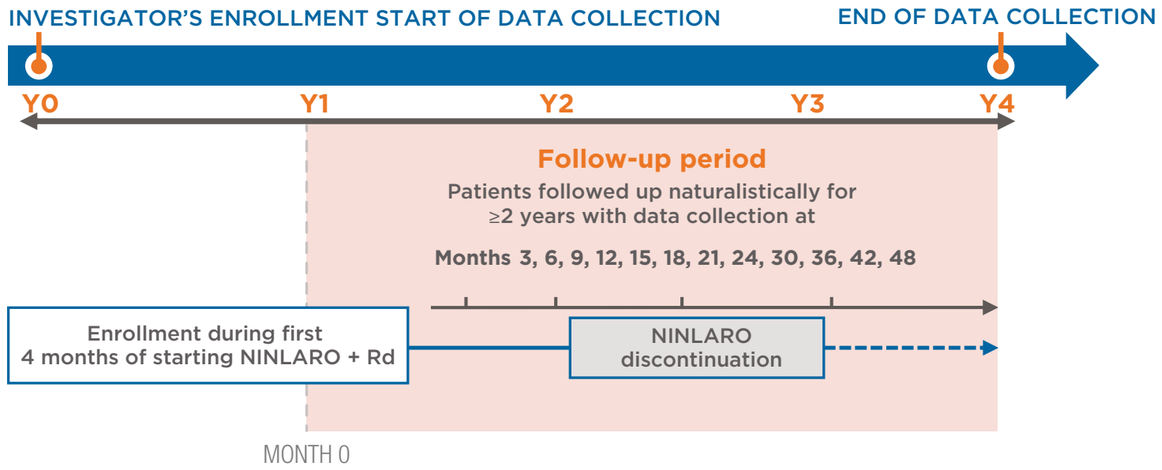
- **Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting:** In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

REAL-WORLD STUDY: NINLARO + Rd DEMONSTRATED EFFECTIVENESS AND A MANAGEABLE SAFETY PROFILE[25]

STUDY DESIGN[25]

REMIX was a multicenter, non-interventional, prospective study conducted at 60 sites in France that evaluated the effectiveness and safety of NINLARO + Rd in 376 real-world patients with RRMM who initiated the regimen in 2L or later:*

- The primary endpoint was mPFS† and PFS† rates assessed at 12, 18, 24 and 36 months
- Key secondary endpoints included OS,‡ DOR§ and RR (CR, VGPR, PR and SD)
- Safety endpoints included the incidence of AEs, SAEs, TRAEs and TRSAEs, and AEs leading to treatment discontinuation
- Patients who received lenalidomide more than 6 weeks before NINLARO + Rd were excluded from the study



Adapted from Macro M, et al. 2023.[25]

90.4% (n=340) of patients initiated NINLARO at the full dosage of **4 mg/day.** The remaining 36 patients were prescribed 3 mg/day or less[25]

*The study started in August 2017 when NINLARO + Rd became available in a compassionate program in France, and ended in October 2019.[25]
†PFS was defined as the time interval from the date of first dose of NINLARO to the date of disease progression or death, whichever occurred first.[25]
‡OS was defined as the time interval from the date of first dose of NINLARO to the date of death at Months 12, 18, 24, 36, 42 and 48.[25]
§DOR was defined as the time interval between the best response to treatment to progression or death, whichever occurred first among patients with at least a PR.[25]

2L, second-line; AE, adverse event; CR, complete response; DOR, duration of response; mPFS, median PFS; OS, overall survival; PFS, progression-free survival; PR, partial response; Rd, lenalidomide + dexamethasone; RR, response rate; RRMM, relapsed/refractory multiple myeloma; SAE, serious AE; SD, stable disease; TRAE, treatment-related AE; TRSAE, treatment-related SAE; VGPR, very good PR.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in the NINLARO regimen compared to placebo in combination with lenalidomide plus dexamethasone, respectively were thrombocytopenia (85%, 67%; pooled from adverse event and laboratory data), neutropenia (74%, 70%; pooled from adverse event and laboratory data), diarrhea (52%, 43%), constipation (35%, 28%), peripheral neuropathy (32%, 24%), nausea (32%, 23%), edema peripheral (27%, 21%), rash (27%, 16%), vomiting (26%, 13%), and bronchitis (22%, 17%). Serious adverse reactions reported in ≥2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%).

Real-world analyses are often non-randomized, observational, retrospective or prospective studies that may have unobserved confounding and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials.

Outcomes should be interpreted with caution because of small sample size, limited follow-up and limited maturity of data.

Observational, retrospective and prospective analyses are not intended for direct comparison with clinical trials.

Rd, lenalidomide + dexamethasone; Y, year.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

Avoid concomitant administration of NINLARO with strong CYP3A inducers.

IN THE STUDY POPULATION, 48.8% OF PATIENTS WERE FRAIL AND 62.8% HAD AT LEAST 1 COMORBIDITY[25]

PATIENT POPULATION[25]

Baseline characteristics[25]	All patients (N=376)
Median age at NINLARO + Rd start, years (IQR)	**71** (65.0–77.5)
≥75, n (%)	**133** (35.4)
≥80, n (%)	**69** (18.4)
Male, n (%)	**185** (49.2)
ECOG PS at NINLARO + Rd start, n (%)	**n=209**
0	**69** (33.0)
1	**102** (48.8)
≥2	**38** (18.2)
Simplified frailty score* at NINLARO + Rd start, n (%)	**n=283**
Frail	**138** (48.8)
Non-frail	**145** (51.2)
Charison Comorbidity Index,†[26] n (%)	
0	**246** (65.4)
1–2	**100** (26.6)
3–4	**21** (5.6)
≥5	**9** (2.4)
Cytogenetic features at NINLARO + Rd start, n (%)	
Standard risk	**167** (44.4)
High risk‡	**45** (12.0)
Data not available	**164** (43.6)
Creatinine clearance (mL/min) at NINLARO + Rd start, n (%)	**n=304**
>50	**238** (78.3)
30–50	**43** (14.1)
≤30	**23** (7.6)

Baseline characteristics[25]	All patients (N=376)
Median time since diagnosis, years	**4.0**
Line of treatment at NINLARO + Rd start, n (%)	
2L	**227** (60.4)
3L	**68** (18.1)
4L+	**81** (21.5)
Prior PI therapy, n (%)	**349** (93.1)
Bortezomib	**344** (91.7)
Carfilzomib	**28** (7.5)
Prior IMiD therapy, n (%)	**244** (65.1)
Lenalidomide	**147** (39.2)
Pomalidomide	**44** (11.7)
Thalidomide	**159** (42.4)
Prior exposure to other therapy (>10%), n (%)	
Melphalan	**170** (45.3)
Cyclophosphamide	**76** (20.3)
Daratumumab	**52** (13.9)
At least 1 ASCT during previous therapy, n (%)	**167** (44.5)
Median duration of exposure to lenalidomide, months	**17.0**
Median duration between lenalidomide and NINLARO + Rd start, months	**16.0**
Refractory to lenalidomide,§ n (%)	**26** (6.9)

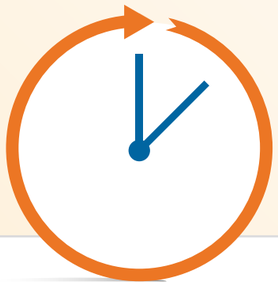
*Frailty score was calculated using a simplified adaption of the IMWG algorithm of frailty to categorize patients with MM as either frail or non-frail based on age (≤75 years; 76–80 years; >80 years), Charlson's Comorbidity Index (≤1; >1) and ECOG PS (0; 1; ≥2).[27] Due to missing data on ECOG PS, the simplified frailty score was only available for 283 patients (75.0%).[25]
†A weighted index that classifies prognostic comorbidities for use in longitudinal studies based on the number and seriousness of certain comorbidities.[25]
‡High-risk cytogenetic abnormalities: Deletion(17p) and/or translocation(4,14) and/or translocation(14,16).[25]
§Based on the investigator's assessment.[25]
2/3/4L+, second-/third-/fourth or further-line; ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; IQR, interquartile range; MM, multiple myeloma; PI, proteasome inhibitor; Rd, lenalidomide + dexamethasone.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.
- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-617-6468 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.



Time intervals from diagnosis to initiation of NINLARO + Rd, lines of treatment, Charlson score, and cytogenetic abnormalities, were similar in the age groups, except for frailty score (≥80 years: 96.7% and <80 years: 35.9%)[25]

Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia:** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14–21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

NOTES:

RWE IS USUALLY A GOOD REFLECTION OF ROUTINE CLINICAL PRACTICE BUT THERE ARE IMPORTANT LIMITATIONS THAT MUST BE CONSIDERED[28]

REMIX STUDY LIMITATIONS[25]

The REMIX study includes limitations inherent to real-world observational studies, notably concerning treatment response or progression assessments, which are determined as per investigator assessment

Frailty score calculation was based on ECOG PS if patients were ≤80 years, which is collected less frequently in routine clinical practice than in RCTs. Missing data on ECOG PS resulted in the simplified frailty score only being available for 283 patients (75%)

The prospective patient recruitment at the initiation of treatment does not predict treatment response and limits the impact of this bias on the efficacy assessment

Although the centers were encouraged to propose the study to all patients that met the eligibility criteria, the sample may not accurately represent the overall patient population

ECOG PS, Eastern Cooperative Oncology Group performance status; RCT, randomized controlled trial; RWE, real-world evidence.

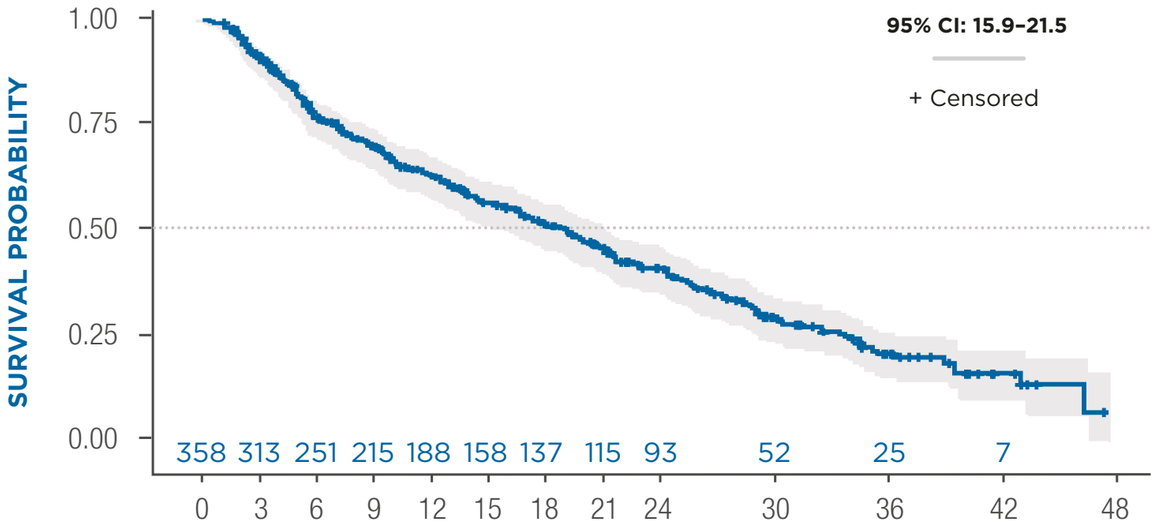
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Gastrointestinal Toxicities,** including diarrhea, constipation, nausea and vomiting were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

mPFS WITH NINLARO + Rd WAS CONSISTENT WITH TOURMALINE-MM1, WHICH REPORTED AN mPFS OF 20.6 MONTHS[19,25]

PFS FOR OVERALL COHORT OF PATIENTS RECEIVING NINLARO + Rd[25]



Adapted from Macro M, et al. 2023.[25]

With a median follow-up of 28.7 months, REMIX demonstrated an mPFS of 19.1 months (95% CI: 15.9–21.5) with NINLARO + Rd in real-world patients with RRMM[25]

The effectiveness of NINLARO + Rd in 3L (21.9 months) was similar to that in 2L (21.5 months), but was lower in 4L+ (5.8 months)[25]

In patients with cytogenetic abnormalities, mPFS was 21.2 months (95% CI: 14.7–25.6) in the standard-risk group, 19.8 months (95% CI: 16.4–29.0) in the high-risk group* and 15.4 months (95% CI: 11.6–21.0) in the group for which cytogenetic risk data were not available (p=0.07)[25]

Unadjusted, indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

Observational, retrospective and prospective analyses are not intended for direct comparison with clinical trials.

CI, confidence interval; mPFS, median PFS; PFS, progression-free survival; Rd, lenalidomide + dexamethasone; RRMM, relapsed/refractory multiple myeloma.

This study was not powered to detect statistical significance in subgroup analyses. A sample size of 250 patients per subgroup (including age group) would provide an accuracy of 6.2% in describing the study results.[25]

*High-risk cytogenetic abnormalities defined as patients with deletion(17p) and/or translocation(4,14) and/or translocation(14,16).[25]

2/3/4L+, second-/third-/fourth or further-line; CI, confidence interval; mPFS, median PFS; Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

IMPORTANT SAFETY INFORMATION (cont'd)

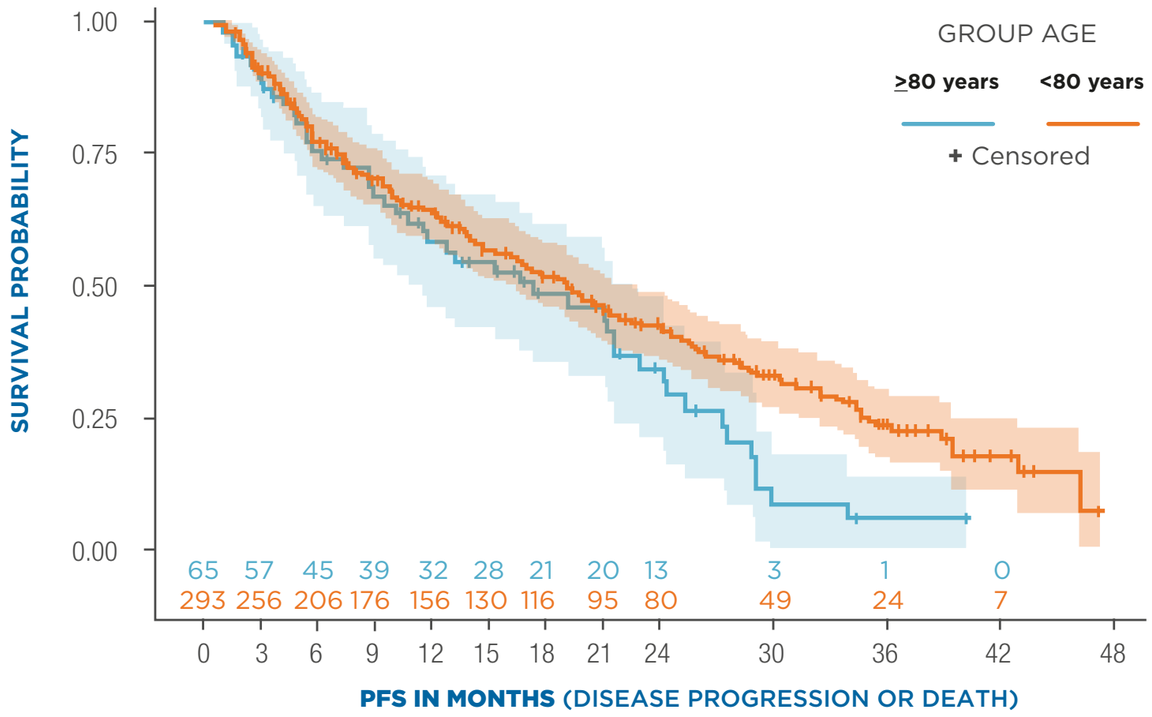
WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Neuropathy** was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.

- **Peripheral Edema** was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.

mPFS WAS SIMILAR IN THOSE AGED 80 YEARS AND OVER VS YOUNGER PATIENTS RECEIVING NINLARO + Rd[25]

PFS IN PATIENTS RECEIVING NINLARO + Rd BY AGE GROUP[25]



Adapted from Macro M, et al. 2023.[25]

mPFS, median PFS; PFS, progression-free survival; Rd, lenalidomide + dexamethasone.

mPFS in patients **younger than 80 years** was 19.1 months (95% CI: 15.9–21.9) and 17.4 months (95% CI: 10.8–23.0) in those **80 years or older** (p=0.06)[25]

This study was not powered to detect statistical significance in subgroup analyses. A sample size of 250 patients per subgroup (including age group) would provide an accuracy of 6.2% in describing the study results.[25]

CI, confidence interval; mPFS, median PFS; RWE, real-world evidence.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Cutaneous Reactions.** Stevens-Johnson syndrome and toxic epidermal necrolysis, including fatal cases, have been reported with NINLARO. If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, discontinue NINLARO and manage as clinically indicated. Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

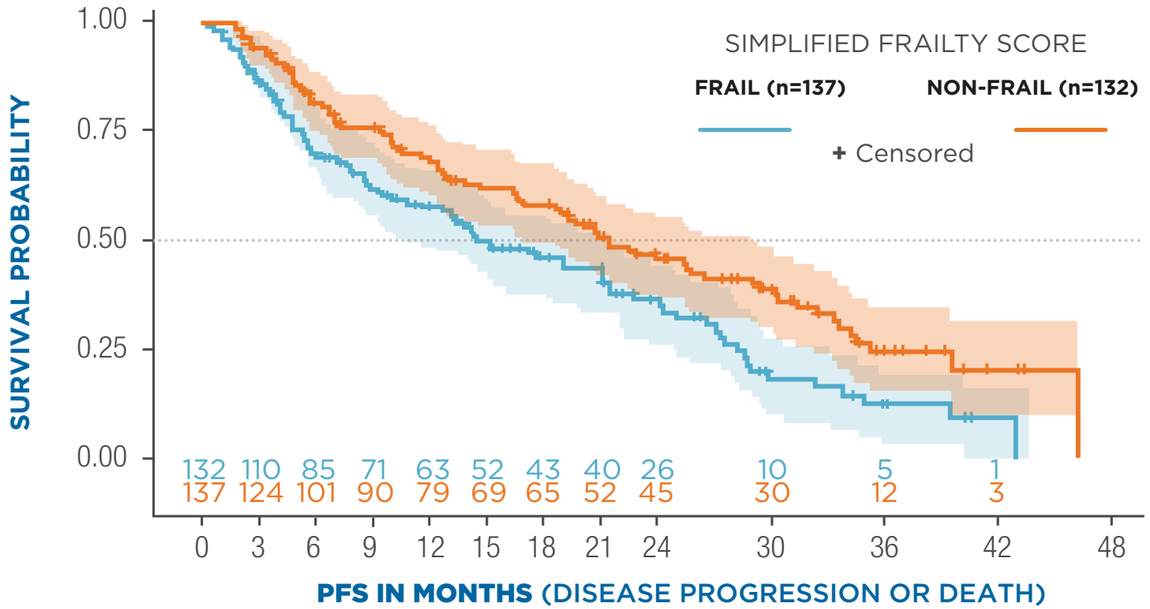
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Thrombotic Microangiopathy** has been reported with NINLARO. Fatal cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

mPFS WAS SIGNIFICANTLY SHORTER IN FRAIL VS NON-FRAIL PATIENTS RECEIVING NINLARO + Rd[25]

PFS IN PATIENTS RECEIVING NINLARO + Rd BY FRAILTY STATUS[25]



Adapted from Macro M, et al. 2023.[25]

mPFS in frail patients receiving NINLARO + Rd was 14.6 months (95% CI: 10.8–21.3) vs 21.5 months (95% CI: 17.0–29.1) for non-frail patients receiving NINLARO + Rd (p<0.01)[25]

Although mPFS was shorter in frail vs non-frail patients, frail patients included in REMIX also benefited from NINLARO + Rd[25]

This study was not powered to detect statistical significance in subgroup analyses. A sample size of 250 patients per subgroup (including age group) would provide an accuracy of 6.2% in describing the study results.[25]

mPFS, median PFS; PFS, progression-free survival; Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

CI, confidence interval; mPFS, median PFS; Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

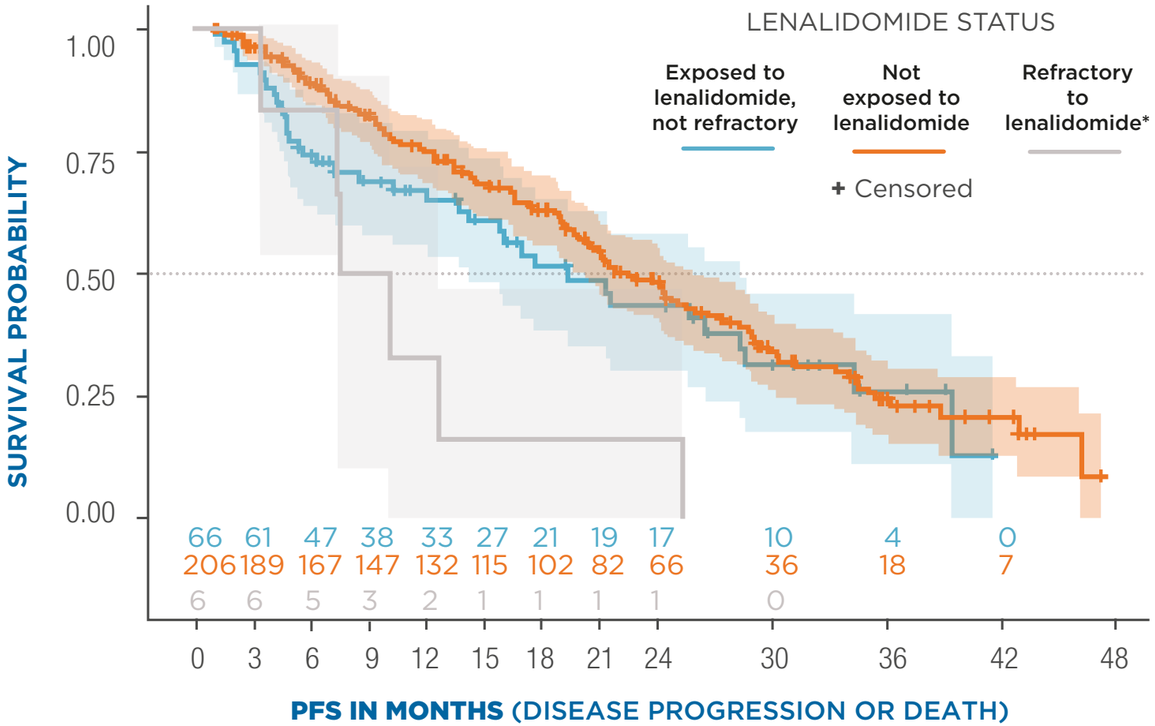
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

mPFS WAS SIMILAR IN PATIENTS PREVIOUSLY TREATED WITH LENALIDOMIDE AND LENALIDOMIDE-NAÏVE PATIENTS (in 2L and 3L)[25]

PFS IN PATIENTS RECEIVING NINLARO + Rd IN 2L AND 3L WHO HAD PRIOR LENALIDOMIDE EXPOSURE[25]



Adapted from Macro M, et al. 2023.[25]

2/3L, second-/third-line; mPFS, median PFS; PFS, progression-free survival; Rd, lenalidomide + dexamethasone.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting:** In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

Among patients receiving NINLARO + Rd in 2L and 3L, mPFS was 22.6 months (95% CI: 20.0–26.7) in patients not exposed to lenalidomide and 19.5 months (95% CI: 14.3–28.4) in patients previously treated with lenalidomide (p=0.29)[25]

mPFS was not reported in patients refractory to lenalidomide[25]

This study was not powered to detect statistical significance in subgroup analyses. A sample size of 250 patients per subgroup (including age group) would provide an accuracy of 6.2% in describing the study results.[25]

As data are limited in patients with primary refractoriness to lenalidomide, a careful risk–benefit assessment is recommended before initiating NINLARO + Rd.

2/3L, second-/third-line; CI, confidence interval; mPFS, median PFS; Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

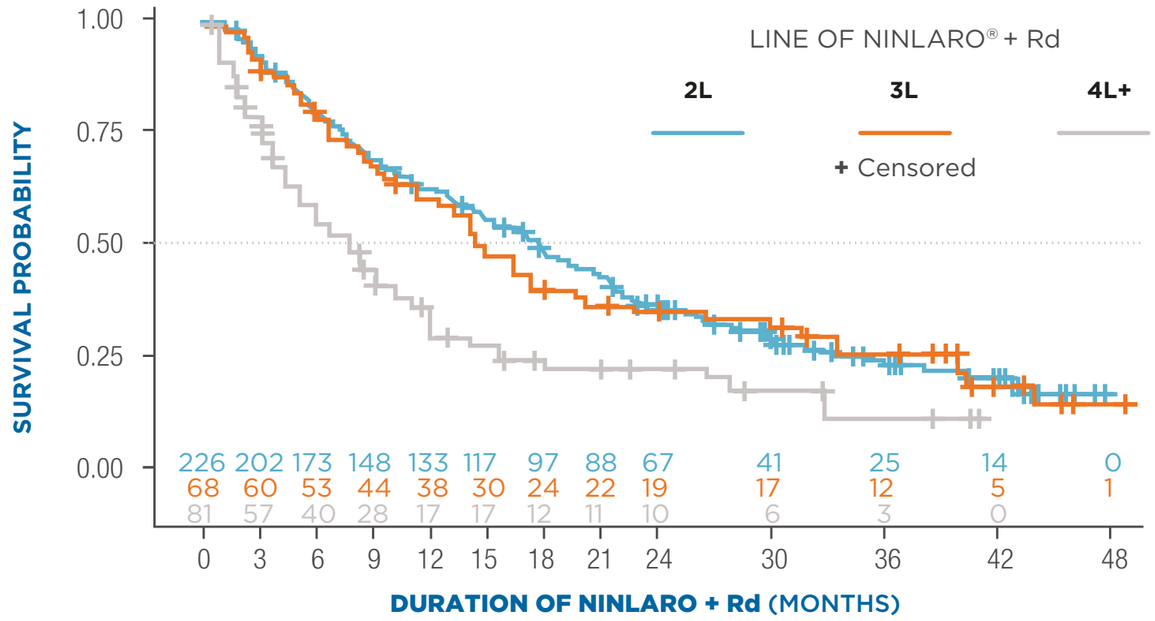
IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

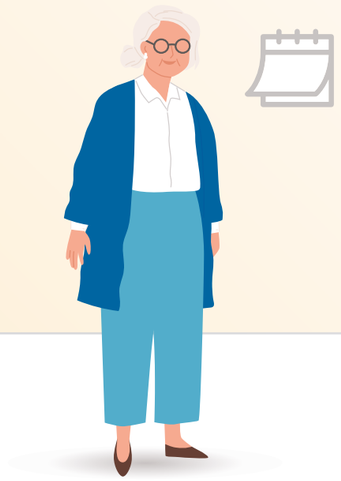
- The most common adverse reactions (≥20%) in the NINLARO regimen compared to placebo in combination with lenalidomide plus dexamethasone, respectively were thrombocytopenia (85%, 67%; pooled from adverse event and laboratory data), neutropenia (74%, 70%; pooled from adverse event and laboratory data), diarrhea (52%, 43%), constipation (35%, 28%), peripheral neuropathy (32%, 24%), nausea (32%, 23%), edema peripheral (27%, 21%), rash (27%, 16%), vomiting (26%, 13%), and bronchitis (22%, 17%). Serious adverse reactions reported in ≥2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%).

DOT WITH NINLARO + Rd WAS LONGER IN THE 2L OR 3L SETTING THAN IN 4L+[29]

DOT (MONTHS) WITH NINLARO + Rd ACCORDING TO PREVIOUS LOT*[29]



Adapted from Data on File. Takeda Pharmaceuticals America, Inc 2023.[29]



DOT was numerically longer among patients who received NINLARO + Rd in the 2L or 3L setting than in patients who received NINLARO® + Rd as 4L+ (15.8 and 13.9 vs 5.8 months, respectively)[29]

This study was not powered to detect statistical significance in subgroup analyses. A sample size of 250 patients per subgroup (including age group) would provide an accuracy of 6.2% in describing the study results.[25]

*This is the analysis population with at least one follow-up.[29]

2/3/4L+, second-/third-/fourth or further-line; DOT, duration of treatment; LOT, line of treatment; Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- Avoid concomitant administration of NINLARO with strong CYP3A inducers.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.
- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-617-6468 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ORR WITH NINLARO + Rd WAS CONSISTENT WITH TOURMALINE-MM1, WHICH REPORTED AN ORR OF 78.3%[19,25]

BEST REPONSES RATES AND OS IN OVERALL POPULATION[25]

BEST RESPONSE AND OS	All patients (N=376)
Best response, n (%)	**N=331**
CR	**48** (14.5)
VGPR	**101** (30.5)
PR	**93** (28.1)
SD	**35** (10.6)
PD	**54** (16.3)
mDOR, months (95% CI)	**N=242**
	10.9 (8.7–14.8)
OS, months (95% CI)	**N=375**
mOS	NE*
12-month OS	**82.2** (78.3–86.1)
24-month OS	**71.6** (67.0–76.3)
36-month OS	**58.3** (52.6–63.9)
42-month OS	**55.4** (49.4–61.5)
48-month OS	**52.4** (44.2–60.5)

Adapted from Macro M, et al. 2023.[25]

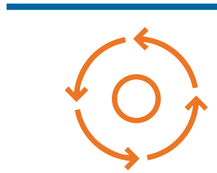
*mOS was not reached at time of analysis.[25]

CI, confidence interval; CR, complete response; mDOR, median duration of response; mOS, median OS; NE, not estimated; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; Rd, lenalidomide + dexamethasone; SD, stable disease; VGPR, very good PR.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia:** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14–21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.



The investigator-assessed ORR was 73.1%.*[25] This is consistent with TOURMALINE-MM1, which reported an ORR of 78.3% with NINLARO + Rd[19]

Younger (<80 years) vs older (≥80 years) patients had a similar ORR† (72.4% vs 76.8%)[25]

ORR was increased among patients who received NINLARO + Rd in 2L or 3L setting (80.3% and 70%, respectively) and decreased in patients who received NINLARO + Rd in 4L+ (54.4%)[25]

Unadjusted, indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

Observational, retrospective and prospective analyses are not intended for direct comparison with clinical trials.

*ORR combined CR, VGPR and PR.[25]

2/3/4L+, second-/third-/fourth or further-line; CR, complete response; ORR, overall response rate; PR, partial response; Rd, lenalidomide + dexamethasone; RWE, real-world evidence; VGPR, very good PR.

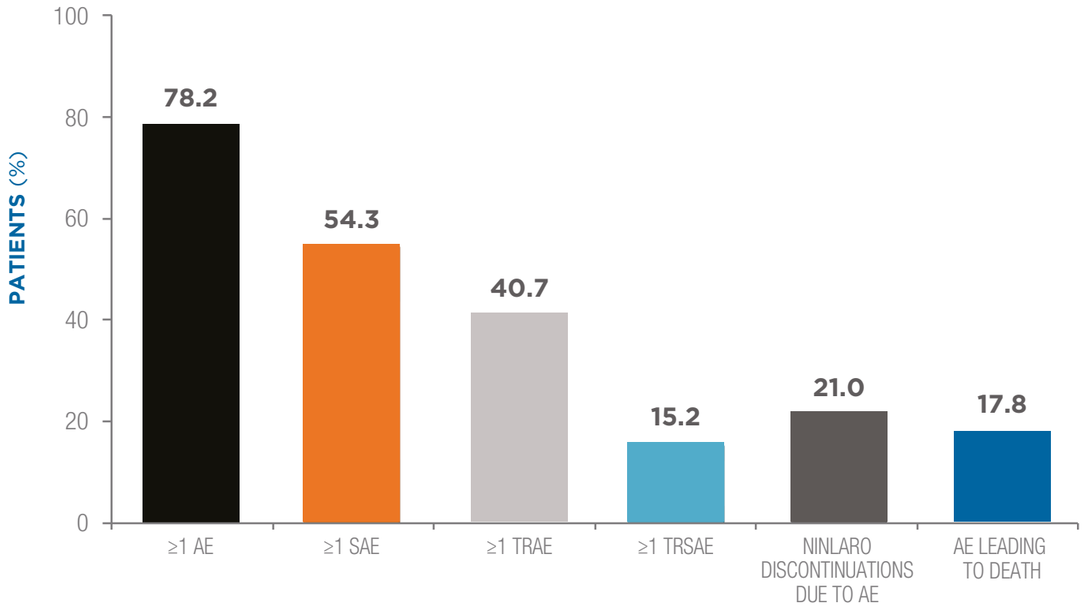
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Gastrointestinal Toxicities,** including diarrhea, constipation, nausea and vomiting were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

NINLARO + Rd DEMONSTRATED A SAFETY PROFILE THAT WAS GENERALLY CONSISTENT WITH TOURMALINE-MM1[19,25]

AEs REPORTED IN PATIENTS TREATED WITH NINLARO + Rd (N=376)[25]



Adapted from Macro M, et al. 2023.[25]

The most frequently reported AEs >10% (n=294) included diarrhea (26.2%), thrombocytopenia (23.1%), asthenia (15%), neutropenia (11.9%), nausea (11.6%) and anemia (11.2%)*[25]

Thrombocytopenia (12.2% of patients with ≥1 AE) and plasma cell myeloma (9.5%) were the most common SAEs[25]

*In TOURMALINE-MM1, the incidence of these AEs (any grade) in the NINLARO + Rd and placebo + Rd groups, respectively, were: diarrhea (45% vs 39%), thrombocytopenia† (31% vs 16%), neutropenia† (33% vs 31%), nausea (29% vs 22%) and anemia (29% vs 27%). No data were available on asthenia.[19]

†Represents a pooling of preferred terms.[19]

AE, adverse event; Rd, lenalidomide + dexamethasone; SAE, serious AE; TRAE, treatment-related AE; TRSAE, treatment-related SAE.

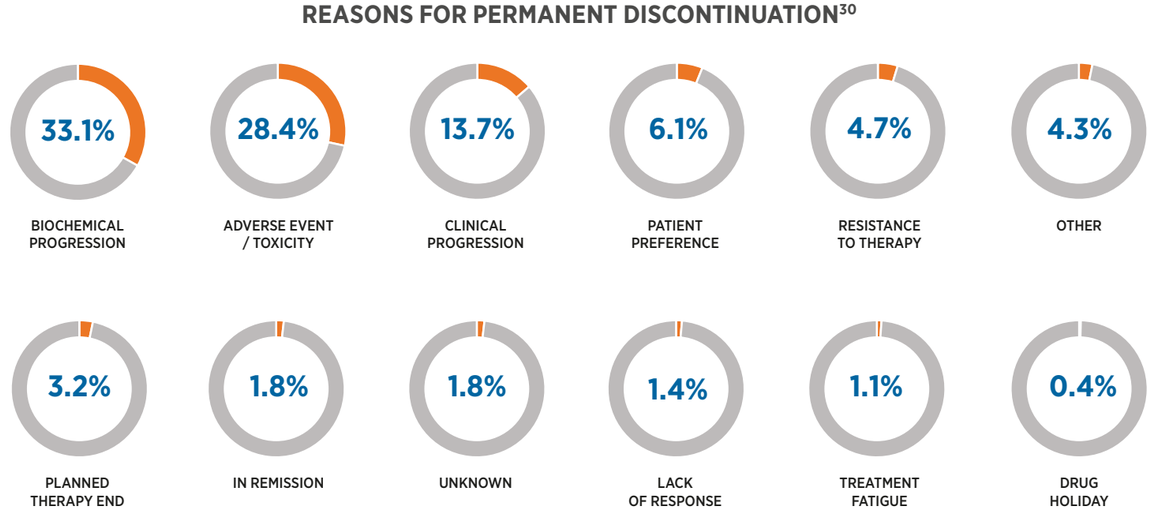
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Neuropathy** was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.

AT FINAL ANALYSIS, 74.1% (278/375) OF PATIENTS HAD PERMANENTLY DISCONTINUED NINLARO[25]

REASONS FOR PERMANENT DISCONTINUATION[30]



Unadjusted, indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

Observational, retrospective and prospective analyses are not intended for direct comparison with clinical trials.

*Median follow-up of 28.7 months.[25]

AE, adverse event; Rd, lenalidomide + dexamethasone; RWE, real-world evidence; SAE, serious AE.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Edema** was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Cutaneous Reactions.** Stevens-Johnson syndrome and toxic epidermal necrolysis, including fatal cases, have been reported with NINLARO. If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, discontinue NINLARO and manage as clinically indicated. Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

KEY TAKEAWAYS

PATIENT POPULATION[25]

90.4% of patients initiated NINLARO at the full dosage of **4 mg/day***

Median age at NINLARO + Rd start was **71 years** (IQR: 65.0–77.5)

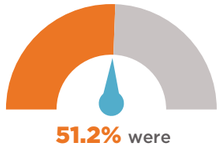
18.4% of patients were **≥80 years** of age

93.1% had received prior **PI therapy**

35.4% were **≥75 years** of age

62.8% had at least **1 comorbidity**

39.2% had received prior **lenalidomide therapy**



51.2% were **considered non-frail**

OUTCOMES[25]

- REMIX demonstrated a mPFS of 19.1 months (95% CI: 15.9–21.5) with NINLARO + Rd in real-world patients with RRMM
- The effectiveness of NINLARO + Rd in 3L (21.9 months) was similar to that in 2L (21.5 months), but was lower in 4L+ (5.8 months)
- 21.0% (79/376) of patients reported NINLARO discontinuation due to AEs
- The most frequently reported AEs were digestive or hematological

NINLARO + Rd DEMONSTRATED EFFECTIVENESS AND A MANAGEABLE SAFETY PROFILE IN RRMM IN THE REAL-WORLD SETTING[25]

*The remaining 36 patients were prescribed 3 mg/day or less.
2/3/4L+, second-/third-/fourth or further-line; AE, adverse event; CI, confidence interval; IQR, interquartile range; mPFS, median progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide + dexamethasone; RRMM, relapsed/refractory multiple myeloma; RWE, real-world evidence.

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