Takeda | ONCOLOGY

CONSIDER NINLARO® (ixazomib) + Rd FOR PATIENTS WHO MAY BENEFIT FROM LONG-TERM* PROTEASOME INHIBITION IN THE REAL WORLD

*Used herein to refer to treatment to disease progression or unacceptable toxicity.[1]
Rd, lenalidomide + dexamethasone.

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

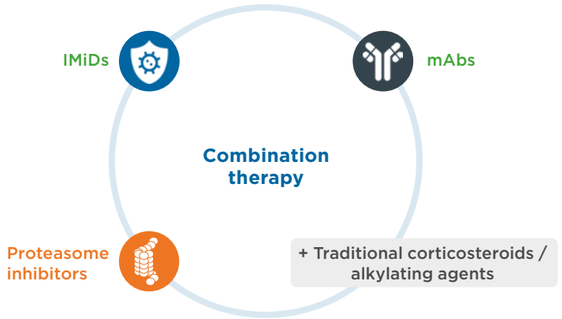
- **Thrombocytopenia,** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14–21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was 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.

Please see additional Important Safety Information throughout and NINLARO (ixazomib) full Prescribing Information.

NINLARO® (ixazomib) capsules

DRUGS WITHIN DIFFERENT CLASSES CAN BE COMBINED IN DOUBLET, TRIPLET, OR QUADRUPLET REGIMENS OR USED AS MONOTHERAPY[2–5]

STANDARD OF CARE[2–5]



EMERGING AGENTS[2–4]

Monotherapy

Anti-BCMA/GPRC5D bispecific antbodies

Anti-BCMA CAR-T-cells

PROTEASOME INHIBITION REMAINS A CORNERSTONE OF TREATMENT[5]

Proteasome inhibitors can help to control the disease by selectively inducing MM cell apoptosis[5]

What is the impact of proteasome inhibition on your patients?

PIs are a mainstay of treatment within the RRMM space. Triplet regimens for MM consisting of a PI, an IMiD or an alkylator, and dexamethasone have been evaluated and widely used in the clinical setting.[6]

In the real world,* 50–71% of patients with MM received triplet therapy – this typically included a **PI** (ixazomib, carfilzomib or bortezomib), and dexamethasone.[7]

HOW IS CLINICAL DECISION-MAKING SUPPORTED BY RCTs AND RWE?

In recent years, RCTs have shown that current therapies have demonstrated significant efficacy improvements.[8]

RCTs remain the gold standard for therapeutic evaluation and regulatory approval.[8]

- **RWE** is important for determining whether efficacy outcomes observed in RCTs are reflected in real-world practice; this is not always the case due to a range of factors[8,9]
- RWE often reflects the heterogeneity of patients treated in clinical practice[8–10]
- RWE provides information on real-world treatment patterns[8,9]

Real-world analyses are often non-randomized, observational, retrospective 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.

*INSIGHT MM was a large, global, prospective, RWE, observational study of 4,188 patients with MM, conducted across 15 countries between July 2016 and July 2021, which aimed to describe contemporary real-world treatment patterns and outcomes.[7]
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; IMiD, immunomodulatory drug; mAbs, monoclonal antibodies; MM, multiple myeloma; RCT, randomized, controlled trial; RRMM, relapsed/refractory multiple myeloma; RWE, real-world evidence.

NINLARO® (ixazomib) capsules

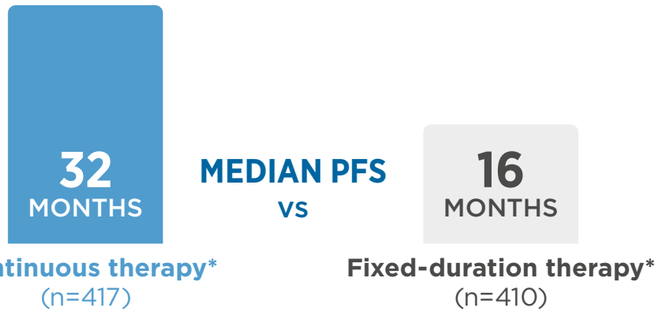
CONTINUOUS OR LONG-TERM THERAPY IMPROVES OUTCOMES WITH PIs VS FIXED-DURATION THERAPY[5,11]

Injectable PI therapy can be difficult to continue because of:[12]

- Adverse reactions[13,14]
- Restricted mobility[15]
- Burden of repeated IV or SC injection impacting patients' HRQoL[15]
- Patient desire to avoid hospitals or clinics for drug administration[15]

POOLED ANALYSIS OF THREE PHASE 3 RCTs

INCLUDING PI-BASED THERAPY*[11]



2x
median PFS with continuous therapy for MM

Adapted from Palumbo A, et al. 2015.[11]

ORAL PIs OFFER CONVENIENT ADMINISTRATION FOR CONTINUOUS THERAPY[16]

*Patients received ASCT and/or immunomodulatory drugs in various combinations with a PI, chemotherapy or CSTs.[11]
ASCT, autologous stem cell transplant; CI, confidence interval; CST, corticosteroid therapy; HR, hazard ratio; HRQoL, health-related quality of life; IV, intravenous; MM, multiple myeloma; PFS, progression-free survival; PI, proteasome inhibitor; RCT, randomized controlled trial; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous.

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.
- **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 IS AN ORAL PI[1,16]

INDICATION AND USAGE[1]

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.

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.

GLOBAL, PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY[1,16]

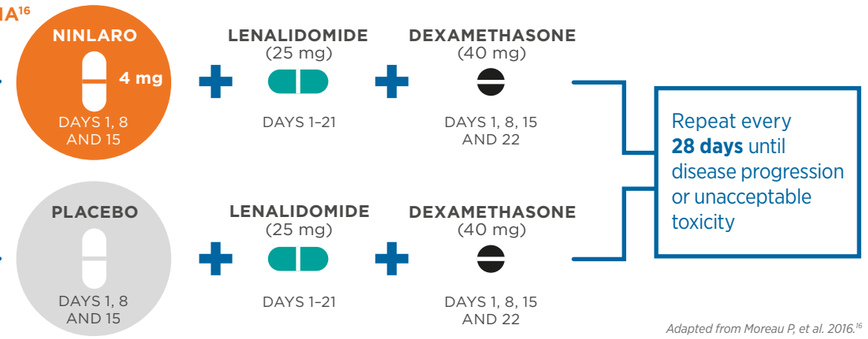
TOURMALINE-MM1 EVALUATED THE SAFETY AND EFFICACY OF NINLARO + Rd VS PLACEBO + Rd[1,16]

722 patients with RRMM[1,16]

SELECTED INCLUSION CRITERIA[16]
- RRMM
- 1–3 prior therapies
- ECOG PS 0–2

RANDOMIZATION* (1:1)

SELECTED EXCLUSION CRITERIA[16]
- Lenalidomide or PI refractory



Adapted from Moreau P, et al. 2016.[16]

PRIMARY ENDPOINT[1,16]
- 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[16]
- OS
- OS in del(17p)

OTHER SECONDARY ENDPOINTS[16]
- ORR
- PFS in patients with high-risk cytogenetics†
- Change in GHS
- CR and VGPR rate
- DOR
- Safety

*Stratification: 1 vs 2 or 3 prior therapies. PI exposed vs proteasome naïve; and ISS Stage I or II vs III.
†Defined as patients with del(17p), t(4;14) and/or t(14;16).[16]
CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GHS, global health status; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; ORR, overall response rate; NE, not estimable; 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)

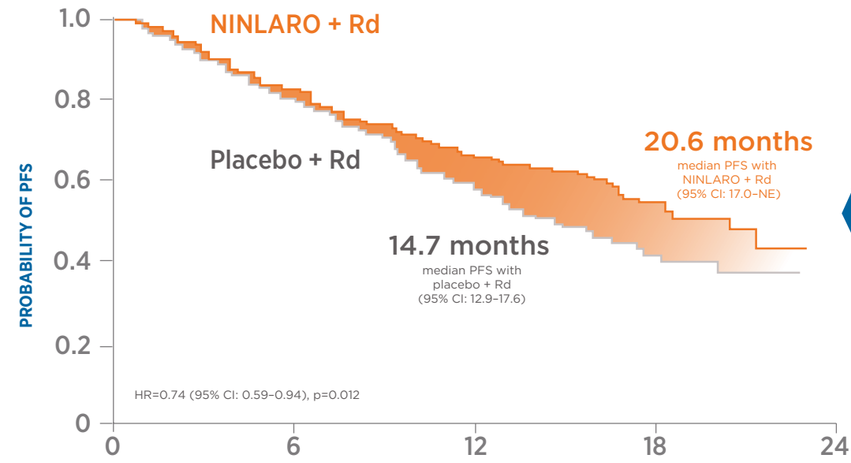
WARNINGS AND PRECAUTIONS (cont'd)

- **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.

NINLARO® (ixazomib) capsules

NINLARO + Rd PROLONGED MEDIAN PFS VS PLACEBO + Rd[1,16]

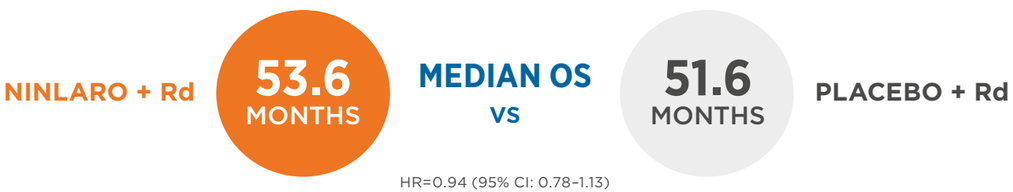
PRIMARY PFS ANALYSIS[1,16]



Adapted from Moreau P, et al. 2016.[16]

~6 month median PFS benefit[1,16]

FINAL OS ANALYSIS[1] (median follow-up of ~85 months)



HR=0.94 (95% CI: 0.78–1.13)

NINLARO + Rd IS AN ORAL PI THAT OFFERS EXTENDED EFFICACY VS PLACEBO + Rd IN PATIENTS WITH RRMM[1,16]

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; RRMM, relapsed/refractory multiple myeloma.

IMPORTANT SAFETY INFORMATION (cont'd)

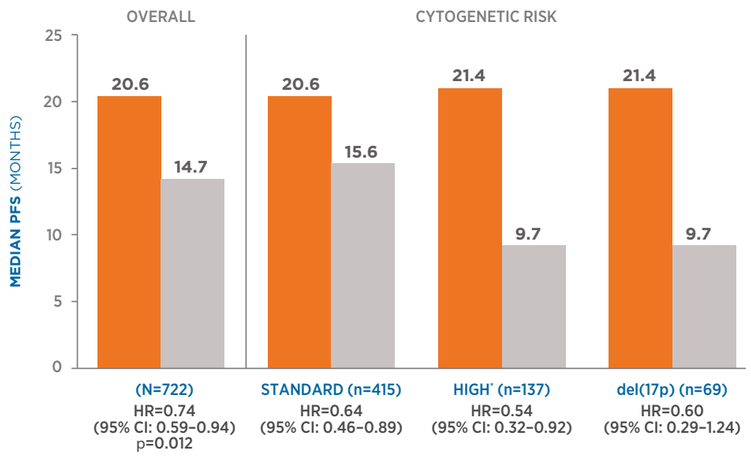
WARNINGS AND PRECAUTIONS (cont'd)

- **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 IMPROVED MEDIAN PFS IN PATIENTS WITH HIGH-RISK CYTOGENETIC ABNORMALITIES*[16,17]

Patients with high-risk cytogenetic abnormalities such as del(17p), t(4;14) and t(14;16) have a poor prognosis in MM[16,17]

NINLARO + Rd SUBSTANTIALLY INCREASED MEDIAN PFS VS PLACEBO + Rd IN HIGH RISK CYTOGENETIC GROUPS*[16,17]



>2x
MEDIAN PFS IN HIGH-RISK* PATIENTS (n=137)[17]

NINLARO + Rd
Placebo + Rd

- This study was not powered to show significance in PFS across these prespecified subgroups
- Cytogenetic-risk data were not available for 24% of patients in the study[16,17]

Adapted from Avet-Loiseau H, et al. 2017.[17]

TRIPLET THERAPY WITH NINLARO + Rd MAY IMPROVE OUTCOMES VS Rd DOUBLET THERAPY IN PATIENTS WITH HIGH-RISK CYTOGENETICS[16,17]

*Defined as patients with del(17p), t(4;14) and/or t(14;16).[16]
CI, confidence interval; HR, hazard ratio; OS, overall survival; MM, multiple myeloma; PFS, progression-free survival; RCT, randomized controlled trial; 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.

NINLARO® (ixazomib) capsules

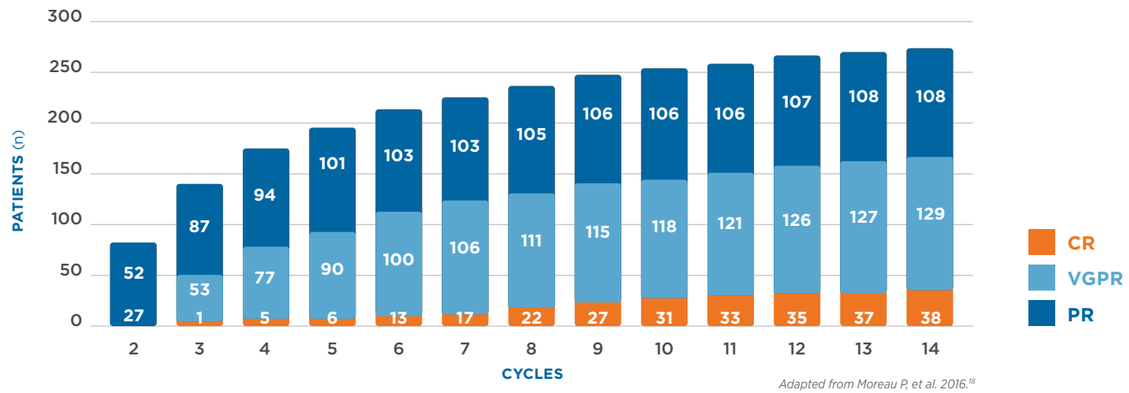
NINLARO + Rd ACHIEVED RAPID RESPONSES* THAT DEEPENED WITH LONG-TERM† TREATMENT[1,16]

MEDIAN TIME TO INITIAL RESPONSE[1,16]

1.1 months with NINLARO + Rd

1.9 months with Placebo + Rd

CUMULATIVE BEST RESPONSES SEEN WITH LONG-TERM NINLARO + Rd (ITT population)[18]



Adapted from Moreau P, et al. 2016.[18]

Depth of response for NINLARO + Rd vs placebo + Rd, respectively:

- ORR:‡ 78% vs 72%; CR: 12% vs 7%; VGPR + CR: 48% vs 39%; PR: 30% vs 33%[1]
- Responses improved over time in both arms of the study[16]

The study was not powered to detect differences in response rates between arms.

WITH INCREASING DURATION OF NINLARO + Rd TREATMENT THE NUMBER OF PEOPLE WITH A VGPR OR CR INCREASED[18]

*Vs placebo + Rd.
†Treatment to disease progression or unacceptable toxicity.[1]
‡ORR = CR + VGPR+PR.
CR, complete response; ITT, intention-to-treat; ORR, overall response rate; PR, partial response; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; VGPR, very good partial response.

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 MANAGEABLE LONG-TERM* TOLERABILITY[1,19–21]

FINAL SAFETY ANALYSIS[†1]

THE MAJORITY OF PATIENTS DID NOT EXPERIENCE PERMANENT DISCONTINUATION OF NINLARO DUE TO ARs[1]

10%

After a median follow-up of ~85 months, permanent discontinuation of NINLARO due to an AR occurred in 10% of patients[1,19]

THE MAJORITY OF PATIENTS CONTINUED AT THE STARTING DOSE OF NINLARO WITHOUT DOSE REDUCTION[20]

75%

of patients (n=269/361) receiving NINLARO + Rd in TOURMALINE-MM1 continued on their starting NINLARO dose[‡20]

- The median relative dose intensity for NINLARO + Rd and placebo + Rd was high and similar between both arms: 97.8% and 100%, respectively[21]
- Relative dose intensity was calculated as: 100 x (total amount of dose taken) ÷ (total prescribed dose of treated cycles)[§21]

AE management in TOURMALINE-MM1[23]

Dose modification:
- Toxicities graded using NCI-CTCAE v4.0; toxicity attributed to drug/s by investigator
- If significant toxicity, drug was withheld until toxicity resolved
- Drug was restarted at a reduced dose or discontinued if persistent toxicity

*Treatment to disease progression or unacceptable toxicity.[1]
†Data cut-off for the final analysis 28 September 2020.[20]
‡Median duration of exposure to NINLARO was 457 days (range: 1–2768 days).[22]
§Total prescribed dose equals (dose prescribed at enrollment × number of prescribed doses per cycle × the number of treated cycles).[21]
AE, adverse event; AR, adverse reaction; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone.

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.

NINLARO® (ixazomib) capsules

RCT: TOURMALINE-MM1

SAFETY PROFILES IN PATIENTS WITH CYTOGENETIC RISK WERE CONSISTENT WITH THE OVERALL POPULATION[17]

SAFETY PROFILE IN HIGH-RISK* PATIENTS[17]

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[17]

DISCONTINUATION OF REGIMEN DUE TO AEs

HIGH RISK

8% vs **13%**

with **NINLARO + Rd** (n=74) vs placebo + Rd (n=62), respectively

STANDARD RISK

21% vs **14%**

with **NINLARO + Rd** (n=200) vs placebo + Rd (n=214), respectively

COMMON AEs IN HIGH-RISK* PATIENTS[17]

As seen in the overall population, in both high-risk and standard-risk cytogenetics patients, common AEs were primarily:[17]

GRADE 1 OR 2 IN SEVERITY

- Diarrhea & constipation
- Neutropenia
- Anemia

AE management in TOURMALINE-MM1 continued[18,23]

Hematological toxicities:
- Platelet count measured monthly, or weekly in first 3 cycles[23]
- Neutropenia treated with G-CSF and dose modification[23]
- Red blood cell and platelet transfusions as clinically indicated[18]

Non-hematological toxicities:
- Anti-diarrheal medications, primarily loperamide, and dose modification[23]
- Routine measures for constipation, including diet and laxative adjustments[23]
- Standard antiemetics, e.g. 5-HT3 antagonists for emesis if occurring during treatment[18,23]

*Defined as patients with del(17p), t(4;14), and/or t(14;16).[18]
AE, adverse event; G-CSF, granulocyte colony-stimulating factor; RCT, randomized controlled trial; 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.

NINLARO + Rd DEMONSTRATED A COMPARABLE SAFETY PROFILE TO PLACEBO + Rd[1]

NON-HEMATOLOGIC ARs OCCURRING IN ≥5% OF PATIENTS WITH A ≥5% DIFFERENCE BETWEEN NINLARO + Rd AND PLACEBO + Rd IN TOURMALINE-MM1[1]

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. 2022.[1]

- Serious ARs reported in ≥2% of patients treated with NINLARO + Rd included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%)[1]
- Incidence of thrombocytopenia in patients treated with NINLARO + Rd and placebo + Rd, respectively: Any grade, 85% vs 67%; Grades 3–4, 30% vs 14%[1]
- Incidence of neutropenia in patients treated with NINLARO + Rd and placebo + Rd, respectively: Any grade, 74% vs 70%; Grades 3–4, 34% vs 37%[1]

THE NINLARO TRIPLET REGIMEN MAY OFFER EXTENDED† EFFICACY WITH SAFETY THAT IS SIMILAR TO A DOUBLET IN PATIENTS WITH RRMM[1,16]

*Represents a pooling of preferred terms.[1]
†At the time of the final analysis, these ARs no longer met the criterion for a ≥5% difference between NINLARO + Rd and placebo + Rd.[1]
‡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)

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%).

NOTES

RCTs PROVIDE ROBUST EVIDENCE OF THE SAFETY PROFILE AND EFFICACY OF THERAPEUTIC AGENTS[10]

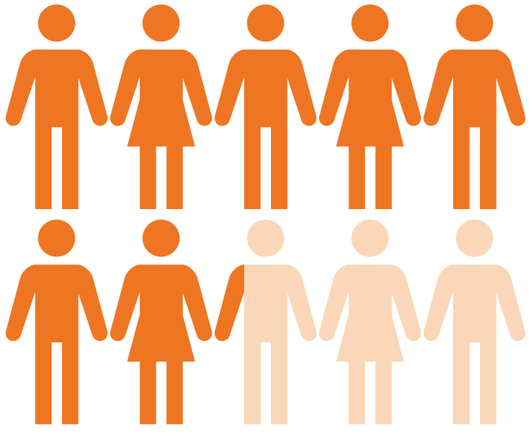
By utilizing randomization and strict patient inclusion and exclusion criteria, investigators can minimize bias and the influence of confounding variables to gather robust evidence of the safety and efficacy of medical interventions.[10]

HOWEVER, RCT POPULATIONS MAY NOT BE REPRESENTATIVE OF YOUR TYPICAL PATIENTS

MANY COMMON PATIENT POPULATIONS YOU SEE WITH MM ARE TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIALS, INCLUDING:[8,24,25]

- Elderly patients
- Patients from ethnic minorities or underprivileged socioeconomic backgrounds
- Patients with comorbidities or low performance status

FOR THOSE WITH RRMM, RECEIVING ROUTINE CARE IN THE UNITED STATES



UP TO 72%

OF REAL-WORLD PATIENTS WITH RRMM DO NOT MEET THE ELIGIBILITY CRITERIA FOR CLINICAL TRIALS*[24]

Adapted from Chari A, et al. 2020.[24]

*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 + dexamethasone; RRMM, relapsed/refractory MM; RWE, real-world evidence; Vd, bortezomib + dexamethasone.

IMPORTANT SAFETY INFORMATION (cont'd)

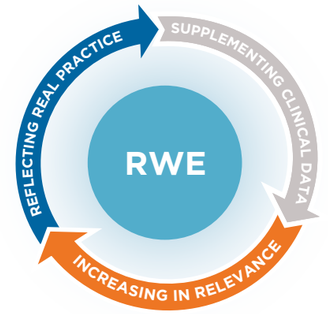
DRUG INTERACTIONS

- Avoid concomitant administration of NINLARO with strong CYP3A inducers.

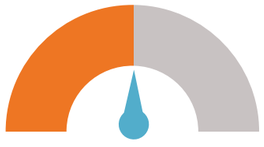
RWE COMPLEMENTS RCTs, PROVIDING INSIGHTS INTO REAL-WORLD TREATMENT PRACTICES AND THERAPEUTIC OUTCOMES[9]

Real-world studies have become increasingly important in providing valuable information that informs payers, clinicians and patients on the effectiveness and safety of drugs in large heterogenous populations in real-world practice settings.[10]

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.[8,10]



KEY DIFFERENCES IN OUTCOMES BETWEEN RCT RESULTS AND RWE[8,24]



50%

Increased risk of **mortality*[24]**

In real-world studies, patients with MM had an increased risk of mortality[24] and disease progression[8] compared with patients in clinical trials.

WHY RWE OUTCOMES MAY DIFFER FROM RCT RESULTS†[8]

- **ARs**
- **Challenges with administration**
- **Patient adherence**
- **Significant differences in patient populations**
- **Burden of having to travel to a treatment center**

*RCT-ineligible vs RCT-eligible patients had a significantly greater mortality risk (HR: Rd, 1.46; Vd, 1.51).
†Based on a review of patients with relapsed and/or refractory MM in the real world.[8]
AR, adverse reaction; HR, hazard ratio; MM, multiple myeloma; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; RWE, real-world evidence, Vd, bortezomib + 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.

REAL-WORLD STUDIES GIVE INSIGHTS INTO PATIENTS TREATED IN CLINICAL PRACTICE

REAL-WORLD PATIENT POPULATIONS AND STUDY DESIGNS

	TERPOS ET AL, 2020[26]	HÁJEK ET AL, 2021[27]	MINARIK ET AL, 2021[28]
	MULTICENTER, RETROSPECTIVE STUDY	RETROSPECTIVE STUDY	PROSPECTIVE STUDY
Study group / duration	12 clinical centers between December 2015 and October 2017	Pooled analysis of data from 2 discrete sources or registries* July 2016 – September 2019 (15 countries) and May 2007 – February 2020	Comparitive study of patients treated with NINLARO regimen vs Rd regimen between 2016 and 2018
Patient population	• 155 patients† • RRMM • Median of 1 prior line of therapy • Some patients would not have been eligible for TOURMALINE-MM1	• 263 patients† • RRMM • Median of 2 prior lines of therapy • Some patients would not have been eligible for TOURMALINE-MM1	• 344 patients† • RRMM • Median of 1 prior line of therapy • Some patients would not have been eligible for TOURMALINE-MM1
Treatment regimen	NINLARO + Rd through early access program	NINLARO + Rd used in INSIGHT MM (n=132) and Czech RMG (n=131)	NINLARO + Rd used in INSIGHT MM (n=127) vs Rd regimen (n=217) as part of Named Patient Program
Key study endpoints	• ORR • CBR • DCR • Safety	• Best response to therapy • DOT • TTNT • PFS • OS	• PFS • Response rates • OS

Real-world analyses are often non-randomized, observational, retrospective 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.

*Many of the patients included in the analysis were treated at academic centers; therefore, these results may not be representative of the community practice setting.[27]
†Key exclusion criteria for Minarik et al. included: Active 1L therapy; patients with missing data for primary endpoints; patients in clinical trials; patients who switched combination regimens. In Hájek et al. patients from INSIGHT MM were excluded if they had missing or incomplete data or had signed the study informed consent form more than 3 months after starting NINLARO + Rd. This analysis also excluded patients from RMG with missing or incomplete data. In Terpos et al. no exclusion criteria were identified.[26–28]
1L, first line; CBR, clinical benefit rate; DOT, duration of treatment; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide + dexamethasone; RMG, Registry of Monoclonal Gammopathies; RWE, real-world evidence; TTNT, time to next treatment.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS (cont'd)

- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment*

RWE IS USUALLY A GOOD REFLECTION OF ROUTINE CLINICAL PRACTICE BUT THERE ARE IMPORTANT LIMITATIONS THAT MUST BE CONSIDERED[29]

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. In addition, each real-world study should be examined individually to understand any study-specific limitations.[10]

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[10]

SPECIFIC LIMITATIONS FOR REAL-WORLD STUDIES WITH NINLARO + Rd

Outcomes should be interpreted with caution because of small sample size, limited follow-up, and limited maturity of data[27]

There is an unknown overlap in study populations across the RWE studies due to inclusion of patients from the same registries (all studies included patients from the Czech Republic and 2 included patients from the Czech RMG)[26–28]

These RWE studies included patients ineligible for TOURMALINE-MM1 based on refractory status to lenalidomide and/or PIs, comorbidities, performance status, and median lines of previous therapy.
These RWE studies lack adequate controls to establish safety and efficacy in these subgroups[26–28]

These RWE studies included analyses of PFS across select patient subgroups. In certain subgroups, the median PFS observed was not consistent with the overall PFS observed. These studies were not powered to show significance in PFS across these subgroups[26–28]

PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide + dexamethasone; RMG, Registry of Monoclonal Gammopathies; RWE, real-world evidence.

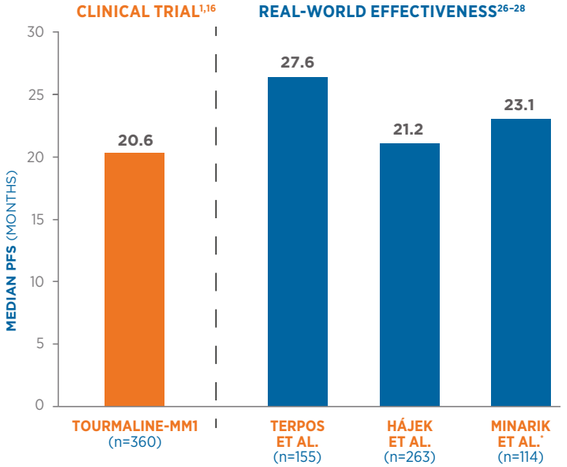
IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS (cont'd)

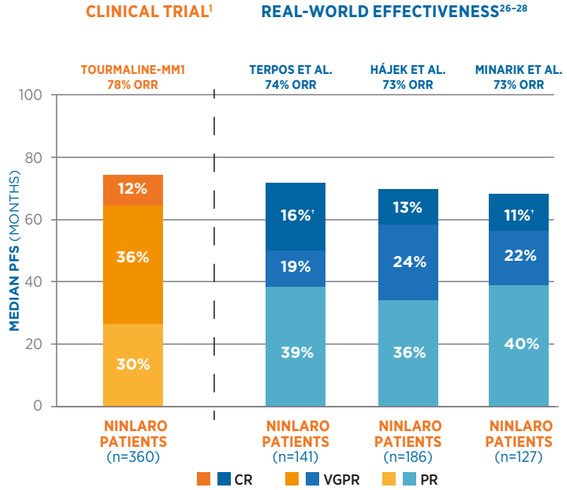
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

CONSISTENT PFS WAS SEEN WITH NINLARO + Rd IN THE REAL WORLD

NINLARO + Rd ACHIEVED CONSISTENT EFFICACY OUTCOMES IN THE REAL WORLD



NINLARO + Rd ACHIEVED CONSISTENT RESPONSE RATES IN THE REAL WORLD



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

*Treatment lines 2–4.
†Includes CR and stringent CR.
CR, complete response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; RWE, real-world evidence; VGPR, very good partial response.

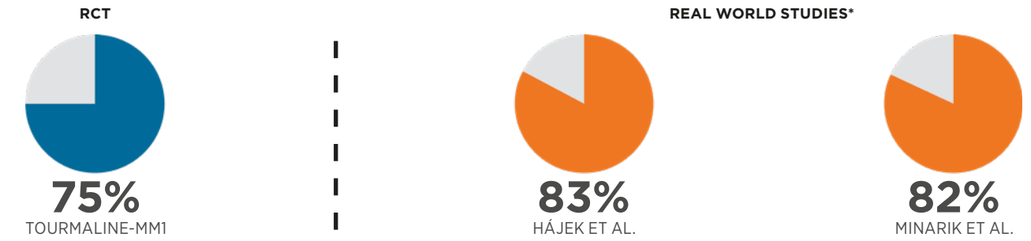
IMPORTANT SAFETY INFORMATION (cont'd)

- 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.

NINLARO® (ixazomib) capsules

ARs SEEN IN REAL-WORLD SETTINGS WERE CONSISTENT WITH THE KNOWN SAFETY PROFILE

THE MAJORITY OF PATIENTS CONTINUED ON STARTING DOSE OF NINLARO WITHOUT DOSE REDUCTION IN RCTs AND REAL-WORLD STUDIES[20,27,28]



ARs OCCURRING WITH NINLARO + Rd IN THE REAL WORLD WERE CONSISTENT WITH TOURMALINE-MM1[1,26–28]

TERPOS ET AL. 2020 (N=155)[26]

RATES OF SPECIFIC SAFETY ASPECTS OF INTEREST

	RWE	RCT
PN	35%	27%
PN Grade >2	3%	2%
Thrombo-embolism	5%	8%
Herpes zoster	5%	5%
Hypertension	4%	6%

HÁJEK ET AL. 2021 (N=263)[30]

MOST COMMON ARs LEADING TO DISCONTINUATION

NINLARO + Rd			
Infection	19%	Rash	4%
Neutropenia	6%	Nausea	3%
Thrombocytopenia	6%	Fatigue	2%
Diarrhea	3%	Other†	32%

MINARIK ET AL. 2021 (N=127)[28]

GRADE ≥3 AEs IN ≥10% PATIENTS

	NINLARO‡	Rd‡
Anemia	12%	26%
Neutropenia	28%	23%
Thrombocytopenia	21%	23%
Infection	21%	23%
Exanthema/rash	25%‡	0%
Other	19%	32%

NINLARO + Rd OFFERS MANAGEABLE TOLERABILITY IN RCTs AND REAL-WORLD STUDIES[1,26–28,30]

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

*Dose reduction data not available for Terpos et al.[26]
†More than 1 AE could be assigned to 1 patient; each AE was counted only once for each patient.[30]
‡Grade ≥3 exanthema/rash was reported in 1 patient receiving NINLARO + Rd (n=1/4).[28]
AE, adverse event; AR, adverse reaction; PN, peripheral neuropathy; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; RWE, real-world evidence.

NINLARO + Rd DEMONSTRATED LONG-TERM* PROTEASOME INHIBITION IN AN RCT

TOURMALINE-MM1 RCT DATA

CONVENIENT ALL-ORAL
PI-based triplet therapy[1,16,31,32]

EXTENDED† EFFICACY
~6 months median PFS vs Rd doublet therapy[1,16]

MANAGEABLE TOLERABILITY
- Permanent discontinuation of NINLARO due to an AR occurred in 10% of patients[†1,19]
- Serious ARs comparable to Rd doublet therapy[1,16]
- Serious ARs reported in ≥2% of patients treated with NINLARO + Rd included diarrhea (3%), thrombocytopenia (2%) and bronchitis (2%)[1]

COMPLEMENTED BY RCT-CONSISTENT EFFECTIVENESS AND TOLERABILITY IN REAL-WORLD PATIENTS

Median PFS
20.6 months in RCT[1] and 27.6, 21.2 and 23.1 months in 3 real-world studies[26–28]

ORR
78% in RCT[1] and 74%, 73% and 73% in 3 real-world studies[26–28]

Continued at NINLARO starting dose without dose reduction
75% of patients in RCT[20] and 83% and 82% in 2 real-world studies[27,28]

NINLARO + Rd OFFERS EXTENDED† EFFICACY AND MANAGEABLE TOLERABILITY FOR THE PATIENTS YOU SEE EVERY DAY[1,16,26–28]

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.

*Treatment to disease progression or unacceptable toxicity.[1]
†Extended refers to NINLARO + Rd vs placebo + Rd.
‡After a median follow-up of ~85 months at final analysis.[19]
AR, adverse reaction; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone.

NINLARO® (ixazomib) capsules

REFERENCES:

1. NINLARO (ixazomib). Prescribing information. April 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208462s012s013lbl.pdf. Accessed: April 2024.
2. International Myeloma Foundation. Multiple myeloma medications. Available at: https://www.myeloma.org/multiple-myeloma-drugs. Accessed: April 2024.
3. Ni B and Hou J. *Hematology* 2022;27:343–52.
4. Dimopoulos MA, et al. *Ann Oncol* 2021;32:309–22.
5. Gandolfi S, et al. *Cancer Metastasis Rev* 2017;36:561–84.
6. Ito S. *Cancers* (Basel) 2020;12:265.
7. Puig N et al. Blood 2022;140:4269–72.
8. Richardson PG, et al. Blood Cancer J 2018;8:109.
9. Costello C, et al. Future Oncol 2019;15:1379–85.
10. Blonde L, et al. Adv Ther 2018;35:1763–74.
11. Palumbo A, et al. *J Clin Oncol* 2015;33:3459–66.
12. Chari A, et al. *Clin Lymphoma Myeloma Leuk* 2019;19:645–55.
13. VELCADE (bortezomib). August 2022. Prescribing information Available at: https://www.takedaoncology.com/medicines/united-states/. Accessed: April 2024.
14. KYPROLIS. Prescribing information. June 2022. Available at: https://www.kyprolis-hcp.com/. Accessed: April 2024.
15. Baz R, et al. *Support Care Cancer* 2015;23:2789–97.
16. Moreau P, et al; for *N Engl J Med* 2016;374:1621–34.
17. Avet-Loiseau H, et al. *Blood* 2017;130:2610–8.
18. Moreau P, et al. for *N Engl J Med* 2016;374:1621–34 (Supplementary data).
19. Takeda Pharmaceuticals America, Inc. Data on File [Ref 51154]. 2023.
20. Takeda Pharmaceuticals America, Inc. Data on File. Ref 51158. 2023.
21. Takeda Pharmaceuticals America, Inc. Data on File. Ref 51157. 2023.
22. Takeda Pharmaceuticals America, Inc. Data on File [Ref 60031]. 2024
23. Kumar S, et al. *Br J Haematol* 2017;178:571–82.
24. Chari A, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:8–17.e16.
25. Yong K, et al. *Br J Haematol* 2016;175:252–64.
26. Terpos E, et al. *Ann Hematol* 2020;99:1049–61.
27. Hájek R, et al. *Future Oncol* 2021;374:1621–34.
28. Minarik J, et al. *BMC Cancer* 2021;21:73.
29. Visvanathan K, et al. *J Clin Oncol* 2017;35:1845–54.
30. Hájek R, J, et al. *Future Oncol* 2021;374:1621–34 (Supplementary data).
31. REVLIMID (lenalidomide). Prescribing information. May 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021880s057lbl.pdf. Accessed April 2024.
32. HEMADY (dexamethasone). Prescribing information. Oct 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211379s000lbl.pdf. Accessed April 2024.

Takeda | ONCOLOGY

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.

Takeda Oncology Here2Assist®

We're here to help your patients with their coverage, financial, and educational resource needs

From helping patients understand coverage options to identifying available financial assistance, **Takeda Oncology Here2Assist™** is committed to offering your patients comprehensive support.

Takeda Oncology Here2Assist™

- Works with your patients' insurance company to help get your patient started on their medication
- Identifies available financial assistance that may be right for your patients
- May help eligible patients get started on treatment in the event of an insurance delay
- Identifies specialty pharmacies to help fill and ship your patients' prescriptions appropriately
- Conducts regular follow-up calls to patients
- Sends text message status updates and reminders to patients*

*Patients will need to enroll in the texting program to receive text messages.

For more information about access support and financial assistance that your patients may qualify for, call **Takeda Oncology Here2Assist™** at **1-844-817-6468, option 2.**

Let's talk. We're available Monday–Friday, 8am–8pm ET, or visit us at www.here2assist.com to learn more.