WHEN NAVIGATING THE DIFFICULTIES OF MULTIPLE MYELOMA IN THE REAL WORLD, YOU NEED

DURABLE STRENGTH

THE NINLARO® (ixazomib) REGIMEN* OFFERS EXTENDED EFFICACY AND MANAGEABLE TOLERABILITY FOR THE TYPES OF PATIENTS YOU SEE EVERY DAY[1-6]

CONSIDER THE NINLARO REGIMEN FOR PATIENTS WHO COULD BENEFIT FROM **LONG-TERM**† PROTEASOME INHIBITION

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.

*The NINLARO regimen includes NINLARO+lenalidomide+dexamethasone.
†**Defined as treatment to disease progression or unacceptable toxicity.**[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. 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. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.
- **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 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

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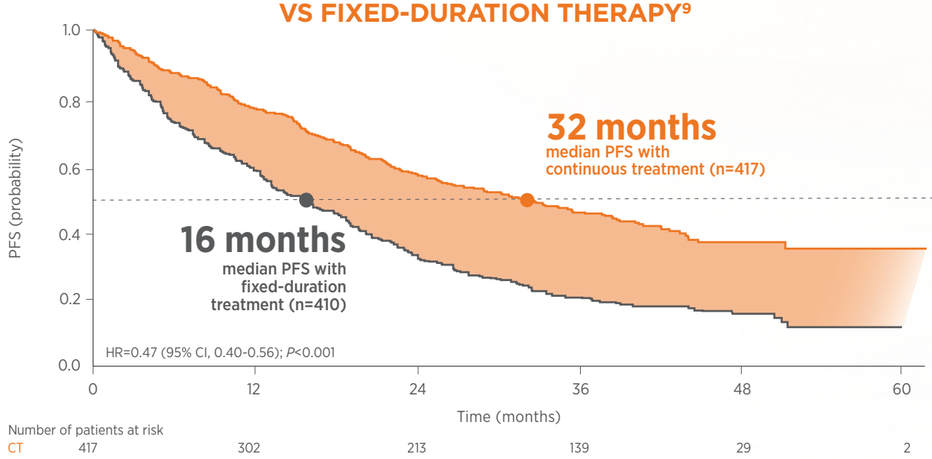
NINLARO®
(ixazomib) capsules
4mg | 3mg | 2.3mg

In multiple myeloma

CONTINUOUS PROTEASOME INHIBITION REMAINS A CORNERSTONE OF TREATMENT WITH OPTIMAL OUTCOMES[2,7,8]

Proteasome inhibitor (PI)–based triplet regimens have demonstrated superior efficacy vs doublet regimens[2,8]

CONTINUOUS THERAPY DOUBLED MEDIAN PFS VS FIXED-DURATION THERAPY[9]



2x
mPFS WITH CONTINUOUS THERAPY[9]

Adapted from Palumbo et al, 2015.[9]
Results of a pooled analysis of three phase 3 studies.
CT=continuous treatment; FDT=fixed-duration treatment; mPFS=median progression-free survival.

- Proteasome inhibition has been a standard of care in the treatment of multiple myeloma for more than 15 years[7]

IN CLINICAL PRACTICE, MOST PATIENTS RECEIVE INJECTABLE PROTEASOME INHIBITORS FOR ONLY 4-7 MONTHS[10,11]

INJECTABLE PIs CAN BE DIFFICULT TO MAINTAIN BECAUSE OF[3]:

- **ADVERSE REACTIONS**
- **BURDEN OF REPEATED IV OR SQ ADMINISTRATION IMPACTING PATIENTS' HRQOL**
- **RESTRICTED MOBILITY**
- **DESIRE TO REMAIN OUTSIDE OF A HOSPITAL OR CLINIC**

HRQOL=health-related quality of life; IV=intravenous; SQ=subcutaneous.

WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% 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 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.
- **Cutaneous Reactions:** 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.
- **Thrombotic Microangiopathy:** Cases, sometimes fatal, 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.

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. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.
- **Embryo-fetal Toxicity:** 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 final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. NINLARO can cause fetal harm.

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

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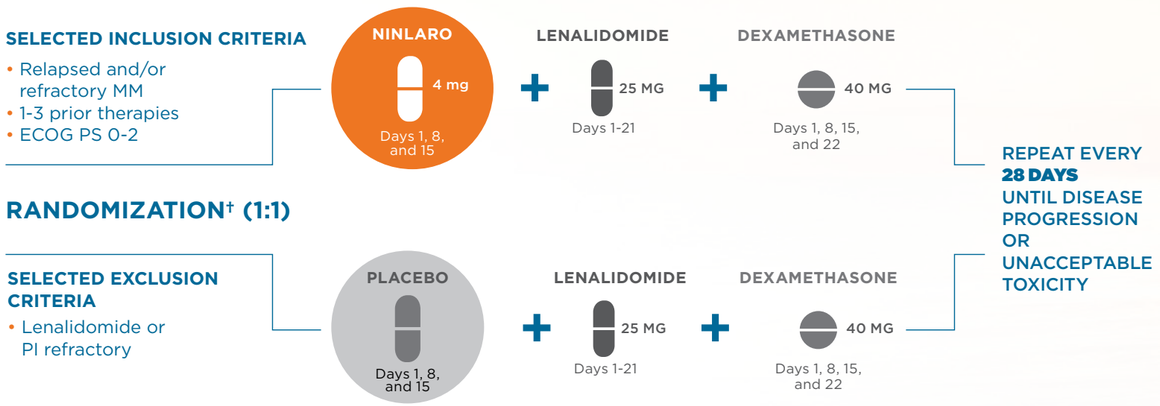
TOURMALINE-MM1 EVALUATED LONG-TERM* TREATMENT WITH THE ALL-ORAL NINLARO® (ixazomib) REGIMEN[1,2,12,13]

A global, phase 3, randomized, double-blind, placebo-controlled study of patients with relapsed and/or refractory multiple myeloma (N=722)[1,2]



- The primary endpoint of PFS, according to 2011 IMWG criteria, was assessed every 4 weeks until disease progression by a blinded IRC and was based on central laboratory results[1]
- Key secondary endpoints included OS and OS in del(17p)[2]
- Other secondary endpoints included ORR, PFS in patients with high-risk cytogenetics,[‡] and safety[2]

69% OF PATIENTS WERE PREVIOUSLY TREATED WITH VELCADE® (bortezomib)[2]

***Defined as treatment to disease progression or unacceptable toxicity.**
†Stratification: 1 vs 2 or 3 prior therapies; PI exposed vs PI naive; and ISS stage I or II vs III.
‡Defined as patients with del(17p), t(4;14), and/or t(14;16).
ECOG=Eastern Cooperative Oncology Group performance status; IMWG=International Myeloma Working Group; IRC=independent review committee; ISS=International Staging System; MM=multiple myeloma; ORR=overall response rate; OS=overall survival.

IMPORTANT SAFETY INFORMATION (cont'd)

SPECIAL POPULATIONS

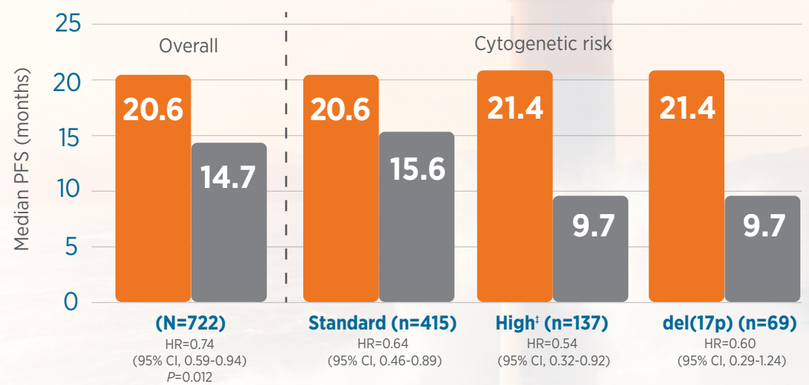
- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.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

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. 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. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.
- **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 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.
- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% 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 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

~6-MONTH MEDIAN PFS BENEFIT AND DURABLE RESULTS SEEN IN DIFFICULT-TO-TREAT PATIENTS[1,2]

MEDIAN PFS IN OVERALL POPULATION AND CYTOGENETIC RISK SUBGROUPS[1,2,14]



>2x
mPFS IN HIGH-RISK‡ PATIENTS (n=137)[2]

Study limitations:
- 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[2]

NINLARO regimen
Rd regimen

THE NINLARO REGIMEN DEMONSTRATED A SAFETY PROFILE AMENABLE TO TREATMENT TO DISEASE PROGRESSION[1]

DISCONTINUATION RATES DUE TO ARs WERE SIMILAR TO THOSE IN THE Rd REGIMEN[15]

13% vs 11%

with the NINLARO and Rd regimens, respectively

- The most common ARs (≥20%) in the NINLARO regimen and greater than the Rd regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%)[1]
- Serious ARs reported in ≥2% of patients included thrombocytopenia (2%) and diarrhea (2%)[1]
- 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[14]
- As seen in the overall population, in both high-risk‡ and standard-risk cytogenetics patients, common adverse events were primarily of grade 1 or 2 severity and included diarrhea, constipation, neutropenia, and anemia[14]

AR=adverse reaction; Rd=lenalidomide, dexamethasone.

WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.
- **Cutaneous Reactions:** 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.

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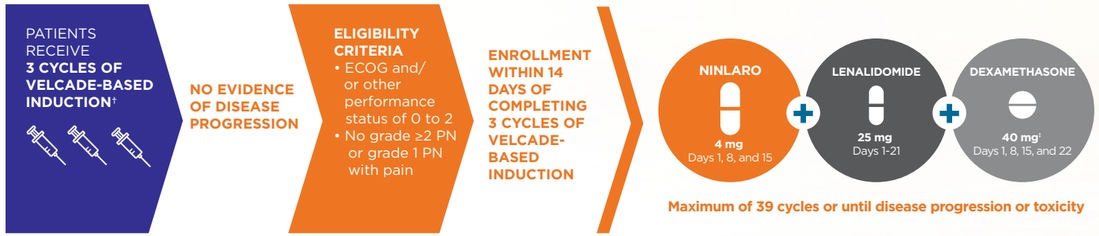
US MM-6 studied

LONG-TERM* PROTEASOME INHIBITION FACILITATED BY IN-CLASS TRANSITION FROM VELCADE® (bortezomib) TO NINLARO® (ixazomib)[3]

An ongoing US community-based, open-label, single-arm, phase 4 study in adult patients with newly diagnosed multiple myeloma who are:

- Transplant ineligible or for whom transplant would be delayed ≥24 months
- Receiving first-line VELCADE-based induction (85% of patients received VRd)

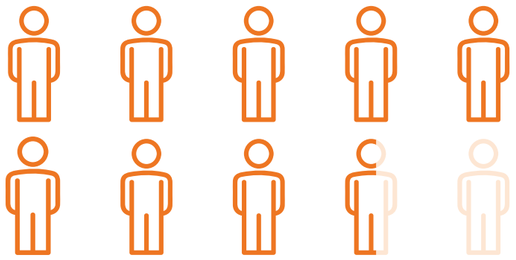


- This study included real-world patients who are often underrepresented in clinical trials because of eligibility criteria
  - 44% of patients were aged ≥75 years, 15% were Black or African American, 10% were Hispanic/Latino, 29% had creatinine clearance <60 mL/min, and 99% had any concurrent medical condition
- The primary endpoint is 2-year PFS, from the first administration of the NINLARO regimen
- **Study limitation:** Study is a single-arm, open-label trial, which may limit interpretation of the results
- As of November 18, 2019, 84 patients had been enrolled

***Defined as treatment to disease progression or unacceptable toxicity.**[1]
†Per regimens listed in NCCN Guidelines®.
‡Patients aged >75 years received 20 mg.
PN=peripheral neuropathy; VRd=bortezomib, lenalidomide, dexamethasone.

With in-class transition from VELCADE to the NINLARO regimen

>8 OF 10 PATIENTS WERE PROGRESSION FREE AT 1 YEAR[3]



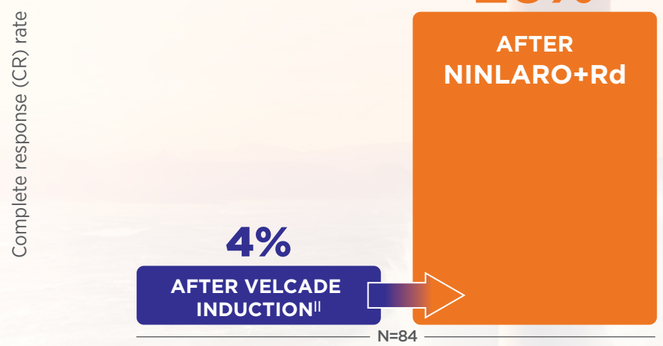
86%
OF PATIENTS WERE PROGRESSION FREE AT 12 MONTHS[3§]

§Preliminary results based on the first 84 patients enrolled in the study (at a median follow-up of 8 months).

WARNINGS AND PRECAUTIONS (cont'd)

- **Thrombotic Microangiopathy:** Cases, sometimes fatal, 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.
- **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. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.

RESPONSES DEEPENED WITH A TRANSITION TO THE NINLARO REGIMEN[3]

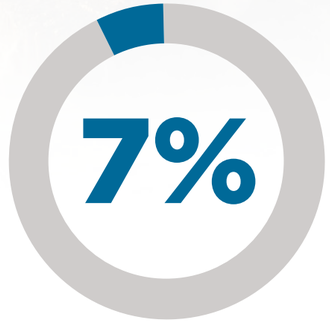


MORE THAN **6x CR** CONVERSION

- Transition to the NINLARO regimen increased ORR¶ from 62% (95% CI, 51-72) to 70% (95% CI, 59-80)

IN US MM-6, PRELIMINARY SAFETY# WAS CONSISTENT WITH PREVIOUS CLINICAL TRIAL DATA[3]

Discontinuation due to TEAEs



- Grade ≥3 TEAEs occurred in 48% of patients
- Serious TEAEs occurred in 36% of patients
- The serious TEAE occurring in >2 patients was pneumonia (5%)

‖Three cycles.
¶ORR=CR+VGPR+PR.
#N=84.
PR=partial response; TEAE=treatment-emergent adverse event; VGPR=very good partial response.

WARNINGS AND PRECAUTIONS (cont'd)

- **Embryo-fetal Toxicity:** 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 final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. NINLARO can cause fetal harm.

ADVERSE REACTIONS

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MAINTAIN THE DURABLE STRENGTH OF LONG-TERM* PROTEASOME INHIBITION WITH THE NINLARO® (ixazomib) REGIMEN[1-3,15]

EXTENDED EFFICACY

In TOURMALINE-MM1[1,2]:

- mPFS was extended by ~6 months overall with the NINLARO regimen† vs Rd regimen†
- Greater than 2X mPFS was achieved in high-risk‡ patients with the NINLARO regimen vs Rd regimen

In US MM-6[3]:

- 86% of patients were progression free at 12 months
- 6X CR conversion after transitioning from 3 cycles of VELCADE® (bortezomib) to the NINLARO regimen

MANAGEABLE TOLERABILITY

- 13% discontinued the NINLARO regimen vs 11% with Rd regimen due to ARs in TOURMALINE-MM1.[15] Serious ARs reported in ≥2% of patients included thrombocytopenia (2%) and diarrhea (2%)[1]
- 7% discontinued the NINLARO regimen due to TEAEs in US MM-6[3]

CONVENIENT ALL-ORAL, PI-BASED REGIMEN

The NINLARO regimen is the first and only PI-based therapy with the convenience of all-oral administration for long-term treatment[1,12,13]

NEXT TIME YOU SEE A PATIENT WHO COULD BENEFIT FROM LONG-TERM PROTEASOME INHIBITION, CONSIDER THE NINLARO REGIMEN

***Defined as treatment to disease progression or unacceptable toxicity.**
†The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The Rd regimen included placebo+lenalidomide+dexamethasone.
‡Defined as patients with del(17p), t(4;14), and/or t(14;16).

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

SPECIAL POPULATIONS

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REFERENCES: 1. NINLARO. Prescribing information. Takeda Pharmaceutical Company Limited; 3/2021. **2.** Moreau P, Masszi T, Grzasko N, et al; for TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-1634. **3.** Manda S, Yimer HA, Noga SJ, et al. Feasibility of long-term proteasome inhibition in multiple myeloma by in-class transition from bortezomib to ixazomib. *Clin Lymphoma Myeloma Leuk*. 2020;20(11):e910-e925. **4.** Terpos E, Ramasamy K, Maouche N, et al. Real-world effectiveness and safety of ixazomib-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma. *Ann Hematol*. 2020;99(5):1049-1061. **5.** Hájek R, Minařík J, Straub J, et al. Ixazomib-lenalidomide-dexamethasone in routine clinical practice: effectiveness in relapsed/refractory multiple myeloma. *Future Oncol*. Published online March 26, 2021. doi:10.2217/fon-2020-1225 **6.** Minarik J, Pika T, Radocha J, et al. Survival benefit of ixazomib, lenalidomide and dexamethasone (IRD) over lenalidomide and dexamethasone (Rd) in relapsed and refractory multiple myeloma patients in routine clinical practice. *BMC Cancer*. 2021;21(1):73. **7.** Gandolfi S, Laubach JP, Hideshima T, Chauhan D, Anderson KC, Richardson PG. The proteasome and proteasome inhibitors in multiple myeloma. *Cancer Metastasis Rev*. 2017;36(4):561-584. **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.7.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 26, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **9.** Palumbo A, Gay F, Cavallo F, et al. Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma. *J Clin Oncol*. 2015;33(30):3459-3466. **10.** Jagannath S, Roy A, Kish J, et al. Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. *Expert Rev Hematol*. 2016;9(7):707-717, Supplemental Table 2. Accessed April 26, 2021. https://www.tandfonline.com/doi/suppl/10.1080/17474086.2016.1195254. **11.** Hari P, Romanus D, Palumbo A, et al. Prolonged duration of therapy is associated with improved survival in patients treated for relapsed refractory multiple myeloma in routine clinical care in the United States. *Clin Lymphoma Myeloma Leuk*. 2018;18(2):152-160. **12.** Revlimid. Prescribing information. Celgene Corporation; 10/2019. **13.** Hemady. Prescribing information. Acrotech Biopharma, LLC; 2/2020. **14.** Avet-Loiseau H, Bahlis NJ, Chng W-J, et al. Ixazomib significantly prolongs progression-free survival in high-risk relapsed/refractory myeloma patients. *Blood*. 2017;130(24):2610-2618.
15. Data on File. Takeda Pharmaceutical Company Limited; 2021.

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Takeda

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