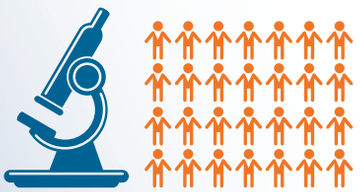
NINLARO™
ixazomib capsules

NINLARO is a proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. NINLARO enables appropriate patients to receive a fully oral proteasome inhibitor-based triplet combination therapy.

KEY MOMENTS IN TIME

09 — 2009 Ixazomib's First Use in Human Trials



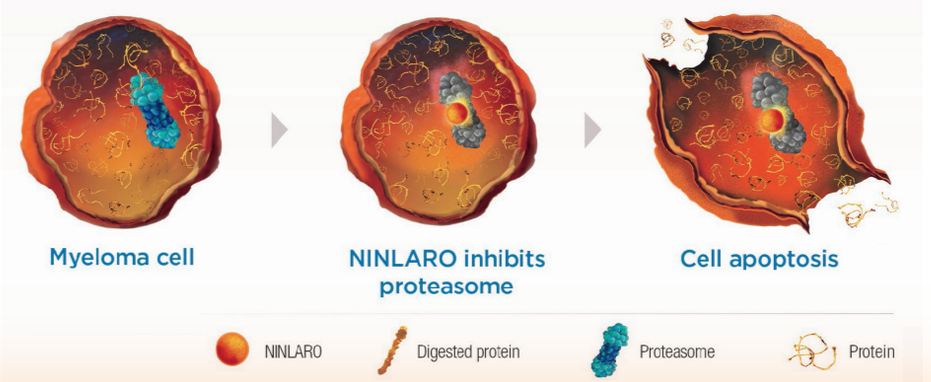
12 — 2012 TOURMALINE-MM1 Clinical Study for People with Relapsed and/or Refractory Multiple Myeloma Begins

14 — 2014 Ixazomib Granted Breakthrough Therapy Designation by U.S. FDA for Relapsed or Refractory Systemic Light-chain Amyloidosis

15 — 2015 NINLARO Receives U.S. FDA Approval November 2015

16 — 2016 NINLARO Receives European Commission Approval November 2016

HOW IT WORKS



1. NINLARO temporarily blocks proteasomes from breaking down proteins.

2. This causes a buildup of proteins in the cell.

3. The buildup of proteins can result in cell death.

NINLARO CLINICAL DATA[1]

Based on TOURMALINE-MM1

- NINLARO was evaluated as part of an all-oral regimen in a global, phase 3, double-blind, placebo-controlled study of 722 patients with relapsed and/or refractory multiple myeloma who have received one to three prior therapies, treated to progression or unacceptable toxicity (TOURMALINE-MM1). Treatment with NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen) demonstrated an improvement in median progression-free survival (PFS) compared with placebo plus lenalidomide and dexamethasone (placebo regimen).
- The primary and final statistical analysis of the PFS occurred at a median of 14.7 months' follow-up, where the NINLARO regimen demonstrated approximately 6-month PFS advantage compared to the placebo regimen (20.6 months vs. 14.7 months in the control arm; 95% confidence interval [CI] [17.0-non-estimable] and 95% CI [12.9-17.6], respectively; Hazard Ratio [HR] 0.74; 95% CI [0.59-0.94]; p = 0.01). Patients treated with the NINLARO regimen achieved rapid responses, with a median time to response of 1.1 months compared to 1.9 months in the placebo regimen. Overall response rate was 78% in the NINLARO regimen and 72% in the placebo regimen.
- NINLARO offers the convenience of oral administration. It should be taken weekly for 3 of every 4 weeks on days 1, 8, and 15 of a 28-day treatment cycle.
- Warnings and precautions associated with NINLARO include thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, hepatotoxicity, and embryo-fetal toxicity (see Important Safety Information below for more information).
- 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%).
- NINLARO offered a safety profile amenable to treatment to progression. Discontinuation rates were 13% for the NINLARO regimen and 11% for the placebo regimen. 80% of patients continued at the starting dose of NINLARO without dose reduction.

1 US National Institutes of Health of Health Clinical Trials Registry. A Phase 3 Study Comparing Oral Ixazomib Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma. https://clinicaltrials.gov/ct2/show/NCT01564537. Updated May 3, 2016. Accessed October 26, 2016.

PATIENT-CENTRIC INNOVATION

- Takeda's clinical development program embodies its commitment to patient-centric innovation for people living with multiple myeloma.
- Takeda strives to meet the unique and urgent needs of people living with cancer, their loved ones, and the healthcare providers around the world who support them.

Additional information about Takeda Oncology is available through its website, **www.takedaoncology.com**.

NINLARO™ (ixazomib): GLOBAL IMPORTANT SAFETY INFORMATION

SPECIAL WARNINGS AND PRECAUTIONS

- Thrombocytopenia has been reported with NINLARO (28% vs. 14% in the NINLARO and placebo regimens, respectively) with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. It did not result in an increase in hemorrhagic events or platelet transfusions. Monitor platelet counts at least monthly during treatment with NINLARO and consider more frequent monitoring during the first three cycles. Manage with dose modifications and platelet transfusions as per standard medical guidelines.
- Gastrointestinal toxicities have been reported in the NINLARO and placebo regimens respectively, such as diarrhea (42% vs. 36%), constipation (34% vs. 25%), nausea (26% vs. 21%), and vomiting (22% vs. 11%), occasionally requiring use of antiemetic and anti-diarrheal medications, and supportive care.
- Peripheral neuropathy was reported with NINLARO (28% vs. 21% in the NINLARO and placebo regimens, respectively). 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%). Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- Peripheral edema was reported with NINLARO (25% vs. 18% in the NINLARO and placebo regimens, respectively). Evaluate patients for underlying causes and provide supportive care, as necessary. Adjust the dose of dexamethasone per its prescribing information or the dose of NINLARO for severe symptoms
- Cutaneous reactions occurred in 19% of patients in the NINLARO regimen compared to 11% of patients in the placebo regimen. The most common type of rash reported in both regimens was maculo-papular and macular rash. Manage rash with supportive care, dose modification or discontinuation.
- Hepatotoxicity, drug-induced liver injury, hepatocellular injury, hepatic steatosis, and hepatitis cholestatic have been uncommonly reported with NINLARO. Monitor hepatic enzymes regularly and adjust dose for Grade 3 or 4 symptoms.
- Pregnancy- NINLARO can cause fetal harm. Advise male and females patients of reproductive potential to use contraceptive measures during treatment and for an additional 90 days after the final dose of NINLARO. Women of childbearing potential should avoid becoming pregnant while taking NINLARO due to potential hazard to the fetus. Women using hormonal contraceptives should use an additional barrier method of contraception.
- Lactation- It is not known whether NINLARO or its metabolites are excreted in human milk. There could be potential adverse events in nursing infants and therefore breastfeeding should be discontinued.

SPECIAL PATIENT 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 (ESRD) requiring dialysis. NINLARO is not dialyzable and, therefore, can be administered without regard to the timing of dialysis.

DRUG INTERACTIONS

Co-administration of strong CYP3A inducers with NINLARO is not recommended.

ADVERSE REACTIONS

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen, and greater than in the placebo regimen, were diarrhea (42% vs. 36%), constipation (34% vs. 25%), thrombocytopenia (28% vs. 14%), peripheral neuropathy (28% vs. 21%), nausea (26% vs. 21%), peripheral edema (25% vs. 18%), vomiting (22% vs. 11%), and back pain (21% vs. 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

For US Prescribing Information:
https://www.ninlarohcp.com/pdf/prescribing-information.pdf

For Canada Product Monograph:
http://www.takedacanada.com/ninlaropm

Takeda ONCOLOGY