GIVE YOUR PATIENTS THE POWER OF PROTEASOME INHIBITION THROUGHOUT THEIR TREATMENT JOURNEY

TAKEDA ONCOLOGY HAS ADVANCED THE MULTIPLE MYELOMA TREATMENT LANDSCAPE WITH 2 INNOVATIVE PIs[1-3]

VELCADE® (bortezomib) FOR INJECTION

VELCADE® (bortezomib)

The **first FDA-approved PI** for the treatment of patients with multiple myeloma

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

NINLARO® (ixazomib)

The first and **only FDA-approved oral PI** for patients with multiple myeloma who have received at least 1 prior therapy

PI=proteasome inhibitor.

INDICATION FOR VELCADE® (bortezomib) FOR INJECTION

VELCADE is indicated for the treatment of adult patients with multiple myeloma.

DOSAGE AND ADMINISTRATION: VELCADE is for subcutaneous (SC) or intravenous (IV) administration only. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

CONTRAINDICATIONS

- VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions.
- VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

INDICATION FOR NINLARO

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.

CONTRAINDICATIONS

NINLARO does not have any contraindications.

Please see Important Safety Information for VELCADE and NINLARO throughout and accompanying VELCADE (bortezomib) full Prescribing Information and NINLARO (ixazomib) full Prescribing Information.

WITH ESTABLISHED BENEFITS ACROSS THE TREATMENT CONTINUUM, PROTEASOME INHIBITION IS A CORNERSTONE OF MULTIPLE MYELOMA TREATMENT[1-5]

PROTEASOME INHIBITION IS A PROVEN MECHANISM IN MULTIPLE MYELOMA TREATMENT[1,3-5]

- Proteasome inhibition results in the accumulation of proteins within the myeloma cell, which ultimately induces apoptosis[1]
- For more than a decade, the effectiveness of PI-based regimens has been evaluated, with additional trials ongoing
- Continuous treatment with a PI-based regimen is associated with clinical benefits, including for patients with high-risk cytogenetics[3,6,7]

IMPORTANT SAFETY INFORMATION FOR VELCADE® (bortezomib)

WARNINGS AND PRECAUTIONS

- **Peripheral neuropathy**, including severe cases, may occur. Patients with preexisting symptoms may experience worsening peripheral neuropathy (including ≥Grade 3). Patients should be monitored for symptoms and managed with dose modification or discontinuation. Starting VELCADE subcutaneously may be considered for patients with preexisting or at high risk of peripheral neuropathy.

IMPORTANT SAFETY INFORMATION FOR NINLARO® (ixazomib)

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.

PROTEASOME INHIBITION HAS BEEN A STANDARD OF CARE IN THE TREATMENT OF MULTIPLE MYELOMA FOR MORE THAN 15 YEARS[1]

VELCADE received **accelerated approval** in 2003 for patients with progressive multiple myeloma after prior treatment

In 2008, approval was expanded to include **frontline treatment** of newly diagnosed multiple myeloma patients

Subcutaneous formulation was approved in 2012 for all indications

VELCADE® (bortezomib) FOR INJECTION

2005 2010 2015 2020

NINLARO, **the first oral PI that can be taken long term**,* was approved in 2015, in combination with **lenalidomide and dexamethasone**, for patients with multiple myeloma who have received at least 1 prior therapy

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

PATIENTS MAY NEED MORE THAN 1 PI OPTION THROUGHOUT THEIR TREATMENT JOURNEY[2,3]

***Defined as treatment to disease progression or unacceptable toxicity.**

Please see Important Safety Information for VELCADE and NINLARO throughout and accompanying VELCADE (bortezomib) full Prescribing Information and NINLARO (ixazomib) full Prescribing Information.

VELCADE AND NINLARO HELP PATIENTS ACROSS THE TREATMENT CONTINUUM[2-4]

VELCADE® (bortezomib) FOR INJECTION

VELCADE is indicated for the treatment of adult patients with multiple myeloma.

Induction therapy | 2nd line | 3rd+ line

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

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.

Induction therapy | 1 prior therapy | 2nd line | 3rd+ line

The NINLARO regimen in the multiple myeloma treatment paradigm for relapsed and/or refractory patients.

VELCADE WARNINGS AND PRECAUTIONS (cont'd)

- **Hypotension:** Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension. Management may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

NINLARO 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 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

VELCADE
AN INJECTABLE PI

NINLARO
AN ORAL PI

Please see Important Safety Information for VELCADE and NINLARO throughout and accompanying VELCADE (bortezomib) full Prescribing Information and NINLARO (ixazomib) full Prescribing Information.

VELCADE AND NINLARO HELP PATIENTS ACROSS THE TREATMENT CONTINUUM[2-4]

THE POWER OF PROTEASOME INHIBITION

VELCADE® (bortezomib) FOR INJECTION

VELCADE is indicated for the treatment of adult patients with multiple myeloma.

Induction therapy | 2nd line | 3rd+ line

Treatment Highlights[8]

- **Sustained OS advantage***
- **Responses improved with longer therapy**
- **Well-characterized safety profile**

Study Design

VISTA trial: a randomized, open-label, international phase 3 trial (N=682) evaluating the efficacy and safety of VELCADE administered intravenously in combination with melphalan+prednisone (MP) vs MP in patients with previously untreated multiple myeloma. After progressive disease was established, all patients were eligible to receive subsequent therapies. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and OS. At a prespecified interim analysis (median follow-up: 16.3 months), VELCADE+MP resulted in significantly superior results for TTP (median: 20.7 months with VELCADE+MP vs 15 months with MP [*P*=0.000002]), PFS, OS, and ORR. Further enrollment was halted, and patients receiving MP were offered VELCADE in addition. Updated analyses were performed.[4,9]

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

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.

Induction therapy | 1 prior therapy | 2nd line | 3rd+ line

The NINLARO regimen in the multiple myeloma treatment paradigm for relapsed and/or refractory patients.

Treatment Highlights[3]

- **Significantly extended PFS†**
- **Responses deepened with continued treatment**
  - Responses improved over time in both arms of the study
  - **Study limitation: The study was not powered to detect differences in response rates between arms**
- **Safety profile amenable to treatment to disease progression**

Study Design

TOURMALINE-MM1 trial: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of the NINLARO regimen (ixazomib+lenalidomide+dexamethasone) vs the placebo regimen (placebo+lenalidomide+dexamethasone) until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.[3]

- 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 lab results
- Key secondary endpoints included OS and OS in del(17p)[3]
- Other secondary endpoints included ORR, PFS in patients with high-risk cytogenetics,‡ and safety[3]
- Patients who were refractory to lenalidomide or PIs were excluded from the study

*Median OS of 56.4 months with VELCADE+MP vs 43.1 months with MP alone; HR=0.695 (95% CI, 0.57-0.85); *P*<0.05.
†OS data for the NINLARO regimen are not yet mature.
‡Defined as patients with del(17p), t(4;14), and/or t(14;16).[3]
CR=complete response; IRC=independent review committee; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTP=time to progression.

VELCADE WARNINGS AND PRECAUTIONS (cont'd)

- **Hypotension:** Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension. Management may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

NINLARO 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 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

Please see Important Safety Information for VELCADE and NINLARO throughout and accompanying VELCADE (bortezomib) full Prescribing Information and NINLARO (ixazomib) full Prescribing Information.

VELCADE® (bortezomib) was studied in a variety of patients with NDMM[4]

Selected baseline characteristics	VELCADE+MP (n=344)	MP (n=338)
Median age in years (range); ≥75 years	71 (57-90); 31%	71 (48-91); 30%
Male	51%	49%
Race (white/Asian/black/other)	88%/10%/1%/1%	87%/11%/2%/0
Karnofsky performance status score ≤70%	35%	33%
Median hemoglobin (g/L) (range)	104 (64-159)	106 (73-165)
Median platelet count (µL) (range)	221,500 (68,000-515,000)	221,500 (33,000-587,000)
Type of myeloma: IgG/IgA/Light chain	64%/24%/8%	62%/26%/8%
Creatinine clearance: <30/30-60/>60 mL/min	6%/48%/46%	5%/50%/46%
ISS stage: I/II/III	19%/47%/35%	19%/47%/34%

- In post hoc analyses, the efficacy of VELCADE+MP was assessed within the following subgroups that were defined as having a poor prognosis[4]:
  - Aged ≥75 years
  - Impaired creatinine clearance (<60 mL/min)
  - High-risk cytogenetics defined as the presence of del(17p), t(4;14), or t(14;16)

ISS=International Staging System; NDMM=newly diagnosed multiple myeloma.

VELCADE WARNINGS AND PRECAUTIONS (cont'd)

- **Cardiac toxicity**, including acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction, has occurred. Isolated cases of QT-interval prolongation have been reported. Patients with risk factors for, or existing, heart disease should be frequently monitored.

VELCADE achieved significantly superior results across key endpoints

Initial VISTA trial analysis (16.3-month median follow-up)	VELCADE+MP (n=344)	MP (n=338)	Statistical results
Median TTP* (months)	20.7	15	HR=0.54; *P*=0.000002
Median PFS (months)	18.3	14	HR=0.61 *P*=0.00001
ORR† (%)	69	34	*P*<0.0000000001
CR†‡ (%)	30	4	*P*<0.0000000001

*Primary endpoint.
†Responses were based on criteria established by the European Group for Blood and Marrow Transplantation.
‡28% of CRs were achieved after 24 weeks of therapy.[8]

VELCADE Delivered a >1-year Sustained OS Advantage

Updated VISTA trial analysis (60.1-month median follow-up)

- Median OS of 56.4 months with VELCADE+MP vs 43.1 months with MP alone; HR=0.695 (95% CI, 0.57-0.85); *P*<0.05
- Results achieved using twice-weekly followed by weekly dosing for a median of 50 weeks (54 weeks planned)[10]

Adverse Reactions in the VISTA Trial

The most commonly reported adverse reactions (ARs) for VELCADE+MP (n=340) vs MP alone (n=337) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), and leukopenia (32% vs 28%).

A total of 25% of patients receiving VELCADE+MP experienced serious ARs vs 18% receiving MP. The most commonly reported serious ARs with VELCADE+MP vs MP alone included pneumonia (5% vs 4%), diarrhea (4% vs 0%), thrombocytopenia (3% vs 1%), vomiting (3% vs <1%), nausea (2% vs <1%), anemia (2% vs 2%), herpes zoster (2% vs <1%), and dehydration (2% vs <1%).[11]

VELCADE WARNINGS AND PRECAUTIONS (cont'd)

- **Pulmonary toxicity:** Acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology have occurred, sometimes fatal. Pulmonary hypertension, in the absence of left heart failure or significant pulmonary disease, has been reported. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.

Please see Important Safety Information for VELCADE throughout and accompanying VELCADE (bortezomib) full Prescribing Information.

VELCADE® (bortezomib) FOR INJECTION

VELCADE® (bortezomib) dosing guidelines

- The recommended starting dose of VELCADE is 1.3 mg/m^2. VELCADE is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL
- VELCADE is administered in combination with oral melphalan and oral prednisone for 9 six-week treatment cycles as shown below
- In cycles 1 to 4, VELCADE is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29, and 32). In cycles 5 to 9, VELCADE is administered once weekly (days 1, 8, 22, and 29). At least 72 hours should elapse between consecutive doses of VELCADE
- Discontinuations due to ARs were 11% for VELCADE+MP and 10% for MP alone[12]
- Use a lower starting dose for patients with moderate or severe hepatic impairment
- May re-treat starting at the last tolerated dose
- Dose must be individualized to prevent overdose

Dosing Regimen for Patients With Previously Untreated Multiple Myeloma

Twice-weekly VELCADE (cycles 1 to 4)

Week	1				2		3	4		5		6
VELCADE (1.3 mg/m^2)	Day 1	—	—	Day 4	Day 8	Day 11	Rest period	Day 22	Day 25	Day 29	Day 32	Rest period
Melphalan (9 mg/m^2) **Prednisone** (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	—	—	Rest period	—	—	—	—	Rest period

Once-weekly VELCADE (cycles 5 to 9 when used in combination with melphalan and prednisone)

Week	1				2		3	4		5		6
VELCADE (1.3 mg/m^2)	Day 1	—	—	—	Day 8	—	Rest period	Day 22	—	Day 29	—	Rest period
Melphalan (9 mg/m^2) **Prednisone** (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	—	—	Rest period	—	—	—	—	Rest period

VELCADE WARNINGS AND PRECAUTIONS (cont'd)

- **Posterior Reversible Encephalopathy Syndrome (PRES)** has occurred. Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.
- **Gastrointestinal toxicity**, including nausea, diarrhea, constipation, and vomiting, has occurred and may require use of antiemetic and antidiarrheal medications or fluid and electrolyte replacement. Ileus can occur. Interrupt VELCADE for severe symptoms.

VELCADE WARNINGS AND PRECAUTIONS (cont'd)

- **Thrombocytopenia/Neutropenia** that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle have occurred. Complete blood counts should be monitored frequently during treatment. Measure platelet counts prior to each dose of VELCADE. Adjust dose/schedule for thrombocytopenia. There have been reports of gastrointestinal and intracerebral hemorrhage. Support with transfusions and supportive care, according to published guidelines.
- **Tumor Lysis Syndrome** has been reported. Closely monitor patients with high tumor burden and take appropriate precautions.
- **Hepatic toxicity**, including acute liver failure, has been reported. Monitor hepatic enzymes during treatment. Upon occurrence, interrupt therapy with VELCADE to assess reversibility. There is limited re-challenge information in these patients.
- **Thrombotic Microangiopathy:** Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received VELCADE. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop VELCADE and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing TTP/HUS is not known.
- **Embryo-fetal Toxicity:** VELCADE can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use effective contraception during treatment and for at least seven months after the final dose of VELCADE. Women using hormonal contraceptives should also use a barrier method of contraception. Advise males with female sexual partners of reproductive potential that they must use contraception during treatment with VELCADE and for four months following treatment.

ADVERSE REACTIONS

- **Previously untreated multiple myeloma (MM):** In the phase 3 study of VELCADE administered intravenously with melphalan and prednisone (MP) vs MP alone, the most commonly reported adverse reactions (ARs) (≥ 30%) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), and leukopenia (32% vs 28%).
- **Relapsed MM:** In the phase 3 study of VELCADE administered intravenously vs dexamethasone, the most commonly reported ARs (≥ 20%) were nausea (52% vs 9%), diarrhea (52% vs 11%), fatigue (39% vs 25%), peripheral neuropathies (35% vs 4%), thrombocytopenia (33% vs 3%), constipation (30% vs 8%), vomiting (29% vs 3%), anorexia (21% vs 2%), and pyrexia (20% vs 6%). The most commonly reported serious ARs were diarrhea (3%), dehydration, herpes zoster, pyrexia, nausea, vomiting, dyspnea, and thrombocytopenia (2% each) in the VELCADE treatment group and pneumonia (4%), hyperglycemia (3%), pyrexia, and psychotic disorder (2% each) in the dexamethasone treatment group.
- **Relapsed MM subcutaneous vs IV:** In the phase 3 study of VELCADE administered subcutaneously vs intravenously in relapsed MM, safety data were similar between the two treatment groups. The most commonly reported ARs (≥ 30%) in the subcutaneous vs IV treatment groups were peripheral neuropathy (37% vs 50%) and thrombocytopenia (30% vs 34%). The incidence of serious ARs was similar in the subcutaneous treatment group (20%) and the IV treatment group (19%). The most commonly reported serious ARs were pneumonia and pyrexia (each 2%) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (each 3%) in the IV treatment group.

DRUG INTERACTIONS

- Avoid concomitant use with strong CYP3A4 inducers.
- Closely monitor patients receiving VELCADE in combination with strong CYP3A4 inhibitors and consider dose reduction of VELCADE if it must be administered with strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise nursing women not to breastfeed during treatment with VELCADE and for two months after treatment.
- **Renal Impairment:** No starting dosage adjustment is recommended for patients with renal impairment. In patients requiring dialysis, VELCADE should be administered after the dialysis procedure.
- **Hepatic Impairment:** No starting dosage adjustment is recommended for patients with mild hepatic impairment. Reduce the starting dose in patients with moderate or severe hepatic impairment.
- **Patients with Diabetes:** Patients on oral antidiabetic agents receiving VELCADE may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

Please see Important Safety Information for VELCADE throughout and accompanying VELCADE (bortezomib) full Prescribing Information.

VELCADE® (bortezomib) FOR INJECTION

TOURMALINE-MM1 is the first clinical trial using an all-oral PI-based treatment to disease progression or unacceptable toxicity[3,13,14]

The NINLARO® (ixazomib) regimen extended median PFS by ~6 months vs the placebo regimen. Median PFS: 20.6 vs 14.7 months for the NINLARO and placebo regimens, respectively; HR=0.74 (95% CI, 0.59-0.94); *P*=0.012[3]

Selected baseline characteristics		NINLARO regimen* (n=360)	Placebo regimen* (n=362)
Median age in years (range)		66 years (38-91)	66 years (30-89)
Male/Female		58%/42%	56%/44%
Prior line(s) of therapy (median: 1) 1† | 2 or 3†		62% | 38%	60% | 40%
Type of prior therapy Bortezomib containing† | Carfilzomib containing† Thalidomide containing | Lenalidomide containing Stem cell transplant		69% | <1% 44% | 12% 59%	69% | 1% 47% | 12% 55%
Creatinine clearance <30 mL/min | 30-59 mL/min | ≥60 mL/min		1% | 21% | 78%	1% | 26% | 72%
Status at baseline Relapsed | Refractory | Relapsed and refractory		77% | 12% | 11%	77% | 11% | 12%
Myeloma ISS stage	I or II† | III†	87% | 13%	88% | 12%
High-risk cytogenetics	del(17), t(4;14), and/or t(14;16)	21%	17%
ECOG PS	0 or 1 | 2 | Missing	93% | 5% | 2%	92% | 7% | 1%

*The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The placebo regimen included placebo+lenalidomide+dexamethasone.
†Stratification factor.
ECOG PS=Eastern Cooperative Oncology Group performance status.

NINLARO Regimen Dosing Guidelines

NINLARO should not be taken with food.

- NINLARO is administered orally on days 1, 8, and 15 of a 28-day cycle
  - NINLARO should be taken once a week on the same day and at approximately the same time for the first 3 weeks of a 4-week cycle
- Lenalidomide is administered orally on days 1-21 of a 28-day cycle
- Dexamethasone is administered orally on days 1, 8, 15, and 22 of a 28-day cycle

Please note that there is NO DOSING on days 23-28.

- The recommended starting dose of NINLARO is 4 mg (one capsule) in combination with lenalidomide and dexamethasone
- A 3-mg starting dose is recommended for patients with moderate or severe hepatic impairment and patients with severe renal impairment or end-stage renal disease requiring dialysis. A 2.3-mg dose is also available for subsequent dose reductions due to ARs

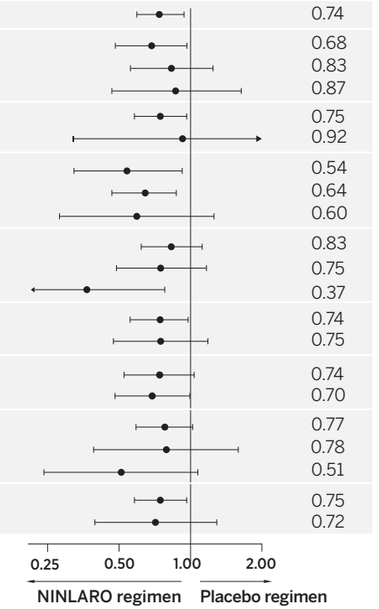
Please refer to the accompanying NINLARO full Prescribing Information for dose modification guidelines for hematologic and nonhematologic toxicities, as well as dose reduction instructions for patients with hepatic or renal impairment.

Positive PFS Trends Seen Across Selected Prespecified Subgroups: Hazard Ratios

PFS analysis in overall population and selected patient populations

- **Study limitations:**
  - **This study was not powered to show significance in PFS across these prespecified subgroups[15]**
  - **Cytogenetic risk data were not available for 24% of patients in the study[3]**
- Other prespecified subgroups not included in this figure were gender, race, region, Western countries, prior bortezomib exposure, thalidomide refractory, creatinine clearance at baseline, and refractory to last prior therapy[15]
  - The PFS results in the above subgroups were consistent with those represented in the figure below[3,16,17]

Variable	Subgroup	Hazard ratio (95% CI)
Subjects	N=722	0.74
Years of age	≤65 (n=344) >65-75 (n=270) >75 (n=108)	0.68 0.83 0.87
ECOG PS	0 or 1 (n=670) 2 (n=42)	0.75 0.92
Cytogenetic risk	High risk (n=137) Standard risk (n=415) del(17p) (n=69)	0.54 0.64 0.60
Prior therapies	1 (n=441) 2 (n=208) 3 (n=73)	0.83 0.75 0.37
Prior PI	Exposed (n=503) Naive (n=219)	0.74 0.75
Prior immunomodulatory drug	Exposed (n=397) Naive (n=325)	0.74 0.70
Relapsed/refractory	Relapsed (n=556) Refractory (n=82) Relapsed and refractory (n=83)	0.77 0.78 0.51
ISS stage at screening	I or II (n=632) III (n=90)	0.75 0.72



Warnings and Precautions

Warnings and Precautions associated with NINLARO include thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, thrombotic microangiopathy, hepatotoxicity, and embryo-fetal toxicity.

NINLARO 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.

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

NINLARO® (ixazomib) capsules
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Feasibility of long-term proteasome inhibition in multiple myeloma by *in*-class transition from bortezomib to ixazomib

Manda S, Yimer HA, Noga SJ, Girnius S, et al. Feasibility of long-term proteasome inhibition in multiple myeloma by *in*-class transition from bortezomib to ixazomib. *Clin Lymphoma Myeloma Leuk*. Preprint posted online July 6, 2020. doi:10.1016/j.clml.2020.06.024

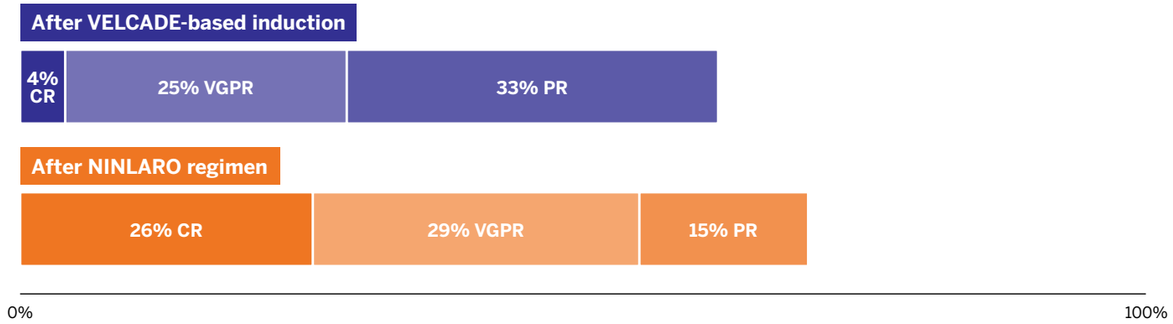
US MM-6 is an ongoing US community-based, real-world, open-label, single-arm, phase 4 study in patients with newly diagnosed multiple myeloma who are transplant ineligible or for whom transplant would be delayed ≥24 months and who are receiving first-line VELCADE-based induction. This study included real-world patients who are often underrepresented in clinical trials because of eligibility criteria. In US MM-6, 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.[18]

- Patients receive 3 cycles of VELCADE-based induction (per regimens listed in NCCN guidelines)[18]
- Patients who have no evidence of disease progression after 3 treatment cycles are enrolled to receive the NINLARO regimen (ixazomib+lenalidomide+dexamethasone) for a maximum of 39 cycles or until disease progression or toxicity[18]
- The primary endpoint is 2-year PFS, from the first administration of the NINLARO regimen[18]
- **Study limitation: Study is an open-label trial lacking a comparator arm, which may limit interpretation of the results**

Preliminary Results Based on the First 84 Patients Enrolled in the Study (at a Median Follow-up of 8 Months)[18]

- **The preliminary 12-month PFS rate was 86% (95% CI, 73-93) both from the start of VELCADE-based induction and from the start of treatment with the NINLARO regimen***

ORRs Were 62% After VELCADE-Based Induction and 70% After Treatment With the NINLARO Regimen (N=84)[18†]



Preliminary safety was consistent with previous NINLARO studies[18]

78%-92% of patients reported high medication adherence in cycles 1-5 of treatment[18‡]

At data cutoff,[§] patients had received a mean of 10.1 months of continuous PI therapy, with 7.3 months on the NINLARO regimen. Sixty-two percent remained on therapy.[18]

*PFS data from US MM-6, including in patients with high-risk cytogenetics, were immature.
†ORR=CR+VGPR+PR.
‡Includes patients who reported medication adherence as "excellent" or "very good" in cycles 1–5. At the time of this analysis, the number of evaluable patients was <30% after cycle 5.
§As of November 18, 2019.
PR=partial response, VGPR=very good partial response.

NINLARO 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.
- **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.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO. Women using hormonal contraceptives should also use a barrier method of contraception.

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.

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 nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

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

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

VELCADE® (bortezomib) FOR INJECTION

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

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Committed to the treatment of multiple myeloma

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Please see Important Safety Information for VELCADE and NINLARO throughout and accompanying VELCADE (bortezomib) full Prescribing Information and NINLARO (ixazomib) full Prescribing Information.

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