Ninlaro (Ixazomib): First Oral Proteasome Inhibitor Approved for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma

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Multiple myeloma is a cancer of plasma cells in the bone marrow that often leads to bone destruction and bone marrow failure.[1,2] According to the American Cancer Society, more than 26,800 new cases of multiple myeloma were diagnosed in 2015, and 11,240 deaths were attributed to the disease.[3]

Representing approximately 1% of all cancers, multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma.[4] The incidence of multiple myeloma is higher among men than in women.[1] Individuals aged ≥65 years, those with a family history of the disease, and those with a history of monoclonal gammopathy of undetermined significance are at increased risk for multiple myeloma.[1] Several common complications of multiple myeloma include bone pain, kidney dysfunction, bone loss, impaired immunity, and anemia.[5]

Although the overall incidence of multiple myeloma continues to increase, the mortality rates associated with this malignancy have declined during the past 20 years.[1,6] Specifically, the advent of novel therapy options for multiple myeloma, as well as improvements in high-dose therapy and supportive care have contributed to extended survival for patients with multiple myeloma.[6]

New anticancer drugs and novel combinations have emerged in part because of improved understanding of the bone marrow microenvironment and the biology of multiple myeloma.[7] Immune modulators and proteasome inhibitors now represent the cornerstones of initial treatment for multiple myeloma based on their ability to enhance the overall response rates and survival.[2,7]

Because novel agents have had a considerable impact on the US healthcare system, understanding their relative cost-effectiveness is important for ensuring efficient use. Overall, 2 recent evaluations of the economics of new agents in multiple myeloma resulted in similar conclusions.[8,9] Using claims data from more than 2600 patients with multiple myeloma, one study showed that the 1-year cost of bortezomib-based therapy was similar to the cost of older drug combinations (approximately $112,000 each), whereas the costs of thalidomide- and lenalidomide-based regimens were significantly higher (approximately $130,500 and $159,200, respectively) than older combinations.[8] In addition, patients taking thalidomide and lenalidomide had higher out-of-pocket costs because of Medicare Part D coverage gaps.[8]

The second study modeled the cost-effectiveness of novel agents combined with melphalan and prednisone in patients with newly diagnosed multiple myeloma who were ineligible for a transplant.[9] The researchers concluded that adding bortezomib to melphalan and prednisone was more cost-effective than adding thalidomide or lenalidomide to the same drug combination.[9]

Despite strides in the treatment of patients with multiple myeloma, patients will experience disease relapse after initial treatment, and multiple lines of therapy are typically required. Considerations for patients with relapsed or refractory multiple myeloma include the duration of response to previous treatment and the risk for toxicity. There remains a marked need for additional therapeutic options for this patient population.[10]

Ixazomib Approved for Relapsed or Refractory Multiple Myeloma

On November 20, 2015, the US Food and Drug Administration (FDA) approved ixazomib (Ninlaro; Takeda Oncology) capsules in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who received at least 1 previous therapy.[11,12] Ixazomib is the first oral proteasome inhibitor approved by the FDA for this patient population.[11]

The safety and efficacy of ixazomib were demonstrated in the TOURMALINE-MM1 study, an international, phase 3, double-blind clinical trial.[11-14] More than 720 patients with relapsed and/or refractory multiple myeloma were randomized to ixazomib plus lenalidomide and dexamethasone or to placebo plus lenalidomide and dexamethasone.[11-14] After the first prespecified interim analysis, treatment with ixazomib plus lenalidomide and dexamethasone significantly ex-

tended progression-free survival (PFS) compared with placebo plus lenalidomide and dexamethasone.[11-14]

Richard Pazdur, MD, Director of the FDA's Office of Hematology and Oncology Products, said, "As we learn more about the underlying biology of multiple myeloma, we are encouraged to see the development of new ways to treat this disease. Today's approval…provides patients with a new oral treatment that slows disease progression when other therapy has failed."[11]

Mechanism of Action

Ixazomib is a reversible proteasome inhibitor that preferentially binds to the beta 5 subunit of the 20S proteasome and inhibits its chymotrypsin-like activity.[12] Based on in vitro studies, ixazomib induces apoptosis of multiple myeloma cell lines. It was also cytotoxic against myeloma cells from patients whose disease relapsed after previous therapies, including bortezomib, lenalidomide, and dexamethasone.[12]

Dosing and Administration

The recommended starting doses of each component of the 28-day regimen are ixazomib 4 mg once weekly on days 1, 8, and 15; lenalidomide 25 mg once daily on days 1 through 21; and dexamethasone 40 mg once weekly on days 1, 8, 15, and 22.

The recommended starting dose of ixazomib in patients with moderate or severe hepatic impairment, severe renal impairment, or end-stage renal disease requiring dialysis is 3 mg.[12]

Ixazomib should be taken on the same day of the week and at approximately the same hour of the day. Ixazomib should be taken at least 1 hour before or at least 2 hours after eating. The capsule should be swallowed with water and should not be crushed, chewed, or opened.[12]

If a dose of ixazomib is delayed or missed, the dose should be taken only if the next scheduled dose is ≥72 hours away. The patient should not take a double dose of ixazomib to account for the missed dose. Overall, 3 capsule strengths are available for ixazomib—4 mg, 3 mg, and 2.3 mg.[12]

Clinical Trials

TOURMALINE-MM1

TOURMALINE-MM1, a multinational, randomized, double-blind study, compared ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in patients with multiple myeloma whose disease progressed during or after 1 to 3 previous therapies.[11-14] Overall, 722 patients were randomized in a 1:1 ratio to the active triple-drug regimen or to placebo plus lenalidomide and dexamethasone until disease progression or until unacceptable toxicity.[12-14]

Table The TOURMALINE-MM1 Clinical Trial: Ixazomib plus Lenalidomide and Dexamethasone versus Placebo plus Lenalidomide and Dexamethasone

Efficacy parameter	Ixazomib/ lenalidomide/ dexamethasone (N = 360)	Placebo/ lenalidomide/ dexamethasone (N = 362)
Progression-free survival		
Events, N (%)	129 (36)	157 (43)
Median, mo	20.6 (95% CI, 17.0-NE)	14.7 (95% CI, 12.9-17.6)
Hazard ratio	0.74 (95% CI, 0.59-0.94)	
Stratified log-rank *P* value	.012	
Response rate		
Overall response, %	78	72
Complete response, %	12	7
Very good partial response, %	36	32
Partial response, %	30	33

CI indicates confidence interval; NE, not evaluable.
Source: Ninlaro (ixazomib) capsules prescribing information; November 2015.

The treatment cycles were repeated every 28 days in both study arms. Randomization was stratified according to the number of previous lines of therapy (1 vs 2 or 3), myeloma International Staging System (stage I or II vs stage III), and previous therapy status with a proteasome inhibitor (exposed vs not exposed).[12-14]

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The primary efficacy end point in TOURMALINE-MM1 was PFS according to the 2011 International Myeloma Working Group Consensus Uniform Response Criteria.[12] The response assessments were conducted every 4 weeks until disease progression.[12-14]

Demographic and baseline characteristics were similar between the treatment arms.[12] The patients' median age was 66 years.[12]

The majority (87%) of patients who received ixazomib

plus lenalidomide and dexamethasone had stage I or II disease and 62% had received 1 previous therapy for multiple myeloma.[12] Overall, 59% of the patients receiving ixazomib plus lenalidomide and dexamethasone had undergone stem-cell transplantation for multiple myeloma.[12]

The PFS was significantly improved in the active combination arm compared with the placebo arm (**Table**).[12] The median PFS was 20.6 months among patients receiving the ixazomib-based combination compared with 14.7 months in the placebo arm, a significant (P = .012) difference (hazard ratio, 0.74; 95% confidence interval, 0.59-0.94).[12]

The median time to response was 1.1 months with ixazomib compared with 1.9 months with placebo.[12] In the response evaluable population, the median duration of response was 20.5 months versus 15 months, respectively.[12]

After a median follow-up of 23 months, a planned interim analysis of overall survival (OS) was conducted with 35% of the required number of deaths for the final OS analysis; an OS benefit was not demonstrated.[12]

Adverse Events

Among patients receiving the ixazomib combination regimen in TOURMLINE-MM1, the most common adverse reactions (all grades) reported at a rate of ≥20% compared with the placebo arm included thrombocytopenia (78% vs 54%), neutropenia (67% vs 66%), diarrhea (42% vs 36%), constipation (34% vs 25%), peripheral neuropathies (a pooled term; 28% vs 21%), nausea (26% vs 21%), peripheral edema (25% vs 18%), vomiting (22% vs 11%), and back pain (21% vs 16%).[12]

Serious adverse reactions reported in ≥2% of patients receiving the active regimen included thrombocytopenia (2%) and diarrhea (2%).[12] For each of these adverse reactions, ≥1 of the 3 drugs was discontinued in ≤1% of patients receiving ixazomib plus lenalidomide and dexamethasone.[12]

Various eye disorders were reported in 26% of patients receiving the ixazomib combination regimen compared with 16% of patients in the placebo arm.[12] The most common eye disorders that were more common with ixazomib than with placebo included blurred vision (6% vs 3%, respectively), dry eye (5% vs 1%, respectively), and conjunctivitis (6% vs 1%, respectively).[12] Grade 3 eye disorders were reported in 2% of patients receiving the ixazomib combination and in 1% of patients receiving the placebo combination.[12]

Ixazomib does not have any contraindications.[12]

Drug Interactions

Ixazomib should not be used concomitantly with strong cytochrome P3A inducers (ie, rifampin, phenytoin, carbamazepine, and St. John's wort).[12]

Warnings and Precautions

Thrombocytopenia. Platelet nadirs associated with ixazomib therapy typically occurred between days 14 and 21 of each 28-day cycle and recovered to baseline levels by the beginning of the next cycle.[12] The discontinuation of ≥1 of the 3 drugs in the regimen because of thrombocytopenia occurred in <1% of patients who received the ixazomib combination and in 2% of patients who received the placebo combination.[12]

Platelet counts should be evaluated at least monthly during treatment with ixazomib.[12]

Gastrointestinal toxicities. Diarrhea, constipation, nausea, and vomiting occasionally required the use of antidiarrheal and antiemetic medications.[12]

Peripheral neuropathy. The majority of peripheral neuropathy reactions were grade 1 or 2.[12] Grade 3 peripheral neuropathy was reported in 2% of patients receiving both regimens.[12] Patients taking ixazomib should be monitored for symptoms of neuropathy.[12]

Peripheral edema. The majority of peripheral edema reactions observed with ixazomib were grade 1 or 2.[12] Ixazomib dosing should be adjusted if grade 3 or 4 peripheral edema occurs.[12]

Cutaneous reactions. Grade 3 rash—typically maculopapular and macular—was reported in 3% of patients receiving ixazomib and in 1% of patients receiving placebo.[12] Supportive care and dose modification should be considered if grade ≥2 rash occurs with ixazomib.[12]

Hepatotoxicity. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic, and hepatotoxicity have each been reported in <1% of patients taking ixazomib.[12] Patients receiving ixazomib should be tested for hepatic enzymes regularly, and the ixazomib dose should be adjusted if grade 3 or 4 events are observed.[12]

Specific Populations

Pregnancy. Ixazomib can cause fetal harm when administered during pregnancy. Women should avoid becoming pregnant while taking ixazomib.[12] Females of reproductive potential should be advised to use effective contraception during treatment with ixazomib and for 90 days after the final dose.[12]

Lactation. It is not known whether ixazomib or its metabolites are present in human milk.[12] Women taking ixazomib should discontinue nursing.[12]

Men and women of reproductive potential. Effective contraceptives should be used while taking ixazomib and for 90 days after treatment with ixazomib.[12]

Pediatric use. The safety and effectiveness of ixazomib have not been established in children.[12]

Geriatric use. Of the patients with multiple myeloma in clinical studies of ixazomib, 55% were aged ≥65 years

and 17% were aged ≥75 years.[12] No differences in safety were observed between the younger and older cohorts.[12]

Hepatic impairment. In patients with moderate or severe hepatic impairment, blood levels of ixazomib increased by 20% compared with patients with normal liver function.[12] The starting dose of ixazomib should be reduced in this patient population.[12]

Renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis, blood levels of ixazomib increased by 39% compared with normal renal function.[12] The starting dose of ixazomib should be reduced in this patient population. Because ixazomib is not dialyzable, it can be administered without regard to dialysis timing.[12]

Ixazomib is the first oral proteasome inhibitor to demonstrate clinical benefit and an acceptable safety profile in patients with relapsed or refractory multiple myeloma.

Conclusion

Ixazomib is the first oral proteasome inhibitor to demonstrate clinical benefit and an acceptable safety profile in patients with relapsed or refractory multiple myeloma. The TOURMALINE-MM1 study demonstrated that adding ixazomib to lenalidomide and dexamethasone significantly enhanced PFS compared with placebo plus lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. The combination of ixazomib plus lenalidomide and dexamethasone represents the first all-oral triple therapy for patients with relapsed or refractory multiple myeloma.

In addition to the TOURMALINE-MM1 clinical trial, 4 global phase 3 trials are ongoing for ixazomib, including TOURMALINE-AL1, ixazomib plus dexamethasone in patients with relapsed or refractory amyloid light-chain amyloidosis; TOURMALINE-MM2, ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma; TOURMALINE-MM3, ixazomib versus placebo as maintenance therapy in patients with newly diagnosed multiple myeloma after induction therapy and autologous stem-cell transplantation; and TOURMALINE-MM4, ixazomib versus placebo as maintenance therapy in patients with newly diagnosed multiple myeloma who have not undergone autologous stem-cell transplantation. ■

References

1. National Cancer Institute. A snapshot of myeloma. November 5, 2014. www.cancer.gov/researchandfund ing/snapshots/myeloma. Accessed December 8, 2015.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): multiple myeloma. Version 2.2016. September 22, 2015. www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed December 8, 2015.
3. American Cancer Society. What are the key statistics about multiple myeloma? Revised March 9, 2015. www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics. Accessed December 8, 2015.
4. Smith L, McCourt O, Henrich M, et al. Multiple myeloma and physical activity: a scoping review. *BMJ Open*. 2015;5:e009576. Erratum in: *BMJ Open*. 2016;6:e009576corr1.
5. Mayo Clinic staff. Diseases and conditions: multiple myeloma: treatments and drugs. December 4, 2015. www.mayoclinic.org/diseases-conditions/multiple-myeloma/basics/treatment/con-20026607. Accessed December 11, 2015.
6. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111:2516-2520.
7. Andrews SW, Kabrah S, May JE, et al. Multiple myeloma: the bone marrow microenvironment and its relation to treatment. *Br J Biomed Sci*. 2013;70:110-120.
8. Teitelbaum A, Ba-Mancini A, Huang H, Henk HJ. Health care costs and resource utilization, including patient burden, associated with novel-agent-based treatment versus other therapies for multiple myeloma: findings using real-world claims data. *Oncologist*. 2013;18:37-45.
9. Garrison LP Jr, Wang S-T, Huang H, et al. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment. *Oncologist*. 2013;18:27-36.
10. Munshi NC, Anderson KC. New strategies in the treatment of multiple myeloma. *Clin Cancer Res*. 2013;19:3337-3344.
11. US Food and Drug Administration. FDA approves Ninlaro, new oral medication to treat multiple myeloma. Press release. November 20, 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473771.htm. Accessed December 11, 2015.
12. Ninlaro (ixazomib) capsules [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc; November 2015.
13. Takeda. Takeda presents data from phase 3 TOURMALINE-MM1 study for Ninlaro (ixazomib), first and only once-weekly oral proteasome inhibitor recently approved for multiple myeloma. Press release. December 6, 2015. www.takeda.com/news/2015/20151207 _7238.html. Accessed December 9, 2015.
14. Moreau P, Masszi T, Grzasko N, et al. Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRd), significantly extends progression-free survival (PFS) for patients (Pts) with relapsed and/or refractory multiple myeloma (RRMM): the phase 3 Tourmaline-MM1 study (NCT01564537). *Blood*. 2015;126. Abstract 727.