

Elotuzumab and ixazomib join the therapeutic arsenal for multiple myeloma

Last year, 2015, was a banner year for multiple myeloma treatment, with 5 new drugs approved by the US Food and Drug Administration. Two of those drugs, the monoclonal antibody elotuzumab and the proteasome inhibitor, ixazomib, were approved in November, following promising phase 3 clinical trial results, in combination with standard multiple myeloma therapies, the immunomodulatory agent lenalidomide and the corticosteroid dexamethasone, in the second-line setting. Notably, the approval of ixazomib marks the availability of the first all-oral regimen for multiple myeloma.

Elotuzumab was evaluated in the phase 3 ELOQUENT-2 study in which patients aged 18 years or older, with measurable disease, who had documented disease progression after their most recent therapy, and had creatinine clearance of 30 mL/minute or higher, were randomly assigned in a 1:1 ratio to receive elotuzumab in combination with lenalidomide and dexamethasone (elotuzumab group) or lenalidomide and dexamethasone alone (control group). Randomization was stratified according to baseline beta-2-microglobulin level, the number of previous therapies, and previous immunomodulatory drug therapy (previous treatment with lenalidomide was allowed in a maximum of 10% of patients).

Patients received elotuzumab intravenously at a dose of 10 mg/kg of body weight on days 1, 8, 15, and 22 during the first 2 28-day cycles, and then on days 1 and 15 starting with the third cycle. Lenalidomide was administered orally at a dose of 25 mg/day on days 1-21 of each cycle in both groups. In the elotuzumab group, dexamethasone was given at a dose of 40 mg/day during the week without elotuzumab and as a mixture of an 8-mg intravenous dose and 28-mg oral dose on the day of elotuzumab administration. In the control group, patients received a 40-mg oral dose of dexamethasone on days 1, 8, 15 and 22 of every cycle.

Patients also received mandatory premedication consisting of 25-50 mg diphenhydramine, 50 mg ranitidine, and 650-1,000 mg acetaminophen, or their equivalents, which was administered 30-90 minutes before elotuzumab infusion. Thromboembolic preventive treatment was administered according to institutional guidelines or at the investigator's discretion.

During June 2011-November 2012 at 168 sites globally, 646 patients underwent randomization and 635 were

What's new, what's important

For patients with multiple myeloma, it has been amazing to see so many therapeutic options emerging in the past 5 years. In 2015, both elotuzumab and ixazomib were approved for patients with melanoma who have received previous treatment.

Elotuzumab is a SLAMF7-directed immuno-stimulatory antibody approved for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received 1 to 3 prior therapies. The dose is 10 mg/kg administered intravenously every week for the first 2 cycles, and every 2 weeks thereafter. The patients should be pre-medicated with dexamethasone, diphenhydramine, ranitidine, and acetaminophen. The most common adverse reactions with elotuzumab are fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper-respiratory tract infection, decreased appetite, and pneumonia.

Ixazomib is a proteasome inhibitor also indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. The recommended starting dose is 4 mg administered orally once a week on days 1, 8, and 15 of a 28-day treatment cycle. The recommended starting dose of lenalidomide is 25 mg administered daily on days 1-21 of a 28-day treatment cycle and of dexamethasone, 40 mg administered on days 1, 8, 15, and 22 of a 28-day treatment cycle. The most common adverse reactions ($\geq 20\%$) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain.

— Jame Abraham, MD, FACP (abraha5@ccf.org)

treated. Over a median follow-up of 24.5 months, patients in the elotuzumab group experienced significantly longer progression-free survival (PFS) compared with those in the control group (median PFS, 19.4 months vs 14.9 months, respectively), a 30% relative reduction in risk of disease progression or death. The PFS benefit was consistent across subgroups examined, but seemed greatest in patients in whom multiple myeloma diagnosis had occurred more than 3.5 years before study entry. Overall, 79% of patients in the elotuzumab group experienced an objective response, compared with 66% in the control group, and responses were durable, lasting a median of 21 months in the elotu-

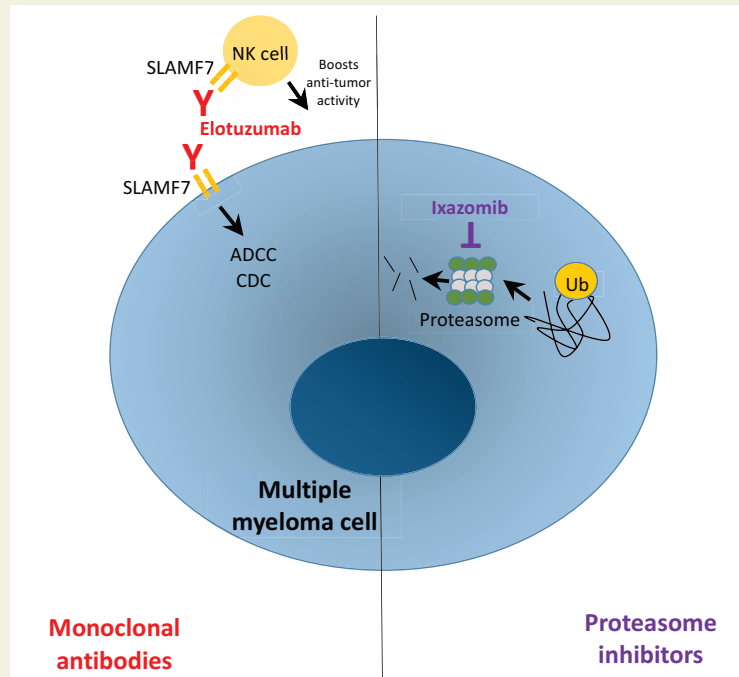
Mechanism of action: elotuzumab and ixazomib

Next-generation proteasome inhibitor and first-in-class monoclonal antibody

In 2015, an unprecedented number of new drugs were approved for the treatment of multiple myeloma. Two of those approvals, for elotuzumab and ixazomib, have unique mechanisms of action and came in a single month. Elotuzumab is the second monoclonal antibody approved for the treatment of multiple myeloma, but the first in a new class of drugs targeting the signaling lymphocyte activation molecule 7 (SLAMF7) protein. SLAMF7 is expressed on the surface of more than 95% of multiple myeloma cells, but not on the surface of most normal cells, offering an ideal target for a drug to specifically kill cancerous cells and spare healthy ones.

Elotuzumab binds to multiple myeloma cells expressing the SLAMF7 protein on their surface and induces cell death in a number of different ways. These include antibody-dependent cellular cytotoxicity (ADCC), in which the fragment crystallizable (Fc) domain of the antibody interacts with the Fc receptors on the surface of immune effector cells, activating the cytotoxic activity of the immune system. Antibodies can also induce the complement system, a cascade of proteins that assemble a complex that inserts itself into the cell membrane of a target cell and causes the cell to break apart and die. Elotuzumab has also been shown to target SLAMF7 on the surface of natural killer (NK) cells, boosting their antitumor activity, and increasing tumor cell destruction.

Ixazomib is a next-generation proteasome inhibitor, designed to have a shorter half-life than previous drugs in this class, in an effort to increase potency while reducing side effects. Proteasome inhibitors are designed to block the effects of the cellular machinery that removes surplus or damaged proteins from the cell. These proteins are tagged for destruction by the addition



Elotuzumab is a monoclonal antibody that targets signaling lymphocyte activation molecule 7 (SLAMF7), a protein that is highly expressed on the surface of multiple myeloma cells, and activates the immune system to attack and kill multiple myeloma cells. Ixazomib is a proteasome inhibitor that inhibits the activity of the ubiquitin-proteasome pathway, allowing accumulation of abnormal proteins within multiple myeloma cells, which triggers cell death.

of ubiquitin molecules that are recognized by the proteasome.

Multiple myeloma is a cancer of malignant plasma cells, the antibody producing cells. Proteasome inhibitors offer a particularly effective treatment strategy for this type of cancer because cancerous plasma cells produce a lot of abnormal antibody proteins and are heavily dependent on the proteasome to clear these proteins to prevent them accumulating and triggering cell death.

zumab group. The follow-up on overall survival (OS) was not mature at the time of study publication.

The addition of elotuzumab produced a modest increase in adverse events (AEs). AEs of any grade that occurred in more than 25% of patients included lymphocytopenia, anemia, fatigue, diarrhea, and constipation. Serious AEs were reported in 65% of patients in the elotuzumab group, and 57% of patients in the control group. The rates of discontinuation were 65% and 79%, respectively, most commonly a result of disease progression. A similar number of patients in each group died from an AE: in the elotuzumab group, due to infections, pulmonary embolism, gastrointestinal cancer, and myelodysplastic syndrome;

and in the control group, due to infections and pulmonary embolism.

Meanwhile, TOURMALINE-MM1 was the first double-blind, placebo-controlled trial of a proteasome inhibitor. In this phase 3 study, eligible patients with relapsed and/or refractory multiple myeloma, with measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2 (on a scale of 0-5, with 0 indicating no symptoms and increasing score indicating more disability), who had received 1-3 previous therapies, with adequate hematologic and hepatic function were enrolled.

A total of 722 patients at 147 sites in 26 countries were

randomized 1:1 during August 2012-May 2014 to receive either 4 mg oral ixazomib or matching placebo on days 1, 8, and 15; 25 mg oral lenalidomide on days 1-21; and 40 mg oral dexamethasone on days 1, 8, 15, and 22 of 28-day cycles until disease progression or unacceptable toxicity. Randomization was stratified according to the number of previous therapies received, previous exposure to proteasome inhibitors, and International Staging System disease stage. Patients also received mandatory thromboembolic prophylaxis.

Median follow-up was 14.7 months in the ixazomib group and 14.6 months in the control group and patients in the ixazomib group experienced significantly greater PFS (20.6 months vs 14.7 months, respectively), representing a 40% increase in PFS, with a consistent benefit across prespecified subgroups. Overall response rates were 78.3% and 71.5%, respectively and responses were rapid and durable. Median OS had not yet been reached in either group.

The addition of ixazomib to lenalidomide and dexamethasone was well tolerated. Treatment was discontinued in a similar proportion of patients in both study groups, and disease progression was the most common reason for dis-

continuation. Patients ended treatment as a result of AEs at a rate of 17% in the ixazomib group, compared with 14% in the control group. The most common hematologic AEs were neutropenia, thrombocytopenia, and anemia, while non-hematologic AEs included diarrhea, rash, constipation, and fatigue.

Elotuzumab is marketed as Empliciti by Bristol-Myers Squibb, and ixazomib as Ninlaro by Takeda Pharmaceuticals. As per the prescribing information, the recommended doses are 10 mg/kg administered intravenously every week for the first 2 cycles and then every 2 weeks thereafter for elotuzumab and 4 mg administered orally once a week on days 1, 8, and 15 of a 28-day treatment cycle for ixazomib.

There are warnings and precautions for elotuzumab including infusion reactions, infections, second primary malignancies, hepatotoxicity, and interference with the determination of complete response and possibly relapse from complete response in patients with immunoglobulin kappa myeloma protein. For ixazomib, the prescribing information details warnings and precautions including thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, hepatotoxicity, and embryofetal toxicity.

References

1. Ninlaro (ixazomib). Prescribing information. Cambridge, MA: Millennium Pharmaceuticals Inc. <https://www.ninlaro.com/prescribing-information.pdf>. Issued November 2015. Accessed June 20, 2016.
2. Empliciti (elotuzumab). Prescribing information. Princeton, NJ: Bristol-Myers Squibb Company. http://packageinserts.bms.com/pi/pi_empliciti.pdf. Issued November 2015. Accessed June 20, 2016.
3. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621-631.
4. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374:1621-1634.