Dr Mikhael Video Transcript

Narrator:

Welcome. In this video we will explore the utility of XPOVIO (selinexor) in the treatment of multiple myeloma.

INDICATION

XPOVIO® (selinexor) is a prescription medicine approved:

In combination with bortezomib and dexamethasone (XVd) to treat adult patients with multiple myeloma who have received at least one prior therapy.

This promotional XPOVIO video was developed in conjunction with Dr. Joseph Mikhael. Dr. Mikhael was compensated for his participation in this video.

This video is not intended to provide medical advice or replace the directions of the healthcare team.

Dr. Mikhael:

Hello, my name is Dr. Joseph Mikhael. I'm a hematologist and a professor at the Translational Genomics Research Institute in Phoenix, Arizona which is part of the City of Hope Cancer Center.

I am a multiple myeloma physician who's had the privilege of being involved in clinical trials and care of myeloma patients for over 20 years.

Before we get into XPOVIO (selinexor) mechanism of action, let's take a look at the current Multiple Myeloma landscape.

In the current treatment paradigm, patients often progress on commonly used combinations, including those of daratumumab, thus making physicians re-challenge patients with the same class or classes. This is where I believe XPOVIO, an XPO1 inhibitor, has its utility. With FDA approved indication in adult patients with at least one prior therapy, and an NCCN category 1 recommendation, XPOVIO provides you with an opportunity to introduce a different class that may demonstrate efficacy benefits for your Multiple Myeloma patients. Now let's see how different the MOA of XPOVIO is.

XPOVIO helps restore the body's own tumor defense system, leading to cell cycle arrest, and apoptosis of cancer cells. Healthy cells have a protein called XPO1 that is responsible for carrying important materials in and out of the core of the cell, the nucleus. Many of these materials help fight cancer, but only when they are inside the nucleus. XPOVIO helps to restore the body's own tumor defense system by blocking XPO1. The XPOVIO plus Vd treatment regimen is a combination of 3 different medicines that work together to kill certain cancer cells.

BOSTON was a phase 3, global, randomized, open-label study of patients with multiple myeloma who have received 1 to 3 prior therapies that compared XVd with Vd. The primary endpoint was progression-free survival, or PFS. Secondary endpoints included overall response rate, very good partial response rate or greater, and peripheral neuropathy of grade 2 or higher.

XVd demonstrated an early and sustained PFS benefit when compared with Vd. Median progression-free survival was 13.9 months vs 9.5 months with a hazard ratio of 0.7. This translates into a 30% reduction in the risk of progression or death. Outcomes were similar across select subgroups that included cytogenetics, renal impairment, prior therapy, and age 65 years and older.

Efficacy outcomes were similar across select subgroups. The risk of progression or death was lower in these represented subgroups including patients 65 years of age and older, patients with high-risk cytogenetic abnormalities, and patients with 1 previous line of therapy. Please note that these subgroup analyses were exploratory in nature. It does not control for type 1 error and was not powered or adjusted for multiplicity to assess PFS.

There were significantly higher rates of deep responses with XVd vs Vd. Overall response rate 76.4% vs 62.3%. Greater than or equal to VGPR rates of 44.6% vs 32.4%. Responses were rapid and durable. Median time to response was 1.4 months vs 1.6 months. And the median duration of response was 20.3 months vs 12.9 months.

The most exciting thing about the BOSTON trial is that it supports the use of an agent with a new mechanism of action earlier in the course of treatment. XPOVIO plus Vd can be used as early as first relapse. Identifying and using active regimens as early as possible is what we do now in multiple myeloma.

Narrator:

Thrombocytopenia: XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma.

Thrombocytopenia is the leading cause of dosage modifications. Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Monitor patients for signs and symptoms of bleeding. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia: XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection.

Monitor more frequently during the first 3 months of treatment. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity: XPOVIO can cause severe gastrointestinal toxicities in patients.

Nausea/Vomiting/Diarrhea: Provide prophylactic antiemetics or treatment as needed.

Dr. Mikhael:

The safety profile of XVd was generally manageable and/or reversible with appropriate prophylactic measures and supportive care.

Warnings and precautions include thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infections, neurologic toxicity, embryo-fetal toxicity, and cataracts.

Most common adverse reactions with XVd greater than or equal to 20% with a difference between the arms of greater than 5% vs Vd: fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, weight decrease, cataract, and vomiting. Serious adverse reactions with XVd in 52% of patients. Serious adverse reactions in greater than 3% of patients: pneumonia (14%), sepsis (4%), diarrhea (4%), and vomiting in 4%.

Fatal adverse reactions within 30 days of last treatment were seen in 6%: pneumonia in 3 patients, and sepsis in 3 patients. Additionally, XVd was not associated with major organ, cardiac, pulmonary, renal, or liver toxicities in the BOSTON trial.

Permanent discontinuation of XPOVIO was seen in 19%. The most common adverse reactions leading to discontinuation included fatigue (3.6%), nausea (3.1%), thrombocytopenia, decreased appetite, and peripheral neuropathy and vomiting at 2.1% each.Dose interruptions of XPOVIO in 83% and dose reductions of XPOVIO in 64%.

One should also remember that the dosing schedule of XPOVIO in BOSTON was weekly compared to that of twice weekly in STORM Part 2 trial. Patients receiving XVd experienced lower levels of grade 2 or higher peripheral neuropathy vs those receiving Vd. This point may reflect once weekly administration of bortezomib versus administering it twice weekly.

Treatment-related nausea with XVd is manageable and transient. The percent of patients experiencing nausea decreased in the first month of XVd treatment using appropriate antiemetic measures. In the XVd trial, about 92% of the patients had their nausea events resolved within the first month. Patients were only required to take 1 concomitant antiemetic, a 5-HT3 antagonist.

Adverse reactions related to XPOVIO are largely dose and schedule dependent, and may be mitigated with prophylactic measures, vigilant monitoring and management, and dose reductions. Before starting XPOVIO, provide 2 prophylactic antiemetics, including a 5-HT3 antagonist with olanzapine or an NK1R antagonist such as rolapitant. During therapy, provide additional antiemetics as needed. Please note, management recommendations for specific hematologic and non-hematologic ARs can be found in the full XPOVIO USPI.

Narrator:

Anorexia/Weight Loss: Monitor weight, nutritional status, and volume status at baseline and throughout treatment and provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia: XPOVIO can cause severe or life-threatening hyponatremia. Monitor sodium level at baseline and throughout treatment.

Serious Infection: XPOVIO can cause serious and fatal infections. Atypical infections reported after taking XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Neurological Toxicity: XPOVIO can cause life-threatening neurological toxicities.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities until the neurological toxicity fully resolves. Institute fall precautions as appropriate.

Dr. Mikhael:

Patients in the BOSTON trial had a broad range of characteristics, including reduced kidney function, high-risk cytogenetics, and were ages 65 years and older.

Please note these subgroup analyses were exploratory in nature. It does not control for type 1 error and was not powered or adjusted for multiplicity to assess PFS.

126 patients in the Boston trial had reduced kidney function at baseline.

In patients with a Creatinine Clearance of 30 to 60 mLs per minute, median progression-free survival was 16.6 months vs 7.3 months with a hazard ratio of 0.49. Overall response rate was 79.2% vs 56.7%.

About half of patients had high-risk cytogenetics, including deletion 17p. In patients with high-risk cytogenetics, median progression-free survival was 12.9 months vs 8.3 months with a hazard ratio of 0.67. Overall response rate was 77.3% vs 55.8%.

In the BOSTON trial, the overall response rate was significantly higher in the XVd group regardless of age. 241 patients, or about 60% of all patients, were 65 years of age or older. In patients age 65 years or older, median progression-free survival was 21 months vs 9.5 months with a hazard ratio of 0.56. The overall response rate was 76.1% vs 64.4%.

Yes, gladly. I have a wonderful 64-year-old patient in my practice. She was initially diagnosed with standard-risk multiple myeloma and was treated with standard therapy of VRd: bortezomib, lenalidomide and dexamethasone. She went on to an autologous stem-cell transplant and lenalidomide maintenance therapy. She remained in remission for about 3 years and then had a rising M spike, and so her second line of therapy was DPd, or daratumumab, pomalidomide dex. Unfortunately, this lasted only about a year, and when she started relapsing, we noticed that her M spike was relapsing very quickly and when we did a bone marrow evaluation, she now had acquired the high-risk feature of the p53 deletion. At that point, we decided to treat her with XVd: XPOVIO, bortezomib and dexamethasone.

Yes, the patient had a rapid response to XVd. Her M spike came down quite nicely and she had a deep response and now remains in that response after 6 months of therapy.

Yes, in addition to the dexamethasone that is part of the XVd regimen, we provided her two antiemetics with ondansetron and olanzapine. Furthermore, particularly in the first month, we monitor them very closely and give them IV fluids on a weekly basis. I was prepared to give her an NK1R antagonist as further antiemetic if she required it, but she did well with the two of olanzapine and ondansetron.

The patient tolerated the XVd regimen quite well. She did experience a nausea in the first month, but it continued to decrease over time, and by the third month, she has been tolerating the regimen very well.

She has not experienced any peripheral neuropathy and now, several months later, she continues in a deep response and is tolerating the regimen well.

Thanks very much for joining me today. I trust that this has been helpful to you as you care for your patients with multiple myeloma.

Narrator:

Embryo-Fetal Toxicity: XPOVIO can cause fetal harm when administered to a pregnant woman.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Cataracts: New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataract requiring clinical intervention was reported.

ADVERSE REACTIONS

The most common adverse reactions (ARs) (≥20%) in patients with multiple myeloma who received XVd were fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract, and vomiting.

Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

Fatal ARs occurred in 6% of patients within 30 days of last treatment. Serious ARs occurred in 52% of patients. Treatment discontinuation rate due to ARs was 19%. The most frequent ARs requiring permanent discontinuation in >2% of patients included fatigue, nausea, thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting. Adverse reactions led to XPOVIO dose interruption in 83% of patients and dose reduction in 64% of patients.

USE IN SPECIFIC POPULATIONS

No overall difference in effectiveness of XPOVIO was observed in patients >65 years old when compared with younger patients. Patients ≥65 years old had a higher incidence of discontinuation due to an adverse reaction (AR) and a higher incidence of serious ARs than younger patients.

The effect of end-stage renal disease (CLCR <15 mL/min) or hemodialysis on XPOVIO pharmacokinetics is unknown.

Please see full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact Karyopharm Therapeutics Inc. at 1-888-209-9326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.