Dr. Gasparetto Video Transcript

Narrator:

Welcome – In this video we will explore the utility of XPOVIO (selinexor).

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.

Important Safety Information:

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.

This promotional XPOVIO video was developed in conjunction with Dr. Cristina Gasparetto. Dr. Gasparetto was compensated for her participation in this video.

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

Dr. Gasparetto:

Hello, my name is Cristina Gasparetto. I lead the myeloma program at Duke University, North Carolina.

We're currently five physicians dedicated to see myeloma patients. We probably see 10 to 12 new patients each week, and then we follow our patient longitudinally throughout the disease course. So currently we have a few hundred, three hundred patient we are currently treating in our myeloma practice.

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, selinexor provides you with an opportunity to introduce a different class that may demonstrate efficacy benefits for your Multiple Myeloma patients.

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 X-Protein 1 that is responsible for carrying important materials in and out of the core of the cells, or 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 this protein, X-Protein 1. The XPOVIO plus bortezomib dexamethasone treatment regimen is a combination of 3 different medicines that work together to kill certain cancer cells.

Narrator:

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. Gasparetto:

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 XPOVIO bortezomib dexamethasone with bortezomib dexamethasone.

The primary endpoint was progression-free survival, with secondary endpoints including overall response rate, very good partial response greater than or equal to VGPR rate, and peripheral neuropathy of grade 2 or higher.

XPOVIO bortezomib dexamethasone demonstrated an early and sustained progression-free survival benefit compared with bortezomib dexamethasone.

The Median progression-free survival was 13.9 months for XPOVIO bortezomib dexamethasone, vs 9.5 months for the doublet bortezomib dexamethasone arm.

The hazard ratio was 0.7, and this translates to a 30% reduction in risk of progression or death.

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. Note that these subgroup analyses were exploratory in nature. It doesn't control for type 1 error and was not powered or adjusted for multiplicity to assess progression-free survival.

There were significantly higher rates of deep responses with XPOVIO bortezomib dexamethasone vs bortezomib dexamethasone. With an overall response rate of 76.4% vs 62.3%, and a VGPR or higher of 44.6% vs 32.4%.

Responses were rapid and durable with a median time to response of 1.4 vs 1.6 months. And a median duration of response of 20.3 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 bortezomib dexamethasone can

also be used as early as first relapse. Identifying and using active regimens as early as possible is what we do now in multiple myeloma.

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, neurological toxicity, embryo-fetal toxicity, and cataracts.

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

Fatal adverse reactions within 30 days of last treatment were 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 19% and the most common adverse reactions leading to discontinuation were fatigue in 3.6%, nausea: 3.1%, thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting, each at 2.1%.

Dose interruptions of XPOVIO was 83% and dose reductions of XPOVIO was 64%.

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 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 required to take 1 concomitant antiemetic, a 5-HT3 antagonist.

Adverse reactions related to XPOVIO are largely dosage 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 olanzapine or an NK1R antagonist such as rolapitant, and during therapy, provide additional antiemetic as needed. Please note, management recommendations for specific hematologic and non-hematologic adverse reactions can be found in the full XPOVIO US Prescribing Information.

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. Gasparetto:

The 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 doesn't control for type 1 error and was not powered or adjusted for multiplicity to assess progression-free survival.

126 patients in the BOSTON trial had reduced kidney function at baseline. And in patients with the creatinine clearance between 30 and 60 mL per minute, the median PFS was 16.6 months vs 7.3 months with a hazard ratio of 0.49. Overall response rate was 79.2% vs 56.7%. Also, about half of patients had high-risk cytogenetics, including the deletion 17p. And in those patients with high-risk cytogenetics, the median PFS was 12.9 vs 8.3 months with a hazard ratio of 0.67. The 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. In fact, 241 patients, about 60%, were ages 65 years and older. In those patients, 65 years and older, the median PFS was 21 vs 9.5 months with a hazard ratio of 0.56. And the overall response rate was 76.1% vs 64.4%.

Dr. Gasparetto:

Yes, I have a patient who was 65 years old at time of diagnosis. He was considered ineligible for transplant due to his history of coronary artery disease and congestive heart failure. He also had some mild renal insufficiency. We treated the patient with first-line DRd: daratumumab lenalidomide dexamethasone. The patient did well, but eventually relapsed two years later with increasing levels of M protein. We decided to switch both mechanisms of action, so patient then received XVd combination.

Dr. Gasparetto:

Yes, the patient experienced a deep response to XVd. He has been on treatment now for 6 months and continues to respond. His monoclonal protein has decreased from initiation of this therapy.

Dr. Gasparetto:

Yes, we generally support patients, particularly during the first cycle with IV fluids, antiemetics, in fact the patient received two prophylactic antiemetics: ondansetron and olanzapine.

Dr. Gasparetto:

Well, the patient reported some nausea in the first month, and actually we provided him with the antiemetics as I mentioned, but also we made some dose reduction modifications of XPOVIO to 80 mg once a week. The nausea subsided, and by month 4, the patient was actually taking the combination XPOVIO bortezomib dexa with minimal toxicity with minimal trouble.

The patient has not experienced significant peripheral neuropathy to date and continues to respond and is tolerating the regimen quite well actually.

Dr. Gasparetto:

Well, thank you so much for your attention today. I hope I was able to provide you with good, useful information about the combination of XPOVIO bortezomib dexamethasone, that now we can use with patients with Multiple Myeloma in first relapse. Thank you.

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 (CL^{CR} <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.