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PRESENTATION

Operator

Good morning. My name is Matt, and I will be your conference operator today. At this time, I would like to welcome everyone to Karyopharm Therapeutics XPOVIO Expanded Approval Conference Call. (Operator Instructions) Please be advised that this call is being recorded at the company's request.

I would like now to turn the conference over to Mr. Ian Karp, Karyopharm's Senior Vice President, Investor and Public Relations. Please go ahead.

Ian Karp - *Karyopharm Therapeutics Inc. - SVP of Investor & Public Relations*

Thanks so much, Matt, and thank you all for joining us on today's conference call to discuss the expanded FDA approval of XPOVIO for the treatment of patients with multiple myeloma who have received at least one prior therapy. This is Ian Karp, and I'm joined today by Dr. Michael Kauffman, Chief Executive Officer; Dr. Sharon Shacham, President and Chief Scientific Officer; Mr. John Demaree, our Chief Commercial Officer; and Mike Mason, our Chief Financial Officer.

On the call today, Dr. Kauffman will reveal details regarding the expanded approval of XPOVIO for the treatment of adult patients with multiple myeloma and will describe some of the key clinical features from the updated label, which will help us differentiate XPOVIO in the current multiple myeloma treatment landscape.

Following Dr. Kauffman's remarks, John Demaree will highlight the commercial positioning for XPOVIO in this new and expanded indication and where we believe the once-weekly XPOVIO, Velcade and dexamethasone regimen will be particularly appealing for physicians and patients. We will then open up the call to answer your questions.

Earlier today, we issued a press release detailing the FDA approval of an expanded XPOVIO label. This release as well as this webcast presentation are available in the Investors section of our website at karyopharm.com.

Before we begin our formal comments and for those following along on the slide presentation, please turn to Slide 3. I'll remind you that various remarks we will make today constitute forward-looking statements for purposes of the Safe Harbor provisions under the Private Securities Litigation Reform Act of 1995. These include statements about our future expectations, clinical development, regulatory matters, timelines, potential success of our products and product candidates, including our expectations related to the commercialization of XPOVIO, financial projections and our plans and prospects.

Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors including those discussed in the Risk Factors section of our most recent quarterly report on Form 10-Q, which has been filed with the SEC and in other filings that we may make with the SEC in the future. Any forward-looking statements represent our views as of today only. And while we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so even if our views change. Therefore, you should not rely on the forward-looking statements as representing our views as of any date subsequent to today.

I'll now turn the call over to Dr. Michael Kauffman, our Chief Executive Officer.

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Thank you, Ian, and great afternoon to everybody. We are absolutely delighted today to announce that the FDA has now approved once-weekly oral XPOVIO for patients with multiple myeloma as early as first relapse, significantly expanding the patient population to whom we can now offer a new important treatment option.

More specifically, XPOVIO is now indicated in combination with once-weekly bortezomib, also known as Velcade; and low-dose dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. We call this regimen XVd or XPOVIO + Vd.

This latest indication is now XPOVIO's third FDA approval in less than 2 years and its first full approval. The previous 2 indications in myeloma and DLBCL were approved out of the FDA's accelerated approval program and contingent upon verification of clinical benefit from a confirmatory trial. Thus, today's news is also a critical development from a regulatory standpoint.

Additionally, this is now XPOVIO's first approval as part of a combination regimen with another potent anticancer therapy. And this is ultimately where we see the future for XPOVIO, namely as a partner of choice with other active anticancer medicines.

XPOVIO, of course, is the only approved drug that specifically targets the XPO1 protein. XPO1 over-expression is observed across numerous tumor types, both in hematologic as well as solid tumors, and is a fundamental driver of cancer. XPO1 carries tumor suppressor proteins out of the nucleus, which results in the activation of these natural cancer fighting molecules.

XPOVIO treatment leads to the retention of a large number of tumor suppressor proteins in the nucleus, leading to their functional activation. Based on this important and fundamental mechanism of action, XPOVIO has demonstrated synergistic activity in combination with many different drugs, including Velcade, an important part of the regimen approved by the FDA today.

Please now turn to Slide 5. As expected, there is also important safety information included in the updated XPOVIO product label. Notably, there are still no black box warnings or contraindications in the label. A patient medication guide is available to educate patients on the expected adverse reaction profile for XPOVIO.

Additionally, there are some important details regarding patient monitoring instructions and warnings and precautions included. All of these details are consistent with the safety information previously included in XPOVIO's label based on its accelerated approval last year for the treatment of patients with penta-refractory myeloma.

We continue to expect that these instructions, including the recommended supportive care guidelines and dose modification criteria, to be straightforward and easy for health care providers and patients to follow. And importantly, the dose of XPOVIO approved in this new expanded indication is 100 milligrams taken only once per week as compared to the 80-milligram twice-weekly dose, which was previously approved.

A lower dose and the simple once-weekly administration is associated with improved tolerability with fewer adverse events as compared with the previously approved regimen. And this newly approved once-weekly XVd regimen can be used in any patient with at least one prior therapy.

Finally, it's recommended that as first reactions we address using dose modification standard supportive care with specific recommendations for both included in the prescribing information. Complete details of these guidelines, along with the complete information, can be found at www.xpovio.com.

Moving now to Slide 6, you'll get a sense of just how much larger the expanded patient population is for this new indication relative to XPOVIO's previously approved penta-refractory indication. In 2020, there are estimated to be over 20,000 multiple myeloma patients being treated in the second-line setting and over 12,000 patients treated in the third-line setting as well as 6,000 or more in the 4th Line+ setting.

Additionally, these numbers continue to grow each year due to both increasing incidents of myeloma, but also because newer and more effective myeloma drugs are keeping patients alive longer, which is a wonderful achievement for the greater multiple myeloma community. These numbers greatly expand on the prior indication of XPOVIO in only penta-refractory or 4th Line+ patients.

As we move to Slide 7, I'll briefly highlight some of the key differences between the STORM study, which served as the basis for XPOVIO's accelerated approval in patients with penta-refractory disease; as compared to the BOSTON study, which supported today's expanded approval.

As you can see, the patients who participated in the BOSTON study had received far fewer therapies than those in STORM and had myeloma that was far less refractory to treatment. Specifically, patients in BOSTON had a median of 2 prior therapies, as compared to 8 prior therapies in STORM.

In BOSTON, the median progression-free survival and the response rate as well as the time on selinexor seen in the BOSTON study was substantially higher than in the STORM study. This was also driven by the mechanistic approach of combining 2 drugs with different mechanisms of action in the BOSTON study, such as XPOVIO, an XPO1 inhibitor and given in combination with once-weekly Velcade, a proteasome inhibitor, along with dexamethasone. And to reiterate, the mean duration of treatment was 10 months in the BOSTON study as compared to 3 months in the STORM study.

This comparison of studies is key to why we believe XPOVIO has just begun to make an impact on the treatment paradigm in multiple myeloma. We believe the greatest utility for XPOVIO in the future will be as a combination therapy with other potent anti-myeloma drugs such as Velcade and taken only once per week instead of the currently approved dose of twice per week.

As we move to Slides 8 and 9, I will highlight some of the critical data from the BOSTON study that is most important to treating physicians.

Once-weekly oral XPOVIO plus once-weekly Velcade and low-dose dexamethasone delivered an early and sustained progression-free survival advantage compared to twice-weekly Velcade and dexamethasone. More specifically, the XVd regimen demonstrated a 30% reduction in risk of disease progression or death and demonstrated a median progression-free survival of 13.9 months compared to 9.5 months in the Vd arm. And only one of the nearly 200 patients of the XVd arm in BOSTON actually progressed as compared to 10 on the Vd arm.

And what makes these results even more impressive is that in the study arm with XPOVIO, Velcade, and dex, the Velcade was dosed at only once per week so that patients received approximately 40% less Velcade. Along with this, they received 25% less dexamethasone as compared with the control arm.

In addition, patients receiving XPOVIO had approximately 35% fewer clinic visits compared to those who received standard twice weekly Velcade regimen. In fact, this is the first Phase III trial of a Velcade-based regimen that utilized only once-weekly Velcade in the experimental arm for patients with previously treated myeloma. This is critical because many physicians employ only once-weekly Velcade in combinations in general clinical practice.

Responses observed with oral once-weekly XPOVIO + Vd were also rapid and durable compared to twice-weekly Vd. More specifically, the median time to a partial response or better was just 1.4 months on the once-weekly XVd regimen compared to 1.6 months on Vd, and the median duration of response was 20.3 months on XVd compared to 12.9 months on Vd.

Additionally, the depth of response observed with once-weekly XPOVIO + Vd was significantly longer -- higher than twice-weekly Vd. The overall response rate was 76.4% on XVd compared to 62.3% on Vd. And even more importantly, the rate of deep responses as defined by a very good partial response or better, meaning at least a 90% reduction in myeloma levels, was 44.6% for patients on the XVd arm compared to 32.4% on the Vd arm.

Finally, higher response rates were observed regardless of prior therapies received. The presence of high-risk cytogenetics, which were -- which occurred in 50% of the patients on trial. Patients with renal impairment or advanced age. And this is very important as our commercial team now goes out to educate treating physicians on XPOVIO's updated indication and label.

Moving to Slide 10. I'll also highlight the key safety data from the BOSTON study, now included in the updated XPOVIO product label. The most common adverse event is over 20% in patients with myeloma who received XVd are fatigue, nausea, reduced appetite, diarrhea, peripheral neuropathy, upper gastrointestinal infection, decreased weight, cataracts and vomiting. The most common grade 3-4 laboratory abnormalities are thrombocytopenia, lymphopenia, neutropenia, anemia and low sodium.

These adverse events were generally self-limiting, reversible and proved manageable with dose modifications and supportive care. Most of the cytopenias were not accompanied by clinical sequelae. And importantly, the once-weekly XVd regimen resulted in significantly lower rates of peripheral neuropathy compared to the control group receiving twice-weekly Velcade. This is a particularly important feature as peripheral neuropathy is one of the most common causes of treatment limitation and discontinuation for all Vd combination regimens and for Vd itself.

Additionally, the rate of grade 2 or higher peripheral neuropathy, which was a prespecified secondary endpoint in the BOSTON trial, was significantly lower in the XVd arm. This is particularly important and one which we believe will be well received by both patients and physicians alike.

With my review of the clinical data and label now update complete, I'd like to ask John Demaree our Chief Commercial Officer, to highlight some of the key commercial messaging we plan to employ beginning today. John?

John Demaree - *Karyopharm Therapeutics Inc. - Chief Commercial Officer*

Thank you, Michael. And let me echo your excitement and sentiments on just how important today's announcement is for the myeloma community and the Karyopharm commercial organization's ability to serve as many patients as we possibly can in their fight against this unfortunately far-too-common blood cancer.

As we move to Slide 11, I will highlight some of the key messaging our team will be taking to health care providers and patients.

First, as you may know, there are currently a number of different therapeutic options available to myeloma patients in the second and third-line settings. So it will be critical for Karyopharm to clearly highlight the key unmet need that XPOVIO can help address.

Importantly, in multiple myeloma, we believe treating with different mechanisms as early as possible is vital for success. And thus, one of the key advantages XPOVIO brings is a novel mechanism of action that is synergistic with a proteasome inhibitor like Velcade. But the primary focus of our messaging will be on the efficacy and safety XPOVIO demonstrated in the pivotal BOSTON study.

The weekly XPOVIO + Vd regimen conferred a rapid and sustained PFS benefit. And patients achieved a clinically significant durable response with once-weekly XPOVIO + Vd regardless of cytogenetics, renal impairment or prior therapeutic exposure. And of course, XPOVIO is the first and only FDA-approved oral XPO1 inhibitor that gets to the cell's nucleus, which leads to cell cycle arrest and apoptosis in cancer cells. In fact, it is the first new mechanism approved since 2016 for the treatment of myeloma patients who received at least one prior line of therapy and has a strong synergistic effect with proteasome inhibitors, leading to cancer cell death.

Another important feature for the once-weekly oral XPOVIO + Vd regimen is that it can reduce the burden of having to come to the physician's office or hospital clinic for twice-weekly Velcade injections. Moreover, many patients may prefer an oral drug option to other options that require intravenous infusions at the hospital or physician's office, which can mean many hours spent in the clinic.

Also, our discussions with health care professionals will include a manageable safety profile that weekly XPOVIO + Vd offers to a broad range of patients and a side effect profile that is reversible and manageable with dose modifications and supportive care.

Finally, as I move to Slide 12, let me explicitly identify the kinds of patients that we believe physicians are most likely going to consider for treatment with the newly approved once-weekly XPOVIO + Vd regimen. And these include patients who received revlimid and Darzalex in the front-line setting and are Velcade-naive following their first relapse, patients who received only a short course of Velcade in the front-line setting prior to a stem cell transplant and thus may be appropriate to receive another course of a Velcade-based regimen, patients who have high-risk disease and/or cytogenetic abnormalities, patients who have renal dysfunction, patients who prefer a once-weekly oral drug and once-weekly injection rather than IV infusions or more frequent visits to the clinic and finally, patients who might benefit from a drug with a completely novel mechanism of action that is synergistic with a proteasome inhibitor.

In summary, we believe there are many different types of patients who can benefit from XPOVIO + Vd therapy, and we can't wait to meet with our customers and begin to educate them on this new, expanded and exciting indication. We believe this new indication will allow us to greatly increase our recent sales trajectory and significantly expand XPOVIO's peak sales potential.

With that said, we are, of course, still in the midst of a surge in the global COVID pandemic. So patient visits to their physician offices may remain impacted, and we will continue to largely access our customers via digital methods over the next handful of months. Once our sales force can get back to regular face-to-face interactions with customers, we believe we will be able to drive even greater adoption of the once-weekly XPOVIO + Vd regimen.

And with that, we would now like to open the call up to questions. Matt, turn it over to you for Q&A.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from Maury Raycroft with Jefferies.

Maurice Thomas Raycroft - *Jefferies LLC, Research Division - Equity Analyst*

Much congrats on the update today. I guess first question is just on you getting this approval earlier than expected. I'm wondering if you can comment on just preparedness for the expansion with supply. And commercially, are you full go right now or what you have to do in order to get to the full go [onset for the 4th, for example]?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Thanks, Maury. We've been working very closely with FDA on this. The trial was clean and clear. The review was very expeditious by the agency back and forth. There was absolutely no slowdown, if anything, there seemed to be an acceleration.

Obviously, the FDA is well acquainted with this drug. This is our third approval with the same division. And of course, the side effect profile, despite the fact that this treatment is more than 3x longer than the previous 2 approvals, the side effect profile is better than the previous approval. So that was easy there. And then clearly, we hit the primary and many of the secondary endpoints.

So we've had a very good interaction with the agency. I think they're thrilled that this confirmed their initial decision to approve the drug in the accelerated approval fashion, both literally confirmed it and legally confirmed it. And now we've been ready for a while now gearing up for this on the commercial side.

I'll turn it over to John now. But I can say the preparation on the commercial side as well as on our medical science liaisons, our nurse practitioners who worked -- work in here and all of our groups in commercial have been just great. John?

John Demaree - *Karyopharm Therapeutics Inc. - Chief Commercial Officer*

Thank you, Michael. In order to ensure we can bring this advance to patients immediately at approval, we set a launch readiness date well in advance of the PDUFA date. All of our teams have been trained, the sales teams, the nurse teams, our market access teams, our medical science liaison teams, and they're ready to fully go as of today. We have prepared all of our materials in advance, and we'll start rolling those out within the next few hours. So we can immediately start communicating the good news and educating physicians.

So good news is we're ready to go across functions, and that begins right now.

Maurice Thomas Raycroft - *Jefferies LLC, Research Division - Equity Analyst*

Great. And maybe just a quick follow-up. You also had the NCCN Guideline update recently too. So in addition to XVd, the SPd and [SDd] added to the NCCN guidelines, just wondering how that's going to factor in -- commercially, how that could be -- how that could come into play for prescribers?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Sure. Thanks. Just to be clear, our sales and marketing teams will, of course, only promote XPOVIO based on the approved FDA label, which obviously now includes the combination with bortez and dex for the treatment of patients with myeloma who've received at least one prior therapy. So that regimen can be used in anyone that is getting second-line or later therapy in myeloma. It applies to everybody.

We do know that many physicians and particularly the payers rely on the NCCN guidelines to help them make treatment decisions, like you said. And as you know, the NCCN recently added the XVd combination to the guideline with a category 1 recommendation, meaning the strongest recommendation for treatment of relapsed disease.

They also, based on the presented Phase I/II data and the very high response rates and progression-free survival, they added the SDd, the selinexor, daratumumab, dexamethasone combination; and the SPd, or selinexor, pomalyst, dexamethasone combination. And this latter combination, importantly, is one of the most potent all-oral regimens for the treatment of relapsed myeloma. So it can be very convenient, particularly in the setting of a pandemic. But if you just think about it outside the pandemic, for patients who have a long distance to travel and would prefer an all-oral regimen and not have to visit the clinic.

So all of these regimens are now in the NCCN. In addition to that, we're already aware of a significant minority of patients who are receiving XVd prior to today as well as other X combinations, XPOVIO combinations, including with Kyprolis and Revlimid. And these have been generally reimbursed without any trouble. Previously, they were only reimbursed in the penta treatment setting, but now we believe that the combination regimens would generally be reversed -- would be reimbursed even in a second-line setting as is typical with other myeloma drugs.

And we just close this by reiterating again that the commercial team will only promote based on the FDA label. Does that answer it?

Maurice Thomas Raycroft - *Jefferies LLC, Research Division - Equity Analyst*

Got it. Yes, that sure does. Congrats again.

Operator

Our next question comes from Brian Abrahams with RBC.

David Szeto - *RBC Capital Markets, Research Division - Senior Associate*

This is David Szeto on for Brian. Congratulations on this early approval, a great way to cap off 2020.

I just have, I guess, one question and then maybe a quick follow-up. Just looking at Slide 12, again, on the types of patients that your market research suggests might most likely prefer XPOVIO in the earlier line settings. Could you speak a little bit to how maybe you're aligning or realigning the commercial strategy for this expansion relative to the penta-refractory setting? And maybe, for example, you might find more of these patients in the community setting.

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

So yes, you're correct. About 75% of these patients are in the community setting. And we have updated the positioning and the strategy accordingly to drive the combination therapy, and we've trained the teams as such. As we've done a significant out of market research and a number of ad boards, the patients you see here are all types of patients that are both community oncologists and the academic oncologists said would be appropriate for this new XVd regimen.

David Szeto - *RBC Capital Markets, Research Division - Senior Associate*

Got it. And maybe just to follow up a little bit on Maury's last question on NCCN and access. I guess, could you speak a little bit to the expected cadence of access here? For example, might we perhaps see a bit of a bolus initially with immediate access enabled by NCCN, followed by your typical kind of slower expansion of access as plans work through the approval and work XPOVIO earlier line into their policies?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. I mean I think the reality is, as I'm sure you appreciate, payers have their own individual policies and some will follow NCCN, some won't. I think ultimately, obviously, we're thrilled with the approval today. And clearly, especially with the NCCN category 1 designation, there's a clear benefit from the XPOVIO Vd regimen.

I think let's let sort of time tell and individual payers. And physicians as they get more and more experience with XPOVIO, I think they'll be the ultimate deciders of exactly how and where they plan to use it. So I think at this stage, we wouldn't be prepared to kind of project what the cadence of sales or reimbursement policies might look like. That will take some time to see.

Operator

Our next question comes from Jonathan Chang with SVB Leerink.

John Christopher Barrett - *SVB Leerink LLC, Research Division - Associate*

This is John Barrett on for Jonathan. Congrats on the approval. Your press release mentions you're still working with the EMA on a decision there. Is that decision still expected by year-end? And if not, what are your discussions sort of centering around? And do you have any updated thoughts on your launch plans for Europe?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Sure. Yes, we can update on that. So our discussions with CHMP and EMA have progressed regarding the approval of XPOVIO in patients with penta-refractory myeloma. They are ongoing at this time, and we do expect to receive a definitive decision in January of 2021. And additionally, we do expect to submit a separate MAA based -- medicines agency application for XPOVIO approval based on the BOSTON study population shortly after we have the definitive decision from CHMP or EMA. And we'll update, for sure, when we learn more. I'll turn it over to Mike Mason just to comment on the launch in Europe and the plans in Europe.

Michael P. Mason - *Karyopharm Therapeutics Inc. - Senior VP, CFO & Treasurer*

Sure. I mean we see the real value in Europe from a commercialization perspective, really post-BOSTON approval. So we're certainly targeting being commercial ready, whether on our own or with a partner when BOSTON will get approved and -- potentially get approved in Europe.

John Christopher Barrett - *SVB Leerink LLC, Research Division - Associate*

Got it. That's helpful. Just one more follow-up. Given we're near the end of 4Q, can you provide any color on the sales trajectory for XPOVIO through October and November? And do you expect to provide preliminary unaudited 4Q numbers at JPM like you did last year?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. I mean, I think at this stage, we're not really able to provide much detail on fourth quarter sales. I mean that's clearly we're -- there's still a few weeks left in the quarter. So -- and we're focused, obviously, right now on the launch of Boston.

We do expect to provide some additional guidance at the JPMorgan conference. We have a scheduled presentation that's been confirmed for January 11. And so I think that's probably a more appropriate time to give an update there.

Importantly though, and clearly, today's approval from the FDA will allow us to immediately provide access to a significantly expanded patient population. And so as we move into the first quarter, that's obviously the key and most important thing that we'll be working on.

Operator

Our next question comes from David Lebowitz with Morgan Stanley.

David Neil Lebowitz - *Morgan Stanley, Research Division - VP*

When you look at launching into the BOSTON population pushing earlier in line, how do you see it moving into second-line versus third-line as far as physicians, I guess, employing it? Given especially that there's been a lot of movement of the various therapies that are already being used in those earlier lines and reshuffling as far as how they're being used currently.

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. So I'll start, and John will follow up. I think the considerations you saw on Slide 12 are really relevant here. But as you suggest, physicians have developed their preferred sort of first-line, second-line, third-line regimen, and there are a lot of choices to make. One of the -- some of the considerations they'll be looking at as they think about use of second versus third-line are really the ones that are up here.

So there is a desire in myeloma as in most other cancers to switch mechanisms when moving from one line to the next. And certainly, for patients who have Revlimid Darzalex in the front-line setting who've not yet received a proteasome inhibitor, this combination can provide a really convenient and effective regimen in the second line. And it would make sense because you'd switch out the IMid for a proteasome inhibitor and the Darzalex would switch out for seli. It is the only single once a week regimen that would be approved in that second-line.

And then for patients who received a transplant either in first or second-line, but only got a short course of Velcade prior to the transplant, we've shown really great activity. I think those are the 2 major indications for the use in second-line.

There are another subset of use of patients, though, that can be done in second-line who have specific issues, and we listed some of them here. I'll turn it over to John now to add to this.

John Demaree - *Karyopharm Therapeutics Inc. - Chief Commercial Officer*

Yes. Thanks, Michael. We know from the market research and from the ad boards that physicians have an ingrained class switch behavior that they already deployed in the context of multiple myeloma. And they have a desire to use all backbones early in a patient's course of therapy.

We're going to look at it on a patient-by-patient basis as we talk to our HCP customers. And we know XPOVIO will be used some in second-line, some in third-line. It will depend on the sequence of drugs that they have. The primary goal though is to make sure they receive this new background in XPOVIO before they're reexposed to another PI, another IMid or another anti-CD38.

Operator

Our next question comes from Eric Joseph with JPMorgan.

Eric William Joseph - *JPMorgan Chase & Co, Research Division - VP & Senior Analyst*

Congrats on the early approval here, really great. And just from going through the label, it seems that there's a difference in the rate of all-grade neutropenia relative to the Lancet publication, I'm seeing 48% versus 15% in the publication. What accounts for the discrepancy there? And sort of to what extent does neutropenia guide treatment selection in the earlier line when treating between options in the earlier-line treatment myeloma setting?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. We're not sure we really understand the issue. I think it's a grade 3 versus grade 3-4 versus overall grade. We'll get back to you on that, Eric. But there was really no meaningful difference. It's a lower rate of neutropenia in general in the BOSTON study. And again, even with the 3x longer treatment, just given the fact that our drug has minimal neutropenia associated with it. And Velcade has a little bit, but not too much either.

And can you just reiterate the second question you had?

Eric William Joseph - *JPMorgan Chase & Co, Research Division - VP & Senior Analyst*

Well, it just is just related to whether the rate of neutropenia that's showing here in the label is going to have an impact on treatment decisions when choosing between options?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

I think for all cytopenias, I think you have to remember, for all cytopenias, first of all, hematology oncologists are very comfortable handling cytopenias. This is their the bread and butter. This is what they absolutely know.

These rates of overall neutropenia are really not relevant. What's relevant, as you know, in clinical practice is grade 3-4 neutropenia, and in particular, rates of febrile neutropenia. We have extraordinarily low rates of febrile neutropenia. So even in patients who have grade 3, 4 disease, they have -- primarily, they receive GCSF in various types. And they have a quick response. They don't tend to develop infections. And that's the thing that doctors most worry about.

As you know, febrile neutropenia causes -- can be fatal and is a very significant issue, and we don't see it with this drug. That does distinguish XPOVIO and particularly the XPOVIO Vel dex from a lot of the other combinations with an overall lower rate of neutropenia than many of them. But the clinically significant neutropenia grade 3-4, in particular, febrile neutropenia, really are not part of our typical adverse effect profile.

Eric William Joseph - *JPMorgan Chase & Co, Research Division - VP & Senior Analyst*

Got it. And congrats again.

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. I can say from the label, we had a 12% grade 3-4 risk of neutropenia, and that's a very, very low level. I think that compares very favorably to the vast majority of the other triplet regimens.

Operator

Our next question comes from Peter Lawson with Barclays.

Peter Richard Lawson - *Barclays Bank PLC, Research Division - Research Analyst*

Congratulations on the label expansion. Just I guess, firstly, for John, just thanks for highlighting the groups of patients that you target for XVd. Is there any way you can kind of rank those or kind of break out the number of patients that you could potentially address by going after those subgroups?

John Demaree - *Karyopharm Therapeutics Inc. - Chief Commercial Officer*

Yes. We've certainly done that internally in terms of ranking and giving a prioritization to the sales force. I don't think it's something that we want to provide publicly based on competitive reasons as to our ranking as to which patients are the primary target versus which patients are the secondary target.

Peter Richard Lawson - *Barclays Bank PLC, Research Division - Research Analyst*

Great. Okay. Understand. And just going through the label, it seems that -- I may be wrong on this, but that cataracts were mentioned as a new precaution and low phosphate level. Just how we should think about that and the potential for using the drug?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. Ironically, the most common pre-existing condition across both arms of the BOSTON study coming in was cataracts in over 2/3 of the patients. And for reasons that remain unclear, we did have an onset of -- we had a higher onset of late cataracts. Typically, it was without -- typically after 24 weeks as compared to what we've seen previously.

Part of this is because we're giving longer therapy. But the cataracts in both arms, but particularly in the XVd arm, are treated with standard cataract surgery, and this is the most common surgery in these older folks. So we don't really understand the mechanism. It certainly was -- it led to 0 discontinuations. It actually led to a very tiny number of even dose modifications or misdose because cataract surgery is so relatively straightforward and effective.

The other one, the low level phosphate is just something we've noticed. It has had no real impact in the study we try to correlate. Typically, you might see a slight increase in fatigue or muscle aches associated with that. Again, there was really no clinical associations with the phosphate decrease.

I do -- I will address, if you can, I will just go back to Eric's question. The difference in the label, and you are correct, is that the FDA has moved to laboratory abnormalities that are based purely on the laboratory results and not on whether the events were reported as adverse events. So in the label, what you see is the actual take count of people who had neutrophil counts decrease. What you saw in the Lancet paper with a number of 15% for all grade was patients whose doctors reported this as an adverse event.

And that's consistent with what I said, which is to say that doctors really don't consider grade 1 and 2 neutropenia to be an adverse event. They note it. And that's why the Lancet paper has a lower number. The grade 3-4 events for both The Lancet and the packages are differing slightly but are essentially the same, consistent with the notion that doctors will consider a grade 3 or 4 neutropenia to be an adverse event. So they report it both as a number and as well as an actual AE. I hope that clarifies that.

Peter, did you have another one? I'm sorry.

Peter Richard Lawson - *Barclays Bank PLC, Research Division - Research Analyst*

Yes. Just a quick question around the emergence of BCMA therapies and potential impact they could have on the use of selinexor and then the potential for you to combine with those, if that's something you're thinking through?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Yes. I think the second part is easy. I mean XPOVIO, so far, has been effectively combined with at least NCCN guideline support and publication support with all of the other major anti-myeloma drugs to date. And we know that these combinations are in use. So we will be looking at the combination with Blenrep. We're aware of a couple of patients who appear to be receiving the combination already who have highly refractory myeloma.

But our focus really now is on the BOSTON population, which is second-line and later as the XVd regimen on label. And then, of course, as doctors choose to follow the NCCN on an other guidelines, to go further. Whether -- Blenrep is a good drug. It acts well. I want to be clear that the ocular events that are seeing with XPOVIO, which are cataracts, are not the same at all the keratitis that's seen with Blenrep.

I don't think that this will preclude the combination. And I think history in myeloma has told us that taking different mechanisms and combining them can lead to very good effects. So at the end of the day, we want XPOVIO to be a partner for essentially any drug in myeloma, Blenrep included.

Operator

Our next question comes from Ed White with H.C. Wainwright.

Edward Patrick White - *H.C. Wainwright & Co, LLC, Research Division - MD of Equity Research & Senior Healthcare Analyst*

Congratulations. So thinking about your market research, I'm just curious as to what you're seeing for Velcade use in the second and third-line. And the docs you talk to, is lowering the administration of Velcade that important to them that they would increase the use of Velcade in the second and third-lines?

And then the follow-up is just what you're expecting to see the impact on XPOVIO use in the penta-refractory if it's used in second and third line.

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Sure. Look, we think that having another option for Velcade combination has got to help patients, whether it gets used in second or third-line, depending largely on what they got in first-line. And also depending on things like renal dysfunction and high-risk cytogenetics.

The use in the real world of Velcade in second and third-line is almost always with once a week Velcade, and it is used prevalently. So I don't know that will increase necessarily the use of once-weekly Velcade in the second and third-line. But we do believe that selinexor, because of the new mechanism, because it doesn't -- it's not affected by renal dysfunction, it is active in high-risk cytogenetics and so on, provides some really important and potentially very meaningful benefits to patients.

And the last point to really hammer home, and we're talking to physicians all the time, and this was seen at our advisory boards, is that the clinical data that came out of BOSTON are directly relevant to their clinical practice. This is the first Phase III study that we're aware of in relapsed myeloma where the results of a Velcade-based triplet regimen can probably move directly to their practice because all other Velcade triplets are studied with twice-weekly Velcade in the experimental arm. And really, you don't know what you're going to get in practice when you cut the dose of Velcade down by 40%.

The other thing we've learned, to answer the second part of your question, we don't have a lot of great data on retreatment with selinexor. But the previous view and the emerging view for Velcade and even IMids and more recently for Darzalex or at least CD38 antibodies is that somewhere between 6 and 12-month hiatus for the reuse of drugs tends to allow for the tumors to reacquire sensitivity to those mechanisms.

So we wouldn't expect anything different regarding selinexor at this point. And we think that retreatment with XPOVIO-based regimens could happen in later lines. And we would generally say that based on history, some kind of a hiatus since the last time they received XPOVIO would be warranted, but we don't have data yet to directly support that.

Operator

(Operator Instructions) Our next question comes from Arlinda Lee with Canaccord.

Arlinda Anna Lee - *Canaccord Genuity Corp., Research Division - Analyst*

Congratulations on the early approval. I had a couple of questions about maybe -- I know you guys are not promoting or do not promote off-label. But I think in some of your earlier earnings slides, you had indicated things that would have suggested that you were getting off-label use. Do you think you can provide updates on that information? And maybe another way, can you talk about what the durability is on commercial drug currently?

And then lastly, can you maybe talk about feedback that you've been getting from KOLs and prescribing docs coming out of ASH?

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Let me start, and then I'll turn it over to Ian and John. I think when we get into the off-label discussion, we should just be clear that there's 2 aspects. One is the place in someone's therapy and therapeutic journey that they get XPOVIO or any other drug. The penta-refractory label could come in as early as third-line therapy and can come on any time later, provided they received the 5 drugs that are on-label.

Generally, physicians and payers are okay with whatever cocktail is used in a line, provided it is on -- it is for the patients that are on-label. And as you're correct, we have said that a significant minority of patients have received triplet therapy in the penta-refractory setting, and this was reimbursed very well across the country because it was applying to the patients who were in this penta-refractory group. So there's a distinguished -- important to distinguish between the patient population and exactly what combination therapy they get. Typically, payers have left it up to the doctor thankfully to make those decisions to optimize therapy for the patient. Ian?

Ian Karp - *Karyopharm Therapeutics Inc. - SVP of Investor & Public Relations*

Yes, maybe just a couple of points. In terms of future earnings presentations, I think we'll have to wait and see. I mean, certainly, there is -- as you know, this is a competitive space with a number of branded drugs that we're now directly competing with. So I think what the types of commercial data that we show may or may not change, I think time will tell. So I don't want to sort of promise anything in terms of what future slides might look like.

In terms of the durability, and then maybe I'll let John talk about what he and his team are hearing post-ASH, what I will say is on our last earnings call and in the presentation, we did provide the latest average number of cycles or average number of months of drug per patient within our specialty pharmacy network, and it was approaching 3 months. And so that's consistent with what we saw in the STORM study, which was an average of about 3 months of treatment.

I think now what you're going to -- hopefully, what you'll see is as this drug moves in combination with bortezomib and moves earlier lines of therapy, and as Michael noted in the slide presentation, the average duration of treatment in BOSTON was 10 months compared to 3 months in STORM. We would expect to see the durability of the time on treatment to increase over time.

Again, time will tell, and we won't have that data immediately. It will take a number of months to start probably seeing those kinds of averages increase. But it's certainly our expectation that the average duration of therapy increases. I don't know, John, do you want to comment on post-ASH.

John Demaree - *Karyopharm Therapeutics Inc. - Chief Commercial Officer*

Thank you, Ian. Just to further address the comment on current use in the market and then post-ASH. As Michael mentioned, most of our use is in the penta-refractory setting today, most of that is 4th Line+. The majority of that use is with the Xd combination with some limited use of XVd, which is why we're really excited now to get the approval of XVd and be able to promote that in the second, third-line setting where the size of the patient population is roughly 6x the size of our prior indication. So much bigger opportunity to help patients.

And others can comment also, but I'd say the feedback we've heard post-ASH in terms of one-on-one discussions in ad boards and different exchanges with our customers has all been very positive, and people are ready and excited for the XVd day to be available to patients.

Operator

This concludes our question-and-answer session. I would like to turn the conference back over to Michael Kauffman, CEO, for any closing remarks.

Michael G. Kauffman - *Karyopharm Therapeutics Inc. - Co-Founder, CEO & Director*

Thanks very much. I'm -- just close with saying that this is a great day for patients and their families and their physicians and other health care providers for the patients with myeloma, a tough, tough disease, but now they have a new and very convenient option to help them treat their disease. I do want to thank all of the patients and the health care providers, the KPTI staff and especially the FDA for making all of this happen in such an expedited time frame. And I wish everybody happy holidays, and thank you again for joining us today. Have a great day.

Operator

The conference has now concluded. Thank you for attending today's presentation. You may now disconnect.
