Understanding the FDA approved New Drug, Selinexor and its Use in Multiple Myeloma

Recently, the FDA approved a new cancer drug called Selinexor. This drug has been found to be successful in treating multiple myeloma in patients who have exhausted all other existing treatment options.

Selinexor works on a different mechanism compared to other drugs.

It enters a cell and targets mechanisms that move molecules into and out of the cell. We are talking to Dr. Dan Vogl, who lead the Phase II studies on Selinexor, on how the drug works, how it should be used, potential side effects and who should consider using it.

Full Transcript:

Priya Menon: Good afternoon and welcome to another episode of CureTalks. I'm Priya Menon, your host and today the topic of our discussion as the FDA approved new drugs for multiple myeloma, Selinexor. Helping us understand the drug and its use in myeloma is Dr Dan T Vogl from the University of Pennsylvania. On the patient panel, discussing the patient perspective will be patient advocates, Gary Peterson, Jack Aiello and Cynthia Chmielewski. To begin with the discussion we have with us, Dr Dan Vogl, one of the leaders of the Phase II studies on Selinexor which led to its FDA approval. Dr Vogl, thank you for joining us today.

Dr Dan Toby Vogl: Thank you so much, it's a pleasure to be here.

Priya: Dr. Vogl, the new drug Selinexor is definitely exciting and since we have another new drug to treat myeloma, it would be great if you could just start off with explaining in as simple terms as possible for our audience what this drug is and how it works.

Dr Vogl: Sure. Selinexor is the first approved drug in a class, a new class of anti cancer therapies called Selective Inhibitors of Nuclear Export. Selinexor specifically blocks of protein called XPO1 which serves as a

chaperone for the nuclear export system. It turns out that all cells have a system for regulating the movement of molecules into and out of the nucleus, the command center, the cell where the cell reads its genetic code from DNA molecules and turns that code into proteins that then go out into the rest of the cell; and movements of proteins and other molecules into and out of the nucleus is controlled by chaperone or carrier proteins that essentially carry their cargo through pores or holes in the nuclear membrane. And the central insight that led to the development of Selinexor was that cancer cells depend on one particular export protein called XPO1 to export certain molecules from the nucleus that would otherwise signal the cancer cells to stop growing or stop surviving.

That represents a vulnerability for those cancer cells so that if XPO1 is blocked or inhibited, those target molecules remain within the cell and lead to decreased cancer cell growth and decreased cancer cell survival, which is what we're trying to achieve with anticancer drugs. So Selinexor by blocking XPO1 is essentially locking the cancer cells from exporting from the nucleus, things that they don't want there, and keeping those things in the nucleus of the cell to signal to the cancer cells to slow down and to stop surviving. And it turns out that at least in multiple myeloma, that can be a really effective way to lead to cancer responses.

Priya: So what I understand is Selinexor works in a different mechanism as compared to other drugs and it enters a cell and targets mechanisms that move molecules into and out of the cell. Would that be right?

Dr Vogl: It targets molecules that move into and out of the nucleus of the cell, of the command center of the cell.

Priya: Okay. Got it. It's great. So Dr Vogl, now that we have this drug approved, who are the patients who qualify for being treated with Selinexor?

Dr Vogl: So Selinexor is specifically improved right now for patients who have penta exposed myeloma, that means that they've been treated already with all of the effective medications or all of the most effective medications for treating myeloma. That includes lenalidomide which is Revlimid and pomalidomide, which is Pomalid. Those two drugs are known as IMiDs as well as two drugs in the proteasome inhibitor class bortezomib, which is Velcade and carfilzomib, also known as Kyprolis. And then also the antibody treatment, Daratumumab or Darzalex.

And because those five medications together are the most effective current anti myeloma medications, when patients have received all of them, we invented the term Penta exposed to refer to that. And in addition, Selinexor is specifically approved for patients whose myeloma is also refractory, which means it's grown despite treatment with at least one IMiD, either lenalidomide or pomalidomide, at least one proteasome inhibitor, either bortezomib or carfilzomib and the monoclonal antibody Daratumumab. So this is really for patients who have received all of the known effective treatments and for whom the major classes of effective myeloma therapy are no longer working.

Priya: So how can these patients get this drug? Can their doctors prescribe this drug or do they have to participate in trials now?

Dr Vogl: So Selinexor is now by approved by the US Food and Drug Administration, which means that it's available for any doctor to prescribe. My recommendation would be that it be prescribed by an oncologist or hematologist who has experience in managing the side effects of cancer therapies and is prepared to deal with some of the side effects that we see with Selinexor, because I do think that it really does take some close attention to side effects during the first month of therapy. But this is something that patients can get as part of the regular cancer treatment and not necessarily by participating in a clinical trial.

Priya: Okay. You were one of the leaders of the STORM trial that led to the accelerated FDA approval of the drug. Can you briefly talk about the trials results and its significance?

Dr Vogl: Sure. So the STORM trial, which stood for Selinexor Treatment Of Refractory Myeloma was a trial that tried to take this completely new drug with a completely new mechanism of action that we were pretty sure worked differently from any other treatment out there and show that it could effectively cause responses in patients with myeloma who really didn't have any other good treatment options. So the trial enrolled 122 patients in the United States, in Europe who had received all of the most effective myeloma therapies and whose myeloma was refractory to those three classes of myeloma treatment that I just talked about. And in this group of patients, we could see a good response, a partial response or better, which means the myeloma shrinking by at least half in 26% of the patients who received a combination of Selinexor given twice a week along with the steroid medication, dexamethasone also given twice a week.

Twenty six percent may not sound that high but in patients who really don't have any other good treatment options we think it's pretty good and clearly indicates that Selinexor can work for patients with myeloma and can cause good responses. And in turn, one of the things that we saw as part of the trial is some of the patients really did get tremendous clinical benefit from that meaning that they were able to continue living their lives and do so with side effects that for some of them were not too bad and allowed them to stay on study for many months.

Priya: So the STORM trial showed that Selinexor in combination with dexamethasone is effective. What other combinations are in the pipeline? And how does it work in conjunction with the other therapies like probably immunomodulators or proteasome inhibitors?

Dr Vogl: So we've seen some clinical trial results of combinations of Selinexor with other myeloma therapies. The ones that have been most promising have been the combinations of Selinexor with either proteasome inhibitors or monoclonal antibodies. So the combination of Selinexor with bortezomib or Velcade has shown some very promising early results and is actually a combination that's being studied in the large comparative trial that Selinexor is manufactured by Carrier Pharma hopes that we'll get it full approval after publication of the results where patients are either being treated with Selinexor or bortezomib and dexamethasone or just bortezomib and dexamethasone.

Selinexor has also had some promising early results in combination with carfilzomib, also known as Kyprolis and in combination with Daratumumab or Darzalex. The combination that doesn't seem to be as well tolerated, are combinations of Selinexor with the immunomodulatory drugs or IMiDs like lenalidomide or pomalidomide, revlimid or pomalyst. That seems to lead to a lot of low blood counts and those combinations are probably not going to be widely used.

Priya: Thank you doctor. My last question before I actually hand it over to the patient panel is that you did mention the side effects. So if you could talk a little bit about the side effects that were observed and how we can manage these for practical purposes.

Dr Vogl: Sure. Probably this is one of the most important things about Selinexor. Selinexor is an oral pill., so it's relatively easy to take. It's taken as several pills, usually four pills twice a week two days apart. So you usually say on a Monday and Wednesday along with dexamethasone given on the same days. And so it's a medication that you can take at home. You don't necessarily have to go into the doctor's office and that makes it very attractive. But it does come with a fair amount of side effects. The most prominent side effects are fatigue and gastrointestinal side effects, like decreased appetite, nausea, vomiting and diarrhea.

And then we also have noticed that you can see a lot of low blood counts with Selinexor and that's primarily low platelet counts. Those are the cells that help stop the bleeding by causing blood clots and also low levels of white blood cells that fight infection and red blood cells that carry oxygen around. So our experience has been that patients need a lot of close attention to side effects, especially within the first month of treatment. And that means that we give anti-nausea medications along with Selinexor right from the beginning to try to limit how much nausea patients feel.

We tend to use calorie supplements, nutritional shakes in order to make sure that people don't lose too

much weight from the decreased appetite. Sometimes we use psychostimulants like methylphenidate or Ritalin to help improve people's energy level and ability to maintain their attention while they're on Selinexor. And we tend to follow the blood counts very closely, at least once a week during the first month in order to look out for any low blood counts that might require either transfusions or growth factor injections or adjustment in the Selinexor dose because we usually started at a full dose and then back off from the dose of people have side effects that are a little bit too intense.

Priya: Thank you doctor. With that, I'm going to hand over to Gary Petersen to lead the patient panel. Gary you are live. Please ask your questions.

Gary Petersen: Yes, thank you. Dr Vogl and thank you for all you've done for the myeloma patient community. What I'd like to do, if I might, is I'll let Jack go first. So Jack, are you online?

Jack Aiello: I am. And I'm happy to ask some questions. Thank you also Dr Vogl and nice meeting you over the phone. You mentioned that Selinexor and Velcade have shown or are thought to be shown some efficacy. Can you, I don't know, if you mentioned it. When might you expect some real time results on that, when might that type of combination receive approval?

Dr Vogl: Sure. So, early trials have already been published showing good response rates are encouraging response rates of Selinexor combined with Velcade and dexamethasone and the trial that's ongoing, the Comparative trial, which is known as the BOSTON trial has already completed its accrual. All the patients have been signed up for that trial and so everybody's on treatment or in follow up.

And I think we're expecting to see results that will be sufficient for publication and to be made public sometime around the middle of next year with the hope that the FDA would have those results to review during the year next year and perhaps grant Selinexor full approval, which would either be just in combination with dexamethasone right now. And then the addition of the combination along with Velcade and dexamethasone.

Jack: When the ODAC committee, which makes recommendations for approval or non-approval to the FDA, reviewed Selinexor, they recommended not approving it. And so I guess I was wondering, do you think FDA had early results in this BOSTON trial? What caused the FDA to decide to go ahead and approve Selinexor in your opinion?

Dr Vogl: So that's a very reasonable question. I'm pretty certain that the FDA didn't have any early access to the results of the BOSTON trial in part because I don't think those results have been actually put together yet. The Oncology Drugs Advisory Committee or ODAC is a group of experts, both physicians and statisticians and also patient representatives whose job it is to listen to the evidence for and against a new drug and make a recommendation to the FDA. And there were certainly people on the Oncology Drugs Advisory Committee who listened to that evidence and thought that Selinexor should be approved. And that there was sufficient evidence to approve it although the tally of the votes from the committee generally were in favor of delaying consideration of approval for Selinexor until the results of that larger trials were available.

I think what the FDA eventually had was some updated results and subgroup analyses of the same data that were presented from our Phase II STORM trial and had a chance to really pay attention to what we as a myeloma physician community were telling them, which is that we have too many patients who don't have any good treatment options, who need a drug and here's a drug that can certainly work for them. I think the FDA had had some concerns about the amount of side effects that we were seeing with Selinexor, which I certainly think is a valid concern.

It's something to be worried about and also with the fact that the trial that we did wasn't a controlled trial. There was no placebo or standard treatment group. Everyone in the STORM trial got Selinexor and dexamethasone and they were a little bit worried that it's hard to tell whether those patients did better than they might have done with any other treatments. And I think what they heard from me and from other

myeloma physicians was that because of the group of patients that we included in the trial, there really wasn't any chance that they would have done even as well as they did without getting Selinexor that it truly did provide benefit to patients who got a response from the drug. And I think ultimately they found that information compelling.

Jack: Well, thank you to you and other physicians for voicing those opinions. I had just one other question. Based on the mechanism that you're talking about, it would seem that Selinexor could be a viable treatment in other cancers including myeloma, even related cancers such as amyloidosis or maybe myelodysplastic syndrome or PCL or such. Do you expect Selinexor to be tested and used for treatment and other cancers?

Dr Vogl: So Selinexor has been in clinical trials, in many different types of cancer including what we call solid tumors like lung cancer and colon cancer and sarcomas. And honestly I don't know the full results of all of those trials because of how sub-specialized my own practices and multiple myeloma. There's no question that the clearest evidence of Selinexor being an effective medication has come from the multiple myeloma trials. And, and certainly that's where we're going to see it used initially.

And that's what the initial FDA approval is. But I'm very eager to see what some of the results are for those other trials in other cancers. There are a couple of conditions that are essentially the same as multiple myeloma in terms of the type of underlying cancer cell, the plasma cell, which is an immune antibody producing cells. So that plasma cell leukemia, which you mentioned, which is essentially a very aggressive form of multiple myeloma,

I think it would make perfect sense to consider using Selinexor and I would feel very comfortable doing that for patients who otherwise would meet the criteria for using it in myeloma, meaning that they had been through all of the other effective therapies. For conditions like amyloidosis, which is closely related to myeloma, it would be reasonable to consider using Selinexor with the caveat that people, patients with amyloidosis often have more side effects from treatment than patients with multiple myeloma.

And so for a medication like Selinexor that already has a somewhat rough side effect profile, I would be very careful about doing that. Myelodysplastic syndrome or MDS is a somewhat but not as closely related bone marrow cancer and there are trials ongoing using Selinexor and other next generation XPO1 inhibitors that might have somewhat better side effect profiles in myelodysplasia and in other cancers as well.

Dr Vogl: So I, so I think the answer is yeah, I think we're probably going to see more trials looking at XPO1 inhibitors in other cancers and I'm really interested to see how well they work.

Jack: For myeloma patients that would be qualified to use Selinexor, is there a type of patients that you would not lean towards giving someone Selinexor?

Dr Vogl: That's a really good question because I think that deciding to use a medication like Selinexor or requires a patient to honestly assess how willing they are to go through some side effects. Because what you want to do if you're going to try a medication like Selinexor is prepare for the likelihood that they're going to be a bunch of side effects in the first month and kind of get yourself ready to start a medication. Try as hard as you can to stick with the dosing, stay in close contact with your oncologist about the side effects that you're experiencing and working on getting those side effects under control and then seeing if the Selinexor treatment is getting the results that we would want.

And if it is, then thinking about, okay, how bad were those side effects? How much can we control them with supportive care? How much can we make them better with lower doses of the Selinexor, and then is it worth it to continue that treatment? What you wouldn't want to do is try a single dose of Selinexor, decide that the side effects are too much and just give up on it because I'm not sure that would be worth it.

And some patients might look at that plan of really toughing it out for the first month and decide that they're just not willing to try something that has such a high chance of causing side effects and therefore or their

doctor might look at them and say, you know what, you really a little bit too frail. I think that going through side effects like that would just make you too miserable for too low a chance of getting a result. That said, we had patients on our trial of Selinexor who were up to 80 years old and patients who came in relatively sick from their multiple myeloma and patients who were able to tolerate the medication and continue on therapy. Some of them did really well. So I think I would consider using Selinexor in almost any patient , some patients might think about it and decide that it's not for them.

Jack: Thanks very much Dr Dan Vogl. I'll turn it over to Cindy from here.

Cindy Chmielewski: Hi Dr Vogl, this is Cindy. How are you doing?

Dr Vogl: Good. How are you doing Cindy?

Cindy: I've been great. Boy with all that that was talked about, a lot of my questions have been answered but I still have a few that may be some things just to reiterate because they're important. And I guess one of the things that I hear most from myeloma patients and physicians is they're really concerned just because Selinexor is such a hard drug to take. And we talked about the main side effects. The things I want to ask, are these side effects reversible? If you go through the month that you decide that you really can't handle these side effects if you stop taking the drug, are there any long lasting side effects?

Dr Vogl: So that's actually a really good point because I think our experience with Selinexor has generally been that when we stopped the medication, the side effects get better and they get better pretty quickly within a week or two. So that most of my patients, if we needed to take a break from the treatment, we're feeling better relatively quickly. And then sometimes we would restart the treatment with a dose reduction.

And even the patients who ended up having to come off of this study because their myeloma was starting to grow despite Selinexor treatment as they stopped the Selinexor, we generally saw improvements in their blood counts and then how they were feeling. And most of them were able to go on and receive other myeloma treatments including some times on other clinical trials of new myeloma medications. So that, I think that overall there was very little long term downside to trying Selinexor and dexamethasone. And then for some of my patients, even though it did have a lot of side effects initially through supportive care and dose modification, we were able to make those side effects tolerable and allow for ongoing therapy so that I had at least one patient who stayed on Selinexor for over a year. And I think overall really benefited from being able to take this drug.

Cindy: Okay, great. And when we're talking about the side effects, we're talking about things that make you feel pretty badly, but we're not talking about side effects that are damaging your organs. Is that correct?

Dr Vogl: I think that's a fair characterization, meaning that we didn't see much in the way I think, or even any of kidney injury or liver injury or injury to the heart or lungs from Selinexor. What we really saw was gastrointestinal symptoms, fatigue and low blood counts. And yeah, all of those are symptoms that are generally reversible when you stop the drug itself.

Cindy: And I keep on hearing like if you get through the first month or if you get through the beginning part of it, the side effects get better. Is it because you become used to them or is it because your doctors learnt how to manage them? Could you talk a little bit about that?

Dr Vogl: So I know that that's something that has been said about Selinexor and I think it is true for some, but not necessarily all patients. So I think it's a combination of improving supportive care or figuring out what the right regimen is as you get through that first month of treatment along with dose reductions because many patients who start off at the full dose of Selinexor or which right now is 80 milligrams twice a week end up on lower doses, either 80 or 100 mgs once a week and and that dose reduction can make the side effects more tolerable. And then some of it may actually be from just getting used to the side effects and realising that they're actually not bothering you as much as they did earlier in the treatment course.

Cindy: Good. what good dose reduction are you still seeing efficacy with the drug?

Dr Vogl: So I think it's fair to say that most patients who are on the clinical trial of Selinexor that we ran did end up having at least some reduction in their dose over the course of the trial. And that despite that we saw are encouraging preliminary results. And so I do think that it's very reasonable to reduce doses without being too worried that you're going below the minimum effective dose. And so we have generally been pretty aggressive in our clinical trial therapy and as we started using Selinexor about reducing doses to minimize side effects, although I do still tend to start off with the full dose of Selinexor to try to at least get the best initial response that we can tell.

Cindy: Okay, great. And are you seeing any less side effects when Selinexor is used in combination with either rituximab or gyro or one of the other drugs?

Dr Vogl: Well, one of the things about the combination studies that have been done is that they've also generally used lower doses of Selinexor, either 80 or 100 mgs once a week in combination. And I do think that makes the side effect profile overall better. My guess is that's the main thing affecting the side effect profile. Although I know that some of my colleagues who are running those trials think that there has been a qualitative difference in side effects based on that they in the combination treatments compared to just Selinexor and Dexamethasone by itself.

Cindy: Okay, fair enough. And I've heard people worrying that, okay, that maybe this will be a treatment that a myeloma specialist can prescribe, but they're concerned that maybe a community or local oncologist prescribing Selinexor may not know how to effectively manage treatment. What are your thoughts on that and if a patient is being seen in the community setting, what could they be proactively doing to make sure they're getting the supportive care they need?

Dr Vogl: I think that the main thing about providing effective supportive care for patients getting Selinexor is paying close attention. So that I think a myeloma specialist who's too busy and only able to see a patient once a month and doesn't have a nurse practitioner or physician assistant or nurse working with them who can pay close attention weekly to side effects and keep an eye on the blood counts closely. We'll have just as much chance of mismanaging side effects as a community oncologist who doesn't pay enough attention. And conversely, I think that a general oncologist working in the community who is willing to see patients frequently pay close attention to side effects, monitor blood counts carefully, can do just as well as an expert who's done this many times.

The medications that we use as supportive care for Selinexor are generally medications that we use as supportive care for other cancer chemotherapy treatments. And so I think that getting Selinexor in a community oncology office is certainly possible. As a patient, I'd want you to make sure that your oncologist is actually paying attention. You should be wary of anyone who hands you a prescription for Selinexor, tells you to start it and come back in a month to talk about how things are going. Because that first month is when we have to deal with a lot of side effects and we generally want to keep a much closer eye on our patients than that.

Cindy: Okay. And I guess Carrier Pharm or someone provides information on how to manage those side effects or is that kind of common knowledge? I know when I was at the ODAC meeting, some of the doctors were saying there was a learning curve for them to manage the side effects, but once they got it they were quite easily able to manage them.

Dr Vogl: So I think that's very true. There is a lot of information about managing the side effects that comes in the package insert and Carrier Pharm, which manufacturers Selinexor has put together a team of nurses who work with the pharmacies, the specialty pharmacies that dispense Selinexor in order to provide support both to patients who are taking the medication and to the doctors who are prescribing it to make suggestions on what supportive care medications might be the most useful and to help keep a look out early on for those side effects that might cause problems and might stop patients from taking the medication if they're not

managed well.

Cindy: So patients will have a support number that they can call if they need to?

Dr Vogl: I think that's the case, certainly through the specialty pharmacy itself. And then, the other thing to keep in mind is that I think it's generally a good idea for patients with myeloma to have their care done in conjunction with a myeloma specialist at a large academic medical center who has access to all the latest information so that if you run into problems with your treatment on a day to day basis being managed by your primary oncologist, there's always someone to reach out to for advice who has a little bit more experience managing the side effects of this particular medication.

Cindy: Okay, great. From your honest opinion, do you think this is a good drug to be added to the myeloma treatment arsenal or do you think when you will be seeing this in combination earlier on?

Dr Vogl: So I do think that Selinexor is a good addition to our anti myeloma armamentarium because I think it has a different mechanism of action. We can clearly see responses in patients who have disease that has become refractory to other treatments. And I do think that for the most part, that's my biggest problem as a myeloma doctor, that too many of my patients develop disease that won't respond to any of our current effective medications. So I'll always welcome a new medication that gives me another option for how to control their disease, especially if it clearly works like Selinexor does.

I think that the side effect profile of Selinexor may stop us from using it very early in the course of disease. I think earlier in the course of of myeloma therapy, we already have some very effective combinations that are very well tolerated. And so I think it would take some evidence of a major benefit, clear evidence that patients aren't just doing well but doing much better with the Selinexor combination to have me put it ahead of some of the combinations that we're already using in our first, second and third line of myeloma treatment.

Cindy: Okay. And my last question is about Selinexor and you stopped responding, does that disqualify you for many clinical trials or I've also heard that Selinexor sometimes could be used as a bridge to clinical trials, maybe getting your numbers low enough so you could qualify. Can you just talk a little bit about Selinexor in critical trials?

Dr Vogl: Sure. So I actually do think that one of the advantages of Selinexor is that because it has a completely different mechanism of action from other myeloma treatment I have not yet heard of any clinical trials of new myeloma therapies that would exclude somebody just because they had previously gotten Selinexor, and that's not necessarily true for some of our other types of myeloma treatment where they share some common target or mechanism of action that are, would be excluded from other clinical trials aimed at the same target or using the same mechanism of action.

So I think that using Selinexor really only adds a treatment option and doesn't take anything away. I think that the idea of using Selinexor as a bridge to a clinical trial make some sense in that if you're not eligible for a clinical trial right this minute, it part because of how bad your myeloma has gotten, Selinexor offers a chance to get a good myeloma response in a way that might improve some parameters that would then make you more eligible for clinical trial participation. And compared to some of the other chemotherapy regimens that we use sometimes to bridge patients with refractory myeloma to a clinical trial combination intensive chemotherapy regimens like the D pace regimen for instance. I think Selinexor offers some advantages. It's not probably as intensive as those inpatient in intravenous chemotherapy regimens and it's certainly more convenient to take than those other regimens. So I think it can be a great option to use, especially if clinical trials of new therapies are not an option for some reason.

Cindy: Thank you so much for your time and Gary, it's all yours.

Gary: Okay. Thank you. Cindy. Doctor, the STORM trial was approved for like, almost like a single agent or

SD – Selinexor – Dexamethasone and has like a 26% overall response rate. But there's other trials going on, one of which is the BOSTON trial where the Selinexor Velcade and dexamethasone and it has an overall response rate of 63% so far. And then there's this STOMP trial, which has many different segments to it, one of which is a Kyprolis Selinexor Dex with an overall response rate of 78% with the caveat that the patients have to be Kyprolis naive. So I don't know what the significance of that is, but you might be able to let us know and with Darzalex Selinexor Dex and that has a 73% overall response rate. But again, the patients have to be Darzalex naive. But so given that, and the fact that they say that the once a week use of Selinexor during these other trials has fewer side effects, how do you think the patients will be treated in practice? Is it really, will they be asking at the major centers, are they going to be asking for compassionate use of Selinexor with Kyprolis and Dex or with dexamethasone or with the Darzalex and Selinexor with Velcade and Selinexor?

Dr Vogl: So there's a few questions packed into that one and I think I'll start off by saying that it's important not to really compare response rate to cross clinical trials that included patients with different treatment histories. So that I wouldn't look at the response rates that you just quoted and say, Oh, it's clear that Selinexor is much more effective in combination with other drugs than by itself. Because the patients who enrolled on our STORM trial that just led to its approval really were patients who were refractory to all of the available effective therapies. They had been through more therapies and were more refractory to those therapies than any other clinical trial of myeloma treatment that has ever been conducted. And so I think that's part of what kept the response rate so low at 26% was because these were patients who really had already been through absolutely everything and had so little chance at the beginning of the study that they were going to have a response to anything that it made an even a low response rate clinically significant to us.

The other trials had patients whose disease was much less refractory and certainly what's impressive about those response rates is that they are higher than we would have expected with the partner drugs alone. So that in a patient who had never received Kyprolis before getting a combination of Kyprolis with dexamethasone, we might expect that about a third of those patients would respond. And so seeing 78% of those patients respond when you add in Selinexor or definitely looks impressive and does point us towards using Selinexor in combination with other effective myeloma therapies, which I think is a trend that we have in myeloma treatment overall. These days we tend to use most of our medications in at least what we would call triplet combinations to myeloma therapy classes along with steroids like dexamethasone or prednisone. So I think it's likely that in the long run we'll want to use Selinexor in combination with other drugs.

And the truth is even right now, there's not necessarily a true barrier to doing that. Selinexor is approved by the FDA in combination with dexamethasone in a very refractory patients. But doctors actually have a lot of freedom to prescribe FDA approved medications in any way they want. Carrier Pharm isn't allowed to advertise the medication in combinations right now or tell people that it's a good idea to use it, but we have published regimens that incorporate Selinexor in other medications. So right now there isn't anything that stops me as a myeloma doctor from prescribing Selinexor or in combination with Velcade or Kyprolis or Daratumumab unless my patient's insurance company notices that I'm giving the combination and object to paying for it which insurance companies may either be very good at doing or not so good at doing.

So I actually think even right now, we are going to see patients using Selinexor in combination. Now, whether that's the right thing to do for patients who have disease that's already refractory to the partner drug that I'm not so sure about. It might be a waste of time and effort to give Daratumumab or Darzalex, which is a long intravenous infusion in combination with Selinexor instead of just giving the Selinexor and dexamethasone by itself. So if may not always be worth it to do the combination, but I don't think there's anything that's stopping us and I think we're going to see more of that.

Gary: I'd also heard along that line that if you use Selinexor say with somebody who's refractory to Velcade that it somehow makes Velcade refreshed and is now something that works where it didn't work before that it has some kind of a rebirth, a mechanism in it for some drugs like Velcade and Kyprolis. Do you have any comment on that?

Dr Vogl: I think it can be really difficult to tell the difference between that effect between overcoming a resistance mechanism to an existing drug and the actual effect that Selinexor just has in killing myeloma cells. So, and I'm not sure that it matters. In the end, what you're looking for is a regimen that will work for an individual patient. And I think it's going to take us some time to figure out in the long run and probably some additional clinical trials, whether it's better to do that with an earlier combination or with using Selinexor later on, either just with dexamethasone or in a different combination. Those aren't easy questions to answer with clinical trials. But I think the simple answer is that it's going to be worth it to try Selinexor in some regimen at some point in myeloma treatment for most patients.

Gary: Okay. Well thank you doctor. Now the other thing that I think everybody has mentioned is that the experience with Selinexor that doctors who have experience with Selinexor believe that the application of effective supportive care is recommended and that also a single dose of a hundred milligrams seems to be better than the two doses weekly. And I just read not too long ago, something that concerned me significantly. And that is that with current medications for my multiple myeloma, they say that 50% of the patients over 65 years, which is of age, which is approximately 65% of all myeloma patients do not get supportive care like antiviral or bone hardening drugs and standard treatments. And if that'd be the case, given the need for effective supportive care, how does one ensure that that happens so that the risk is, it that you have a higher treatment related mortality if you don't get the supportive care, and it sounds like at least half of that 65% of patients currently don't get it. And why would we expect them to have it with Selinexor unless something changes?

Dr Vogl: Well, so one of the good things about when we're talking about the supportive care per Selinexor is that I don't think the consequence of not getting the supportive care is dying from the side effects of Selinexor. The side effects of Selinexor can be very unpleasant, but I don't think they're generally going to be fatal. So I think the bad consequences of not getting enough supportive care is going to be going off the drug too early and not being able to benefit from, from its anti myeloma effectiveness. But I do agree with you that having patients not get enough supportive care and concentrating just on the anti myeloma drug is a problem in clinical practice. And I think there are a few ways to address it.

Carrier Pharm is doing their part by embedding nurses with specialty pharmacies so that when Selinexor is prescribed, there's some contact with patients and with the physician offices to make sure that supportive care measures are in place. There's some role for me as a myeloma specialist to educate my colleagues both my colleagues who treat myeloma because I'm one of the doctors that treated patients on clinical trials of Selinexor and for my colleagues out in the community. And I think there's a large role for an informed patient population who recognizes that this is something that we are going to have to pay attention to and demands of their doctors that we do a good job giving them the supportive care that they need, not just for Selinexor but as you said for all of the effective supportive measures that we use for our myeloma patients.

Gary: All right, well thank you Dr. I don't want to be, I just ask these questions because having some concerns but and wondering how it's going to be accomplished in practice, but obviously in my own mind, it seems like every time we have a new class of drug, whether it be an IMiD or a proteasome inhibitor or an antibody, the overall survival goes up by about 20 to 25%. So, to have a new one that's effective, here we go again another bump in our survival just because we've got a new mechanism of action. Another way to go after this very, very shady little myeloma cell, which keeps on changing. So, I think this is, this is wonderful. I'm glad to see that we've got other ones that are coming up like CAR-T and antibody drug conjugates and the like. So I think it's a brave new world for us. So thank you very much for all that you do. So at this point I'd like to open it up for the callers, Priya could you see if you can get some caller questions?

Priya: Yes. Thank you, Gary. Thank you for all those great questions. Dr Vogl, we have questions getting posted on our page. I'm going to just probably read through them because we have addressed a couple of them before in the discussion. It'd be great if you could just reiterate very briefly for the people who asked them again. So the first one is do the side effects lessen after a month?

Dr Vogl: And, as I said before to Cindy, I think it's less a time issue, it's less of an issue that the side effects

lessen after a specific amount of time and more that the combination of dose adjustments and tailoring the supportive care mechanisms to the individual patient's needs mean that the first month usually is the toughest and that after that if patients are benefiting from treatment with Selinexor and their myeloma is responding, we can usually find ways to make the treatment tolerable and allow them to continue the treatment.

Priya: Thank you doctor. The next question is what is it about this drug that makes it classified for use only after all other treatment options? Is it risky?

Dr Vogl: So I don't think it's so much that Selinexor is risky but it's side effect profile does mean that it's not something that I would necessarily want to give patients with myeloma very early on in their treatment course where I do have other effective anti myeloma medications that don't have as many side effects. And part of the reason right now that it's approved for use only after everything else has stopped working is that that's one of the ways to get a new myeloma medication approved right now you can either show that it's better than something that's already out there or you can show that it's effective when everything out there no longer is. And that latter argument is the argument that we've ended up making for Selinexor. And I think part of the reason that we did that is because of how much side effects the drug has and therefore the patients who are willing to try it and willing to undergo those side effects are patients who tend not to have that many other good treatment options.

Priya: Thank you doctor. The next question which just came in by email is what is penta refractory multiple myeloma.

Dr Vogl: So Penta refractory multiple myeloma is a term and a category that we actually had to make up for this trial. And it comes, if you go back a few years, myeloma physicians realized that patients who had gotten through both lenalidomide, Revlimid and bortezomib Velcade had disease that was more refractory than other patients and had particularly poor outcomes and started talking about this group of patients with dual refractory myeloma. And we started writing clinical trials for patients who had dual refractory myeloma. When we came out with a new class of medication with Daratumumab or Darzalex, we started talking about triple refractory myeloma. But by the time we started doing trials with Selinexor, we realized that we couldn't just look at patients who were refractory to Revlimid Velcade and Darzalex. We also had to include drugs like POMALYST and Kyprolis and when you include those five drugs that's where we ended up with Penta refractory myeloma. And along the way, actually it was right before Daratumumab was approved.

We had patients who had quad refractory myeloma, but as soon as Darzalex Daratumumab was approved, it became clear that that was going to be used frequently and early for patients. And so we wanted to address patients for whom even Darzalex was no longer going to be effective. And that's where we came up with with the classification of Penta refractory myeloma. This process clearly is going to have to keep on going because as we add new treatments, we're going to extend how long people live and end up with patients who unfortunately end up being refractory to even more classes of drugs. And the naming system might eventually become ridiculous. But in the end what we're looking at is groups of patients who have been through all of the other treatments and are in need of something that's really new and different.

Priya: Thank you very much. Doctor. I just have one more question before we can wrap up today's episode. So Dr Vogl, the approval of Selinexor did draw some harsh criticism from some doctors from myeloma fraternity on its pricing and want of randomized controlled trials. So what are your comments on this?

Dr Vogl: So a randomized control trial I think is the ultimate proof of clinical benefit for any new drug. And I think that the FDA's current insistence that all drugs eventually have a randomized controlled trial to support their ongoing approval is very important. But as a myeloma physician taking care of patients, I also know that when a new drug has been shown to have efficacy it can be an agonizing wait for completion of the randomized controlled trial that will eventually prove that that's truly better in some ways than what we have already available. I am generally in favor of the currently available mechanism for what we call accelerated approval of a drug based on an uncontrolled trial showing that it has efficacy for patients with myeloma. And

although I think there's some valid criticism of Selinexor side effect profile and whether looking at just myeloma responses in the setting of having a lot of side effects is the right way to judge a drug.

I think for Selinexor in my mind, based on the results that I saw from these trials, I think balances out in favor of the drug. And I think the FDA made the right decision in granting Selinexor accelerated approval. I think the cost of oral, especially oral medications, but even intravenous medications in the United States is a real problem. And it's a problem in part because there is no effective mechanism for cost control. No government regulation of costs, no real bargaining power that patients or insurance companies or even government programs are forbidden from bargaining within with drug companies over prices of drugs. And the FDA is not permitted to consider the cost of a medication in its approval decisions unlike some of its counterparts in Europe. That is where regulatory agencies are allowed or are required to consider the cost of a therapy, which I think does keep costs down in Europe for similar drugs. And I think it would be a great idea for the American health system to undergo some reforms, to include some mechanisms for keeping drug prices under control or at least having some mechanism for influencing them downwards because I do think that the cost of these therapies will eventually catch up with us.

Priya: Thank you, doctor. The accelerated approval of Selinexor based on the STORM study of 123 enrolled patients achieving a response rate of 26.2% is important as its target. XPO1 is novel and this oral medication is a first in class agent. Selinexor was granted both orphan drug and fast track designation by the FDA because of the urgent unmet need in the clinic. More clinical trials are underway using Selinexor in combination with other myeloma therapies, as we heard Dr Vogl explain. Certainly this drug is good news for patients with a few options for continued myeloma care. And on that note, we are wrapping up today's episode. Thank you Dr Vogl for joining us today.

Dr Vogl: Thank you so much to all of you for your very perceptive questions.

Priya: Gary, Jack and Cindy, a pleasure to have you on board as usual with your great questions. Thanks a lot. We also thank the University of Pennsylvania and the audience. The talk will be available on curetalks.com. Please visit our website for details on upcoming talks. Thank you and have a great evening.