Dr. Ratan on Nirogacestat - DTRF 2022 Patient Meeting Webinar #2

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Jeanne Whiting: Okay, we're moving on to our next presentation, which has been much anticipated in the desmoid community presentation on nirogacestat for the treatment of desmoid tumors. Presented by Dr. Ravin Ratan, associate professor in sarcoma at MD Anderson Cancer Center. We had a major presentation on this trial at the ESMO conference a couple of weeks ago, and he's just going to summarize that all for us here.

I have to point out that this trial in this drug has been a 16, sorry, a 13 year journey. Phase one was done in 2009. Phase two, several years after that, we were involved in that, working with the National Cancer Institute, made our patients aware of it. There were 17 patients. And now finally we reached the end of phase three. And Dr. Ratan we really appreciate your explanations.

Dr. Ravin Ratan: Okay, great. I'm starting my timer to make sure we stay on time. Good afternoon everybody. I hope you can hear me okay. Someone interrupt me if you can't. So my name's Ravin Ratan. I'm like Jeanne said, an associate professor at MD Anderson. And this is the title slide from the presentation that I gave yesterday, which is derived from the presentation that was given two weeks ago at a large international meeting.

So we're gonna be talking about the results of DeFi, which is a phase three trial of nirogacestat for progressing desmoid tumors. I've modified this a little bit. This is not quite the presentation that the doctors got, although it's certainly very similar. And so I retitled it. It's a summary for the patients and caregivers - really for all of you.

These are my declarations. These are companies that I work with in the course of doing my job. So a couple notes on today's discussion. I think this is really important to emphasize because as Jeanne mentioned, I know there's a lot of excitement in the community, but as of today, nirogacestat is not approved for the treatment of desmoid tumors or any other disease.

It shouldn't be considered standard therapy for patients that have reasonable alternatives outside of participation in a clinical trial. And the data that I'm gonna show you here today is the exact same data that was shared with researchers and clinicians around the world at the European site of medical oncology meeting approximately two weeks ago.

I've tried really hard to make sure that I left all the data containing slides in, but I am gonna explain them differently from the way that I did yesterday to the researcher group. And notably SpringWorks, which is the company that sponsored this study. I mean, I think they're sort of generally supportive of sharing this data with you, but they have not no direct involvement in the development of today's talk and what I'm gonna say, however, some of the data containing slides, which were used at the original presentation were developed in, in, cooperation with them.

So, some key background in desmoid tumors as this audience knows really well these are rare, locally aggressive and invasive soft tissue tumors. And the clinical behaviors really vary ranging from patients who can have their tumors improve or even resolve without any kind of treatment to tumors that are very aggressive and can quickly cause very significant problems, which are even occasionally life threatening.

And as was emphasized by the last presentation, the treatment needs to be highly individualized, and goals can vary for some patients, tumor shrinkage. Trying to make sure that the tumor doesn't cause some kind of anatomical complication. And for others, symptom control is gonna be the key goal irrespective of whether the tumor grows or shrinks, it's making sure that they can live their lives relatively normally. So nirogacestat is a class of medication called a gamma secretase inhibitor, which was noted initially in studies that sort of enrolled a wide range of tumor types and then later in studies just for desmoids to be associated improvement with improvement in the tumors.

And coming out of that, there was a search and a mechanistic rationale developed by which we think that the gamma secretase inhibitors might be working in desmoids, but we don't fully understand that yet. So you'll hear a

little bit about the protein notch which is expressed in desmoids, and the activation of which can be blocked by GSIs.

But we don't fully understand exactly how these drugs are working in this disease. So the study defi was a global randomized and randomization is important. It's a way that we reduce something that we're always very concerned about in clinical trials, which is bias. It was double blinded, which means none of neither the patients on the study nor the physicians treating them, nor the people reading the imaging knew what the patients were getting, whether they were getting placebo or getting the drug. And this particular trial was randomized to placebo. So half the patients got the medicine and half the patients did not get a medicine at all. They simply got pills that were similar in appearance.

When you're doing a clinical trial, the first thing that you want to define is what you're trying to prove. And for statistical purposes and for designing a study, you have to come up with something that you're gonna measure to decide whether your drug is effective. And so for DeFi it was progression of free survival, which is defined as how long from the time the patient starts on the trial to when they have their tumor progress or grow by more than 20%.

Secondary important outcomes that were also looked at were the response rate, which is how likely the tumor is to shrink, slightly different from progression-free survival. And then very importantly, patient reported outcomes including symptom burden, physical functioning, and overall quality of life.

Some of you who participated in this study or cared for people who did, might have been aware that there was a huge burden of questionnaires and surveys. And part of the reason that I wanted to show you the data from the study today is to share with you the fruits of that. It was so important and as an investigator on the study, we've been so appreciative of the participants taking the time to do those cause it's truly been critical to understanding how this drug works.

So this red box on the bottom here is what happens on the study. So patients who are adults with progressive desmoid tumors, and I'll just mention the definition of progressive, was very rigorous here. Most of the patients that I treat with desmoids were not eligible for the study. You had to have a tumor that was well and truly growing over the previous year. Half of the patients got nirogacestat 150 milligrams twice a day, and half the patients got a placebo pill, a sugar pill that they took twice a day and they did not know which that they were getting. For those patients who got placebo and had progressive disease on on the trial, they were allowed to switch over to nirogacestat.

And of course at that time they knew that they were taking nirogacestat. And so this is the baseline demographics and characteristics. And this is a figure that physicians scrutinize very carefully. And what we're looking for is to make sure that the randomization was successful. You wanna see that the numbers in these two columns kind of roughly match each other.

You wanna make sure that the two populations were relatively comparable. So the patients that ended up getting on the study were young in their early thirties, 33 to 34 years of age. About two thirds of them were women and one third were male. And that's kind of how it goes with desmoid tumors.

That's who's affected by this disease. There's a two to one female predominance. Most patients had mutations in a gene called beta catenin, and that's most patients with desmoid. It's about 80%. And then the remaining 20% had APC mutations. And these are generally patients with the syndrome that many of you may know of as familial adenomatous polyposis. It's a colon cancer syndrome that also is associated with the formation of desmoids. So both groups were represented more beta catenin mutations because that's who gets these tumors. And the representation was similar. I'd point out that DeFi had a large percentage of patients with multifocal tumors, so approximately 40% of patients had tumors. Not just one desmoid tumor, but multiple tumors. And we certainly have many patients with desmoids that have multiple tumors, but 40% is on the high end of what one someone might expect. And so there this study included a lot of patients with multiple tumors.

And then I'd also just point out that a number of the patients had prior therapies. Approximately 75%, 75 to 80% of patients had prior therapy. And then the other remaining 20 to 25% were treatment naive, meaning they'd never received any other treatment for their desmoid tumor.

So this is the the headline, right? So nirogacestat reduced the risk of progression. And so this is called a Kaplan Meyer Curve. The top line here in blue. The top line here in blue is nirogacestat, and the black line here is placebo. And every time someone in one of these arms has progression of their disease, the line drops a little bit and this is going forward in time.

So you can see that pretty early on, within about two or three months, you start to see that the black line starts to separate because more patients on placebo are progressing. And then the the blue line stays stays a little bit higher. There are still patients that progress on that side as well.

So by 15 months, half the patients on placebo have already progressed. But for nirogacestat, we have not yet seen that happen. This is a subgroup analysis. It's looking to see if the nirogacestat treatment effect is seen preferentially in one arm versus another, and it is not. So this is actually all of the groups they looked at, including prior chemotherapy patients, responded equally.

Going to response rate, this is tumor shrinkage. 41% of patients with nirogacestat had their tumors shrink by more than 30% in contrast with 8% of patients on placebo. And the complete response rate was 7%. So there actually patients on the niorgacestat arm had their tumors essentially completely disappear, which was not true on the placebo arm.

And this could happen reasonably quickly. So patients on nirogacestat got that response of at least 30% within less than six months versus 11 months for those patients who did get responses on placebo. And notably, there were some of those. This is a waterfall plot. It's looking at how much patients tumors tumors shrink on the study.

And so this red line here is zero, so that's a tumor that didn't change at all. And each of these bars represents an individual patient. So over on the right side here, you see patients that had their tumor shrink all the way. This dotted line here is the cutoff for calling a response. And so you can see above that there are patients that still had their tumors shrink, but did not hit that 30% cutoff.

For the purposes of the study that's considered stable disease. Even though many of these patients probably did get some benefit from nirogacestat, we recognize that as you get closer to zero, some of these bars may be related to errors in measurement and that's why we draw the line at 30%. Going quickly to the patient reported outcomes, and I'll go through this quickly, they were analyzed for statistical purposes at cycle 10, but I will tell you that we, what we see here is in black again, is placebo - and blue is nirogacestat - going down means that the symptom intensity is improving and you can see that very early on by cycle two or three these curves are very clearly separated and they stay that way all the way through the study. So this is pain. Pain was improved by cycle two or three and remained improved throughout the study duration. This is a separate symptom assessment based on patient surveys, looking at desmoid tumor specific symptoms, which could include pain, but also include things like stiffness and limitations and function.

And again, you can see there's an early separation that's maintained throughout the study and it's cycle 10 where it was formally analyzed. It is clearly separate. And then finally, this is the physical functioning, the role, physical and role

functioning, and overall quality of life, which follows the same story. So a quick separation by two or three months that's maintained throughout the study.

Very quickly looking at side effects, because I think this is very important. You have nirogacestat on the left of placebo on the right, and so grade three is classified as a severe side effect. So for example, grade three diarrhea is greater than seven bowel movements over a patient's baseline or requiring hospitalization or IV fluids, or if a patient has an ostomy, greatly increased ostomy output.

And so you can see there were some grade three side effects, but the majority of side effects that we see on nirogacestat are grade one or grade two, so more considered mild. And you can see that even patients on placebo have what we call treatment immersion adverse events. So you can have diarrhea, nausea, and fatigue for reasons that are not related to medication, but clearly diarrhea, nausea, fatigue, low phosphorous level and rash, as well as headaches and mouth sores were all more common in patients getting nirogacestat over placebo.

And then finally, an important side effect that I think this group may partially be aware of is ovarian dysfunction. So this was sort of noted on the study, and fortunately the protocol actually made sure that at the time of enrollment on study, and then in subsequent cycles, we collected hormone levels, reproductive hormone levels in the patients.

And so what we saw was that about of there was 36 women who were sorry, considered of childbearing potential in the nirogacestat arm of the study. And 27 of those 36 women reported some form of ovarian dysfunction, whether that was abnormal hormones or hot flashes or losing their periods. It could be defined in any of those ways.

11 of those 27 women stopped nirogacestat for one reason or another, and in all of those women, the ovarian function as being measured returned to normal. 14 patients out of the 27 are still on nirogacestat at the time that this data was obtained, analyzed. And in those, nine of the patients for approximately two thirds have had resolution of their ovarian symptoms and five patients continue to have symptoms of ovarian dysfunction.

And then two of the 27 patients did not continue with follow up after stopping nirogacestat, and we don't know what the status of their ovarian dysfunction is. So, very briefly, this is the largest and most rigorized, randomized controlled

trial that's been competed, completed in desmoid tumors. It was an enormous undertaking.

The drug demonstrates a rapid sustained and statistically and clinically significant improvement in all of the things that we were looking at in the study, which includes risk of progression, likelihood of shrinkage of tumor, and improvements in quality of life. The safety profile is real. There is side effects to this medication as there is with any, but it seems to be manageable.

And again, I wanna stress that this drug is not currently available for routine use. This is not something that you can go and talk to your doctor about getting today under routine circumstances. And there continue to be a lot of questions that we have as physicians taking care of people with desmoid tumors that I'm sure the community has as well.

You know, even in the placebo arm, there was a low response rate to treatment. 8% of patients had a response to placebo. So we still don't have a great way of knowing who must have treatment and active surveillance remains and option for some patients with desmoid tumors. We don't know how long patients have to be treated for.

We don't know what happens when we take patients off the medication. Do they stay shrunk? Do the tumors all grow back? Can we put the tumor? Can we put the drug back on and have the patient respond in the same way? Those questions have not been answered. And then you know, what we have about the ovarian dysfunction, I think is encouraging with respect to the fact that patients stop the medicine, have their ovarian function apparently returned to normal.

But we don't actually know if there's any sort of adverse effects on fertility down the road and so forth. I think what we know is encouraging, but it remains an unanswered question. Very briefly I want to thank the participants in the study. I recognize that some of you may be listening to this right now.

It is hard to overstate how grateful we are to you for participating in the study, for doing these PRO assessments, which we're burdensome to putting up with multiple scans and clinic visits. I'm thankful to the co-investigators around the country and indeed the world who made this study happen.

And speaking is hard to overstate the impact of the DTRF and the development of this drug really can't be overstated. I mean, DTRF was involved in the development of the patient reported outcomes instruments that were used for

parts of this study. They've advocated for the drug from the very beginning before there even was the SpringWorks.

And publicizing the study to facilitate enrollment in getting patients to a sarcoma center as Jeanne says has all been instrumental in getting this study done. So thank all of you so much and I'm delighted to take your questions.

Jeanne Whiting: Dr. Ratan a big question I think in everybody's minds is, when an application for approval with the FDA is anticipated to be made, and a very brief synopsis of how that approval would take place, how much time it might take?

Dr. Ravin Ratan: Yeah, so the timeline is something that I'm not gonna comment on too much. I think that we are all hopeful that the process unfolds quickly and successfully, but there's no guarantees of any of that. Right. I think that I've tried to stress that this is still an investigational agent. We just have a phase three completed trial.

You know, at some point the company is going to make an application to regulatory agencies around the world trying to get them to approve the drug for marketing for this disease. That's gonna require a rigorous evaluation of this data independently by those regulatory agencies. It's gonna require convening of a panel of oncology experts who will make a recommendation to the FDA as to whether the drug ought to be approved.

And then ultimately the FDA will make a decision on that. So there's still a process that needs to play out. I don't have any information to share about what that timeline is going to be. I will just simply say that I think everyone recognizes that we want this to move forward if if that's what's going to happen.

Jeanne Whiting: Thank you. One other question, as we are short on time, in the press release for the phase three DeFi results, SpringWork's reported a 41% objective response rate, partial plus complete according to RECIST measurements. Are they able to share meeting tumor volume reduction, and two, change in T2 signal intensity in the experimental group versus the control?

Dr. Ravin Ratan: Yeah, so super duper awesome question and I think really important. So all of that data exists. It's, it was all collected. I think that the purpose of this initial disclosure was to report out on the on the primary endpoint of the study. Right. And so I think there will be more information coming out on that over time.

It is just not available yet. But that's coming. I expect both sort of the MRI characteristics and certainly the tumor volumetrics is something that we should expect to hear more about.

Jeanne Whiting: Okay, great. There are a lot of questions in the chat. If you're inclined to go in and answer any of them in writing, I'm sure people would be appreciative, but we'll leave that to you.

Thank you so much. Very exciting. We appreciate your presentation and your time today.

Dr. Ravin Ratan: All right. Delighted. Thanks so much for having me.

Jeanne Whiting: Thank you.

Dr. Ravin Ratan: Thank you all for everything you do.