Dr. Agulnik and Gordon on AL102 - DTRF 2022 Patient Meeting Webinar #2

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Jeanne Whiting: So, as Dr. Ratan mentioned the nirogacestat is a GSI or gamma-secretase inhibitor. There's another trial ongoing with a different gamma-secretase inhibitor by Ayala Pharmaceuticals.

It's called the RINGSIDE trial. They also presented their results at ESMO and we're excited to hear your presentation. We have, sorry, I should introduce Dr. Mark Algunik and Dr. Gary Gordon, who will be sharing the presentation.

Dr. Mark Agulnik: Thank you very much for having us. This is wonderful. It's great to be able to share so much information with the community.

I see so many participants on today a number of my patients. So welcome everyone, and thank you for having us. So what we will go ahead and do is we will discuss the initial results of RINGSIDE, which is a phase two and three trial of a drug called AL102 for the treatment of desmoid tumors.

Dr. Gary Gordon: So this is Gary Gordon, I'm the Chief Medical Officer from Ayala. And I guess the question is, are you seeing my screen?

Dr. Mark Agulnik: We are seeing your screen, yeah.

Dr. Gary Gordon: You are. Okay.

Jeanne Whiting: Good to go.

Dr. Gary Gordon: That makes one of us. Okay. Well thank you very much. As Mark already indicated, Mark and I will be sharing this presentation about the RINGSIDE study. Mark, as you all know, is the section chief for Sarcoma and Medical Oncology at the City of Hope.

And we are really pleased and excited to be here today to talk about the results of RINGSIDE so far. The point I wanted to make before we really get started is that DTRF has really been instrumental in what I would call creating a community around this disease. And that community is first and foremost the patients, the advocates, and the academic investigators as well as the companies.

And it's really through those combined efforts that we're able to conduct these trials, educate practitioners, educate patients, and the like. So we appreciate all the efforts on the part of DTRF to educate everybody involved. And we suspect over time that those efforts will actually bear a lot of fruit, not only across the physician community, but into the regulatory community as well.

Just very briefly to talk about AL102. It's an investigational drug. It's already been mentioned. It's an oral once daily gamma secretase inhibitor. We know that notch is a an important pathway in many different cancers, and that gamma secretase inhibitors as part of their action prevent notch signaling.

And that there is a tie in between notch signaling and the WNT beta cat pathway, as well as the APC pathway that are all active in desmoid tumors. But as indicated earlier, we don't really completely understand how that activity is created. We know the drug is active against desmoid tumors, as you've seen.

And we'll show you here shortly with 102 and RINGSIDE is a phase 2/3 study in desmoid tumors. And we'll show you shortly the results from Part A, which was a dose selection effort in this trial. And these results were also just presented by Robin Jones at the recent ESMO meeting. Just to give you a very high level view of what the study is.

What we call part A is really a phase two study. It's a study that involved 42 subjects that were randomized across three different doses of AL102, a daily dose of 1.2 milligrams. And then we were wondering what would happen if we adjust that, the schedule to be an intermittent schedule of two days on five days off, as well as looking at some of the questions as they relate to efficacy and safety as a factor or as a confounded by dosing.

We have, as you'll see, made the decision to move to part B or the phase three portion of the study, which will be a randomized placebo controlled study. Again, where patients, investigators, and evaluators are blinded to the treatment group that the patient has been assigned to, and we are currently activating sites and open for enrollment in certain centers as we speak.

The next slide really is the total picture of the study. Now, that first part A, where we've looked at these three different doses and part B, which will be the randomized study, and the primary outcome of our study will also be time to progression and response rate in patient reported outcomes.

And the key inclusion criteria for Part B will be individuals who have relapsed or refractory desmoid tumors, or you can be treatment naive as long as you have tumor growth. That's about 20% in the last 12 months, and we will be enrolling individuals as young as age 12. So I'm now gonna turn the presentation over to Dr. Algunik and he'll walk you through the results.

Dr. Mark Agulnik: Perfect. Thank you very much, Dr. Gordon. It's a pleasure. So what we're gonna do is we're gonna look at the initial results of Part A, which is the phase two portion of RINGSIDE. It is a trial of AL102 in the treatment of desmoid tumors as we discussed before.

And so the way that this was is that what we did for our patients that were enrolling in the phase two portion or part A portion, we ended up enrolling them into three different dose levels. So there was a subset of patients who received the drug at a dose of 1.2 milligrams every day. There were two other dose levels.

We had patients receiving it two days on, five days off. We called that the intermittent dose of two milligrams, and then we also had the intermittent dose of four milligrams. All of these patients, if they're currently doing well and still on study, will roll over to an open label extension where they will be over to the 1.2 milligram once daily.

And so if there are any patients currently on this call that have participated in this, that is ultimately the plan. For the part A portion the primary endpoint with safety and the secondary endpoint was to look at the tumor volume and the reduction in tumor volume. These were patients all older than 18 years of age.

These were patients all with measurable disease. These were patients with relapse or refractory or treatment naive with tumor growth or pain in the last 18

months. And let's move to the next slide. So with respect to the design and patient characteristics, we had 42 patients enrolled in phase two of this study.

All had progression seen on a CT or MRI or clinical progression. Clinical progression is documented as worsening of symptoms such as pain. Half of them had prior surgery, two thirds had prior drug based therapy, and one third of patients received AL102 as their first therapy. The average age of the patients were 38 and a half years, so under 40.

Three quarters were female. And what we saw was we saw tumors in the abdomen in other regions such as the head and neck regions, the limb, the back, or the abdominal cavity. And the results are interim. The results could change over time because patients remain on therapy and data continues to be collected for these patients.

And so what we know is that the patients who are 42 of them, this is an ongoing trial of these 42 patients, but it's no longer taking new patients. Any new patients. The intention is for them to go on to Part B, which is a phase three trial, and the dose selection for this phase two will not be mimicked in the phase three, where we will just select one dose level of 1.2 daily.

And so what we saw is rapid activity that was observed across all doses at week 16. And so we have some waterfall plots here, and what we have is that each individual bar represents an individual patient. Everybody starts at zero. Zero would be defined as the volume of tumor that they currently have at study entry, and if the bar goes down, so it decreases. If the change in from baseline decreases, then we see that going down. If the bar goes up, that means that there is an increase. We have two sets of bars here. One is the volume change from baseline, and the other is a central RECIST, which is looking at positive. If it goes beyond 20% growth or beyond 30% shrinkage, anything between those two points are considered stabilization of disease.

Anything greater than a 20% growth is considered progression of disease and anything lower than 30% shrinkage is considered a partial response. And so what we did see as a partial response was observed at 16 weeks and that patient's partial response was confirmed at 28 weeks. And that is a patient in the 1.2 milligram group.

Next slide please.

So here again, we see the activity across all dose, and now we're looking at the 1.2 milligram once daily. So here we see the volume changes with the majority

of patients having shrinkage of their volumes, as well as with a central RECIST review. Majority are having shrinkage of their tumors compared to baseline.

And as I said before, there is one partial response. So if we look at patients who responded at 16 weeks, they continue to respond and develop deeper responses regardless of doses. And so we have 12 patients had at least two MRI scans. Tumors continue to shrink over time at all doses, but what we saw is that there was more shrinkages in the 1.2 milligram group and three of the four partial responders in the 1.2 milligram, three of the four parcel responders were in that 1.2 milligram group.

So over time, the tumors continue to grow and that allows patients to switch over from a stabilization of disease to a confirmed partial response.

So what we often look at is we look at T2 intensity. We considered a T2. MRI reflects the amount of living tissue of a tumor, and what we wanna see is change in intensity.

If you decrease intensity or change intensity, the anticipation is that you're decreasing the cellularity and that living tumor is no longer living.

And so what we did see in several patients is a change in the density which would reflect treatment of the tumor. So as with any drug, what we wanna do is make sure that the drug gets safe. And so here we have the results in the 1.2 milligram group. This is a total of 14 patients. What we could summarize is that AL102 is generally well tolerated.

The most side effects were mild or moderate. Severe side effects were uncommon and there were no grade four or five events. A grade four event would be an event that would be something that would have a major impact on a patient and so that they would either be admitted to a hospital, but certainly they would need to come off of a drug. Grade three events often are events that require a treatment, so whether it be IV fluids, whether it be other drugs. But for these events, often you need to alter the dose of the drug that you're currently on. Most side effects were managed by dose reductions or interruptions. Side effects that cause people to stop taking AL102 included diarrhea, elevated liver enzymes, rash or inflammation of the mouth, and across all doses, we did see ovarian function change in 22% of patients. And so what we have here is our conclusions based on the initial results of RINGSIDE Part A. We know that AL102 was generally well tolerated with a manageable safety profile.

Most side effects were mild to moderate. The most common ones were related to GI, which is so diarrhea, nausea, things like that, or skin toxicity. Severe side effects were uncommon, manageable with dose reductions or interruptions. Activity was demonstrated across all arms of this trial. And what we saw was consistent across measures, meaning we saw it in change in volume, we saw it with respect to change in size, so by RECIST, we saw it in change in the T2, MRIs and T1 responses are seen within 16 weeks and maintained and deepen over time. So the longer you are on this drug, the anticipation is that more response will be seen.

So based on these data the placebo controlled phase, which is the Part B, phase three of RINGSIDE at a dose of 1.2 milligrams daily will enroll patients and give us more information about this drug.

Jeanne Whiting: Thank you. Should we move to questions?

Dr. Gary Gordon: So there's a little bit more we wanna go through. More slides here. This is Gary Gordon jumping back in. Just talk a little bit about the randomized portion of phase three or part B portion of the study. To be eligible for enrollment, you must be 12 years of age or older. You have to have growth defined radiographically by, preferably by MRI or CT within the last year. And you will receive either, if you participate in the study, you'll receive either AL102 or placebo.

And again, given the nature of the randomization and how a blinded study works, no one will know which drug group you've been assigned to. We are very, we very carefully designed the study to say those individuals who do have progression while on study, will be able to cross over to an open label extension with AL102 so that everybody ultimately will be able to get drug.

As I mentioned, this part of the study is now enrolling. Again, the end point is progression free survival and will also be looking at response rate and patient reported outcomes. And for the sake of time, I'm not gonna repeat what we've shown you a couple of times, but just that again, it is a randomized placebo controlled study with a one to one ratio.

As mentioned, these can be, you know, participating in a clinical study does require a little bit more effort, not only on the part of the investigators, but on the part of patients. And what we're just indicating here that participants in the study will get will be asked to undergo some of the items here, such as screening, testing prior to starting the drug.

And then follow up every month around certain issues and an MRI every three weeks. And of course, we'll also be very interested in patient reported outcomes using multiple questionnaires, including those developed by DTRF in part. Lastly, just to give people an idea, the geographic spread of this study, it is in the countries listed on this slide and shown pictorially on the graphic here.

So we are I'm very interested in driving the study forward making the, you know, conducting the study with a broad geographic footprint. And if you are interested in the study, either contact your healthcare provider or Ayala at the clinical trials at Ayalapharma.com for more information.

Thank you.

Jeanne Whiting: Thank you. I would just ask a question practical, a practical nature question. You had one dot on the US. How many centers, for example, within the US will there be an option to enter the trial?

Dr. Gary Gordon: So there'll be approximately 30 to 35 US centers.

Jeanne Whiting: And if a patient were not close to that center, how many visits would there be going actually to this center or can it be administered and checked remotely? How does it impact the patient and travel?

Dr. Gary Gordon: So currently the way the study is written, there would be visits required to the center once the patient is enrolled in the study. And is in the regular schedule. It'll be about quarterly imaging visits and we're working on looking at ways to do some of the intermediate visits remotely.

Jeanne Whiting: Okay. Is there a percentage of tumor growth to required to trigger the unblinding?

Dr. Gary Gordon: Yes. That would be a RECIST defined progression event, and I'll point out, first and foremost, unblinding is not required for one. Progression is required by RECIST to cross over. A patient does not need to be unblinded to cross over.

So for instance, if an individual is still felt to be having clinical benefit, regardless of the radiographic progression, they would count as an event, but they could then move over to the open label extension regardless of the treatment arm they had been assigned to.

Jeanne Whiting: Okay. How many patients again are you enrolling in this final phase?

Dr. Gary Gordon: 156.

Jeanne Whiting: Approximately when, sorry, and when could enrollment end so people know the timing?

Dr. Gary Gordon: So it's a little difficult to answer the second part of your question, but we're aiming to enroll 156 individuals in the study. Enrollment in part A went relatively smoothly over a period of several months. You know, we anticipate enrollment will likely take somewhere in the range of 12 to 18 months.

Jeanne Whiting: Okay. Two questions from Canada. Is there a reason I don't see Canada on the list?

Dr. Gary Gordon: At this point we do not have a Canadian site that was interested in engaging in the study, but if people have suggestions, please let us know and we can reach out.

Jeanne Whiting: Okay. Is the possibility of the ovarian dysfunction result been discovered? And and how has it anticipated that would be?

Dr. Gary Gordon: So, as Dr. Agulnik mentioned, 22% of the patients of who were women of childbearing potential, which was about 23 individuals in the study, did have manifestations of ovarian dysfunction. We have had a couple of individuals stop who have anecdotally begun to show signs of recovery, as mentioned in the previous talk.

This is an area of active interest and you know, needs continued follow up to really answer the questions and understand what are the implications of the findings.

Jeanne Whiting: Okay. And I have so many questions. One more we'll take. Is the trial likely to open up to younger UK based patients, for example, as young as four years old?

Dr. Gary Gordon: At this point, the study is designed for individuals 12 and up. We're, let's say, actively pursuing how we can enroll younger individuals. But at this point in time, the trial is not open to those that are younger.

Jeanne Whiting: Okay. A question one more question. Do you know what dose or dose schedule the patients who had an ovarian issues were on?

Dr. Gary Gordon: We did see that across all three dose groups, so we think it is something that is, you know, fundamentally related to the mechanism of action of gamma secretase inhibitors.

Jeanne Whiting: Interesting. Okay.

Dr. Gary Gordon: And it didn't appear to be a big difference across groups.

Jeanne Whiting: Okay. Thank you so much. How interesting and how important to get this information to the community. We have so many questions in the q and a. If you're inclined to answer them, I'm sure it would be appreciated.

And thank you everybody for your question and participation.

Appreciate it Dr. Gordon.

Dr. Mark Agulnik: Thanks for having us. I appreciate it.

Dr. Gary Gordon: Thanks for the opportunity.

Jeanne Whiting: Thank you.