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Volumetric Assessment of NF Related Tumors
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>> DR. DOMBI: First of all, let me say thank you for three things, first putting together this symposium and giving me the opportunity to be here, second thanks for Dr. Tonsgard for his hospitality, I have to say, he treated us very well.

And the third and most important thank you is for all of you. Thank you for coming here and showing interest in what we do because clinical research is nothing without the patients. We appreciate the participation of patients and families. For me, to be here is a great opportunity to explain what we do, to ensure that you understand our research goals, really do the things required by the protocols, such as handing in the forms to Staci's questions, follow through with plans and stay the course on a treatment study.

Diana asked me to talk about volumetric assessment of NF-related tumors. I would be hard to do that without a little background.

What you see on the picture is the brand new NIH clinical center. It houses over 200 inpatient beds and some outpatient units. It's the largest research hospital in the United States, I can say among the largest in the world. And it's a terrific place to do research, with multidisciplinary experts and a nationwide patient base. The hospital conducts about 1500 clinical studies. About half are natural history studies focusing on rare diseases such as NF, the others are treatment studies to develop new therapies to improve the patients life.

So in an overview: I will start with talking a little bit about clinical drug development, steps the drugs go through before they are approved for a certain indication.

Next I show the efforts of REiNS collaboration to standardize NF clinical trials. It may seem trivial that we want to compare

different drugs and say is this better than the other one? But that's actually not done for NF yet.

The REiNS collaboration that Staci was mentioning for the PROs is a broader effort to standardize every step of clinical trials, the evaluation of the patients, the measures that they use to assess a drug effect with the hope to be able to compare different treatments.

And then I will talk about tumor measurements. I describe the volumetric method that I use and the imaging requirements for volumetric analysis. The print outs are available for you, and you can show these imaging parameters to your doctor and ask if your tumor can be imaged in a way to do volumetric measurement.

And then I show a lot of growth data from the NF 1 natural history study on mostly plexiform neurofibromas. We have precious little data in NF 2, but there is some.

I will show some tumor response data from clinical trials that are looking promising.

And at the end, I would take a look at you as a clinical trial candidate.

Clinical drug development starts out in the laboratories. There are lots of preclinical studies in cell cultures and in animals. But at a certain point when a drug seems promising, it goes to the stage when you have to administer the drug to the first human subject.

First in human trials for tumors are usually done in cancer patients who exhausted all standard treatment options. And goal of this first phase in development is to find a dose that will be used for treatment and describe common side effects.

A phase one trial is typically a fairly involved study where you have many visits and checkups to make sure that the drug is safe. We want to know what happens to your heart, to your liver, to your other organs, whatever is affected by the drug we want to monitor. No drug is affecting just what you target. There are always untoward effects. Sometimes it's a bigger effect than you wish it would be.

We also want to know what happens to the drug; how much is absorbed; how is it distributed; does it ever get to the tumor?

"Dose finding" studies start with a lower drug dose and escalate to higher doses. At the end the phase one study helps to determine the optimal drug dose or maximum tolerated dose. Maximum tolerated dose is used in cancer setting when you want to push the dose to be as high as possible because that's where you expect the most effect. In the case of modern designed drugs we aim for an optimal dose that blocks the intended target.

At the same time you want to see what is happening to your tumor,

is there a sign of activity, either tumor shrinkage, slowing of the tumor growth or any clinical benefit, such as hearing improvement in an NF 2 trial or in some other pre-defined patient reported outcome.

In the second phase of drug development there is more emphasis on demonstrating benefit from drug activity, while still evaluating side effects and safety. So you still have many, many measures and tests to make sure that the drug is safe.

Phase 3 trials are conducted in a larger patient population, where you confirm the drug efficacy, monitor the side effects and compare the new drug with existing treatments. We have not advanced to phase 3 trials with any drug for NF yet.

Now let's talk about clinical trials specifically for NF. This is hard to say, but no drug company is focusing solely on NF. There is no one sitting in a lab and developing a drug to cure NF. At this point everything is borrowed from the cancer field. That's the bad news.

But there are overlapping targets in cancers and NF tumors. So those treatments that work in cancer actually can be very effective in NF. And that's the good news. Some of these drugs have been extensively tested in large patient populations and have established effective doses and side effect profiles.

Still, there is reason to do the phase 1 studies in the NF population because cancer patients and the NF patients are so very different, as summarized in the table.

Cancer is typically a disease of older age. You need a certain time to develop cancer because it is related to your genetic material being degraded by mutations and that takes some time. Pediatric cancer patients for the most part are older than kids diagnosed with NF. The median age of patients on cancer trials is around 14 years, while the median age of NF1 patients we were treating was about 8 years. Way younger.

There is difference in the progression rate of tumors between cancer and NF. NF tumors progress slowly over many years. Their outlook in life and life expectancy is different.

There is difference in the level of daily activity and quality of life. NF patients are more likely to be in school full time and have a demanding workload.

Many cancer patients had prior chemotherapy, radiation, and all kinds of things that affect their ability to tolerate toxic treatments. NF patients rarely have that.

NF patients need long-term treatment, the time frame that we are looking at may be several years. An average cancer patient is on a

study for one or two months. So the toxicities that develop over time can be different in NF.

Also, in NF, we have to pay attention to toxicities that affect long term life. We have to think of these patients 20, 30, 40, 50 years after the trial. We have to make sure that the drug and treatment is safe.

So all in all, the goal of the phase 1 trial is to optimize the dosing for NF 1 patients and find the lowest effective dose. We do not want to push the dose as high as it can be, but to have an effect with the drug that is sustainable on the long term.

Now I move on to phase 2 trials that evaluate the possible benefits from drug treatment. Long-term survival is one measure of benefit.

In the cancer setting of course your primary goal is to cure the patients. This often means a short, very intents course of highly toxic therapy. People are willing to accept that therapy in the hope that after completing the treatment they will be cancer free and recover fully. The proportion of patients surviving 5 years, or 10 years later indicates the effectiveness of the therapy.

While NF can be deadly, it does not have the predictably dismal outcome as most cancers, so the 5 or 10 year overall survival is not a useful measure.

What other measures of benefits can we consider? We do not expect to cure NF with the options we have now. The drugs we are using at this point offer maintenance of status quo or some tumor shrinking.

Tumor shrinkage can be regarded as a benefit of treatment. You hope it improves life as a smaller tumor may lead to less pain or more mobility. In a cancer study, what you want to see is drastic shrinkage of tumors, you want those tumors just melt away. You know that subtle changes would not affect the final outcome.

The picture is different in NF. While NF tumors change typically slowly, even the slightest increase in critical locations can have devastating consequences. On the other hand marginal decrease in size may relieve some of the symptoms. Measuring tumor volume helps us to sensitively measure small changes.

Another end point that we use in clinical trials is delay in progression. Even if you cannot shrink the tumors or cannot make them go away, maybe you can make them grow more slowly. And again in that case, you need a sensitive measure to assess change in tumor size.

And finally we can evaluate clinical improvement. Staci just talked about this in her presentation. This is hugely important for the NF field. In the cancer setting improvement in pain is relevant,

but it won't save the patient. I the setting of NF we are thinking about clinical trials where clinical improvement is the primary end point. So even though your tumor is not going away, you feel better, you function better.

Going back to the REINSs collaboration: REiNS brings together an international group of experts, that really covers a large portion of the NF field from all across the U.S., England, Germany, Belgium, Australia with the goal to develop comparable objective assessment methods of treatment responses for NF-related tumors.

I am involved in the tumor-size working group. We work on developing standardized image acquisition protocols and standardized imaging schedules, so patients would be restaged at certain intervals, and therefore their progression rate would be comparable. We also want agreement on what we call response criteria, how much shrinkage, how much growth we consider significant.

Other groups focus on functional outcomes. I mentioned hearing improvement before. For NF 2, facial functioning is also very important. Facial disfigurement and paralysis affects the patient's life very significantly. We can evaluate walking as an outcome, pulmonary function can be used mostly for NF 1.

And there is the PRO group focusing on Patient Reported Outcomes. Staci talked about the pain assessment and quality of life measures that we want in a standardized format on all studies.

Now I move on to tumor measurements. The examples that I show here are plexiform neurofibromas in 4 different patients. Just recently maybe two or three years ago we started to do whole body MRIs to fully assess the extent of these tumors. The patients I show here have very extensive tumors. These are the kind of patients who come to us for clinical trials. One on the left has a large facial tumor. Facial tumors tend to be very diffuse and very disfiguring. Patients with facial tumors are over-represented in clinical trials, because their tumor is just so unfortunate.

The next little boy has a large arm tumor starting from the neck nerve roots extending down to the left arm.

Next is another patient with a very large flank and abdominal tumor. Overwhelming as it is, most of these patients are actually doing physically very well.

So I would encourage you to look at your own scans and face what kind of tumor you have. I am just mentioning it because it can be scary to see what's inside, but it doesn't determine who you are. But it doesn't determine who you are. You are not a tumor. You can face your tumor and you learn about it. And you are the best judge of what

is happening to your tumor. Your doctor can say it's smaller or bigger, but you have to see it for yourself. So just get a copy and look at your images.

The last image shows a different phenotype. The NF literature describes it as the spinal phenotype. This patient has basically no outward sign of disfiguring tumor but has a very large tumor burden throughout his body. These tumors originate from the spinal nerve roots and go along the major nerves.

These type of patients are often pain-free and very functional and often diagnosed later in life in the late teenage years.

From the images you see here, it's very clear that these tumors are extremely difficult to measure.

Now I'm giving you a course on how to be a radiologist. You really don't have to understand much of what the image shows; it shows a tumor that I point here. And at the next stage we still have that tumor, but it's much smaller. You agree with me? And then the patient comes back he has a problem, the tumor there got bigger- so at the first stage we see tumor response, a partial response because the tumor did not go away completely, just got smaller. And the last image shows disease progression.

In the lower row you see the images of an NF1 patient. On this sequence the plexiform neurofibroma is seen with bright intensity. I measure the tumor at about 5 centimeters. The patient comes back 2 years later and then again four years later. And what we see is no basically change.

Measuring the tumor this way is really not helpful because if we started this patient on a clinical trial, which actually happened on a phase 1 trial, the patient may take a drug for a year or two years or for three years and we would not have any idea of what happened to him during that treatment. We don't know if his tumor was smaller, whether it grew slower than before, or it got bigger, because there is just not all that much measurable difference over four years.

To get a better sense of change we started doing volumetric measurements. The main steps of the volumetric analysis method that was developed at NCI are shown here. I look at every image slice that contains tumor. I outline the tumor with a rough border that includes the entire tumor but excludes anything that also has bright signal. Than the computer takes over, it will use a histogram to analyze how many dark non-tumor pixels and how many bright tumor pixels are in that image, then calculates a threshold between the two groups.

With that threshold the computer will generate the final outline of the tumor. The program does this on every image slice. Adds up all

those slices. And then gives the tumor volume.

It's a very reproducible measure, you can repeat it over and over, and the difference will be within 5% in most cases.

Here I show the requirements for volumetric image analysis. I start with NF1 first, where I have the most experience. You need high quality MRI with a standard technique, the technique is called STIR sequence, which shows the plexiform tumors bright.

Over time, you need to image the tumor exactly the same way. And it applies to every imaging parameter. There are different magnets for MRI. The imaging slice thickness the imaging fief view, and the in-plane resolution all have to be exactly the same every time, so you can consistently measure the tumor.

One thing that seems obvious again is to cover the entire lesion because the volume segmentation requires that you see the outer edge of the tumors in every direction. The image has to include all the peripheral parts. Even if just a little bit of the shoulder is cut off and I see most of tumor, I cannot measure the volume.

Sometimes the tumor is so big that you need multiple image sequences. They have to be continuous, with no gaps, they need to be at the same angle, same resolution, and all other parameters. The patient should not be moving during the scan, so don't twist your head or switch position to get comfortable, because that disturbs the continuity of the image.

For NF 2 tumors, this is an example of a tumor here in one of the acustic nerves. And for these kinds of tumors, the imaging aspect is a little different. You don't have to image the entire body in the large-scale. Your goal is to have a very high resolution image. And it needs to be done with contrast material to enhance the appearance of the tumor.

If your tumor is showing less than 5-10 slices, the image resolution is probably not good enough to assess change by volumetrics.

Here I go back to NF1 tumors. This image shows the completed volume segmentation. So from the top of the head we take each axial slice and you see that the tumor outlined in green contours. This was an orbital tumor.

Next I'm showing you a girl with an abdominal tumor slice by slice we go down in the body and outline the tumor. Using the volumetric method, this tumor is actually fairly measurable and increased very steadily over 10 years since we know the patient.

In terms of comparing volumes to the standard line measurements, here I show a cross section of one tumor. The green line shows you

what is called the longest diameter of that tumor. From baseline it takes over two years to detect over 20% increase that we consider significant change. The blue line shows two-dimensional measurements. And using that method, it takes about a year for this patient to determine progression.

Lastly I show you the volumetric outlines. By the time the 2-dimensional measurement method determines disease progression, the volume increase is over 50%. And by the time the one-dimensional measurement shows progression, the tumor more than doubled in volume.

Using the volumetric data we learned that the tumors tend to grow at a different rate between patients. Some seems to be growing slower, some seems to be growing faster.

We usually define progressive disease as 20% increase in volume. Remember, by the time standard measurement methods detect progression, the volume is by 50% or 60% or 100% larger. Using volume measurement can cut your study time and exposure to potentially unhelpful drugs significantly from five years to one year or less.

And the other observation we made, that interestingly slow growing tumors tended to be in older patients and the fast growing tumors were almost exclusively in the very young.

Drug development is a sensitive issue in very young patients. During early organ development the risk of toxicities is higher, and many drug companies do not want to work with the very young. Not all drugs have liquid formulation for young children. We had to really show hard data to convince the drug companies to let us treat children as young as two-year old. We have drugs that can be given to one-year-olds. And now we are down to six months old children enrolled into one clinical study.

Volumetric analysis helped to generate the progression data that convinced the FDA and the drug companies to allow us to treat young kids because we proved that they are the ones who have the fastest growing tumors.

Unfortunately, some kids go through several clinical trials, like this patient with a large abdominal tumor, and nothing helped him. Treatment or not, we see relentless growth, and the growth is fairly linear. And with increasing tumor size he developed more and more symptoms.

Data that shows linear growth pattern for these tumors is important. We may start a treatment and see slowing of tumor growth. Even though we don't reduce the tumor size, we feel that slower growth is beneficial to the patient as it prevents the development of more symptoms. We need a lot more clinical data to show that tumor growth

will inevitably lead to functional loss or other symptoms that we may be able to prevent by slowing the tumor growth. The goal is to have prevention studies in which we do not treat the late stage established tumors, but patients who have small, growing lesions with a potential for morbidity.

Here I show some more volumetric data. I already pointed out that young patients typically have faster growing plexiform tumors. We collected data from 49 patients who had long-term follow-up and fairly substantial tumors. The median tumor volume in this group was over 400 millimeters. What we observed in that data set, that truly the younger patients had more rapidly growing tumors. Each dot on the plot represents one patient. And kids under the age of 8 or 10 have up to 60% change in their tumor volumes per year. By the age of 15, we rarely see increase that exceeds 20% per year.

Now, one thing that we still don't know is whether the minimal change, like 5% or 10% increase per year, what we see at older ages, is sustained. This small change over 10 years of an adult's life, could lead to doubling in tumor volume, which would be very devastating. Or does this small change just mean measurement variation and there is no real growth over the long term. We simply don't have enough data in adults to show that.

One critique of this data set was that of course young patients grow faster and maybe their tumor just keeps up with the body growth. When we look at the increase in body weight of the same patients shown in the second graph, we can see that their tumors are disproportionately growing faster, so the tumor is always outpacing the increasing in body size.

The tumor growth data from our 49 patients is in agreement with the data from a larger natural history study, conducted by Bruce Korf at UAB. This study included 134 patients, many of them adults. We confirmed that really in the kids you see more rapid growth or variation of growth rates and many more fast-growing tumors. And in the adults, only a few patients had growing tumors.

We still need a lot more natural history data. And we are still working on expanding that data set.

One thing that Dr. Listernick was mentioning in his talk, that puberty may affect tumor growth. We were able to collect 16 patients who had really long term follow-up. At the left you are looking at the percent change in their tumor volume over time, you see an upward trend in tumor size that is fairly steady and linear for the most part. Sometimes you see a little bit of break in growth where the patient may have been on treatment, holding the tumors at bay for

sometime. But overall, we see very steady growth.

And what is important for us, we didn't see any spike in the teenage years suggesting that the growth spurt that occurs in the body would affect similarly the growth of the tumors. And we feel very comfortable in that. We do have a lot of teenagers we followed from a very young age to adulthood. I can say that very clearly, there is no indication that their tumors grow faster at that age group. We don't have any pregnancy data, which is unfortunate. Even though MRI that is used to assess tumor size is considered safe during pregnancy, but still it's only for clinical indications, we are not allowed to do it for research, just to be safe.

The plot on the right compares the tumor growth rate before and after the onset of puberty. And for most colors, where each line corresponds to one patient, the growth rate before and after is basically identical.

And then another question: How long will these tumors keep growing? If the young kids have very fast growing tumors and the older kids show no grows at all, there must be a change in growth rate at some point. We still don’t know at what age the change happens, but tumors eventually stop growing.

And here on the left you see the growth trajectory of a tumor that loses a little bit of volume. This usually happens gradually over a long time, in this example we see 20% reduction in tumor volume in four years. This kind of spontaneous tumor regression will not disturb or assessment of a treatment response. On a clinical trial we expect to see tumor shrinkage from treatment within a year or so, and if it does not happen in that time frame the patient will have to stop the treatment.

Now I move on to clinical trials for plexiform neurofibromas. And this is a long list that doesn't even include all the studies. I'm just showing the list to illustrate that there is a very active drug development program for NF1 plexiforms.

Many of these studies are either phase 1 or phase 2. A large number of patients were evaluated, some included children, others included adults.

The early studies like interferon and thalidomide used standard tumor measurements to assess response. The tipifarnib phase two trial was the first study where we implemented volumetric assessment. The results of most of these studies are very disappointing so far, either no response or very few responses or just minimal slowing of the tumors

Here I highlight the studies that I want to discuss in more

detail. All these studies used volume measurement to assess tumor response. The last one is a very interesting ongoing study that actually shows some promise. Some of the new NF consortium studies didn't even make it to the list because we don't have any patient data yet.

This slide shows the progression free survival of patients on the tipifarnib phase 2 study. With tipifarnib we didn't expect tumor shrinkage, only slowing of tumor growth. All patients entered on the study had documented increase in tumor size before starting treatment. The study included placebo control, because we simply didn't have enough data at that point to show that tumors grow steadily and we needed a comparison group.

On the graph both groups start at at 100%, and every time a patient has progression the line drops, until all patients complete the trial. The placebo group had a median progression free survival of about 10 months, which is the time when half the patients developed progression. For patients receiving tipifarnib the median progression free survival was 19 months. But when you look at the early stage of the trial, the two curves go very close together, and there was no significant statistical difference between the two groups. Tipifarnib didn't seem to make a real difference.

But the study concept was validated. This was the first study that used volumetric assessment to determine disease progression as the primary endpoint. In that sense, the study was very important.

The next trial that I show is the phase 2 study of pirfenidone. Here the progression data is compared to a historical control group, which is previous study's placebo group. You can see that disease progression happens at the same rate in pirfenidone treated and untreated subjects.

And the next drug that I wanted to discuss is PEG-Intron. PEG-Intron is given in weekly injections. For that reason many patients abhor it. But it is only once a week, so that's the good news. And it can be given to very young patients, our youngest is six months old.

First I show two examples of tumor response. Patient 20 on the left had three different tumors. All of them were growing steadily, up to the point that he started treatment. The orange line is the treatment phase. Unfortunately, when he completed two years of study, the tumors started to grow again. We were able to arrange compassionate use of this drug for him, and the drug seemed to work the second time. When he stopped the second treatment, his tumors again started to grow. And giving it a third time he again had good

response. So he seemed to benefit from this treatment, I think, with delayed progression. I would emphasize that without volumetric measurement we would not be able to appreciate this effect.

The patient on the right also had good tumor response, with some shrinkage and very little re-growth after he stopped the drug.

Next you see the overall survival data. You can see that progression in the PEG-Intron treated group is delayed compared to the historic placebo control group. We feel comfortable that this is a real difference.

This drug is accepted as one option to hold tumor growth, at least in young patients with growing tumors.

PEG-Intron was also tested in patients without growing tumors and had no significant effect. So for patients to have a chance of benefit from this treatment, they need to have actively growing tumors.

The last drug I wanted to discuss is a mouthful to pronounce, Selumetinib from AstraZeneca. Currently it is in phase 1 trial in patients with plexiform neurifobromas.

The goal of the phase 1 study is to determine the maximum tolerated dose with long-term dosing in NF1. In our experience, NF patients can have different side effects, than cancer patients. One example of this was seen on the phase 1 trial of Sorafenib, where treatment had to be stopped because of excruciating tumor pain in more than one patient.

So studying toxicity in this population is very important. In addition, even though it is phase 1, dose-finding study, we follow the patients with volumetric MRI to look for signs of tumor response.

The trial was first approved for 12 years to 18, but it is now extended down to three years, which is great. Patients with NF 1 and inoperable plexiforms are eligible to enter the study. The drug is given twice daily. We do response evaluations after 5 and 10 months of treatment and every 6 months afterward.

The starting dose was about 50% of the adult recommended dose. At that dose, we didn't find dose limiting toxicitis. So escalated to a higher dose that is about 75% of the adult recommended dose. This higher dose was not tolerated, we observed some severe side effects. That meant we had to reduce the dose and expand the study of the lower dose. And at this point we are also looking at the intermediate $25mg/m^2$ dose, which is approximately 60% of the adult recommended dose.

Here I am showing some of the toxicities. Dose limiting toxicities are things that affect your health and can be dangerous.

Some other toxicities can be accepted and tolerated.

So as I said, at first we didn't see any dose limiting toxicities at the lower dose. At the higher dose, we had some enzyme changes that suggested that the drug affects muscle function. And one patient had decrease in heart function, which is, of course, a very serious side effect. It's scary that somebody who was basically healthy and young could have a potentially deadly side effect from treatment. Fortunately, he recovered, and he was able to tolerate the drug at a lower dose. And his tumor response data is very exciting.

As the higher dose was not tolerable we extended the lower dose and looked at 9 additional patients. And we pretty much didn't find any severe toxicities, other than skin infections and skin rashes. Next we escalated the dose to an intermediate level, to see if a little more dose would be more effective.

Tumor response data from this study is shown in these graphs. On the left side you see the lowest dose level 20 mg/m^2, middle is the 30 mg/m^2 dose, and then the right is the 25 mg/m^2 dose. And the graphs show that most tumors grow before the patients start treatment. The peak is the start of treatment, labeled time 0. You see that in the first cohort, almost everyone has an upward trend going into the study and a good downward trend on drug.

Now, the same doesn't hold up in the patients who needed dose reductions. So those who didn't tolerate the dose may have a little bit of tumor shrinkage at first, but then the tumors sort of creep up.

There is one line that is kind of hard to show in the middle graph. This is a patient with steady growth before starting treatment, he had a spectacular response of more than 20% decrease in tumor volume; but this is the patient who experienced the heart function decrease, so we had to stop treatment. And we can see that at that point his tumor regrew. After the drug holiday, he was able to restart treatment and have some tumor shrinking again. It's kind of hard to see in here. That's the line I'm talking about. Big drop and then up and down again.

These are the overall responses from the 24 patients who started the study. This graph shows the best response that they achieved as percent change from their baseline volumes. So on the left side, you see several patients who have more than 20% decrease. That is defined as partial response. The very first person that enrolled on the study, and has the longest follow-up, over four years now, had a tumor reduction by -44%. I have to point out, while this response is great, he still has a lot of tumor left.

Another point I want to make here is that this kind of response

is not detectable if you only use line measurements.

Now in summary, 14 of the 24 patients, 58% of this cohort achieved partial response, which is defined as more than 20% decrease in tumor volume.

Some patients had improvement in pain and function. But since this was a phase 1 study, we didn't systematically collect that data. We have plans to do that with the phase 2 expansion. So far, most patients completed almost a year of treatment, and we can stay that the therapy is sustainable over the long term.

Now, I show some patient examples. Patient No. 1, who I mentioned before, had over 40% decrease in tumor volume. What you see on the image is the cross section of the abdomen, showing a huge abdominal tumor. It is visibly smaller on therapy. The starting volume was over 2 liters, and decreased to 1.5 liters.

Patient No. 2 started with a smaller neck tumor, but similarly you can see decrease in the bright area of tumor.

The third example, patient No. 7, who had the unfortunate event of the cardiac toxicity, had visible response at five months when we had to stop treatment.

But how does the tumor response look clinically? Here you see a 6-year-old that is one of the best responders. She has a left leg tumor with overgrowth of that leg. Do you see any difference? I don't really, I have to be honest. I have to push myself to say that this is any different, maybe the standing position is a little better. She had about 30% decrease in tumor volume, and looking at the MRI, you can clearly see that the tumor is smaller, but still she has a lot of tumor.

So where do we go from here? We plan a phase-2 expansion cohort with this drug for children with the goal to evaluate efficacy.

While we will look at tumor response at one year of treatment, we also look at long-term tolerability and safety. This study will incorporate patient-reported outcomes to see if the minimal tumor shrinkage is actually a benefit in making the patient’s life better, and we hope very much that it will.

Selumetinib is not FDA-approved, it is not on the market, and it's not available for off-label use as of yet. We were in conversation with the FDA, and they understand that NF patients need treatment options. And they are very willing to approve this drug for the use of plexiform tumor treatment if we can prove that the treatment provides clinical benefit.

Additionally, we plan a study for adults. We will look at tumor shrinkage as the primary end-point of the study. But we want to also

do biopsies of the tumors in order to understand what makes a tumor respond or not, and what happens when the tumor starts to grow back. This can help us to develop drug combinations to make the therapy more efficient and maybe avoid drug resistance.

Before I finish I wanted to say a few words about clinical trial participation. Patients play a critical role in drug development, and their collaboration truly appreciated. It is very important for us to explain what we do and we need your help to develop new treatments for NF.

First I want to emphasize that in every early phase trial, the primary goal is to learn about the drug. Is it safe and is it effective? They wouldn't give you a drug that they don't have the scientific rationale to believe will help, but there's no guarantee that it will actually work. Having realistic expectations about the study is crucial.

On a clinical trial, the most important thing is to collect the data and prove that a drug is actually working.

Every clinical trial is set up with eligibility criteria. These criteria are designed to make the drug safe for you. So if you enroll into a study where the drug can affect your heart, you need to make sure that before you start your heart is healthy.

The other important aspect of this eligibility is to make sure that you will provide good clinical data. For example we have to be able to measure your tumor in order to prove whether the drug has any effect or not. This is an obligation we have to do. It may happen that your physician tells you that you are not eligible for the study because your tumor is not measurable. If we can’t do proper assessment, the trial is a waste for everyone. It's a waste for the scientific field, and it's a waste for all the patients involved.

Signing the informed consent is a very lengthy process. It takes a lot of time to explain all the potential risks of the treatment. You have to understand that going into a phase 1 trial, there are unknown risks. At that phase our knowledge of the drug comes from animal studies and people may experience different side effects. There are a lot of questions, but we disclose everything that we know.

And also the informed consent is to explain what benefits you may have from the study. For example, if you have a large tumor and it shrinks, it may make you feel better. But if you had a long-standing tumor and already lost neurological function, that function may never come back. We hope that going into the study, you understand what these possible outcomes are. You may or may not experience tumor shrinkage, and you may or may not feel any difference from the smaller

tumor. The informed consent helps to ensure that you really start with the study understanding what you take on.

Participating in a clinical trial, as I mentioned many times before, is a major commitment. You have multiple doctor's visits, you have lab tests, you go through MRI scans. I had an MRI myself, and it was horrible. That makes me really appreciate the time that you spend in that MRI scanner to provide data for us.

Clinical trial participation is always voluntary. When it's enough, it's enough. You can stop any time, there is no obligation to continue. And we understand that if it didn't meet your expectations, you are free to drop off. But the success of the study depends on the completed evaluations. So we really hope that most of you will stay the course.

[Applause.]

>> Is there any questions? Or everybody is hungry? Okay. Thank you. We go to lunch now. I think if you try to come back around 1:15.

You guys could come back down here and 1:15. Go up the stairs to the right.

>> I just wanted to make a couple comments. Dr. Dombi is very modest. She's really done some very important work for our understanding of fibromas, and they're critical for clinical trials. But I don't want you to take away from her talk that these very large plexiform neurofibromas that she was showing are necessarily something that is an inevitable consequence of NF in everybody. These very large tumors definitely occur in a small set of, subset of people, but they don't occur in everybody. And what she tried to point out was that the rapid growth that happens in a number of these patients really happens primarily in childhood. So I don't want you to take away the idea that 10 years from now your 20-year-old or whatever is going to have a massive tumor, because that is probably unlikely.

The second thing that I thought it probably is important to understand is why we're interested in the volumetric analysis. Dr. Dombi had a really nice slide that I just want to emphasize a little bit. Our experience has been that if you do standard MRIs and have the local radiologist measure the tumor size, most of the time the radiologist will tell you that the tumor hasn't really changed in terms of size. Not always, but it oftentimes that's the case.

And that's because they're doing either one or two-dimensional measurements of the tumor, whereas what's shown beautifully in that slide was that small changes in the apparent size of a tumor, when you calculate it in terms of the total volume, make a huge amount of

difference.

And so I've had experience of at the university, for example, where one of my patients who was enrolled in Sirolimus trial had one a large tumor in the right arm, and our radiologist rated it as unchanged, but when Eva read it, it was a 33% change over just a year.

So these volumetric measurements add a tremendously important feature to our understanding of what's happening with these tumors. This is particularly important for the NF 2 patients because with NF 2, we're often talking about very small tumors in crucial places. But, again, if you're thinking about a sphere, and if the sphere just changes by a few millimeters in terms of diameter, that really multiples quite substantially into a substantial increase in volume.

And we make clinical decisions, decisions on surgery, based on significant changes in volume. So having those kind of volumetric measurements is just really important. It could also be for (something) in general. If I could see a plexiform neurofibroma has increased in size by 50% or 30%, that provides me with the impetus, and it also encourages surgeons to move forward and try to think about whether we can remove that tumor.

So the volumetric measurements are really, I think, a critical piece of what we do.