**Transcription of 2021 DTRF Patient Meeting Webinar #1**

**Please remember that desmoid tumors are very complex and the below information is not intended as medical advice for any individual problem, or as a diagnosis, treatment plan, or recommendation for a particular course of action, and should not be used as a substitute for professional medical advice and services. Please do not delay in seeking professional medical advice regarding your individual circumstances**

**Lynne Hernandez (DTRF):** Okay Jeanne, you want to get started?

**Jeanne Whiting (DTRF):** Hello everyone, We'd like to welcome you to the Annual Patient Meeting of the Desmoid Tumor Research Foundation.

This year, again, we're going virtual and we will have two webinars. This first webinar will last a little more than 90 minutes, and we have four topics.

And I'll introduce each presenter before each presentation. It's so exciting that we have more than 275 people registered from 21 countries.

This includes an audience of patients, caregivers, and medical professionals. We always invite our medical professionals to attend and appreciate you being here.

We really appreciate the virtual platform that allows us to be together, I was so touched last night at our

Networking meeting where about 60 patients and care partners joined us for informal connections, via this networking event and I'm just always so touch because we've been doing this for 16 years at DTRF and we

Just love connecting with patients and this annual meeting is so important to us to hear your stories and to know that what we're doing is

is reaching patients and the people who work with them. I'd like to introduce our DTRF team who is here. They're actually behind the scenes, but we have Lynne Hernandez who is our

Great tech person who helps make the meeting work. We have Dr Maneesh Kumar who is our new research director who will be monitoring question and answer and timing, and Marlene Portnoy, co-founder and executive director of DTRF.

We thank our sponsors for our patient meeting SpringWorks Therapeutics who are also in attendance here and Ayala Pharmaceuticals.

And thanks to the presenters who are giving time on a precious Saturday to be here with us when we're most available to hear their presentations.

So, before we start, please, we invite you to follow us on Facebook and on instagram and Twitter our handle is @dtrfoundation

At instagram and Twitter so and also please sign up for our newsletter at dtrf.org. We have a patient newsletter. We have a separate physician newsletter and really appreciate you keeping in touch through that. So this is how the meeting will work.

There are two streams open. You can click on chat and talk with anyone in the general attendee group, but if you have a question for a presenter, you must go to the Q&A stream.

Dr. Kumar will be monitoring the Q&A stream after we have a pre-recorded presentation we're going to open up open that time for live questioning and your questions will be fed through the Q&A.

And also recordings of the webinar will be made available after this on our website.

We won't be able to get to everyone's question, it will be impossible, unfortunately, but if one of your questions either pre-submitted or typed in today is not answered,

Our presenters have generously offered to answer the questions in writing, and we will email the answers out to people who are in attendance.

Okay, so we're hoping to meet all of your needs and questions here. So first I'd like to introduce our first presenter, Dr Bernd Kasper. He's a member of the DTRF Medical Advisory Board.

He is from the Mannheim University Medical Center in Germany. Our board is truly international like all of you are here

And he's done a great pre-recorded presentation, giving an overview of medical medical desmoid tumor treatments. We'll start with the video and then we'll open it live to questions from Dr Kasper.

**Lynne Hernandez (DTRF):** Okay, give me one second.

**Bernd Kasper:** It is indeed my pleasure and honor to speak again at the Annual Patient Meeting of the Desmoid Tumor Research Foundation.

And I would like to talk about challenges in exploiting medical therapies for desmoid tumors. And I would like to give my talk on behalf of the desmoid tumor working group.

As you all know, we are talking about a monoclonal and fibroblastic proliferation, which is characterized by a variable and often unpredictable clinical cost. The incidence of desmoid tumors is around five to six cases per 1 million of the population per annum.

And as you all know, a couple of years ago, we have started a consensus initiative, due to the fact that there was no Level one or two evidence for the treatment approach for desmoid tumors available, and there were only very few prospectively conducted studies and meta-analysis.

So our first roundtable meeting dates back to May 2014 where patients and patient advocates from Sarcoma Patients Euronet

and medical experts from the EORTC soft tissue and bone sarcoma group met in Frankfurt Germany.

And we came up with the first position paper on the management of sporadic desmoid-type fibromatosis which was published in the European Journal of Cancer. This was updated, two years later, in the annals of oncology in 2017

And in 2018

The Desmoid Tumor Working Group went global with a meeting in June 2018 in Milan. And these are the topics which we covered during that meeting. Of course, we talked about pathology and molecular genetics, about indications for an active treatment, including radiotherapy.

We talked about the available medical therapies in different indications, the assessment of treatment effects, pain, quality of life, fertility, and pregnancy and we also dedicated a chapter of this

meeting and have this publication to endpoints, study designs, and regulatory requirements for desmoid tumors.

And I would like to focus now on the systemic treatment landscape for desmoid tumors. Here can you can see the different available systemic treatment options, anti-hormonal therapies

chemotherapies, targeted therapies, which means the tyrosine kinase inhibitors and, most recently gamma secretase inhibitor therapy.

Starting with the anti hormonal therapies, only case reports and small series are available here.

The reported response rates vary up to 50%, however, there is no clear rationale available and a very low evidence. Nevertheless

Anti hormonal therapies are still often used in Europe due to the easy availability, the low cost and the rather few side effects.

But we did not give a general recommendation for the use of anti hormonal therapies. Here, you can see an old overview of case reports and small series evaluating this treatment strategy.

The only the first and only prospective study evaluating the combination of tamoxifen plus sulindac comes from the Children Oncology Group 59 patients

who have been treated with this combination of tamoxifen and sulindac, however, only 10 patients completed the therapy without progressive disease or withdrawl

The overall response rate was 8% in the two years. Progression free survival rate was 36%, which is, by the way, the same as a placebo arm in the sorafenib study.

So this is the first and only prospective study evaluating this combination with rather low activity in terms of overall survival, overall response, and PFS rates.

Regarding chemotherapy, the indication for chemotherapy are non-resectable, rapidly growing, and or symptomatic or even life-threatening desmoid tumors and they should preferably be treated with chemotherapy.

The only perspective phase 2 study evaluating the combination of methotrexate plus vinblastine again comes from the pediatric population 28 patients who have been treated with this

Treatment combination for up to one year overall response rate 19%, which is the same as the placebo arm in the sorafenib study and eight patients remain free of progression at a median of 43 months from study entry.

So this combination of methotrexate and vinblastine demonstrated progression arrest in about one third of the children, and it is definitely the chemotherapy regimen of choice in the pediatric patient population.

Here you can see selected chemotherapy regiments which have been put together here in a publication in the Oncologist, however, no randomized studies are available here.

The French Sarcoma Group retrospectively analyzed 62 patients who have been treated with different chemotherapies, 71% with combination therapy,

29% with monotherapy, 21% with anthracycline-based chemotherapies, and the responses are depicted here - 2% complete responses, 19% partial responses, and 60% of the patients

Had stable disease. The response rate was definitely higher for the anthracycline-based regiments.

So if chemotherapies indicated and a rapid response is needed, then you should go from anthracycline-based regimen and pegylated liposomal doxorubicin may be preferred in this young patient population with less cardiac toxicity.

Moving to the targeted therapy, it has all started with imatinib. There was the US phase 2 study with 19 patients being treated with 800 mg imatinib daily with an overall response rate of 16%.

This study was followed by the phase 2 study from the French Sarcoma Group 35 patients being treated with 400 milligrams imatinib daily overall response rate 11%.

And the progression arrest rates after 3, 6 and 12 montsh were 90, 80, and 70% respectively. The two-year progression-free survival rate was 55% and the overall survival rate 95%.

Within the German Interdisciplinary Sarcoma Group we also run a study evaluating imatinib in RECIST progressive desmoid tumors and we could clearly demonstrate

The sustained progression arrest in this dedicated patient population, and this was published in the European Journal of Cancer in 2017.

The next tyrosine kinase inhibitor which was evaluated in the first large phase 3 randomized study ever performed in desmoid tumors was sorafenib

And the study clearly could demonstrate an advantage for sorafenib compared to placebo in terms of progression-free survival. The overall response rate was 30% in the sorafenib arm compared to 20% in the placebo arm.

The French Sarcoma Group evaluated pazopanib in progressive desmoid tumor patients in the DESMOPAZ trial

Compared to chemotherapy combination consisting of methotrexate and vinblastine. The primary endpoint of this study was the non-progression rate at six months of ever therapy, which was 84% in the pazopanib arm compared to 45% in the

In the chemotherapy arm. So again, there was a clear benefit in favor of the tyrosine kinase inhibitor pazopanib.

The next group of treatment options are the gamma secretase inhibitor and first one, which could demonstrate activity in desmoid tumors was Nirogacestat

which has been evaluated in a small phase 2 study in 17 patients who are depicted here. The responses are shown in this

plot where you can see 5 partial responses and none of the patients demonstrated a progression under treatment with Nirogacestat.

Nirogacestat was overall well tolerated with hardly any grade 3 or grade 2 adverse events. There were only a couple of grade 1 adverse events and based on these findings

A phase 3 study was initiated called Nirogacestat for adults with desmoid tumors/Aggressive Fibromatosis, the DeFi trial, which finalized recruitment about one year ago in summer 2020 and we are of course eagerly awaiting the results of this trial.

This is the design of the Nirogacestat trial a one to one randomization comparing Nirogacestat with placebo

There is the possibility of a cross over from the placebo arm in case of progression to the open-label nirogacestat arm

The primary endpoint of the study is progression-free survival. And here the first patient was dosed in May 2019 and the study finalized recruitment in summer 2020.

Another gamma secretase inhibitor currently being tested in desmoid tumor patients is the one which has been developed from Ayala AL102 which is

tested in a kind of seamless combined phase 2 phase 3 study. In the first part, in the part A, the optimal

Treatment regimen is evaluated and in the second part in the part B in a two to one randomization AL102 is being tested, with placebo, in 156 patients.

This is an efficacy summary of the different studies, with a tyrosine kinase inhibitors and the gamma secretase inhibitors here, you can see, the 4 studies evaluating imatinib

This is the sorafenib study, the DESMOPAZ study with pazopanib, and, last but not least, the

data from Nirogacestat, the gamma secretase inhibitor and what you can also see here that only two studies, the one from Germany and the one from France really required a RECIST progressive disease as an inclusion criteria.

So, in summary, the medical treatment options for desmoid tumors

We did not give any recommendation for the use of anti-hormonal therapies. Chemotherapy may be indicated in rapidly growing and/or symptomatic or even life-threatening desmoid tumors.

Tyrosine kinase inhibitors such as sorafenib and pazopanib clearly demonstrated clinical activity in randomized settings and move into the focus of interest. Gamma secretase inhibitors promise to be effective agents and currently Nirogacestat and AL102

are being evaluated in clinical studies, but you have always keep in mind that the majority of the mentioned drugs do not have a formal registration for desmoid tumors and, therefore, are not available or reimbursed in many European countries.

So let me have a look now to our desmoid global consensus and what we summarized and

are here for the available medical therapies. So due to the lack of comparative studies, we are still not able to propose a definitive sequence of the existing systemic treatment options.

Randomized data only exist for sorafenib, pazopanib and the combination of methotrexate plus vinblastine.

So, in general, it is reasonable to employ the less toxic therapy, initially, followed by more toxic agents in a stepwise fashion.

and out of the variety of possible systemic treatment options, one can be chosen, taking into account the level of evidence, the overall response rate,

The progression free survival rate, the ease of administration and the expected toxicity of the administered drug and this, it can be evaluated in a kind of 5 dimensional model which is depicted here.

And this is the treatment algorithm we developed in our global consensus meeting and publication. So the desmoid global consensus

is available in a nice layout form. It is publicly available over the websites of the Desmoid Tumor Research Foundation and Sarcoma Patients Euronet and it is also available

In in a scientific publication, which has been published in the European Journal of cancer at the beginning of 2020.

And having said that, I would like to take the opportunity to thank all the participants, all the patients and patient advocates, and all the medical experts

who contributed to this work within the Desmoid Tumor Working Group, and I would like to say thank you for your attention, for your interest in this in this disease and I'm happy to take any questions or comments here, thank you very much.

**Jeanne Whiting (DTRF):** Dr. Kasper, Thank you so much for that wonderful presentation. I'd just like to point out again as he just explained, there are two versions of the global consensus paper.

We feel that one of the most important things that we've provided funding for in recent years as a resource for both patients

and treating physicians. There is a patient version and the more scientific longer version

For physicians. They're both available on our website and Lynne perhaps you could put in the chat the link to these papers we just feel it's so important for you to use this resource.

You can give it to your doctors, you can you know use it, however you'd like but a really, really important resource and thank you for going into detail about all of that. So I believe you had some questions presented in advance, Dr Kasper, if you'd like to go ahead with some of those.

**Bernd Kasper:** Yeah, thank you very much, Jeanne, and yeah it's always a pleasure to be here thanks a lot.

I've been attending this now for I think more than five years and it's always a great experience. Yeah I received a couple of questions beforehand, so let me start by answering these and

The first few questions have to do our deal with a let's say the definition of a desmoid tumor, you probably know that there is also some come there is always some confusion about that, because in the in the

WHO and also the International Classification of Diseases say that desmoid tumor is a benign disease so it's not a cancer per definition.

And, as you know, of course, especially from the patients and from the patient groups, it is always emphasized that, of course, these tumors grow or can grow locally very aggressively and

And to better let's say reflect this actual clinical course of a desmoid tumor, there is an initiative now that

A desmoid tumor is or will be better reflected by a certain or by a unique code within this International Classification of Diseases maybe even Maneesh you would just like to say a few words on that because I think this is quite important.

**Maneesh Kumar (DTRF):** Sure, I would just say that currently in the ICD- 10 coding system, desmoid tumors are coded under what's a pretty general category that includes a lot of different types of tumors.

So DTRF is now under in the process of getting a very specific code for desmoid tumors that is still under that same category, but it's now a subcategory that's specific for desmoid tumors.

We think this is going to be really important for epidemiology to better categorize these tumors and then also that code is specific to location so again to help kind of with the epidemiology and being able to define these tumors better. If approved that code would go into effect October 1, 2022.

**Bernd Kasper:** Thank you very much, and the next question was about, are there any lifestyle or dietary factors that can influence the desmoid tumor. So in principle, I have to say no.

The only thing is, which might be something worth to discuss is any kind of trauma, so we, we do have some data that may be an injury or even a surgery itself can trigger desmoid tumor growth, so this is something you have to take into account.

Next questions

deal with the

topic of a possible adjuvant therapy so let's let's say we have

A desmoid that has been operated has been taken out or another situation we have a desmoid tumor that has been treated by a kind of medical therapy and we have achieved a

stabilization a stable disease and the question is, is there any kind of treatment to prevent it from happening again, or from growing again. Again I have to answer this question with no, we do not have any data on any kind of what we call adjuvant treatment.

And unfortunately, they also no tests available which could determine the outcome of any kind of treatment.

The next question I received also beforehand, and I think it was also in the in the Q&A is about radiotherapy.

Yes, I mean radiotherapy still does have a kind of position in the in the treatment algorithm we also mentioned it here but it's

it's correct that it's used let's say, less and less a bit like like surgery, and that has to do with a possible long term side effects that we are also that we are always aware of when treating patients, especially this young patient population with radiotherapy.

Next question I received

Which is always a kind of debate or

Not a debate really but it's a

it's an interesting question. Is there really a difference in the treatment algorithm or in the treatment strategy for sporadic desmoids or for desmoids that are associated

With an FAP. So and in according to the to the consensus in principle there's no difference, so we actually use the same treatments, we use the same kind of treatment algorithm

But what is the difference is that FAP-associated desmoid tumors tend to be more aggressive and that's also the reason why we usually that tend to treat them more aggressively.

Generally spoken. And the last question, I received beforehand has to do that, that question comes from UK, so it is a bit more a European problem.

That has to do with access to treatments. As I also outlined in my presentation, the problem is with a lot of treatments that are possibly active in desmoid tumors, like the tyrosine kinase inhibitors- imatinib, sorafenib - and so on.

They do not, they all do not have a formal registration for this disease.

In Europe, that means that, in a lot of countries they are not even allowed as a doctor to prescribe them for a desmoid tumor

or they are not even reimbursed by the by the medical authorities, so this, for example, imatinib is not able to be used in Italy or something like that and and that's, by the way, the reason why

A lot of my colleagues use pazopanib in our in some countries, even in Japan because pazopanib does have a registration for soft tissue sarcomas or for sarcomas and and that's why you can also use it for

desmoid tumors, so these were my questions that I received beforehand so

**Jeanne Whiting (DTRF):** Hi Dr. Kasper, I'm I'm sorry to say, we're out of time here so we're going to have to move on, but again, if you put questions in the Q&A we'll try to get them answered after the webinar. Thank you so much.

**Bernd Kasper:** I will do my best to.

Thank you.

**Jeanne Whiting (DTRF):** Thank you and thank you for those who submitted questions in advance.

We'll move on now to a presentation on cryoablation. We're going to have

Dr Afshin Ganji was not able to be here due to another commitment that he had at a different conference simultaneous with this one so we're going to play his pre-recorded presentation and then

Dr Sean Tutton will be answering question Tutton sorry will be answering questions and he's also working with Dr Ganji and will be answering questions so go ahead Lynne with the video.

**Afshin Gangi:** Ladies and gentlemen, my name is Afshin Gangi, I'm an interventional radiologist in the University Hospital of Strasburg and King College of

London. The subject of my talk today is cryoablation of desmoid tumors. Desmoid tumors or fibromatosis are scar tissue very hard

tissue which are causing symptoms, pain, and sometimes compression of adjacent organs, as you know, it's classified as a benign tumor.

But the recurrence rate is very high, and it can cause major symptoms that could happen in anywhere in the body, as you can see here could grow in very, very large sizes, if not treated.

There is a mass effect could be very painful the patient are complaining about pain,  functional disability and aesthetical consequences,

Psychological consequences for the patients and their environment. The imaging is quite typical, we need to biopsy them systematically to prove that

it's a desmoid tumors to confirm that sporadic for unconfirmed mutation of those tumors. The incidences very rare, that's five to six cases for a million of ablation 3% of all.

Soft tissue tumors the peak of frequency is usually between 30 to 40 years old, you have two groups, as you know, sporadic one

And finally, part of Familial Adenomatous Polyposis, which is another category of the tumor. The major tumors we are treating are the sporadic form of desmoid tumors with confirmation of beta catenin mutation

As you know. The other form, which is the familial form with APC mutation. It's a more difficult tumor to treat, with higher occurrences and the prognostic is very different.

The diagnostic usually have a previous history of trauma, but sometimes you're not finding any any history of any

trauma in those patient means to cannot eliminate this and you need to biopsy those patients to confirm the diagnostic the treatment.

Usually, you know, desmoid tumors can be stable, they can spontaneously decrease in size and sometimes they are increase in size. We are interested in tumor which are symptomatic and evolutive.

Not the others tumors means, this is what we do. Previously before 2000, all these patients they're going to two category of treatments surgery on radiotherapy or both

Together, that was the problem, and you know to high recurrences of desmoid tumors after surgery I've been not insist much about medical and surgical treatment because we want to talk more about

the percutaneous treatment of this but, as you know, the surgery, is now more reserved to the patient, which are very symptomatic with compression symptom, radiotherapy

is an active treatment which is giving good results, but, as you know, if the patient is young, we try to avoid radiation therapy in young patients if the other treatments are working.

That's why we are you know, reducing the number of radiotherapy. Medical treatment very efficient,

working very good in many patients means you know we are now, for the moment, proposing cryoablation on the patient, which are not responding to medical treatment

or very symptomatic patients are growing tumors. Interventional radiology we have tried many techniques.

We were doing chemical ablation Then we come to thermal ablations and cryo. Cryo seems to be the most promising technique today

For desmoid tumors with HiFU, there are the two treatment proposed. Cryoablation consist of freezing the tumors going below minus 40 degrees.

As you can see many examples of those tumors you need to put every 1.5 to 2 centimeters the cryo probes to treatment, we have done til now they're always done, usually in very large

tumors means, this is not the best cases, but we have done it in large evolutive tumors and it works quite good, you will see the result.

As you can see some cases needing more than 15 nearly 18 probes to freeze the tumor, as you can see here every 1.5 to 2 centimeters the props in the positions to freeze and to destroy

The tumor. Visualization of the iceball is essential that's why we like cryo, because we can see the iceball. This is not possible with ultrasound. With ultrasound we have a shadow, and we cannot see exactly the ice. That's why you need to do it under CT or

MRI. Not following the iceball with ultrasound because you're blind and you cannot see much of this. But with other technique like MRI you can see very nicely the ice balls in different

sagittal axial view. Here you can see the deltoid desmoid tumors, which is very well seen on MRI and you see the iceball visible on it. Another one on the pectoral muscles, you can see the iceball precisely at the end.

We have sometimes good surprise, it is not systematic, this is the immunological effect.

This was done, you know the abscopal effect if you want, but we have seen in

A few cases very good surprise, like this one, you see the other large cervical tumors we have frozen

About 80% of the tumors, but when we have controlled the patient, they have hundred percent necrosis of the tumors happening. Those cases are happening or sometime

Very extended tumors we have effect on the distal part of the tumor we have not frozen.

Today, the indication of cryo just the before the next flow perspective study is biopsy proven this desmoid tumors growing and symptomatic painful or not and

Not tolerating the treatment and resisting to the conventional treatment that means, this is what you're doing. That's an alternative to radiotherapy and surgery is before becoming very aggressive

They go to cryo, before going to radiation or surgery in the major case the major part of the cases we are treating today.

The technique it's a long procedures painful procedures and we need to be very precise that's why those patients should be under general anesthesia so we can very precisely take our time to make it and

To make it safe protecting the surrounding area.

It's painful, especially during the few hours after the intervention during the first three days you have a large edema.

which should be treated and you should be careful with this. You can use ultrasound to position the probes, if you want, but not to follow the iceball that's very important to know.

CT and MRI are mandatory to follow up the cryoablation and to see what you're doing. As you can see, here again, the iceball seen this time for the CT scan

very nicely and very precisely. We are trying to do a complete ablation every time we can. That's important

to note. The number of probes depend how large is a tumor, as I told you before every 1.5 to 2 centimeters one probe should be positioned that the usual architecture of the tumor

with probes positioned in the patient. As I said, for large tumors, you can need a lot of probes. This increase the cost of the treatment and make it more aggressive and you can imagine.

The volume of tumor is proportional to the number of complications, as you can imagine this. Sometimes the tumors has a very strange shape and we have to take care of it needs the probes that come in every direction

To cover the tumors and this could happen that's like this, you see every probe is coming from another direction to cover completely

The tumor. We should be very careful with those surrounding organs. Skin is very near

bone, nerve root, muscles, bowel, pericardium, pelvic organs, an anatomical review is essential to protect digestive organ they're not having major major complication with the iceball.

Sure you're working with small probes but inside you're creating a very large necrosis. That's important that we need to protect those organs by hydrodissection, carbodissection, electro stimulation, evoked potentials, skin warming, dissection of the skin - all this together to do a safe

procedure to avoid major complications, as you can see, you know when you're producing an iceball in the nerve root is real, we need to do a hydrodissection of it different needle to push the nerve root away or make a warm bath

For the tumor. In other case, you can see very near the sciatic nerve hydrodissection is done to put the sciatic nerve is inside this warm fluid

To protect it during the whole procedures associated with evoked potentials to be sure you're not damaging the nerve. In the acute phase

After the procedure we have a huge oedema I'm telling always to a patient it created an omelet you're

Breaking all the eggs and you have all the fluid coming out hyper or smaller and we have this huge oedema which usually double the size of the tumor and you have to take care of this after the procedure and tell the patient about this oedema and the moving fluid along the body

The few days after.

The delayed phase is hard tumors which is desmoid tumors become softer and softer take the shape of a silicon ball that's what

We have, and then the shrinkage is very, very slow. That's something you need to know, an example of a very large abdominal wall desmoid tumors, it's a sporadic case

Very voluminous tumors, very painful and the patient cannot really close the bottom of his shirt.

And that's what you have done, as you can see here, here we are that's taking contrast tumors pushing even the abdominal wall in contact with the colon.

That again a difficulty and that's what we have done CO2 dissection, that is carbodissection, the probes position every 1.5 centimeters inside protecting the bowel with carbodissection, as you can see here.

And this done we are freezing the tumors at the end, freezing completely the whole tumors as if we can. The skin was protected too, as you can see a hydrodissection of the skin, to be sure we don't have any froze by.

that's the iceball at the end - look at the iceball, the whole high density of the tumors the skin is away, and you have still the carbodissections.

A few hours after even the procedure, because we want that to hold. Ice is gone before we are approaching the colon. Look at this M1

Full necrosis of the tumors. M3, we have a nice shrinkage of the tumors and, finally, two years later, you have just a small amount of the tumors and very soft, as I said, the shrinkage is very slow.

When you're working on the MRI we don't have an insulated needle really, and they have sometimes small frostbite of the skin. Each are scarring very good afterwards.

As I said, hydrodissection in the cervical case, all these are fluid to protect the carotid and the nerve roots.

With excellent result complete ablation six months later. This is a Strasbourg experience at the beginning.

Was you know, we have done a few patients, before beginning our perspective study and you can see the follow up was up to five years.

And as you can complete ablation only in 3 of the 11 cases, partial ablation 8, but what is essential is improvement of the symptoms, in all cases that was very encouraging.

We have to get our records, but asymptomatic means if the patient is asymptomatic and the tumor is small, you should not touch it anymore.

And that's what we have, there are a few papers on the literature showing the same thing very efficient treatment on the symptoms.

We are not obtaining complete ablation in many cases, as you can see, here we have 39% of no residual tumor but 95% of the tumors are shrinking and the symptoms are responding to the patient. In other papers

going in the same way, then 80% of tumor reduction and excellent symptoms response. Then we have done the prospective study - the French one, the CRYODESMO one

which was, including prospectively patient resisting and progressing on the conventional treatment.

We have included multicentric study with 50 patients included average age of 40. 96% of the patient had previous treatment, as I said, and as you can see, usually quite very large

tumors means we having to the really very large desmoid tumors inside and what was impressive again it was that no progression at 12 months in 86% of the patients.

You're not talking about complete ablation, but no progression. Minor complication in 77% of the cases but major complication in 22 means those results are very encouraging.

And it lead, finally, that ESMO guidelines included cryoablation in the second line means you in the treatment

is not working, the conventional one we can propose now cryoablations in those guidelines. To conclude now I think cryoablation

And a little bit HIFU, at the same time, are very promising

technique percutaneously to treat desmoid tumors. The current that indication, as I said, but you're pushing it to the next prospective study, which will begin in the next month about including first line.

Cryo comparing the medical treatment, which will include again multicentric studying in France, and we will begin this and we're leading the study.

And we will see if we can introduce cryo as a first line.

Challenging technique, because we have done large tumors but again very promising, but it should be done in good hands of people trained having the exact training and CT and MR in this position to do it. Thank you very much for your attention.

**Jeanne Whiting (DTRF):** We thank Dr Ganji for that wonderful presentation and again I'll announce that these videos will be available for you to look at

as many times, as you want at our website. Now I'll introduce Dr Sean Tutton he is from the Medical College of Wisconsin. Dr Tutton, I'll start with one question.

That we just heard that asked, be a highly specialized doctor who will administer this. Can you talk about the general availability of the procedure, what kind of physicians are really capable of doing this well and insurance coverage for the procedure?

**Sean Tutton:** Thanks for your question.

So cryoablation and other forms of ablation are generally

performed by what are called interventional radiologists. I'm an interventional radiologist. We use image guidance so as you saw in the video ultrasound, CT and MRI.

Can you all hear me?

**Jeanne Whiting (DTRF):** Yes, great.

**Sean Tutton:** And so

ablation is becoming more widely available we we started using ablation in the treatment of liver tumors and kidney tumors and lung tumors.

And it is in the last decade, I would say that we're starting to use it more and bone and soft tissue tumors like desmoid.

And so I can tell you that at many of the major cancer centers around the United States there are interventional radiologists and physicians that have the expertise to offer cryoablation.

One of the interesting things is that not very many people know what an interventional radiologist is, right, it's sort of medical oncologist is a very well understood concept.

But an interventional radiologist is something that is still - there's an awareness issue. So most large centers do have highly specialized interventional radiologists that are treating cancer patients, are working in multidisciplinary tumor boards, sarcoma

teams, as in my as my own situation.

And so I think that seeking us out, it can be a little bit of a challenge, but as I promised, I will make the DTRF I have a list of available physicians that can offer these services around the United States and Afshin can obviously fill in the blanks in Europe.

**Jeanne Whiting (DTRF):** And about general insurance coverage I'm sure it's different from country to country but

**Sean Tutton:** Correct so prior to this year we were having challenges with coverage, because there was really only this small retrospective data and there was no support in the NCCN guidelines and the NCCN guidelines

For better or for worse, a lot of the payers look at those guidelines to to determine whether something is experimental or whether they're going to cover it.

In this year, the NCCN guidelines now have language supporting ablation both cryoablation and HiFU as an option, and so, at least at my own institution we're seeing we're having much better success treating patients with cryo and getting insurance coverage.

**Jeanne Whiting (DTRF):** Maneesh, did you want to bring over any other questions from the Q&A?

**Maneesh Kumar (DTRF):** Yeah I think Bernd and Sean doing a really good job about answering specific questions by text, but maybe i'll just take a step back we've gotten a lot of questions about location

Of desmoid tumors and how that affects treatment options or prognosis so maybe it's a question for Bernd or Sean but Bernd has mentioned that abdominal tumors

tend to be more have a better prognosis. Is that because there's something about the biology of an abdominal tumor or that it's more superficial it's easier to monitor that gives it a better prognosis?

Or do we not know?

**Sean Tutton:** I'll yield to Bernd and then I can follow up.

**Bernd Kasper:** Yeah I mean that

I guess the most important point is that

location is important for the kind of treatment, we can do, and so that, if you look at our treatment algorithm in the in the consensus table you can see that we have we we have different treatments for the different locations and, of course, for let's let's the the.

The most difficult ones are up for us let's say in the head and neck area where we have where you have a lot of nerves, a lot of

Issues that may occur here, then when when you do surgery or when you do other kinds of therapies and that's maybe the most important thing. But yes, we do have different prognosis for the different locations of desmoid tumors.

**Sean Tutton:** I would just generally say that

we heard yesterday that people are being treated with intra abdominal tumors with cryoablation. It is more challenging to treat those tumors because the bowel and other structures are quite close. The extra abdominal tumors are

more amenable to cryoablation and other forms of ablation and so we've treated patients with neck tumors as Dr Gangi showed

who have failed systemic therapies and other treatments. We've treated limb tumors, abdominal wall tumors, flank tumors, you know, or in and around the back.

And one of the one of the attendees asked a specific question, which I think I should address. In all of these retrospective series we've seen that there can be some nerve injuries.

And it is important that we have the conversation with the patient about the potential for those nerve injuries and whether they're going to happen and whether they could be recoverable.

Most of the time with cryoablation the nerve injuries will recover over time, but that's not always the case and that becomes one of the major limitations.

Is is the nerve that would potentially be injured, a very important nerve so that there'd be much there'd be a significant reduction and function. That's always the big question that we have in trying to decide where to put cryoablation. Is it second line is it first line

And is it safe to offer it based on the proximity to a nerve.

**Maneesh Kumar (DTRF):** And I think that's a great segue to maybe the next big topic, which I think we've got a lot of questions about injuries and trauma and one of the specific questions was can cryoablation be considered a trauma that would then cause more desmoids to happen in there?

**Sean Tutton:** Yeah I think we don't know - I think that's the fair answer.

You know what what is nice and unique about cryo is, as you saw in the video, we're putting fairly small needles in, we're not making an incision we're not moving muscles,

we're not causing sort of major trauma, but we are placing these needles into the body going through the skin and into the tissues, and so the honest answer is, we don't know.

But in my experience, and I think in Afshin's experience, we have not seen rapid progression in any of the patients who have been treated with cryo. I think we can say that, if you look at all of the data.

Maneesh Kumar (DTRF): And then related to that kind of question so if a patient has a desmoid tumor let's say in the abdomen should they be avoiding all surgeries like if they need surgery on her arm or something?

Do they are they at higher risk for desmoids due to all surgeries or just in surgeries near their desmoid?

Either Bernd or Sean or Dr. Gangi.

**Sean Tutton:** That's a good question, I mean, I think we talked about

field defects right so where the desmoid has occurred, we talked about the area in that region as the there's a field defect that somehow is predisposing to desmoids but

It it's an excellent question I don't think we know the absolute answer that if you have a an intra abdominal desmoid are you more likely to develop something out on the arm or something like that.

Bernd, maybe you can add to that.

**Bernd Kasper:** No, I mean you're you're explained it excellently so.

I mean the question is, we there is often obviously a defect in the in the

yeah in the

In any, at any located, but the thing is what would we don't know why does the desmoid occur in this location, then and

But, of course, you cannot say generally that you cannot do any surgery, then, because if you need a surgery in for any kind of other disease or whatever you have to go for that surgery, no questions so.

Yeah, but we would not, we do not recommend too many surgeries for desmoids - that's another thing.

**Maneesh Kumar (DTRF):** I think another question that's come up related to that is kind of the ordering of these treatments, I think Bernd, you mentioned active surveillance is always first line we want to try to do first.

But then, how do you know if cryoablation is the next step, or is medical treatment, the next step or surgery, the next step?

I mean that's that's very easy answer - we don't know, and I mean or we can say at the moment that.

**Bernd Kasper:** I would, what I would say is that, with a more and more data coming up for cryoablation, this is definitely something which, which will, which we will discuss maybe in our next consensus meeting and because cryoablation seems to be have more and more a kind of

position in the treatment algorithm and that's something to discuss if we have more and more data on that certainly.

**Maneesh Kumar (DTRF):** And then maybe Sean this is a specific question to you, but it was so would cryoablation ever be considered a first line treatment for maybe small desmoids? And when I say first line, I mean after active surveillance, maybe on progression, the first treatment choice?

**Sean Tutton:** Yeah, thanks for that qualification.

So you know, we had a small retrospective series that we published. One of our residents, Kaila Redifer, did a wonderful job and and it reflects what has changed at our own institution, which is we realized that surgery, radiation, and chemotherapy were really

not working well for these young patients, and so, in the majority of our our patients, we actually use cryoablation as a first line treatment and we had I as I recall 85% you know disease control and so

I think, to bundle the last question, and this question it really does require a group of people that are passionate and focused on desmoid tumors - surgeons, medical oncologists, radiation oncologists, interventional radiologists.

A whole team to sort of consider, along with a patient, what's the best treatment, given that we really don't have that perfect answer yet.

So that's how we function and so whenever you know in those patients that we treated,

It was never my decision alone with a patient, it was always this consensus group of people say, "yeah that really does make sense and that's better than this it's

it's the least invasive thing that we can offer", which is how I think about it, the least offensive least invasive invasive thing that we could offer.

**Maneesh Kumar (DTRF):** And then I think we have time for just one last question, Dr Gangi in is video mentioned that cryoablation is really useful for smaller tumors. Is cryoablation ever used in larger tumors with the intent of slowing growth and not necessarily eliminating the tumor?

**Sean Tutton:** Yeah so I you know the the ideal tumor that's relatively easy to treat is one that's maybe five or six centimeters or less.

Those actually are pretty easily treated by cryo. When they start to get to be above you know 8, 9, 10, 15 centimeters,

It gets to be a big undertaking for anybody right so that's it's just a big lesion with a lot of cells.

We tend to break those up into stage procedures, where we will treat part of the tumor.

And then come back at maybe in four to six weeks and treat the next part of the tumor just so that again we're being more gentle on the patient. But it definitely can be done. I've treated very large tumors in all parts of the body, as has Dr Ganji so it definitely possible.

**Jeanne Whiting (DTRF):** Dr. Tutton, I'll just ask one final question. We saw that there can be multiple treatments required for cryo. In other words, it might shrink, grow again, shrink grow again. How common is recurrence and what is the average number of treatments required?

**Sean Tutton:** Well, I think that we, and looking at all the data, we can sort of generally say that the recurrence rate is similar to surgery, so it can be up to let's say 50%.

So it's not a perfect treatment, we definitely have those patients, where it goes away all together in one treatment and it never comes back so that's the mystic view of this.

On average, in our series, we ended up treating patients, almost two times so if you looked at every patient and you sort of averaged out

That number, it was one to two times.

And again, sometimes that's because we're trying to break up the treatments, to be more on a little bit more to have a patient maintain function and to have a better experience with the treatment, rather than trying to be overly aggressive and get everything in the first go.

**Jeanne Whiting (DTRF):** Okay Thank you so much what an an enlightening

video and answering session. Thank you so much. We'll now move on to discussion of a gamma secretase inhibitor you heard from Dr Kasper's presentation

That we've seen success with Nirogacestat which has is in current phase 3 trial, but it is closed to new patients.

I'll just tell the attendees that you'll learn tomorrow more about how these drugs after a trial is closed

or outside of a trial can possibly be obtained through compassionate use but that's a subject for tomorrow.

And now we have another gamma secretase inhibitor on the horizon developed by Ayala Pharmaceuticals and we'll turn the time over to Dr Gary Gordon and Jason Kaplan for their video and questions after.

**Ayala Pharma:** Hi and welcome to our session, thank you for inviting us and for giving us the opportunity to share with you Ayala, an AL102 Program.

We are glad to be here today and I'm happy to introduce to you my team. Dr Gary Gordon, our chief medical officer, Dr Jason Kaplan,

Our medical director and Dana Gelbaum, our chief business officer.

The company, founded in 2017, so we are a young company is a clinical stage oncology company dedicated to developing and commercializing small molecule therapeutics for patients suffering

From rare tumors and aggressive cancers. The company's current portfolio of product candidates, AL101 and AL102

target the aberrant activation of notch pathway with gamma secretase inhibitors. My incredible team is located in the US and in Israel.

At Ayala, we understand the needs of patients. Like many people listening today and people like Ashley and Kate who are living with desmoid tumors, this can be an especially challenging journey because

As we all know, desmoid tumors are rare, debilitating, and often disfiguring class of soft tissue tumors for which there are currently no approved therapies.

We believe our lead investigational product AL102 has the potential to become a new treatment option

For desmoid tumors because of its ability to inhibit notch pathway activation which we will talk more about during today's presentation.

Both of our product candidates are potent selected gamma secretase inhibitors or, as we call them GSIs

That are being studied across several rare tumors in aggressive cancers, including desmoid, adenoid cystic carcinoma, triple negative breast cancer and multiple myeloma.

And we are making good progress. Ayala is currently conducting a phase 2/3 clinical trial of AL102 for the treatment of progressing desmoid tumors.

We expect to report entering data from the initial part of the study in mid 2022 with Part B commencing there after.

Dr Gary Gordon will now provide an overview of AL102 mechanism faction, some results from phase one studies, with our GSIs and overview of the ringside study design.

Hi, I'm Gary Gordon. I'm the chief medical officer at Ayala and I am very happy to be here today to talk to you about our program with AL102 and desmoid tumors and the ringside study.

So, as many as you know, the notch pathway is an important pathway in the development of the fetus and the embryo during

pregnancies. It plays a really critical role there for cell division and the the normal development of the fetus.

This is shown in an illustration on the left hand side of the slide where you see the notch pathway in blue, you can see the

The ligand or the protein that normally signals for notch receptors to be active and you can see a little pair of scissors here in the membrane.

That play a critical role and releasing the signaling message of the notch pathway. During cancer and other disease states the receptor can become independent of that signal from the other cell - that blue

triggering protein - and then abnormally signal the nucleus to start making additional proteins, and this can, in adults, play a very critical role in the development of tumors, not only in their ability to grow,

Their ability to spread, their ability to get blood vessels, and their ability to resist treatment with certain types of chemotherapies.

On the far right hand side of the slide is an illustration that shows what our drug does.

Our drug, AL102, is illustrated here is the white ball with spikes on it, and again the gamma secretase enzyme is shown as a pair of scissors.

And you can see, obviously, that the drug is preventing the scissors from closing and therefore from triggering the signaling of the notch pathway

By preventing that cutting of the normal notch receptor. The next slide shows you a little bit of information that we've gathered over the years from our experience with both

AL101 and AL102. AL101 and AL102 are both gamma secretase inhibitors. The primary difference is AL102 is the drug that will be studying and the ringside study

And it is an oral drug as opposed to an IV drug. And what you can see in this slide is that

We have had some experience, both as part of the formal studies and as part of expanded access studies, with both of these drugs

Being able to achieve achieve tumor shrinkages in patients. So in AL102 in the phase 1 Program,

There was a patient who had an nearly 20% shrinkage on AL102, and there were additional patients in the AL1 experience consistent with other gamma secretase inhibitors that these agents can

cause dramatic tumor shrinkage, and this is shown in the scans on the right hand side of the slide, where you can see the patient has a large intra abdominal desmoid tumor

That with treatment shrinks very, very dramatically. Hi, my name is Jason Kaplan. I'm one of the medical directors here at Ayala.

And I'm here to discuss the ringside study with you all. Ringside is the name of our phase 2/ phase 3 clinical trial involving our drug AL102, which is a gamma secretase inhibitor. The study is divided into two parts, Part A, and Part B.

Part A, will involve 36 patients and the study does require that patients have

Desmoid tumors that are in the process of what we call "progressing" and what we mean by progressing as the protocol is written now

is patients have to have what we call a RECIST defined progression, meaning 20% or greater growth in their tumor within a 12 month period before going on the study.

So everyone in Part A, will get the study drug, one of three different doses. Once that part is completed, we'll decide which of the 3 dosing regimens is best to move forward with.

And everyone who's on Part A who's taking the drug still who is benefiting from it and tolerating it well,

At the time that we finished part A, everyone will have the opportunity to roll over to this open label extension. So patients will be able to stay on drug, even when Part A completes.

So in Part B, which you can see, on the right side of the screen, patients additional patients will get randomized to AL102, the study drug, or to placebo. Most patients will be randomized to AL102.

And about a third of all the patients in Part B will be randomized to placebo, and to anyone who's getting placebo

Who has their desmoid tumor get worse if you will, or progress on the study, they'll have the opportunity to switch over to AL102, to the study drug, so virtually everyone

In part B, will be able to get the study drug. We're going to be looking at safety, we're looking at how well the drug works, which we call efficacy

Meaning, "does it shrink? does pain get better?" and we're also interested in looking at quality of life, as measured by what we call patient reported outcomes tools or PRO tools.

And we have several of these PRO tools built into the study, one of which is a tool, called the GODDESS PRO tool and that was actually developed at Memorial Sloan Kettering in conjunction with the DTRF so we're looking at all of these things, and ultimately

The primary goal is to determine whether the study drug AL102 is better than placebo and that's really the summary of the study in a nutshell. I also will mention in Part B, it does involve enrollment of

Patients who are 12 years and older, whereas Part A, is for patients who are 18 years and older. Certainly if you have any questions about the study feel free to contact us. Our contact information will

be listed at the end of this presentation. So here's a list of all the countries where the study will be open, as of now, you can see, under Part A, you can see, the list of countries that weire opening in.

And then, at the bottom of the list, you can see, additional countries that we're looking into actually we've decided to move forward with those countries as well.

There are additional countries that are not listed here that we're also considering even for Part A. So, then in Part B, which will open later on, all of these countries that you see here for Part A, will be involved with Part B. Additionally will have other countries for part B as well.

Hi, I'm Dana Gelbaum and I'm leading the patient advocacy work at Ayala. At Ayala, we strongly believe that the patient voice matters. Since I started my career in drug development, one constant has been focusing on the needs of patients.

At Ayala, this commitment informs our work every day from how we develop the clinical trial protocol to putting programs in place to ensure all patients have access to new treatment options.

Fortunately, the FDA is also taking steps to better understand the patient experience by providing more opportunities for patients to share their perspectives. I hope this answers some of your questions about Ayala's work in desmoid tumors

and on our commitment to develop targeted therapies for people living with rare and aggressive diseases.

We want to thank you all today, for being here, we really appreciate your time. If you have any questions or concerns about the protocol, feel free to reach out to us anytime. Here's our information. Please reach out to Gary or myself again, thank you for your time.

**Jeanne Whiting (DTRF):** Thank you so much for that presentation Drs. Gordon

And Jason. You're both here, Dr Kaplan, here to answer questions. I'd like to just start with one question that we think has come up a lot.

When you say, if you do start with the placebo, and you have progression of the tumor, at what level does that progression need to be for you to switch over to the actual drug?

Yeah so i'll take that so thanks for the questions and thanks for having us here. So during part B, the part in which patients could potentially receive placebo, as opposed to AL102,

If there's evidence of progression, as defined by the RECIST

definition of progression, which is 20% growth or greater, that that would prompt us to unblind and

If we learned that the patient had been receiving a placebo, then that patient will have the opportunity to switch over or crossover I should say to AL102. So yes, it is simply stated it's it's 20% or higher growth.

**Jeanne Whiting (DTRF):** And can you just define.

**Gary Gordon:** I mean, I think it's important to add that progression is a key endpoint that the study and patients would need to progress as defined in the protocol in order to switch over.

And we have to do that, to protect the validity of the study and we will work with CRO that we work with to have a way to enable that.

**Jeanne Whiting (DTRF):** Can you just define your life terms the meaning of RECIST? It's an acronym.

**Jason Kaplan:** Right.

**Gary Gordon:** Very good.

Go ahead, Jason.

Jason Kaplan: So, so it is an acronym it's it's well established in the world of oncology research- clinical research- and basically it is a system in which radiologists

measure the size of the tumor they look at the diameter of the tumor and when it involves multiple different tumors in the same patient we add them all up the diameters of each of those lesions up and

You know, and we can look at the percentage change from baseline to later on and

You know, in the case of desmoid tumor many cases there's one tumor, as opposed to multiple but sometimes there are multiple tumors. But even with just one single tumor and

You know it's basically if that the dimension, the diameter of the tumor is increasing from baseline by 20% or greater, that is progression. And that's what I mean by RECIST, the RECIST definition of it.

And that's that's pretty well accepted in the world of solid tumor oncology.

We know that desmoid tumors don't always behave exactly like every other cancer out there. We realize it.

**Gary Gordon:** And critically it's the endpoint that the FDA, at least up until now, has asked for.

Right.

**Jeanne Whiting (DTRF):** Maneesh, did you see any other questions to field here?

**Maneesh Kumar (DTRF):** Yeah, there were a couple of questions that came up earlier that I think are relevant here. There was one question about patient reported outcomes that you mentioned, using the GODDESS PRO in this study and, specifically, they were asking about

Real time, real time details on the results of those PROs so I guess to broaden the question, what are your plans to release results, specifically on the PROs or otherwise, for the study?

**Gary Gordon:** So I'll jump in and take this one and say you know this is meant to be a registration study.

So those results will be reported in a way that's consistent with us to allow us to use them for registration, so we can't prematurely break the blind in a study that we're going to use for registration. As we learn the first part of the study, we will likely be able to report those.

**Jeanne Whiting (DTRF):** Can you please defined registration and in lay terms for us all?

**Gary Gordon:** Sure, registration in lay terms and apologize for using jargon means being able to take the results to the FDA or other regulatory agencies and have them review those results and approve the drug

then for use. And again the goal is to ultimately get the drug approved so that the most patients can benefit from the use of the drug.

And I think we're all probably more aware of

the registration process lately because of all the discussion of vaccines than we might otherwise be.

**Jeanne Whiting (DTRF):** Any other questions that came through, Maneesh? And then I had another question related to genetics or mutation status.

**Maneesh Kumar (DTRF):** I believe in you say there's a biopsy at the beginning, and the question was really around how useful is a genetic test - does it allow us to predict which treatment would be useful?

Does that allow us to predict how useful a treatment will be? I don't know if you have any comments on on that.

**Jason Kaplan:** Yeah that's a good question. Um simple answer is, we don't know yet. We're very interested in learning that so you know by collecting that information

And then later on looking back at all the data together and seeing if there's a correlation between the genetic status and the patient and how well the patient did or how you know how well the tumor responded is of great interest, absolutely.

**Maneesh Kumar (DTRF):** Great that's a great point about clinical trials, while the primary focus is to you know progression free survival, cure the tumor, there's all these other kind of other endpoints that could be really useful.

And and and you know biopsies and mutational status is one, and we also talked about imaging and whether or not imaging could help us define a better way of monitoring these tumors so I didn't know if you want to comment on the imaging aspect as well?

**Jason Kaplan:** Well, we are, we are, of course, you know we were relying on imaging to determine, you know the the primary endpoint which is progression free survival.

So imaging is is an essential part of the study and you know we're, as we said we're looking at the RECIST criteria for response.

But we're also looking at other specific MRI changes, including tumor volume and signaling changes on the MRI that are a little more exploratory at this point, and so

I think that's an important part of the study even it's an exploratory endpoint but it's an important part of this study. Actually it's a secondary endpoint for the for Part A, the tumor volume aspect of it, but the other

features that I mentioned are are a little more exploratory but but as as many of us know it's a great interest to see if we can come up with a way an imaging modality

To assess how these tumors are responding to therapy, other than you know, the more conventional RECIST way of doing things.

**Maneesh Kumar (DTRF):** Great.

And just one

quick question and then we'll move on. Oh, I think I got answered by text so we're fine so Jeanne, if you want to move on, for a minute.

**Jeanne Whiting (DTRF):** I'm going to ask for one more definition, please.

The term progression free survival does not fit well to me with desmoid tumors because very few people actually die from desmoid tumors so how does that what does that tumor mean in the terms of desmoid tumors being studied and reaching that endpoint.

**Jason Kaplan:** Right yeah, and again I apologize for the jargon as well you know so progression and so when we use the term survival "progression free survival" that that generally the term survival indicates, you know mortality and if someone's alive or not.

But what we really mean when we say survival is progression free progression free survival is we mean how, what is the status of

How how long can someone be without having their tumor grow and that's what we mean it's not really specifically addressing being alive or not it's

How long someone can be without that tumor getting worse that's what we mean by "progression free survival" or PFS for short, and again I apologize for that the jargon, but yeah and that's why we have these conferences, so we can talk about things.

**Jeanne Whiting (DTRF):** Thank you so much, and

**Maneesh Kumar (DTRF):** The last question did come back just real fast. Do we have an estimate on when part 2 might open? There was a question that said their doctor has been saying six months for a while. I know it's challenging to really pin down a date, especially on these big trials, but

**Jason Kaplan:** Yeah that's that is a good question. I don't yeah I know we don't have a crystal ball, of course, but you know

It could be in six months is is reasonable, you know no one knows yet just because it all depends on the but six months sounds reasonable, you know it could be more could be less, but I think that's a nice ballpark figure.

**Maneesh Kumar (DTRF):** Fantastic well, thank you both very much it was very helpful. Love the video and all the answers to your question to that.

**Jeanne Whiting (DTRF):** Thank you so much, and were so excited that this is going to be available in so many countries, so please again, you can watch the presentation again at your leisure.

To the patients here and physicians to get that information and send your questions to these two presenters here. I just want to make a few announcements before our last session here.

Please remember to join

RFA Live Virtual Challenge Ceremony tomorrow that takes place at 11am Eastern time and we had such an amazing presentation last year.

Lynne and her team do an amazing job - it's going to be so exciting to learn how we reached our goal, our fun our fundraising goal and and what everybody has done to help with fundraising this year.

These events are all taking place as part of Desmoid Tumor Awareness Month, which is now every September also we're hosting a Facebook

And instagram live broadcast that you're all welcome to attend, it's one of the major questions that comes up for patients.

Is why, why do we use the term cancer or not use the term cancer? The term benign, the meaning, what we call a desmoid tumor.

And the impact of a name and how it's categorized and I know that question was raised a little bit earlier in this meeting.

So that's going to be with Dr. Pollock from Ohio State Cancer Center on Wednesday at 430 Eastern so be sure to

either be on instagram or Facebook at that time to participate in that really important live discussion that I think's going to be of interest to everybody.

You can also share your stories during awareness month still check out more information at our website dtrf.org/awareness

and also you're going to be receiving a survey after this meeting we'd like to ask you to please answer the survey. You help

Us become better by giving us your feedback. It would just be a survey about this meeting and save the date for next year, physicians and patients and caregivers.

Our next year 2022 meetings will be September 23 - 25th you'll hear more about it, but please save the dates on your calendar. I did misspeak that our

discussion about compassionate use was going to meet tomorrow. With all of these meetings these hours are turning into days for me. The compassionate use and other discussions will be today at

At one Eastern.

Correct 130 1:30pm Eastern. And again I misspoke in the chat. It's at 1:30pm Eastern, but are we will be opening

The webinar at 1pm and so you can enter it anytime. So we're so excited to have is our final presenter a discussion about an international pregnancy study.

We, this is an area that we really need to explore - desmoids and pregnancy and we turn the time over to Marianna Coppola

Of the Desmoid Foundation of Italy and Dr Chandrajit Raut of the Dana Farber Cancer Institute for a presentation about the pregnancy study that is ongoing now.

**Marianna Coppola:** My name is Marianna Coppola and I'm the manager director of the Desmoid Foundation of Italy. It's a pleasure for me being here today to speak about desmoid tumor pregnancy and fertility.

A few months ago, we started to collaborate for a new study. This new study is

Divided into sections, the first one is about women and pregnancy and we want to investigate about the behavior of the desmoid tumor during the pregnancy and the second one is about

The psychological effect caused by diagnosis of desmoid tumor on woman choices during their fertile age. How do we interpret our involvement in these studies?

We are actively collaborating with doctors and with other patient advocates from all over the world. From we're collaborating collaborating the from USA, Italy, France and Canada.

The previous study about desmoid tumor and pregnancy is from 2014 and some of the authors are the same that are making the new one, this in your study.

Study involved 92 women and it wanted to investigate about the relationship between desmoid tumor and pregnancy. The conclusion of this study was that

The progression risk for the desmoid tumor during the pregnancy is high but it can be managed, and so it's always advised to speak with your doctor before starting a pregnancy.

But there is no increase of obstetric risk if you are diagnosed with desmoid tumor, so there is no contraindications about having a pregnancy, if you are diagnosed with this disease. You can download the full

Paper of this article from our website.

The new study that started a few months ago

involved five different university centers and international hospitals and it involves the most important doctors

That specialize in desmoid tumor and you can find it in all the most important scientifically correct articles about this disease. So it involves the Institute from Milan, from Padova, from Paris, Boston and Toronto.

And the objective was of this study is

To investigate about the effects of pregnancy on the desmoid progression and the effect of the desmoid on the pregnancy outcome.

So we want to enroll women that are diagnosed with desmoid tumor before or during the pregnancy. How do we make the enrollment? The enrollment can be made directly from

One of the university centers and hospitals that I mentioned before, or it can be made the to the patient advocate associations

Or you can find the online on social media or on our website.

Information about the enrollment for the patients. Our website is available right now in Italian, in English, and in Portuguese. We started to enroll patients few months ago, as I said. Actually, we have no deadline, but this will depend on the

On the number of the women, that will be enrolled in the process of the scouting and the recruiting.

Related to the main study, there is an ancillary study and that's the first time that we want to investigate about the psychological effect

Of the diagnosis of desmoid tumor

When a woman during the fertile age received this diagnosis. So how this changes her fears and her feelings about

The wellbeing of pregnancy and that's the first time that we want to investigate about the quality of life of women that receive this diagnosis, and this is really important, because desmoid tumors has a high incidence in young women.

And, as I said that the patient advocate association has an active role.

There are four patient advocacy associations that are related for from the related with the hospitals that I mentioned before. So that is the Desmoid Foundation of from Italy, DTRF from USA, SOS Desmoid from France, and the Desmoid Foundation from Canada.

But thanks to the internet and thanks to our technology now we want to

To reach all the all the world, so we are already actively collaborating with the Desmoid UK and Desmoid Brazil to enroll the women from these two countries and

that's what will make this study really important to the collaboration from all over the world.

The technology, as I said, it will help us to reach our number of the women from all over the world, but these are so bring us a problem because

We have the, we have to protect the privacy of our patients

That participate in the study and so what how are we doing this? We guarantee the anonymity of this study. The questionnaire are processed full anonymously and

Every name is associated with an identification code. The data will be processed, that are not individually, but aggregated, and we will use all the technical and organizational security measures to

protect the data of the patients that enroll in this study. That's why, after filling the survey, all the patients must sign a privacy form

First of all to verify and validate their identity and then we will guarantee the anonymity.

Unknown Speaker: So I think that you already saw maybe online some post about the study, because, as I said, we started a few months ago.

You if you're a woman, that got a diagnosis of desmoid during or before your pregnancy

Please just contact one of the doctors from the research centers that I mentioned before or one of your patient advocacy associations in your country, just to add information about how to be enrolled and in this study.

You can participate directly so from our website desmoidfoundation.org that, as I said, is available in three languages - Italian, English, and Portuguese right now. The patient advocates are there just to support you and to give you all the information

That you need to participate in this study.

For what

I said about the ancillary study, all the women that received a diagnosis of desmoid during their fertile age

can participate in the study and it's really important that really huge number for this study, so we can have a

Good view of

how this diagnosis changes the young women's life.

And so, so the ancillary study is made

Just with a survey of a few questions, and this is entirely managed by our website so it's just that you have to go on our website desmoidfoundation.org and you have to fill out that survey

And it will be totally anonymous. I'm saying it once again.

What are the objectives of the Desmoid Foundation of Italy and other patient advocate associations? We are actually scouting and recruiting for both studies and we

We made the

on our website some pages where you can find all the info about the the studies and you can be enrolled directly by it just by filling the survey.

That is about desmoid tumor in pregnancy. After filling the survey, you will be contacted by by one of the patient advocate and there are a few questions that that we made to you. For the fertile study, as I said, it's entirely managed online.

All the women from all over the world can participate in these studies

to study that is about desmoid tumor and fertility

and

other women that received a diagnosis of desmoid before or during their pregnancy can participate also, so to the study that is about

Desmoid tumor and pregnancy. If you are eligible after you will be contacted the from a patient advocate from your association

or from one of the doctors who is working in the study. It's not necessary to visit the hospital, it's totally managed through our website. Anyways totally managed it online and by phone, so please, if you are

eligible just participate in this study because this can make a difference for the future.

Before we are leaving I want to thank all of the patient advocate associations that are working with us - the DTRF that remains the world reference point for desmoid tumor, SOS Demsoid from France, Desmoid UK from UK

Desmoid Brazil, Desmoid Foundation of Canada and SPAEN.

We are really proud to work with you and we're very proud of the amazing work that you were making the together to enroll the highest number of patients that are eligible for this study.

And thanks also to all the doctors that are involved in this study, thank you for your commitment and your collaboration, because we really think that

With this working together can make a difference from the future young woman that received a diagnosis of desmoid that we can really help them to face the difficulties of this diagnosis.

And before we're leaving, thank you to Marlene and Lynne for organizing this amazing meeting, and we think that together we are stronger.

**Jeanne Whiting (DTRF):** Thank you for your attention. Thank you for that presentation. Dr Raut, did you want to say anything before questions or do you just want to proceed with questions?

**Chandrajit Raut:** Sure, I think we can proceed with questions. I'm sorry I keep my camera off I'm stuck in traffic coming back from a meeting, so I apologize for that

But yeah something while we just turn it over to questions, so we can get

To those.

**Jeanne Whiting (DTRF):** If I could just clarify.

DTRF will be a site for this study but this study, does not take place on a site like a clinical trial might or something - it is done virtually.

So all you have to do like Marianna said in the presentation is to and we'll send you more information about how to participate through DTRF.

But you just fill out a form and then you'll have about an hour of questions asked where your answers will be taken it all be done remotely so again as Marianna emphasized it's so important that we studied this area. This disease is truly

So many young women have desmoid tumors, young women of childbearing age and the more information that we can get relating

To the impact on your fertile years and the impact on pregnancy decisions, to become pregnant, results after you do with a desmoid. et cetera et cetera, These are the areas that will be covered and that are so important to our research, so Maneesh, did you have questions for Dr Raut?

**Maneesh Kumar (DTRF):** Yeah, Chan a couple of questions came through related to desmoid tumors are often diagnosed during pregnancy or on a C-section scar. Does that mean that for women who are diagnosed during her pregnancy, they should not get pregnant again for fear of growth of their desmoid tumor?

**Chandrajit Raut:** Alright, so that that's that that's a common piece of advice that women have been given in the past we don't have any evidence to suggest that that that there's

A lot of credence behind that. There's a couple of issues, one is if if the woman decides after delivery to not treat the desmoid, meaning just or I mean not remove a desmoid, the desmoid may go away or shrink.

And that's perfectly fine if they want to have another child, the counseling that I give them is that that does more will probably grow.

That doesn't mean that you shouldn't get pregnant and it doesn't and also we don't know for certain if if you should have a desmoid taken out, we just don't necessarily know how to predict the growth rate so

it's possible that the desmoid can grow slowly, or possibly can grow quickly, so I have a long discussion with each woman who presents in that situation about these are the options. We don't have a lot of great data, hopefully this this new study will shed more light on this.

But we don't we can't tell you for certain you shouldn't have a pregnancy. I think that's the wrong thing to do. We just don't know how this is going to play out. Now if the desmoid's removed,

Then I see really no contraindications to getting pregnant. The recurrence rate seems to be a little bit lower for pregnancy-associated desmoid then for, in terms of after surgery, then for say desmoids arising in the context of FAP or trauma or other circumstance.

**Maneesh Kumar (DTRF):** Right, thank you and then another related question, I think this will probably be our last question since we're a little bit over time.

But if a person already has a diagnosis of a desmoid tumor, should they avoid C Sections? I know oftentimes it's impossible sometimes it's just you know mandatory that you get a C section, but if given the option, should they'd be avoiding C sections?

**Chandrajit Raut:** Great question we don't have any data on that, again, I hope we can get gain some information on that from from the survey. We can we have a few patients who have

Desmoids arising in a C section scar, but they were not, they did not have a diagnosis of desmoid fibromatosis before they had their C section, so we just don't we don't have good data.

**Maneesh Kumar (DTRF):** Right, and I think that also answered another question which is that this study will be investigating the idea of cesarean section trauma

And desmoid tumors.

**Chandrajit Raut:** Right.

**Maneesh Kumar (DTRF):** Great. Thank you and I think that probably covers most of the questions that we've had. Any questions that we didn't get to as Jeanne mentioned we'll try to send those out to our expert doctors and try to get all the answers via email.

**Lynne Hernandez (DTRF):** Can we have one

Can we take one more question Maneesh in the in the Q&A?

**Maneesh Kumar (DTRF):** Sure, are you the last question that just came in?

Yes, yes, so, can I just came in is, are there any interventions that can be used, while pregnant or are they all too toxic? That's a great question, thanks, Lynne.

**Chandrajit Raut:** Yeah, great question.

At this point, I think that

We just don't know the impact of, and I also defer to our medical oncologist on this as well, but we don't know the impact of these newer drugs on a

A growing fetus. They haven't been tested necessarily in pregnant women.

So I think it's as long as the desmoid is not symptomatic, we trying to minimize an intervention that might put the pregnancy at risk.

**Maneesh Kumar (DTRF):** Great, did any of our medical colleagues on the line want to comment on that as well? Or perhaps Jason or Gary, how do we study something like that, and in a trial?

**Gary Gordon:** So I think in the context of a trial

You know, we would probably say that if someone becomes pregnant on the trial, they should stop the drug, given the fact that

At least for some of these newer drugs, we don't really have any information to inform that.

There is some experience in the oncology literature that I'm aware of, for instance in treating women with breast cancer, who are pregnant and which agents can be used when and with what degree of safety.

But it has been a while, since I've looked at them.

**Jeanne Whiting (DTRF):** Dr Raut, thank you, Dr Raut, could you please explain again how the pregnancy study, which is done remotely, wherever you are in the world, it only applies in certain languages.

Do you have to be in any certain country to participate or can you participate from anywhere?

**Chandrajit Raut:** Yes, so I think that what we haven't anticipated is the amount of enthusiasm in the study so

Right now, the consent, so that to participate in the consent and in the study have to sign a consent. The consents are currently available in English, French, Italian, Spanish and Portuguese.

Yesterday at the Research Workshop, one of the investigators from Japan offered to translate into Japanese as well.

So those are going to be the languages that we have available  but there's no limitation on where you where you are in terms of being able to participate, the important the important thing, of course, is that

Your each individual is data are gathered only once, so we don't duplicate information and and have error in numbers.

**Jeanne Whiting (DTRF):** Okay, so if you were living in the United States, you can participate through DTRF, but if you speak English.

And you live in some other country, you could still participate through DTRF or through the UK or whatever. You just register online and people will be diverted to the correct language right?

**Chandrajit Raut:** Correct and again when we designed to study we weren't quite sure how much enthusiasm that would be outside of the participating countries obviously there is.

And we want to gather as much information as possible. Our original hope was that if your country is participating that you would

go through either the institution or the advocacy group in your country. That's obviously

only applies to the the the participating countries but for people outside of those countries through participating through any site would be would be fine.

**Jeanne Whiting (DTRF):** Okay thank you so much, and we'll be sending out more information via DTRF about this study.

**Maneesh Kumar (DTRF):** Let's just get one more question real quick. We have a very active chat here.

Chan, can you

Is there any evidence that breastfeeding might influence the growth rate of a tumor?

**Chandrajit Raut:** I get that question a lot actually and we have no data on that.

None at all.

Okay.

**Maneesh Kumar (DTRF):** Great, thank you.

**Jeanne Whiting (DTRF):** Okay, thank you so now we're 45 minutes to our next

To our next webinar, correct, Lynne? 45 minutes, which will be 130 Eastern. Please sign in a little early so you don't run into into tech problems and have time to get signed in.

We're going to have various interesting presentations again on our webinar #2, and these will be actually live so will be a little different from this webinar but we look forward to seeing you all in 45 minutes. Signing off for now take a good break.

**Gary Gordon:** Thank you very much.

**Lynne Hernandez (DTRF):** Thank you, thank you to our panelists. Thank you.

**Bernd Kasper:** It was a pleasure.

Thank you.

Bye bye.