Please stand by for realtime transcripts.

>> [Captioner on Stand By].

>> Dr. Paleologos will answer as many questions as possible at the end of the presentation. Tomorrow, you will receive an invitation to complete a brief feedback survey. Please, we do ask that you take just a few minutes to complete the survey and share comments about today's webinar. Your feedback is very important to us as we plan future webinars. We are recording today's webinar that will post to the [Indiscernible/Name] website shortly. You will receive the webinar link and a follow-up e-mail message wants the webinar is available. Let's pause for a moment so we can begin the webinar recording here.

>> The American Brain Tumor Association is pleased to welcome you back to the webinar series. The webinar today will discuss Oligodendroglioma. And new treatments and updates and care. My name is Jillann Demes, Senior program manager here at the American Brain Tumor Association. I am delighted to introduce our speakers today, Dr. Paleologos. Nina Paleologos is a neuro oncologist at Rush University medical Center. And an investigator on multiple clinical trials including those that lead up to the FDA approval of Temozolomide and Bevacizumab. She has done research and written extensively on Oligodendroglioma. She was recently given a career achievement award unexceptional -- exceptional expertise, knowledge, dedication and recognition in the field of neuro-oncology by the Chicago neurological Society. Thank you for joining us Dr. Paleologos. You may now begin your presentation.

>> Thanks JoAnne. And thanks to all of you who are listening, for attending and for your attention today. We will talk about Oligodendroglioma, new treatments and updates and care. First of all, we will go over what a Oligodendroglioma is and why they are unique. They are unique because of their pathology or the way that they look, when you look at them under a microscope. They are unique because of the epidemiology, who they affect and how they behave, both statistically and the population in general and clinically, in individual patients. They are very unique in that they are responsive to therapy, which is just great. And they are unique in the molecular makeup. They are associated -- many patients with patients with transit -- what Oligodendroglioma have tumor cells with pieces of chromosome called, 1P and/or 19Q. That is important as we will learn today. They are unique in regard to the way we treat them and they are unique in that it -- that the future is bright. Let's get going.

>> What I have in front of you right now is a picture of what a low Grade Oligodendroglioma looks like underneath the microscope. If you can see here -- these cells look like little mini fried eggs. That is very unique for this tumor types. That is the little clear halo around the middle part, the nucleus. That is actually a fixation artifact. It is the way the tumor tissue is fixed for the pathologist to look at. Sometimes you don't see it as clearly as you do in this slide. This is a very unique look. They also have these little skinny sort of than chicken wire type blood vessels. The way they look is very unique under the microscope. A Astrocytoma, which is a different cell type of tumor, are very common compared to the Oligodendroglioma. The Oligodendroglioma is much more rare than Astrocytoma. But sometimes, tumors can have both cell types. And those are called, mixed Oligo-Astrocytoma. This is what a low Grade Astrocytoma looks like under the microscope, which is not what we will talk about specifically today. But just to show you the difference in the way they looked underneath the microscope. And on the slide, what you can see is a mixed Oligo-Astrocytoma -- what that looks like. It can have the behavioral characteristics of both tumors. And it can look like both tumors. You can see in between here that there are little cells with the halos. Those are the oligos cells I am pointing to an in these Brown cells -- they are stained brown specifically so they

show up. These are the astrocytes. They look like little stars. We can test the tissue to see if there are those chromosome. And that can help us tell had to deal with these mixed glioma. There are two categories of mixed glioma. Those that have 1P or 19 Q -- which suggests that they came originally from a Oligodendrocyte stem cell lineage -- - (indiscernible) And then there are others that don't have the deletion but they have other molecular deletions like TP53 mutations which is a just they will behave more like an astrocytes because they probably came from a Astrocytoma stem cell originally. Those are the two main categories of mixed Oligo-Astrocytoma. The pathology of a Oligodendroglioma is unique. But the Grade is also unique and very important. On this slide, on the far left, as you are looking at it, that is the low Grade tumor. The middle is kind of halfway between a high-grade tumor and a low Grade tumor. So you can see, on the far right, that is a much more aggressive high-grade, what we call a anaplastic Oligodendroglioma or a Grade three Oligodendroglioma. The reason I put the picture in the middle is to show you that there really is sort of a transition. And it is a continuum. So you could have -- and this is very important. You could have a tumor were -- say you have a tumor where the doctor could only take a biopsy from or only part of it is able to be removed. You could have pathology like on the far left. Or in the middle -- in the piece under the microscope, but in the middle of the tumor, it might look more like this on the far right. It will end up behaving more like that on the far right. So you may hear me today, and her doctors, talk about something called, sampling error. It is not really an error. It is just that if you take a biopsy of an area that looks like this, the past reports might say, Grade two. But yet your doctor might be talking to you as though you probably have a higher Grade tumor. And that may be because of the way the scam looks and the way they may feel and suspect other areas of the tumor look more like the two pictures on the right. So that is really more of a sampling issue than an error. But that is a very important thing related to these tumors. So how do you know you have a Oligodendroglioma? You can't really completely rely on the MRI scan or the CT scan appearance. You actually have to remove a piece of the tumor for analysis and study. Like the pictures I showed you. So one of the ways that can be done is through a needle biopsy called a stereotactic biopsy. Or it can be done through a operation to remove part of the tumor or at least everything that the neurosurgeon can see possible.

>> When we are talking about how they are unique in regards to the epidemiology and the clinical characteristics, we already mentioned that they are rare. They are only 5-20% of all of that glial tumors, primary brain tumors. And they arise from these specific cells called Oligodendrocyte. It is probably closer to eight up to 10% interest. But there are a variety of studies with that broad range. They tend to happen in the fourth to the sixth decade of life. They are more common in men. Low Grade Oligodendroglioma occur in slightly younger patients than that. They have a relatively low intellect slow course with a long survival time for many patients, especially if a patient has or started out having a low Grade glioma. I have patients that I have been taking care of with Oligodendroglioma, for literally 20 years. So that is a very unique thing, in comparison to patients that have pure Astrocytoma. They more quickly present with seizures compared to the Astrocytoma patients. Over 50% of patients will have a seizure as the first presenting systems -- symptoms. Even if they don't, 85% will have some sort of seizure. It might be small or minor. But eventually, during the course of the disease process. This -- the seizures are common. Other neurological symptoms are more related to the location of the tumor in the size of the tumor. Sort of like real estate. Where is your tumor at? If it is in a motor area, you might have some weakness. If it is in the sensory area, you might have numbness or tingling. We talked about the unique histology. Like the fried egg and this them -- then branching blood vessels. The neuroimaging is nonspecific but there are clues. You can see sometimes, calcium on the CT scan, more than the MRI scan. That is because they tend to be slow growing and the beginning. Sometimes you will see a little tiny hemorrhages, from those branching blood vessels. And you see the tumor invading the cortex, or the most superficial part of the brain. More so than the Astrocytoma does. That superficial cortex is

where seizures come from. Which is why we think that seizures are a little more common in patients that have this type of tumor compared to other types of primary brain tumors. If there is a lot of enhancement -- and I will tell you what that means in a second -- if there is a lot on the MRI scan, that is more typical of a higher Grade, anaplastic or aggressive tumor. Anaplastic means the same thing as Grade three. So if you hear those words, they are interchangeable. Low Grade [Inaudible/Low Volume] of any sort including oligos are considered Grade two tumors. And Grade two tumors tend to progress over time into Grade three tumors. Like I said earlier, there can be parts of the tumor that look more like a Grade two under the microscope where another area Mort -- might look more like a Grade three tumor. These really respond to treatment and are associated with 1P and 19Q solutions. Like I said, they responded to treatment. We did not know that until maybe about 10 years ago or so. And the reason we never knew that was because there were so few patients included in these big clinical trials that were being done. Most of the patients had Astrocytoma. So they were sort of lost in the shuffle. But they are very key most sensitive tumors. And again, they are characterized by 1P or 19Q. I thought everybody might be interested in seeing what the one pop -- 1P19Q looks like. They are fluorescent [Indiscernible/Name] and we shorten that to FISH. Basically it is a fluorescence test that makes a certain chromosomes light up. On the left, you should see -- you can see two copies of every chromosome in every cell. You can see there are two here of 19. And there is only one of the green. There is two of the red and only one of the green. There is two of the red here and one of the green. So the green represents 1P. This is a 1P deleted tumor. On the other side, it is the exact opposite. There is one copy of the red where are -- whereas there are two of the green. This is the deleted one. This is 19Q. So that is what it looks like underneath the microscope. That is the test your doctor is talking about when he or she talks about having or not having 1P19Q deletions.

>> Initially, years ago, when the Red Cross and other colleagues around the country first appreciated the malignant or high-grade or aggressive anaplastic -- all of those words are kind of interchangeable, the Oligodendroglioma -- the anaplastic Oligodendroglioma responded to a combination of chemotherapies called, PCV. There were three drugs. That he stands for -- the P in the C in the V. It was kind of an eye-opening thing. That these tumors -- 100% of them responded to the PCV in this one series they looked at. And I was repeated by others later. And that patients with this tumor types had much more prolonged survival time than patients with that. Astrocytoma. That made everybody go on and unbelievable hunt as to why. And that is when we discovered the 1P19Q. Doctor David look -- doctor David Lewis and Dr. [Indiscernible/Name] first recorded it. And the biggest study, about 80 up to 90% of LGO will have those deletions. About 50 up to 70% of anaplastic Grade three [Inaudible/Low Volume] five will have those deletions. And about half of the mixed Oligo-Astrocytoma patients will have those deletions. And it is not in the regular cells of your body. Just the tumor cells. Tumors that look like those classic fried eggs that I showed you under the microscope -- microscope as opposed to the mixed tumors, the ones that look at classical are more likely to have the deletions. And the chemo sensitivity of the low Grade Oligodendroglioma is probably better predicted by the 1P19Q status than any way it looks under the microscope. So it is a really important test.

>> And it kind of made all of us study a bunch of things to try to see if we could tell if there were different groups. I don't want everybody to take -- pay too much attention to the survival data at the bottom here. Because that has changed over the years. This is old data from over a decade ago. But we really can see that there are different -- four different groups of people, depending on if they have 1P deletion or loss versus if this 1P is intact and they have other types. If you look, and you have 1P loss, the most -- not quite 100%, but almost 100% of patients will respond to chemotherapy. If you don't have 1P19Q lost does not mean you won't respond to chemotherapy. So had is that one pop -- 1P19Q help? It protects which patients will have tumors that might act more

slowly or indolent Lee, meaning they will live long enough -- that perhaps the development of some delayed publication from radiation -- we will talk about that a little bit later. To critics which patients are likely to respond to chemotherapy so that maybe we should use it earlier in those patients. And so it assists us, as your physicians, and U.S. patients, in deciding on what the best individual management is for your particular case. So there are a lot of different treatment options. There is watchful waiting which means you don't do anything but watch carefully with MRI scans. And we do for treatment until -- say the tumor progresses and size or greater symptomatically in some way. And that may be appropriate for some low-grade tumors. But not for anaplastic or high-grade tumors. You can have surgery with a caveat. And the caveat is important. If it is technically feasible, with the goal of preservation and neurological function and inaccessible level of risk. You can have radiation therapy. You can have chemotherapy. The benefits of treatment of course should always outweigh the risks. And the risks of not treating should also be considered in patients that you are considering watching. So surgery. If we talk about reception, would you get from that? You get a verification of the diagnosis and you get more tissue from a recession then you do with small biopsies. So the greeting may be more accurate. There is a release of signs and symptoms in some patients who have large tumors, were there is swelling in a mass effect. You get basically rid of those cells. That is what stereotactic means. Reducing the cell number. And some Oligodendroglioma -- some patients, that might improve outcome. It allows for lower steroid dose. As you know, steroids are used to control swelling and edema. And they have their own set of side effects. So usually, if you have less mass effect of a smaller tumor burden, in the sense you can get away with either no steroids were a lower dose. We already talked about reducing sampling error is because you get a bigger keep -- piece of tissue. It should be done if technically feasible, with the goal of preservation of function. And as long as there is an access -- acceptable level of risk. And the extent of resection is an independent variable associated with survival. (indiscernible) So everything we can see on the MRI scan is gone are very close to it. Like 80 up to 90% of what we can see -- or slightly less than that. You will likely have an improved overall survival. But that should not be done with the cost of say -- some serious neurological -- happening. If we hurt you more then we hope you it is not necessarily a good thing. Some patients can benefit from operation of the time of tumor recurrence. There have been a lot of technical advances that increase our ability to respect -- respect tumor from the Oakland brain. That is like the language area. With a reduced morbidity. FMRI to identify eloquent cortical areas. And DTI can identify white matter pathways. The absolute gold standard is an awake craniotomy when you are actually awake and your cortex is being them -- mapped with electrodes and stimulated. And you are participating in that with the neurosurgeon. Not everybody needs something like that. But if the tumor is in or very near eloquent range, there are definitely some patients that might benefit from that. And that might facilitate -- these things might facilitate a more complete and safer resection in tumors near eloquent rain. I put up a couple pictures to show you what those look like. On the left, is a diffusion test imaging. Those are the white matter normal pathways. And here is the tumor right here I am circling. You can see -- in this case, the white matter pathways are getting pushed out of the way. You wouldn't want to cut that out. Because this is a functional MRI. A language area. This is a language area here. And there are some comp -- comprehensive language back here. Somebody might think that the tumor is right here in between and it is okay to remove. But these two areas are connected. And you need to diffusion image to see if the white matter pathways are going through the tumor or around the tumor. If they are going around the tumor, you might still be able to get away with operating right there. But if they are going right through, even though you are not touching each individual language area, you could have a language problem if the connecting fibers are disrupted. I don't have a picture of an awake craniotomy. But I know that doctor Burns will be talking about that at the family meeting in Chicago in July. Said Mac so there are risks of resection. There is a standard risks that you see with any kind of surgery of any sort. Infection, bleeding, anesthesia convocations, medical complications.

Because they are operating on your brain, you could have a stroke or bleeding or some sort of loss of function. Which many times, you have to give up a little to get a lot. But you don't want to have a large -- or devastating deficit afterwards. And there are important blood vessels nearby that put an impact into whether it is safe to operate or not. Occasionally, people will have seizures right after the surgery just because of the information there. And you can have some plot -- spinal fluid leakage as well.

>> So once the surgery is done, whether you have had a biopsy or an operation to remove part of the tumor or resection, what do you do after? And who should treat? And when should we treat? The timing is controversial in patients with low-grade tumors. Most people -- in fact, pretty much all Nero oncologist in the country would agree that if you have a anaplastic or high-grade tumor, Grade three tumor, that you should have treatment. Low-grade tumors are a little more controversial. But I think most of us can agree that you can probably get away with differing or delaying treatment in a low-grade tumor after a very large or -- like I said before, growth total reception, if there is [Inaudible/Low Volume] or if there was no or very little enhancement, meaning the contrast that you have injected does not leak into the tumor. If it does leak out, that is called enhancement. If there is little of that or none of that. If the seizures are well controlled and there are few or no other symptoms, you might be able to get away with deferring treatment. But you have to watch, with very frequent MRI scans over time. Most people would agree that we should treat people who have Grade three or anaplastic tumors, if there is a low-grade tumor that is progressing. If there was a lot of enhancement on the preoperative MRI scan, that would suggest that it would behave more like an aggressive were Grade three tumor. If there was significant size causing mass effect, or [Indiscernible/Name] symptoms. Radiation therapy is kind of an old therapy. It works pretty well though. It significantly improves survival over doing nothing. Or doing tomorrow -- chemotherapy alone. Or doing an operation alone. And all malignant high-grade gliomas. And I put glioma in quotes because the studies were mostly done when the trend -- Oligodendroglioma was mixed up with the Astrocytoma. So there are very few studies -- in fact, almost no studies, at least from that -- from back then, on Oligodendroglioma all by themselves without other tumor types being in the mix. It became a cornerstone of therapy many years ago. There are a lot of questions I get about proton beam therapy. It is thought to decrease risk to normal brains. However, I always caution people that the efficacy or the ability for it to work has never been compared to standard RT with margins are on the area of abnormality. The risk with proton beam is that you old -- you can't always see the edge of the tumor. And you could under treat the margins and have growth at the edge. It is a big -- a bit controversial. It is never been completely tested. Stereotactic radiation is usually called, things like, cyber knife. That is a very sort of focus the small area, high-dose radiation. It is not usually indicated in Oligodendroglioma. Because Oligodendroglioma is usually more spread out and consultative -- infiltrative. The role or timing in Oligodendroglioma tumors is evolving. The standard radiation protocol is that it is five days a week. Not on Saturday or Sunday or major holidays. And it lasts about five or six weeks. The initial port encompasses the entire abnormality there that you can see. Not on the post [Indiscernible/Name] images but the other images were the tumor shows up best. And you include a one up to 3-centimeter margin that looks normal around it, so you don't miss any records topic -- and then you call them down or target the area where the die might have been leaking out, the contrast enhancing area and give a little boost to that. So the dose for a high-grade tumor is 6000 center grey or the dose for the low-grade tumors is about 5400 centigrade. It depends on the size and shape of the beam in the physics of it. Those are rough doses for the usual treatment protocol. There are lots and lots of studies.

>> I have put up some that are particularly -- strongly related to Oligodendroglioma. But we know that in the anaplastic Grade three Oligodendroglioma, that in improves the time of the tumor progressing. There is an approval in survival in all types of glioma -- again, compared to

chemotherapy alone. Chemotherapy is not necessarily worse than radiotherapy in a trend if it. But I'm talking about the stereotactic -- glioma of all types. In any kind of glioma, it is improved over doing nothing, or surgery alone or chemotherapy. The [Inaudible/Low Volume] five is a little more controversial. And low-grade tumors, most of those studies to know -- they do not look at Oligodendroglioma alone. They look at all kinds of low-grade tumors. What we know from the bulk of the trials -- the biggest one was the one I have up here. The European oncology radiation study that was published in 2002. If you have early radiation like right after the biopsy or right after the diagnosis, versus radiation at the time the tumor grows -- the tumor might take a little bit longer to progress. That is called, time to tumor progression or TTP. But you do not affect the overall survival. The triable -- the trial was not specific to low-grade Oligodendroglioma. It also included some patients that had big surgeries in some that only had biopsies and had a lot of tumor left behind. They are very different. So it is affected. But it also has delayed consequences, which we will talk about. People started to wonder if there were subsets of people that maybe you should defer or delay.

>> Chemotherapy. Most Oligodendroglioma respond to chemotherapy. Sometimes vary dramatically. And sometimes for very prolonged periods. They responded to the protocol I talked about earlier, the procarbazine, CCNU and the cap IN-Christine. They also responded to Temozolomide. And the timing of when you should be that related to the radiation that is still being worked out in the length of treatment is still being worked out. With the PCV protocol, people started to have side effects after about -- somewhere between eight months in a year or six month and a year. So you kind of have to stop. The TMZ -- that drug is a little bit better tolerated. People can stay on it for longer. So a lot of times, they will be treated for many more months than with PCV. But we really don't know what the best amount of time is. 1p/19q really predicts response. So if you have 1p/19q lost, you have an almost 100% likelihood of responding to chemotherapy. Not quite 100%. But almost 100%. But that does not mean -- I have had some patients say that my doctor says I shouldn't have chemotherapy because my 1p/19q is in tact. I am not deleted. That is not really true. You just have a lower% -- lower percentage response rate statistically. I have had plenty of patients -- and studies also show that many patients without 1p/19q also respond to chemotherapy.

>> This is what a low-grade Oligodendroglioma looks like under the microscope. And we have already seen that. And this is kind of what it looks like on a MRI scan. This is the whole tumor here and whites. This is the post contrast study. There is really no enhancement here. There are these little dark areas. Those are little cysts. Some tumors will make those.

>> So why would you treat a low-grade -- we will talk about low-grade treatment first and then go on to the high-grade treatment. So why would we treat these tumors? They progressively infiltrate the brain.They cause increasing neurological disability over time. They cause patients symptoms like seizures, cognitive symptoms, weakness, focal symptoms like weakness or numbness. They ultimately, over time, progress in size and transform in Grade two higher Grade or what we call, anaplastic form. Radiation is probably helpful at the time of progression. It is not so clear that it is helpful early.

>> Unless there is a lot of tumor left behind.

>> Issues that complicate management is -- that under grading we talked about. Is it really low-grade? Or are you just testing that part of the tumor and could it be a higher Grade? You don't want to under treat people. The responses difficult to assess. The tumors tend to grow slowly when their low-grade and sometimes you get somebody chemotherapy and you can't tell that the tumor is shrinking from scan to scan. But if you take care of them for a year and you skip over a few of the previous scans and you look back six months, you will see that the tumor has shrunk. But you don't

see it from scan to scan. The converse is true as well. When you're getting followed over time and people are looking to make sure the tumor has not grown come you don't always see a subtle change in the growth. Sometimes, you have to look back a few scans to see it. The literature is what I like to call, dirty. Mixed tumors are included. Some Astrocytoma are included. It is not a pure literature when you look at all the studies that are done. There are high-grade tumors that are included in some of the studies. We still have a lot of unknowns. The optimal duration of therapy in the long-term consequences of some of the treatments. The radiation is known. But the really longer-term consequences of chemotherapy is not completely known. Now compared to 10 years ago, we know more about that.

>> And there are very few long-term consequences of chemotherapy.

>> We also don't know for sure. But we think that the genetic characteristics can define the diagnosis. But that is not completely proving it.

>> So why would we do radiation in a low-grade tumor? We already know that it improves the time to tumor progression. Several studies show it improve survival in patients with progressing or aggressive tumors. There is no systemic side effects. And it is a very specific to find treatment time. There are a lot of studies done. Most of them are just in any kind of low-grade tumor. Like I said earlier. Some of the studies show benefits and some do not. Some show benefits but not in FISH have had deep -- GTR. And not with patients with really indolent tumors. It is pretty controversial. Why not radiation? There is no clear evidence of improved survival. If you do it early after surgery versus delaying it. And there is something called, delayed radiation induced neurotoxicity. Or encephalopathy. Where you can have problems with memory and thinking processes and imbalance and dizziness. It doesn't happen right away. But it can happen a few years later. And it can get progressively worse. And it is a delayed effect of radiation. One of the biggest studies show that if you had an early radiation, with a low-grade tumor, versus no radiation early -- and only when the tumor progressed, it was the people with the radiation early, performed -- performed worse on the cognitive tests -- that the Karnofsky score, which is a functional level, is lower. That was not accounted for by how much of the tumor got removed or where it was her anything like that. This is what radiation encephalopathy does look like on a scan. All of this I am pointing to right now -- that is all scarring related to the radiation. This is a bad case. This is an old picture. But I wanted you to be able to see what it looks like. Chemotherapy risks are different. You can have suppression of your bone marrow called Milo suppression. That can be right at the time. And it can be chronic or delayed as well. There are other organ toxicities, not so much with [Indiscernible/Name] but with PCV for sure. Quality of life can be affected. You're getting treated over months and months. The toxicity of the PCV protocol is pretty significant. And very dose limiting. So the Temozolomide as much either just -- easier to tolerate. But we don't know how long the treatment.

>> I will skip over this. We already talked about interpreting the literature and why it is so difficult.

>> There were a lot of low-grade studies and years ago. One of mine included, where we gave PCV to low-grade tumors then we thought really high response rates. Then there were several more that occurred with Temozolomide. And we set a good response rate. So we know that they respond. This is a patient of mine that I took care of a few years ago. You can see this hazy white abnormality all around here. That is the tumor. All of -- part of it was removed. All of this stuff around here -- and you didn't see it. You could barely see it from scan to scan. This scan was taken in July of 2003. This was taken in January of 2005. Over the course of that period of time, that patient got -- I think 20 cycles of Temozolomide. You can really see the difference. You did not see it so much from scan to scan the. This is an even more impressive case. This is after 21 cycles of Temozolomide. So 21 months of it. A big tumor. This is the same person here. And this is the scan after that. So you can

see -- you can get really dramatic shrinkage. But it happens over a long period of time in a low-grade tumor. So they respond clinically. Radiographically, they respond. Symptoms can get better. That's what that means. Seizures can get better and weakness can get better. The response occurs slowly over multiple cycles. And both drug regimens have activity. The Temozolomide is less toxic. So it is a reasonable treatment. And a lot of time, especially if there is 1p/19q deletion, that allows us to defer or delay the radiation. So a lot of times, we use chemotherapy in low-grade tumors, particularly if there are deletions of 1p/19q.

>> I think we pretty much went over all of this. In the end, for the low-grade tumors, both are reasonable options. There are no controlled trials comparing these two treatments to each other. I think the histopathology matters. That it is truly low-grade. And I think the 1p/19q is really helpful. If the 1p/19q is intact, especially if it is a mixed tumor, that patient tumor will probably be more of an aggressive manner, more of a Astrocytoma. In that case, radiation might be a better choice.

>> For the high-grade tumors, the Grade three and a plastic Oligodendroglioma, this is what they look like. They can be large. This is what we call, [Indiscernible/Name] when it is pushing like that. Here is the enhancement on the MRI scan. You can see it does not do that everywhere. It is kind of patchy. These are actual pieces of the tumor from this patient. This was an area that was a little more lower Grade. Where it is dark. And this was where that enhancement was. You can see that it can have a really different looking tumor in different areas. This patient had 1p/19q deletion. Years ago, there were studies of patients getting PCV. And all of those patients had already had radiation. Back in the day when that was the only thing we had. And Dr. [Indiscernible/Name] and Dr. [Indiscernible/Name] in Europe. And Dr. [Indiscernible/Name] in Canada did the initial studies. They were all in patients who had previous relation therapy. This is a patient of mine that I put into one of those studies. This was a man whose tumor came back after radiation. This was after one cycle. That is the tumor. And that is the improvement, of the old FISH regimen. And then people started doing more creative things and doing it automatically after radiation. And trying to compare it. And it looked -- at least in the initial studies, that there was really no difference, if you added it to the radiation versus radiation alone. Subsequent studies have actually supported that. Then we started doing it, where we treated it -- treated patients when they were first diagnosed. And we held off on the radiation. We deferred it. We delayed it. Even though the tumors were high-grade. At that time, about the largest that he was one that I published with Dr. [Indiscernible/Name] and Dr. McDonald. And that was, 75% of the high-grade tumors responded. But 30% needed to have radiation earlier because they progressed or had problems with PCV. At that time, we did not know anything about 1p/19q status. We now know that these patients -- were probably the ones that did not have deletion. So this is a picture of a patient who actually responded in one of those studies. The problem is that the PCV is relatively toxic. So you can have a lot of liver toxicity and nausea and vomiting and weight loss and depression a bone marrow can be tough on certain people. We don't even know if we need [Indiscernible/Name] anymore. It can cause one -- numbness or tingling in your fingers and toes. It is a relatively toxic regimen. Temozolomide came along and that was easier to tolerate. It did not cause significant organ toxicity of any sort of the kidneys or the lungs are the heart. Very rare to affect the liver. And the effect on the bone marrow was pretty mild compared to FISH. And it did not add up. It was not cumulative. So you could keep going. Alternately, there were so many different ways we risk -- we were treating these people that we didn't know what to do. And they were pretty rare tumors, as we said. So a few of us did a really large international study where we went back over the records of over 1000 patients with a high-grade anaplastic Oligodendroglioma -- and ultimately -- I will go over the details. But what we learned was that, not surprisingly, patients with the deletions did better. But surprisingly, we found that people that had deletions, some of them are really small numbers. They did worse then we expected. And then we also showed that there were some patients, as we followed people for so many years -- this study

went back 22 years. There were patients that did not have deletions that did do great for decades. We realize from this large study -- which is the largest study ever published, that there are other factors. There are other things like -- -- the repair and John -- enzyme. Or a mutation called IDP. There was a trend that survival was better actually in patients you are treated with chemotherapy first with radiation deferred, must the tumor progressed. And that is the -- the PCV might be a little more robust or get a more durable response. And those are just the curves that show that. So we then did a survey. At that time, at least in this country, 42% of patients were being advised by the oncologist, to start out with chemotherapy alone. At that time, the drug was Temozolomide. Because the PCV was too toxic. And there were other studies here including the one we just went over that we published in the 1000 patients. And overall, based on those studies, up until this last -- maybe couple of years, chemotherapy alone was thought to be reasonable. And that was in selected patients. Usually does with 1p/19q deletion. New studies have helped us with something. But there was no study that was really designed to answer the question of whether it is completely okay or not. There were two large -- so then two -- the new data I have to give you today -- there were two really large studies that came out. They compared radiation a loan to radiation plus chemo. There was a study being done where it is radiation compared to chemo alone. And then compared to both. This is ongoing. And so this is one of the studies that combines -- it is radiation versus regulation plus PCV. The studies were just published last year. Overall, the survival of the entire group of patients was not improved by adding two radiation in either one of the studies. But that does not mean a lot in this age of molecular medicine because now we know about 1p/19q. Both progression free survival [Inaudible/Low Volume] and that by -- that might be because chemotherapy was the key progression free survival and [Inaudible/Low Volume] in the study done in the states. And we also learned from that that the IDP-1 mutation is also important. Really, the bottom line here is that no study has been completed, that compares chemotherapy alone to chemotherapy plus radiation. You would also need to look at the quality of life, not just the survival. Because of the radiation induced change. So we really still don't know, completely, in a big randomized study, whether or not you can safely do that in every patient. Starting with chemo and adding radiation. There is just that one study that is ongoing. And there is no similar prospective randomized study using Temozolomide. That one that I already pointed out is ongoing. So there is definitely the FISH -- patients that do better than most. And there are some factors that play a role. We will talk a couple minutes about new therapies. And I am running a little over my time. Most clinical trials that have been done in any kind of tumor are in high-grade Astrocytoma. So many of the drugs used may be useful in Oligodendroglioma as well. We are headed toward more targeted therapies, more specific therapies and specific routines or receptors. And something called, ANGIO-Genesis inhibitors. They inhibit blood vessel growth. Blood vessel growth is associated with tumor invasion and growth and aggressiveness. So targeted therapies are basically -- tumor cells -- they make receptors for different growth factors, like platelet derived growth factors. And epidermal growth factor. And VEGO. Targeted therapies into inhibit these growth factors -- factor receptors and their Tyrus scene KINASE based intracellular signaling pathways. Changes bind to cell surface receptors and either complete -- compete with or block the normal substrates from binding. In tumors dependent on such pathways for growth, the use of these agents can potentially result in tumor cell growth. The most common is the VEGF. Which is expect in high-grade glioma but not in normal brain. It stimulates blood vessel growth. There is a drug called, Bevacizumab, and it is an antibody. There are a lot of studies -- a couple of them, I was involved in, that show that this hopeful in high-grade -- it is helpful in high-grade Astrocytoma [Inaudible/Low Volume]. And we have used it with Oligodendroglioma. This is a patient of mine that had a high-grade anaplastic Oligodendroglioma that had already -- had already been treated with radiation. And the tumor came back. And this was the response. We do learn from these other trails, even if they are not specific to Oligodendroglioma and we know that they respond to this targeted therapy. With Bevacizumab or Avastin. Which is a

monoclonal antibody against VEGO. Clinically, where do we go? That is the knowledge we have up-to-date. Where we are going clinically is -- we do know now from those two big studies that just got published last year -- that radiation and PCV together is clearly better than radiation alone. But subsets, like patients with 1p/19q deletion, or patients with ICH mutation, there may be subsets like that, where differing or delaying the radiation until later, in order to avoid radiation related toxicity -- that may still be reasonable. Can we do the chemo first and delay the radiation? Phase 3 trials comparing radiation versus chemo in the [Inaudible/Low Volume] are still ongoing. Accrual is slow. There are not that many patients in that category. Temozolomide -- should it replace the PCV? We don't know that. It is a lot less toxic. But there is some trend that PCV might have a little bit of a better duration to response but it is a rougher regimen. Should we bring it back -- with earlier treatment? Or is the toxicity still something we should try to delay and put off? I mentioned earlier that we don't know if the [Inaudible/Low Volume] is that useful. Can you use these individually or in combination? And are there targeted therapies that are more specific to Oligodendroglioma and say, Astrocytoma? And in regards to the genetics, where are we going? And the laboratory, we are trying to find a specific tumor suppressor gene. Like what is located on the [Inaudible/Audio Cutting In and Out]? What Gene is it? What is on those chromosomes that makes somebody -- if you lose them, and your tumor does not have them, why does that make your tumor really, really sensitive to chemotherapy? Or is it just an association? Is it just like a coincidence that that happens? And it is really some other gene or other phenomenon that is their? Can we use the 1p/19q, to tell if you have a [Inaudible/Low Volume] five? And if you don't have that, does that mean that you don't have a oligos? We don't know that yet. We need to learn a lot more about the IDP-1 mutation that was late -- that was a -- that was recently found. And we need to see if there are other factors that we don't quite know about yet. I do know that -- the genotyping -- the 1p/19q is the standard diagnostic procedure with the Oligodendroglioma, that has been for several years. You should know what the 1p/19q status is. And it is pretty standard to test that nowadays.

>> I think I am wrapping up. I am about a minute or two over. I want to thank everybody who attended today, for their time in their attention. I want to thank the [Indiscernible/Name] for all of the work they do. And I want to thank my patients and my family. They are the greatest people that I know.

>> Thank you so much that the Paleologos. That was wonderful. We do have some time left for questions. So if you are open to taking some, I will post them.

>> Absolutely.

>> They have the 19Q deletion but not the 1P. Can you explain that?

>> I can actually. The deletion that is probably most dramatically associated with chemo sensitivity, is the 1P deletion. But patients that have 19Q deletion, that is better than having no deletions at all, in essence of sensitivity to chemotherapy. So if you got -- it is -- if the 1P is intact -- if you don't have the 1P deletion, but you have a 19Q deletion -- so, at least 50% of those patients will respond to chemotherapy.

>> Great.

>> Someone is asking about 5-ALA.

>> 5-ALA -- I think they might be mentioning -- it is a fluorescent compound that is used -- prior to respecting tumors. And it is supposed to attach to compounds within the tumor cells but not in the normal brain cells. And it is supposed to cause the tumor in the operating room to kind of fluoresce so it helps the neurosurgeon see the tumor better. That is in study right now. There have been a few

published reports. And it is being used in clinical trials. Still, it is not part of the standard, as of yet. But it is one way that people are trying to figure out how to get the most tumor out. And the edges of these tumors -- like I said before, especially the low-grade tumors, it is kind of really like thin and fluffy and microscopic. It is like a little routes from a tree. You can't really see the ends of them. And so if there was a way to let the tumor cell light up a little bit, that might help. And so that is what 5-ALA is for.

>> It sounds like some interesting things coming up. Can you have 1p/19q and TP53 together?

>> Usually, you don't. I guess there are times when there may be cases like that. But usually -- you will have a 1p/19q deleted patient.Then you will not have TP53 mutation too. But we are still doing a lot of this work. And most [Indiscernible/Audience Question or Comment] -- [Captioner Lost Audio/Trying to Reconnect] most patients do not have all of those molecular things tested. It depends on the institution you are at. And the level of sophistication of the laboratory there or if they send it out some place. You have to be a little bit careful though because we don't always understand -- the 1p/19q, we know a lot about. But we are still learning about it. We know a lot of stuff about the laboratory affect. And the statistics around TP53. But we don't really know how we should use those results in order to direct here.

>> Thanks. What is the significance of IDP-2 and why is a different than IDP-1?

>> We are still learning that too. IDP-1 and IDP-2 are different molecules. And if you have deletions -- patients that have low-grade tumors and patients that have oligos, are more likely to have IDP-1 and 2 mutations. Then patients that have great four Astrocytoma. The [Indiscernible/Name] patients which is now were talking about to. Mostly, they are associated with a longer survival time. And if it is found in a high-grade patient, a patient with a really aggressive tumor. This is better worked out in the Astrocytoma tumors than in the oligos. So I am really speaking more about those -- those tumors and the oligos specifically. If you see a patient with a great four Astrocytoma that has a oligos-1 mutation, that patient probably started out as a low-grade tumor as opposed to a great four Astrocytoma that popped up -- like it was a great four from the start. So it helps us to know the lineage. Like where the nature of the tumor is. We are still learning a lot about those mutations. So it is associated with a longer survival time. And it is seen more often in patients his tumor started out as low-grade tumors or who have low-grade tumors now.

>> Promising. The next one -- I apologize. I'm not sure how to pronounce it. [Indiscernible/Name].

>> Do you still uses?

>> Not as much as we did. The one slide I showed of the mapping of the anaplastic [Inaudible/Low Volume] five -- that patient has also gotten [Indiscernible/Name]. That is also called CPT-11. It is a drug being used with [Indiscernible/Name] a lot. It is still being used. I have not used it in a while. It tends to be pretty tough on people. It gives them a lot of diarrhea. The blood count, particularly the platelet count falls low. The one randomized study that we did -- it wasn't really statistically powered enough to say whether adding the CPT-11 helped.Or not. But certainly, when we did the study, that compared the Bevacizumab alone to the Bevacizumab plus the [Indiscernible/Name], the patients a couple, had more convocations with toxicity. It has fallen a bit out of favor. But it is still used on occasion. Especially if someone has failed other agents.

>> So there are still options out there.

>> Right.

>> What about RAD-001, to prevent growth in oligos?

>> That is a scientific name -- that is a companies name.

>> Okay. We will skip that one. And then the question that comes up every time I do a webinar. 'S the role that cannabis can play as treatment for any drug that is in relation to oligos obviously.

>> It's funny. I just actually looked at this issue because of a patient's family member who had found some things online, about can avoid whales in cell culture. -- cannabis oils in cell culture. There are some things online and in the literature, especially in Europe, were putting these oils into cell cultures in a petri dish -- have decreased their growth. I don't know what to say about that, in regards to translating it to human beings. There is no study that shows that cannabis, in any form, changes somebody's survival time or prevent the tumor from growing. Or keep that from growing, shrinks it or anything like that. There are some patients -- usually not very many, especially if they are on things like [Indiscernible/Name] that does not cause a lot of nausea and vomiting -- but there are some patients that have nausea and vomiting who don't respond to the usual drugs that -- there may be some symptoms -- but it is not really shown to change outcome, in regards to treating the tumor itself, in any sort of human being trial, any kind of clinical trial.

>> Okay. Again, lots of words that I am not familiar with. I apologize. Did we do this one? MYSOLIDE. Does that sound familiar?

>> I'm not sure if I'm hearing you right. It does not sound like -- there may be somebody doing a clinical trial with that or something.

>> [Inaudible/Low Volume].

>> For treating anaplastic [Inaudible/Low Volume] five.

>> There are a lot of clinical trials out there. I suspect that person is referring to -- a specific compound, where that is part of the name of the compound. But that one word on its own, I am not sure. There are a lot of clinical trials of new novel agents going on right now. Most of them are not specific to Oligodendroglioma. There are a few that are.

>> And that is actually a good place for me to chime in and tell people, if they are looking for a clinical trial, we do have trial connect specialists that they can call here -- and we can connect them to -- and do a clinical trial search for them. It is called, trial connect. And they can call 877-769-4833. A lot of these people are typing in specific manufacturers and drugs -- and proper names like you are saying. So I would encourage any listeners to do that.

>> I think -- one of the things about being asked about a specific experimental agent, is that -- it is like -- what about it? It is probably being tested. But we don't know the outcome of those tests until those tests are done. So it is hard to tell somebody whether that is a promising treatment or a non-promising treatment, until the studies are complete.

>> Sure.

>> What we are at the top of the hour. And one minute over. So I want to be able to wrap it up. And thank you Dr. Paleologos again. It was a wonderful information session as always. We thank you for being such a strong supporter of ABTA. We always appreciate when you present. We have more questions then we had time for. That always happens. We do look forward to you coming again in July for the patient and family conference. So we encourage you to register for that. Him and see Dr. Paleologos in person. You can register at the website at ABTA.org. I will pause for just a moment to into the webinar recording. And I would like to invite you all to continue to check back to the website. ABTA.org. Other brain tumor related series -- the next webinar is Tuesday, May 6, from 1:00 until 2:00 p.m. Treatment of cranial [Indiscernible/Name] an update on current trends and surgical,

medical and radiation treatment. Join Kevin [Indiscernible/Name], professor of the Department of neurosurgery and director of the neuro-oncology program at the University of Colorado Hospital. As he discusses the clinical presentation of cranial [Indiscernible/Name] -- the associated have theological -- pathological features and the [Indiscernible/Name] in management and finally, current trends in there piece. And then Thursday, May 22, we will present [Indiscernible/Name] and the relevance to brain tumors. And join will Parsons, indie, PhD, director of the pediatric center for personal cancer genomics and therapeutics, as he discusses genomics and the relevance to brain tumors. He looks for the biological difference in tumors. And how genomics is deriving personalized medicine. And defining gene sequencing and discussing the pros and cons of population genomic testing. This concludes the webinar. Thank you so much for joining us. And please be sure to complete the feedback survey. You will receive the following the session. You may now disconnect.

>> [Event Concluded].

>>