

Treatments that Excite Your Doctors

- Glenn J. Lesser, MD, FACP, Wake Forest Baptist comprehensive Cancer Center

Dr. Wefel: Okay, everyone. I think we want to try and stay on track here. If you wouldn't mind coming in and finding your seats again, we can continue with the program. I've been asked to provide a few housekeeping pieces for you all.

For those of you attempting to get on the Wi-Fi, the password for you is Fall19. That will give you access to the internet so you can be tweeting and Googling and watching the videos as well.

There's been a request for us as well to get to know each other more. So as we ask questions, if you could please start by introducing yourself and then ask your question, that would be very helpful for everyone.

And for the Livestreaming audience, thank you all for being with us. They would also like to see your shining faces. So when asking a question, if possible, to be able to stand up and introduce yourself with the microphone and then they can see you at home as well and then be a little bit more connected with this technological approach that we're using.

Okay, so, with all that in mind; welcome back now. And I am going to introduce you to our next speaker. A tremendous colleague in the field and a friend, a personal friend who I'm just delighted accepted the invitation and to make time in his really busy schedule to come and be here with all of us, particularly eager to do so as well. And that's Dr. Glenn Lesser who's

going to be telling us about treatments that excite your doctors. Okay. Again, we've given him a challenging title and one I know that he's going to handle nimbly.

Dr. Lesser is the inaugural [inaudible 00:04:09] client-called Miracle Professor and Associate Chief of a section of Hematology and Oncology in the Department of Internal Medicine at the Wake Forest School of Medicine. He is a co-program leader at the Neuro Oncology Research Program at the Wake Forest Baptist Comprehensive Cancer Center, the Director of Medical Neuro Oncology and the Wake Forest PI for the National Cancer Institute funded Adult Brain Tumor Consortium from 1996 until today. Dr. Lesser has recently joined the board at cancer.net which is a patient educational website as the Associate Editor of the Central Nervous System Tumors panel.

His clinical and research interests include the development of novel therapeutic agents to treat adult malignant brain tumors and symptom management issues experienced by patients with cancer. So he's clearly perfectly suited for this topic. Please join me in welcoming Dr. Lesser.

[Applause.]

Dr. Lesser: Well thank you very much, it's really an honor to be here today. My program leader is not very happy with me as we're having our program retreat back at home today, our annual retreat. But you know, here I am and wouldn't miss it for the world. You know, I had the privilege to listen to Jeff with the very kind introduction. I have the privilege of taking care of Louise Miracle for many years. So I do have a named professorship but it's actually from someone I took care of, which is really neat. She's a wonderful lady, but I must

say when I got it, I sat down and realized I'm now the Miracle Professor of Oncology, that sets a very high bar in clinic when people come to meet me. But I hope I'm up to the challenge.

Just some disclosures here. I want to give you an overview here; this is from the top of Everest. We're not going to be quite that high but just a wonderful shot and really, a little bit to talk about what we're going to talk about today.

You know, sort of, this is a very broad topic I could cover. We polled each of the physicians that are going to give a talk over the next few days; the things that excite them will be somewhat different. There'll be some commonalities but there'll be many differences. We could focus on really early things, we could focus on really late things, so I just kind of pulled a few things that today in clinic help me.

I get asked this question a lot, I'm sure we all do. And for the last 25 years that I've been doing this, the answer's really, you know, go up and down in terms of the enthusiasm of my response as to what we're excited for. As new things come the excitement level is extraordinary and then unfortunately, we have a long history of failed or negative clinical trials that sort of sap our enthusiasm and then we move on to the next thing.

I wouldn't say I'm at a high right now, nor am I at a low. I'm sort of day to day -- I'm kind of in the middle because so much is happening. And you're getting a bit of a feel for that today. I will tell you that an unfortunate secret, or not so secret, of the industry is that brain tumors and glioblastomas in particular are known as the place where good drugs go to die.

We have such a long history of lots of work and lots of effort and unfortunately, negative trials. As Tim just so eloquently presented, we're starting to approach how we look at drugs very

differently than we have over the last 30 years. Trying to stack the deck a little bit, to find things that, you know, in very early, very small and quick and small trials give us the excitement and enthusiasm to then spend the resources and effort and energy to really evaluate them fully. And you'll hear a lot more about that from other speakers today.

Because there's a real variety of people in the audience, I want to spend a few slides kind of getting us all on the same page. And forgive me if you're already there. Just going to talk about what we do today and why brain tumors are so hard to treat and then talk about, just really a few things that still excite me. And again, you have to be -- I'm a medical oncologist, neurooncologist -- you have to be an optimist to be in the oncology field and perhaps even more so in the brain tumor field.

And so I'm still quite excited about some things that haven't thus far panned out but may in the future. We'll talk a little bit about personalized medicine, targeted therapy, we'll talk a little bit about immunotherapy, treatments in some other fields, that type of thing. Really, from my interest and background, from the symptom management/quality of life approach, there are a number of things that are exciting and continue to excite me.

And I'll just mention one of those today which is some opportunities in the area of kind of chemo brain/(inaudible 00:08:56) brain, that is the neurocognitive toxicities that I know Jeff is an international expert on.

So again, just to bring us all into the same space. When we talk about brain tumors we can talk about lots and lots and lots of different brain tumors. But as you see from the slide, the majority, the big ones we talk about, are the malignant brain tumors are the ones we talk about,

which tend to be the gliomas. And there are advances being made in each of these small pieces of the pie, but for the purposes of time today -- and because glioblastoma and gliomas sort of are the biggest problem in our field -- we'll really focus on that. But there's great science happening in all of these different niches of brain tumors and you'll hear some of those over the course of two days.

When we talk about gliomas again, the elephant in the room is glioblastoma makes up half of all gliomas we diagnose. Certainly in adults, at least half, and again, you can see a variety of low-grade tumors and then other gliomas like ependymomas. Each of which have their own story, their own advances, their own science, their own clinical trials. And so we have to pick a few things to talk about today, we can't possibly talk about all of them.

Most of our effort is spent trying to deal with glioblastoma which is sort of the representative of the worst tumor we treat and the worst tumor that patients can get. Why is that? Well you see a variety of the histopathologic and biologic reason why. There are kind of two there in the top -- I guess your top right. They're very active; there's a lot of cell division or mitotic activity. These are aggressive, angry, growing tumors.

At the bottom we can see some of the hallmarks of the vascular sort of excitement of these tumors. They're growing new vessels; they're trying to spread and support themselves. And so these are characteristics we've known about for many, many, many years that unfortunately haven't changed but we're learning so much more. We'll touch on that in terms of some of the (inaudible 00:10:56) as Tim alluded to.

So how do we treat these? What's the standard therapy? What should be the standard therapy around the world for a patient who is in reasonable shape -- we call that a performance status -- sort of able to tolerate therapy. What we know is the best?

Fortunately, or unfortunately, this is still the backbone of what we do, we call it the stupor management or concurrent radiation and Temozolomide. First presented in the Neuro Journal in 2005 and it really remains the backbone -- not necessarily we're proud to say that remains the best we have, but it clearly is the best we have and should be at least the starting point in discussion with most patients with newly diagnosed glioblastoma. And we could talk about subtypes and controversies of the lot.

But essentially, as many of you know, it's six weeks of radiation, chemotherapy -- the radiation given Monday through Friday, the chemotherapy given for the duration. A month off, some rescanning, and then about six months -- some people treat with 12, the study really looked at six -- six months of the Temodar/Temozolomide given for five days each month. That is the backbone; that is still the best we know of for most patients.

So why are brain tumors so hard to treat? And when I put this slide in, I didn't know we'd be dealing with a terrific hurricane close to home. I live in North Carolina; sort of in state though, so we're not getting affected, but my thoughts are with my neighbors and friends who are along the South Carolina, North Carolina and Florida coast. Because despite not making landfall, Dorian is creating quite a few problems.

And I wish I could remember from which beach -- this is from Texas, from last year's Category Five hurricane. I was struck by this -- because in some ways, again, as a person who

spends a lot of time thinking about taking care of folks with brain tumors -- I was amazed that in 200 miles an hour winds this single house essentially was unscathed. And it speaks to the sort of the construction and the details and the energy that went into protecting that house. And then I thought a little bit and this really reminds me of what we do with brain tumors; right?

We operate on them; we radiate the crap out of the area to kill cells. You know, we kill normal brain cells -- that's what leads to some of our problems down the road. We annihilate the area and what happens? We still have these well protected cells of glioblastoma that survive that and that are allowed, at some point typically, to come back and grow. So maybe a stretch of the analogy but I thought I'd make it anyway.

So what's unique about brain tumors? So in earlier in part of my career and in other parts of my career and now I take care of patients with lots of different kinds of cancers -- and many of those cancers are undergoing a renaissance in terms of new treatments and new approaches that have just revolutionized some of the success we've had. Yet we've always had to explain why brain tumors may be a little different than lung cancer or breast cancer or colorectal cancer.

Yes, they're all cancers. And in fact, they're all what we call solid tumors, but there's some unique things about brain tumors and they're pretty fundamental and they haven't changed in 100 years. For most of us, the skull has a fixed volume; okay? There's not much room. The brain takes up most of that room. If you start putting other things like a growing tumor in that space, something's got to give. And what gives is the nerves and blood vessels and (inaudible 00:14:22) of the brain and gets squished. And whether it's invaded by the tumor or simply

pressed on, that creates a set of neurologic symptoms that are really different for brain tumors versus most other tumors; unless they spread to the brain. So that's one fundamental issue.

So that's one fundamental issue. We have a hard time measuring success. Because of the blood-brain barrier in particular, we can't depend on some of the things that we as oncologists historically depend on. WE get a scan; did the tumor shrink, did it grow? You know, that tells a story. That's true for lung cancer and breast cancer and colon cancer. It's not always true for brain cancer as I'll show you. Because our brain imaging studies -- our MRIs, our PET scans but particularly the MRIs -- are surrogates. They're not really showing us that tumor. They're showing us the area where the tumor is most bulky and where the blood vessels are leaky -- where the blood brain barrier is leaky. But they really underestimate where the actual tumor is and we always have to factor that in. Plus, those scans can be effected by lots of things we do; radiation, chemotherapy, but most importantly steroids. Glucocorticoids, typically dexamethasone.

And the other thing that's different in brain tumors from when a patient walks in my office -- they may be weak on the right side or paralyzed on the right side. If I got rid of every last tumor cell in the brain, they may still be paralyzed on the right side. Whereas if I have a lung cancer patient who walks in my office short of breath, if I take care of their lung cancer, they may actually breathe better and have better pulmonary functions and be able to do more. So again, a fundamental difference in the tumors we're talking about today.

As I alluded to these tumors are discreet, but they're not so discreet. We point to them on the screen and say there's your tumor. But then in effect we show you where that tumor is from a

great distance from that main site. And again, we'll talk about the blood-brain barrier in a slide of so because from a treatment standpoint, what the blood-brain barrier does is keeps many of our drugs out. And that's at least one of the fundamental reasons we have a harder time treating these tumors than others.

Theologically it makes sense. Our brain needs to be protected and we don't want to have everything we ingest and that goes into the blood stream have free access to the brain. That wouldn't work out so well if we were taking in the wrong things. So just a very, very quick example of something I've sort of been trying to describe for a long time. On the bottom on the left is the leaky blood vessel with the brain tumor up above it. Mr. Smith comes into my office he's got a tumor -- whoops. Can you go back one slide, I'm sorry. Thanks. You know, so this glioblastoma is here -- sort of the grayish area is the enhancing tumor. That central blue area is the necrotic area -- that doesn't change. But that hashed area is really that infiltrating area of that tumor that we can't see. What we see is that kind of off-grey area, which is the area of blood-brain disruption.

WE give steroids and without going through the mechanism -- although we know a lot about it now -- those blood vessels tighten up. So there's less protein, less fluid able to leak out and what happens? Patient comes back -- Mr. Smith comes back and with the steroids he feels better. All his symptoms are better and I get another and lo and behold, his tumor has shrunk dramatically.

Well in fact, his tumor hasn't changed. What has changed is the leakiness of the blood-brain barrier and as a result the imaging has changed, but his tumor is still represented by the

hashed area. That hasn't changed much. And it took about two or three decades for us to factor this into our treatment trials and how we think about it. Because you can imagine, if you can change how a person behaves or feels or functions, and you can change the imaging, that's what we use in other tumors to say we've had success. Whereas here, it's just a result of steroids.

And don't believe my cartoon, believe patients. This is a patient of mine from a few years ago, on the left is the -- on top is the contrasting evidence of a recurrent glioblastoma. On the bottom is what we call T2 flare; shows us the swelling around that tumor. He was quite symptomatic and in fact I wanted to put him on one of our clinical trials. It took a few weeks to get everything out of his system and get him ready and I put him on steroids because he was having symptoms and he came back feeling a lot better. And in fact, that's a scan from one month later. All we did was put him on some steroids.

We learned this lesson in the '70s and '80s, we forgot about it for a while and now we're really sensitized to the fact that in some patients we can see dramatic changes simply with the addition of steroids. And so it's an important thing for us to factor in with all the new therapies we think about.

Eric (inaudible 00:19:17) kindly provided this slide. Again, it illustrates a very important part of -- this is a rat brain with a tumor there. And you can see some blue if the lights were down. That's what we would point to if the rat and his family came into clinic and say, "There's your tumor." But when we actually do scans -- stains to look at proteins on the surface of the tumor cells, what do we see?

Well there's the bulk of the tumor, but these tumors infiltrate in three dimensions at great distances. And again, we knew that at the turn of the century. Harvey Cushing and the great neurosurgeons at Hopkins used to do hemispherectomies. They tried taking out half of the brain in people with malignant brain tumors. Not only did it decimate those patients but the tumors came back on the other side. These are mobile cells that can move through the brain and that's part of our problem. Not only do we have to attack the bulk of the tumor but we have to get these infiltrating cells and that's challenging.

And finally, here's what the blood-brain barrier is. In most of our body our blood vessels are leaky; things come in and things go out and that's how we get rid of garbage and debris in our cells. Well again, in our brain we don't want that. So the brain is equipped with these very tight junctions on the endothelial or lining cells of a blood vessel. Only very controlled things get in and only very controlled things can get out under normal circumstances. So under normal circumstances many of our normal chemotherapies -- nu-uh, you're not getting in. Tumors change that dynamic and of course this is where the swelling and the protein and some of the bad symptoms come in. Also presents some opportunities about getting drugs into the tumors that we can't get into normal brain [tissue].

Here's an example; this happens to be in brain-met model in mice but on the top are [sic]¹ what happens when you give chemotherapy to a model -- an animal model -- with some brain metastasis -- a spread of cancer to the brain from a systemic primary. And you give a drug that

¹ [sic] is used to denote the typed material was transcribed exactly as spoken.

doesn't pass the blood-brain barrier very well like Paclitaxel, you see a little bit gets into the area of the brain mass but for the most part the brain is devoid of active drug.

Whereas down below a drug called Vorinostat that was evaluated in many different tumors, including brain tumors. You can see that's a drug that passes through the blood-brain barrier pretty well. And what happens? You can actually bathe the brain in modest to high amounts of the drug.

That's the interplay between understanding mechanism and understanding targets and then having to have drugs that can actually reach those targets in the brain. Which is different than systemic tumors.

All right, so that's sort of a background in some of the challenges in treating brain tumors. What are some of the things that excite me?

Well I think throughout oncology -- precision oncology, personalized therapy, targeted therapy, lots of names for really trying to treat tumors not with a cannon but really more with a rifle. Okay, a more discreet and targeted approach to tumors. Understanding what's in that tumor that may make it sensitive, as opposed to our traditional chemotherapy drugs which may target dividing cells like those in our gut, those in our bone marrow and those in the tumor.

That's what our cells do every millisecond of every day, okay? It's an extraordinarily complex dance that allows us to be who we are. In fact, it's an amazing, amazing creation. You know, the human body is extraordinary. And each of those areas represents a cellular process that's important and may be sort of screwed up in cancer, maybe partly from treatment -- it's an incredibly complex process that we have to try to understand and target.

We've identified over many years particular signaling areas that might be very important in cancers and I think in the black, sort of on the bottom, you can see there's apoptosis or causing cells to die, there's DNA transcription, there's angiogenesis with blood vessel formation, there's cell cycle progression; getting cells to divide. Invasion, etcetera. Really fundamental processes that we try to target in cancer. And it all looks very easy here because we understand a lot about it and we know the targets. But what happens?

Well what happens when you're in London and they're doing service on one of the lines? Well you just figure out a way around it, right? You go to Piccadilly Square and get on a different one. And that's what happens in our tumors. All those pathways are interrelated so blocks in one area lead to people -- in this case tumor cells -- figuring out ways to get around it. And so we need multiple blocks in multiple areas. So the order of magnitude of complexity really just goes up. It's not simply enough in most tumors to block one way.

When it is, we have tremendous success and oncology is not littered with tremendous success. In particular, tumors that have one line going to them. If you block that one line, you stop them. Lung cancer is probably the perfect example. I think Dr. Brastianos will I'm sure talk more about this in her discussion Brain Metastases. When I started seeing lung cancer patients 20 years ago, the prognosis of lung cancer was dismal. Quite similar to glioblastoma. We had broad chemotherapies that worked, the tumors always came back and the people died from those tumors.

Then over about a ten-year span it has become an extraordinarily treatable tumor. Why? Because of this; we've identified molecular pathways that are drivers. That are the main reason

those tumors exist and grow and survive. Yes, there are a lot of other abnormalities but that's the one that does it. Okay? And if we can block those and for each of those, we found out we can block them out with drugs, we can have tremendous success. This is the model that we're looking for. So ten years ago, 15 years ago, if I were to show this slide, I would show a slide of a drug called Gleevec for a disease called CML. Prior to that everybody died. Bone marrow transplant, Interferon, toxic treatments, everyone died from it, effected young people. We developed a targeted therapy that got that driver mutation; the mutation that caused that cancer. And now everybody survives and maybe even cured and are on those drugs for years if not decades.

And now the question is; well how do we make it easier for people to survive for decades? How long do they need to take the drug? What are the -- how can we minimize the side effects? It's no longer how can we have people last more than a year or two? Ten years, 15 years later, we now have molecular underpinnings of many other cancers. And I think lung cancer is sort of the example that we try to immolate now; where we can take small percentages of the tumors amongst the whole cohort of patients with lung cancer and really target them.

This is what we try to do with many of our tumors, including brain tumors. I have no financial relationship with foundational medicine; our instution has a particular relationship with them and we send our samples there. But there are other companies around the country that do this. We send our tissue samples off and about 300-400 genes are analyzed and those are genes that are commonly changed or mutated or affected in many cancers.

We get a report back like this that says in my patient's tumor these are the changes that were seen. And on that list of genetic changes might be something I can target with a treatment we might use for brain tumors or might use for lung cancer or might use for breast cancer. So this is something that remains quite exciting. It's relatively new that we can now do this in an affordable, quick fashion and use these results to impact the treatments we give to patients. The report has some nice information that helps us understand some of these rare changes that we may not be familiar with; but again, personalized medicine, genetic analysis and Priscilla's going to talk a lot more about that.

This is one example of a patient that we treated on a clinical trial. Actually Dr. Brastianos' clinical trial, who had a particular change in one of their genes. The B-raft gene. Now this is a brain tumor but it's an unusual brain tumor; called a papillary cranial fringedoma. We treated them with targeted therapy that works against that B-raft mutation and you can see from the top to the bottom, within two months, we had a dramatic shrinkage of that tumor. Simply by giving drugs that targeted that specific genetic change. That's not something we're used to in taking care of brain tumor patients, but hopefully represents the future.

I'm going to try and race through a couple other things here. Tumor treating fields; obviously Novacure is out there. Some of you have the device on so many of you are familiar with it. Really came within the last seven or eight years into the clinic; an ability to give low dose electric fields in an alternating fashion by these electrode arrays on the head. The arrays are kind of carefully crafted to try and target the tumors. You see the device has become smaller and lighter and basically can be worn 24 hours a day, 7 days a week if you so choose.

It was interesting, I have Yamen Nascort territory in North Carolina and they actually had a report that said how much they'd used the device of the possible hours in the previous month. And this patient was wearing it like 96% of the time. So 96% of every minute of that month that device was applied and on and their battery went low in clinic and it was like a pit stop. The wife threw the battery to patient -- it was like 15 seconds they had changed the battery and were zooming off to the next -- it was amazing. But really can be relatively easy to do, although not without its effects on your day to day. One of the things that's most interesting is the toxicity is very minimum [sic]. We see some skin changes; sometimes some severe skin changes in patients but it doesn't cause nausea and vomiting, it doesn't cause low blood counts and some other things. So it certainly represents a new way to treat tumors potentially. Electrical fields, electrical therapy, but could potentially be combined with other things. And there are believers and nonbelievers but we can get into that in the questions.

This was the study that really allowed us to use this and have it paid for. The most recent study where standard therapy, essentially with or without the device starting after irradiation. And I didn't put the survival curves in there; it was about five months difference for the folks who used the device. Sort of a stunning number for brain tumors. The trial wasn't perfect; we can talk about that more. What was also interesting if you look out now, five years from the start of the trial the survival in the arms is quite different. It's well over a doubling and that means that some patients are getting sustained and long-term benefit. And we just can't ignore that, we have to figure it out. Figure out how it fits into all the things we do, but that's a number that I think we can ignore.

More recently some other data has come out here that did something interesting. It said let's look at the people who use the device 90% or more of the day; the really heavy users. What we might call in the drug world a dosed response. They used a lot of drug or a dose escalation. In fact, if you look at their survival -- all caveats of looking at subgroups of whatever -- but a huge increase in their five-year survival. Suggesting that maybe like drugs, the more we use of this device the better it is. Unproven, needs to be further looked at, but somewhat exciting, I think.

In all sorts of subgroups; men, women, methylated tumors, unmethylated tumors seem to benefit. So it just works differently than the treatments that we've had up to now.

Again, I'm going to race through here. LIT; Laser Interstitial Therapy. Surgery without surgery; sort of in some patients. This is a technology that allows a laser to be placed in a tumor that can only be biopsied and certain tumors in certain positions of certain sizes are applicable for this approach. The way it works is it's stereo tactically applied with a head frame and the surgeon precisely targets that laser on a long tube or probe, puts it into the tumor and then that laser can be fired and you can sculpt an area that you want to treat with heat.

What that laser does is heats up the surrounding tissue. It's very labor intensive and technologically advanced because it has to be done in an MRI so you can use that MRI to look at that heat signature. What's interesting is that in both brain metastases and primary tumors as well as in radiation necrosis; the death of cells after something like radio surgery, there are some very interesting albeit very early results with this therapy.

(Inaudible 00:32:58) was one of the early adopters of this and we've seen some really neat things in areas of the tumors and areas of the brain we know we couldn't operate on. Here's an example; just some pictures of somebody with radiation necrosis which is sort of that dead tissue, that inflammatory tissue after radiosurgery using LIT as a really effective way to treat those.

I realize I'm moving quickly, so we'll take maybe one minute to do immunotherapy. So the immune system fights off bacteria, infections, all those things quite well; does a lousy job at fighting cancer. Many cells participate; we could talk for hours about this, very exciting. Why does it do a lousy job of fighting cancer? Well we've learned through lots of incredible research that there are extraordinary checks and balances on the immune systems. An immune system untethered causes autoimmune disease; lupus, rheumatoid arthritis, (inaudible 00:33:59), things that we see when the immune system can't discriminate self from non-self.

There's lots of ways that the autoimmune system tries to balance itself and say, "I don't want to attack normal, I only want to attack bacteria and viruses, etcetera." One of the main and early checkpoints that was identified was this PD1, PDL1 access which basically when T-cells -- the autoimmune system try to go and fight something -- a tumor at this point -- that access shuts it off and says "Nah, this is normal. Don't fight it."

We now have blockers of that that say "You know what, don't listen to the tumor cell. That's bad, that's not self. We want you to attack it." And again, we can talk for hours. As it turns out there's lots of subsystems and checkpoints that either turn on or turn off that immune response and that recognition of (inaudible 00:34:52). And I would say our early forays into this

area have not been particularly successful with brain tumors, whereas they have been very successful in a variety of other tumors. But I think as we get smarter and think of combinations and have a better understanding -- and the timing of these approaches we may in fact -- and I'm optimistic that this will be a part of our therapy moving forward.

There have been lots of examples of targeting the immune system and I had some pictures. We won't go through it, but lots of that scenes [sic]. We can either take out the tumors, take out the (inaudible 00:35:27) cells, put them together and then give them back. Try to fight the tumor that way.

We can do an immunization under the skin with some of the proteins that are common in glioblastoma and say "Here, develop an immune response and fight those." Both of those have been done, most of the approaches have unfortunately been negative with most of those studies. We can give viruses that infect cells and cause them to die and then the immune system can do a better job of recognizing a tissue it needs to attack. This is in the early stages of development in gliomas.

And certainly you may have heard, it's all over the news, our T-cells, we can actually take those out and say "Here, we want you to attack this specific protein." And we put those proteins in your machinery and then we give those cells back to patients. For those of us in the field, very exciting a few years ago to see this publication from the Seed of Hope researchers where a patient with advanced glioblastoma was given these RT-cells to a specific antigen on the tumors and in fact had a response.

The RT-cells were given both intratumorally and into the spinal fluid and this was kind of a proof of principle that at least in some cases this approach might work. Much more to come on this.

I'm going to spend one minute on something that's near and dear to me. I actually take lots of pictures of my patients when they come in with t-shirts and tattoos, because they are usually pretty interesting and illustrative. I have lots of folks who talk about the effects. Many of them are X-rated and I can't show those slides.

[Laughter.]

Because it's really bothersome. But certainly those long term neuropositive effects are a huge part of what we need to address with any of our therapies. The ones we have and the ones that are coming. There are -- there's a great deal of science now understanding the mechanism -- at least part of the mechanism of some of the reasons why people get effected by our treatments. Either temporarily or permanently, and a lot of agents have been tried. I'm proud to say at Wake Forest we have a particular interest -- we've been involved with many clinical trials in this particular area and continue to be.

Some of it is home grown science from some more laboratory partners and we hope -- along with folks around the country doing Lamantine and Hippocampal sparing radiation -- all of these approaches will make our therapies less toxic to patients. So that we can deliver it and kill tumor cells but not harm patients in the long term.

I'm going to skip that, it's a disclaimer. This is a picture I got from one of my patients -- I shamelessly steal from anyone that I can. One of my patients came in, he's a brain tumor

survivor who's about ten years out, eight years out. He and his wife just had a baby. Normally when I hear that they've been trying and couldn't and I was just so excited for them. And it turns out they were actually trying not to have a baby for eight to ten years and were successful but then decided it was time and he's stable.

They showed me this baby and I said that's incredibly cute and the baby's not bad looking either. It turns out the Golden Retriever protects their eight-week-old but steals the little bootie socks from under the blanket. But a whole 'nother example of symptom management; young people wanting to have families after our treatment. Can they? What can we do to protect that, etcetera. But was a really great story for this patient.

So I've used way more time than I wanted to, we do have some time for questions. But again, thank you for letting me take up some of your time.

[Applause.]

We've got about five or six minutes for questions, I guess the mikes are coming around.

Q: My name is Allen Dale and a question about Foundation One testing. Could that be a better way of treating patients instead of standard of care? The reason I say that is patients that are methylated negated and methylated positive shows they do better with Temodar. Would doing the gene testing give them better outcomes than the standard of care?

A: See you just shot all six minutes, that's a great topic and one we could talk a lot about. I will say it's a global statement that a molecular understanding of tumors will be essential moving forward. Whether it's through a foundation panel, a genomic panel, whether it's a

metabolic panel, whether it's sort of things we haven't found out; discovered yet. But understanding what makes that particular tumor grow is going to be important.

As Tim showed you with the IDH-1 story, we've got to be splitters and not lumpers because all glioblastomas are not the same. All low-grade tumors are not the same. And it's up to us to parcel out which. Right now, I think the newest kid on the block is the molecular markers. I think everything's more complicated than it appears. So having a panel like that is helpful in certain cases where there are changes that are known to be really important and targetable.

Now again, the elephant in the room is does the drug you're going to target it with get into the brain. The foundation panel doesn't tell you that. We make an assumption. In fact -- I hope there are no insurance people here at the conference -- I will freely tell insurance companies that we need to pay for this test because it tells us if this drug is going to work. I don't tell them that I'm worried that the drug won't get in very well or that its effects we see in other tumors aren't necessarily seen in brain tumors. Because I want that therapy and I want that therapy paid for so we have a shot at a patient.

So I think the answer is ultimately yes. Right now, I think it is very important to again, state what I said at the beginning. The standard of care for most patients involves radiation and temozolomide. It's not a great standard of care but I think to deviate from that you have to have some sound reasons. Could be part of a clinical trial, it could be part of the molecular makeup of your particular tumor or the tumor that's under analysis. There may be other reasons that the doctor and patient get together and decide. But that's what we know so far, we don't have proof

of many of these other novel approaches yet. Doesn't mean they are wrong; you just have to go in with eyes wide open. That may not be better or it may be better; we just don't know yet. I hope I answered your question.

We've got a couple of folks here.

Q: Hi, I was just wondering. Hi, over here. What advice would you give to patients as far as -- once they've gone through the standard of care and what those next steps are for treatment and figuring out what be the best approach? Obviously, figuring out the genetic makeup is part of it, particularly if you're not located next to Wake Forest or MDA Center, UCSF or one of the other major cancer centers. What would you recommend be their next step for treatment?

A: Great question. I think it's always a great thing to know the biases of the people you're asking questions of. You've seen my bias; you know where I practice and sort of what I do day in and day out. So with that as a background, I think it's essential -- perhaps more essential in this disease, although it's getting [sic] true in most cancers. You need to have a relationship with a treating physician. Whether it's a second opinion or a phone consult or in person or they happen to be in your town.

And it doesn't have to be in an academic center. There are incredible physicians and private practices all over the country who have expertise in various areas including brain tumors. But you need somebody who doesn't doubt. You know, somebody who sees one brain tumor patient a year or two brain tumor patients a year. You need someone who's comfortable with the nuances and the controversies and the nuances and such. Doesn't mean if you don't find that

you're necessarily going to do better or worse, because most oncologists are smart and can read what's standard.

But I do think to get people through -- again, a NASCAR analogy, -- I want someone who knows how to change a tire in the pit. I don't want somebody who's reading the book while they're changing the tire. I do think you want some expertise. And now ABTA online and there are lots of ways to get at that.

I will flat out say the reason that I do what I do and the reason that I've done it for 25 years and I daresay most of the folks here will say why they do what they do, is because we want to find better treatments for these tumors. The way we will find better treatments is through clinical trials. One, two, three, four. So the right answer is clinical trial, clinical trial, clinical trial. It is the only way we will make advances from where we are now.

We need well done trials that can carefully control for the things that can make something look good or not look good. The internet is a great source of resources and it's also the worst source because I can say anything I want. What we need are well done trials that prove or disprove whether something works.

So I think expertise, the availability of clinical trials at least to consider and then an open dialogue with the treating professional. There are some patients where more treatment does not make sense. There are other treatment [sic] where ten lines of treatment makes sense. And that has to be a discussion -- that's a flexing that changes from week to week, year to year. And you have to have comfort in that relationship to have challenging and difficult discussions with your

health care team and feel like you're being taken care of. Whether or not you're getting treatment.

I send patients to hospice more often than I'd like, but I still see them. There's a continuum of relationship and much of it involves treatment and much of it may not. But I think having somebody who's there with the team, I think that's the other thing. Right now there are 73 different treatments you could try and I can't tell you one's better than the other because they're unproven.

But I think that's what you need; access to knowledge, clinical trials if appropriate and a relationship with the healthcare team that's a healthy one, that's an open and honest one. I think we're out of time. I will be here for two days I think and during lunch for those of you who may still have questions, because I do still see hands. Thank you very much.

[Applause.]