Latest in Brain Tumor Treatments and Trials

Brain tumors can be among the most challenging cancers to treat. The blood-brain barrier, a natural defense mechanism that shields the brain from harm can also prevent cancer treatments from reaching tumors. However, immunotherapy, precision medicine, and the other new approaches to treatments have been able to get through these barriers and effectively reach tumors. We are discussing the latest in brain tumor research and treatment with neuro-oncologist Dr. Nancy Bush from UCSF Helen Diller Family Comprehensive Cancer Center.

Full Transcript:

Priya Menon: Good morning everyone and welcome to CureTalks. I'm Priya Menon, your host. Today on CureTalks, we are discussing the latest treatments and trials in brain tumor with Dr. Nancy Bush from UCSF Helen Diller Family Comprehensive Cancer Center. Talking to Dr. Bush on the patient panel, are patient advocates Adam Hayden and Jeremy Pivor. To get the discussion started, we have with us Dr. Nancy Bush, assistant professor, neuro oncologist who has extensive experience in treating adult brain tumors, clinical research and teaching at the UCSF Helen Diller family comprehensive cancer center. Dr. Bush, it's a pleasure to have you with us.

Dr Nancy Bush: Thank you so much Priya. I'm happy to be here today.

Priya: Dr Bush, my first question, we know that brain tumors have been some of the most challenging cancers to treat. So let's start with why this is so and then go on to some of the new treatment strategies that you find promising.

Dr Nancy Bush: Brain tumors are very challenging to treat for many reasons. Today, we're mainly discussing primary brain tumors or brain tumors that originate in the brain. They do not come from other organs like the breast or the lung and move to the brain. Those are called metastatic tumors. Primary brain tumors are diffuse and infiltrative. That means they're intermixed with the normal brain cells. And because of this, when a surgeon is able to move everything that we can see on MRI scan, even then there are microscopic cells that are left behind. Because of this, we can't really cure brain tumors. Our goal is really to put the remaining cells into hibernation, typically with a combination of radiation and chemotherapy for higher grade tumors. Another unique aspect of brain tumors is that the brain itself is in a very protective environment because of the blood brain barrier. We actually have excellent chemotherapies that are able to cure many other types of cancers. But the truth is those chemotherapies do not actually enter the brain so they're ineffective against brain tumors.

So again, right now, the standard of care is typically for higher grade tumors, surgery followed by radiation and chemotherapy with a medication called Temozolomide. However, I would like to say there are several exciting avenues that we are pursuing for treatment of primary brain tumors. Like I just mentioned one of the major hurdles is that the blood brain barrier keeps many of our medications out of the brain. So, one strategy to overcome the blood brain barrier by directly injecting drugs into the brain. One very promising technique is called convection enhanced delivery, or we call it CED. This uses convection to basically disperse drug over a tumor. So a patient will undergo a surgery where they place one to three or four catheters in the brain, and then during surgery use convection to move the drug over the entire tumor. And this can actually be watched in real time with MRI scans in the operating room to make sure that the drug is actually covering the tumor correctly.

So this is one very exciting way that we're trying to overcome the blood brain barrier and get good chemotherapies into the brain that otherwise would not be able to reach the tumors. Another strategy that

people have been pursuing is to try to make our current treatments better. Many high grade tumors are treated with Temozolomide, that is a type of chemotherapy that's effective by breaking DNA. However, tumor cells have the ability to repair the DNA damage with other DNA repair machinery. So basically overcoming the damage that our chemotherapy makes. One strategy to overcome this Temodar/Temozolomide resistance is to use that in conjunction with medications that suppress the DNA repair response. These are known as PARP inhibitors. So right now, there are several clinical trials that are combining Temozolomide with PARP inhibitors for both treatment of newly diagnosed and recurrent brain tumors.

A third strategy that we'll just touch on now, but I think I'll go into further later, is precision medicine. We are learning more and more about the genetic makeup of brain tumors. And at this point, one strategy is to look at each person's tumor individually and come up with individualized treatment recommendations based on the genetics of their tumor. And then finally, an exciting strategy is immunotherapy. In brain tumors immunotherapy comes in several different varieties. The first variety is the type of immunotherapy that takes the brakes off your own immune system to fight the tumor. These are called PD-1 or PD-L1 inhibitors, names like Pembrolizumab or Nivolumab and others. And these medications have had excellent results in patients with other forms of tumors, metastatic tumors that have come from other parts of the body and gone to the brain. They are still being studied quite intently in primary brain tumors.

Right now, many of those trials for the PD-1 one and PD-L1 inhibitors have been negative. But we're now looking to see if there are certain patient populations or combinations of treatment that would be more effective, such as using them before surgery using them right after radiation in patients with hyper permutation or again in combination therapy.

Another form of immunotherapy that's very exciting in the brain tumor world is CAR-T therapy. Now, this is when we engineer a patient's own T-cells to recognize the tumor. A patient would have a leukapheresis, which means removal of some of their blood. And then the T-cells are filtered out, and then genetically re-engineered to recognize tumor cells and then given back to the patient. There are several ongoing clinical trials using CAR-T cells in brain tumors. And then finally, the other category is viruses and vaccines. So this would be infusion of things like the engineered polio virus to create an immune response and to kill adenovirus, the cold virus that can actually express cytokines to cause inflammation and kill the cell or vaccines against patients tumors, both in the low and high grade form.

Priya: Thank you, Dr. Bush. I think that was quite a good summary because my next question was on immunotherapy. So what about brain tumors that are benign like the meningiomas? Do you expect immunotherapy to be effective for these types of tumors as well?

Dr Nancy Bush: Yes, I actually do believe that immunotherapy may be beneficial for other types of tumors especially meningioma. There are ongoing trials looking at these PD-1 inhibitors and recurrent meningioma and here at UCSF, we're also developing a clinical trial combining Pembrolizumab with radiation for meningioma. We feel that this is a very promising strategy, because higher grade meningioma have more PD-L1 and PD-1 expression, multiple immune cells have been observed in meningioma and meningioma themselves are actually located near the sinuses or where the lymphatic drainage is happening. So we think that combining the therapy with radiation may be very beneficial, because radiation itself increases immune activation which can increase tumor cell killing and then it also can release to tumor antigens when it's killing the cells, and then this could make immunotherapy more beneficial both for local control and distant control. So I do feel like checkpoint inhibitors are an exciting strategy for other kinds of tumors, especially meningioma and may be important for combining with radiation therapy.

Priya: Yes. Dr. Bush, you also mentioned surgery as a part of standard care that is offered currently. And I want to take an audience question here rather two of them because we're on the topic of treatment. We have an audience question asking does surgery continue to be the most important component of care?

Dr Nancy Bush: I don't know if I would say it's the most important component of care but it is a very

important component of care. We know that the extent of resection or the more a tumor can be removed by surgery, usually the better prognosis, but I do feel like patients who are unable to undergo a surgery because of the location or the size of the tumor can have excellent responses with the combination of radiation and chemotherapy. So I would say it is very important but I'm not sure if it's the most important.

Priya: And we have Brian writing in from Toronto. He says I was just diagnosed with a grade three anaplastic glioma that is inoperable. I have just started radiation and chemotherapy today. Given that the tumor is not resectable due to its location in the motor cortex, I'm looking to all other medical alternative therapies. Could you speak to the possible benefit of DCA tamoxifen, Verapamil, Metformin, Accutane in addition to standard of care therapies?

Dr Nancy Bush: Sure, Brian first I'm so sorry that you're going through this. I think that the treatment with radiation chemotherapy is absolutely appropriate treatment. I'm glad that you started. For these other off label medications, they've been tried many times and in combination and for the most part we really haven't seen a lot of efficacy with that cocktail that you're talking about. And all of them do tend to have side effects and can cause lab abnormalities like problems with your liver and kidneys, making it more difficult for us to give the standard chemotherapies that we do have evidence works. So for the most part, we don't necessarily recommend that particular cocktail. I think the addition of things like Optune, after your radiation, which we may talk about a little bit later, would potentially be very helpful. And then kind of alternative medications that are not FDA approved. There is small evidence coming out of Europe, mainly through Spain, looking at the combination of CBD THC, which is medical marijuana, and its impact on higher grade tumors showing that slows growth and has better prognosis.

So I realized that you're not in California and I am in California, but medical marijuana is legal here and many of our patients will elect to try that in addition to the combination therapy and chemotherapy.

Priya: Thank you, Dr. Bush. Moving on, one of the main advances in all cancers, including brain cancer, as you mentioned, is the understanding of the molecular changes that drive these tumors. And with the National Cancer Institute's project, like the Cancer Genome Atlas, we have been able to characterize molecular changes in both high grade and low grade gliomas. So we understand the molecular drivers of these gliomas. And because of this, we can develop drugs that can target these drivers. Can you talk a little bit about these advances?

Dr Nancy Bush: Absolutely. The Cancer Genome Atlas has really changed the way we think about brain tumors. So prior to 2016 brain tumors were just defined based on their phenotype or how they looked under the microscope. But now that we have more information about their genetics, in 2016, the World Health Organization redefined how we classify brain tumors using their molecular markers. So for lower grade tumors, these are defined by IDH mutations, then tumors with a 1p/19q co-deletion are defined as an oligodendroglioma and oligodendrogliomas can be grade 2 or low grade, or grade three and when they're grade three, they're called anaplastic oligodendrogliomas. In the past, these tumors could become grade fours, but this changed in 2016 when we were, they are defined now by this 1p/19q co-deletion.

Astrocytomas are the other pathway. They're defined by an ATRX mutation. Astrocytomas can be grade two or low grade. When they're grade three, they're called anaplastic astrocytoma. And when they are in grade four, they're called glioblastomas. When these tumors have an IDH mutation, even as a grade four, it means that they started as a low grade tumor and over time became a glioblastoma. So these are called secondary glioblastomas or IDH-mutated glioblastomas and tend to have an overall better prognosis in patients with a primary glioblastoma, which is an IDHwild type glioblatoma. These tumors start as high grades, they do not develop from low grades into high grades. So through next generation sequencing of brain tumors, we're learning more and more about the drivers of tumor genesis. Common mutations that we see in higher grade tumors include amplification of the EGFR receptor or the PDGF receptor, activation of the PI 3-kinase pathway, which then activates the AKT pathway, or Ras activation, which activates the MAP kinase pathway.

All of those are important for keeping the cell alive and increasing cell division. And then we also see

mutations in this gene called CDKN2A/B, those are typically deletions, and they're important for cell cycle controls. So when you see deletions in CDKN2A/B, we know that the cells are able to rapidly divide more. So one future strategy for brain tumor patients is to develop precision medicine. So when a patient is able to have a surgery, we can do next generation sequencing of the tumor tissue and look at all the mutations that person has, then we can take rational choices of medications to treat that patient. So we have a trial at UCSF, called precision medicine, where we use a molecular tumor board to discuss each patient's mutation and then create an individualized treatment strategy for that patient.

So an example would be if a patient has been off Temodar for quite some time, they come back in and they have a recurrence, they have an EGFR amplification, as well as the CDKN2A/B deletion, we may elect to treat them with a combination therapy of Temodar plus a medication called Afatinib which can target EGFR receptor, as well as something called (nonaudible) which could target the CDKN deletion. So kind of using a multi disciplinary approach to fight tumors through precision medicine.

Priya: Great. As Dr. Bush was mentioning every person's tumor is different and to every person, like every person is different. So while we are on the topic of clinical trials, and since you're actively involved in clinical research with extensive training and trial development, implementation analysis, Dr. Bush, how do folks like patients find out about clinical trials? Do you talk to them about this? And when do you recommend a patient for a trial, now it does this come down as initial treatment or is this discussed much later down the road?

Dr Nancy Bush: I am fortunate to work at a large Academic Center, and I believe in clinical trials that I want to be involved in. So we have many clinical trials that are ongoing at any time. And so personally, we have clinical trials at UCSF for both newly diagnosed and recurrent patients – both lower grade patients and higher grade patients. So at all stages of treatment, I will discuss clinical trials with the patient if it's appropriate, and I have something available. If we don't have something available at UCSF, I do encourage patients to seek other opinions from large academic centers. Because each academic center, we may have several of the big trials in common but we'll also have our own individual trial. So it makes sense to kind of see what else is out there. The best resource is truly clinicaltrials.gov and this is the website that will list all of the clinical trials that are ongoing within the United States. And you can search using disease type or location to help you figure out which clinical trials might be an area near you.

But honestly, I would encourage every patient when they're speaking with their oncologist to ask if there are any clinical trials available, or if they could have a referral to an academic center to see if there were any clinical trials available to them.

Priya: Thank you, Dr. Bush. I'm going to hand over to Adam to start with the panel questions now. Adam Hayden is a philosopher, writer, advocate and organizer for the brain tumor community. Diagnosed with brain cancer in 2016. Adam has published on issues germane to medical education, cancer survivorship and the philosophy of illness in both popular and Academic press. His personal blog Glioblastology is a popular peer to peer resource and is in syndication with the Cancer Health magazine. Over to you, Adam.

Adam Hayden: Great, thank you so much Priya and thank you so much for your time, Dr. Bush. It's always funny when I hear that bio read, because around here, I'm just sort of I answer to my kids. So it's always funny to hear the credentials that I try to lay out before myself. Dr. Bush, thanks so much. I thought that discussion on IDH mutant glioblastomas, of which I'm a member of that subclass, was a really terrific and helpful summary. So thanks, I'm benefiting already from this talk. So I wanted to extend this conversation about clinical trials and being someone who's really involved in the patient advocacy space. Of course, many of us know how important clinical trials are to getting to better treatments and ultimately, one day a cure for these, this disease. There are still some kind of common misconceptions about clinical trials. And for example oh, if I enroll in a trial, and I'm not in the experimental arm, will that mean that I don't have any access to treatments at all? So there are some fears. I'm wondering if you could just help dispel some of the misconceptions about clinical trial enrollment.

Dr Nancy Bush: Absolutely. Thank you, Adam so much. So most clinical trials for brain tumors themselves

do not have a ‘no treatment arm’. In general, there are three main phases of clinical trials that a treatment needs to go through to pass safety and become FDA approved. So the first phase is called Phase one and that looks primarily on a drug safety to give to patients. A second phase, Phase two begins to look at efficacy. And the third is the Final phase that looks at an experimental arm compared to the best care of therapy. The gold standard for a Phase three trial is actually a randomized placebo controlled trial, which means it’s randomized, we don’t know which group someone’s going to be in, and there may be a placebo. But this typically means that everybody will get the same standard treatments, and then you have a 50-50 chance of getting an extra medication on top of that.

So it’s not like we’re not treating patients, we’re still giving everybody what we think works. Usually we would give them something on top of that as well because we don’t have a cure. Now I tell my patients there are three rules to a clinical trial. First is they are always voluntary. You can say no at any time, you can stop at any time for any reason. But you just need to let your doctor know, so we can remove you from the clinical trial safely. The second rule is we would never keep you on a medication that is not safe for you and for your body. So if you are having intolerable side effects, lab abnormalities, we would either reduce the dose or stop it altogether because our first goal is to do no harm. And the third role is that we would never continue a medication that is not working. So if it looks like your brain tumor was growing, despite our treatments, we would stop the trial and shift to something else that would work better for you. But I do hear that question a lot. People are worried that if they join a trial, they’re not going to get treatment at all, and that’s usually not the case.

Adam: Great, good. So that’s a great description of kind of the three phases. I’m also a little bit curious about, kind of, trial design. I know there are platform trials and adaptive trials and basket trials and it can all become a bit confusing as to the patient population. So could you describe just kind of the most common clinical trial design?

Dr Nancy Bush: Absolutely. So the most common clinical trial design for Phase one, that first phase is looking at safety and that would be a dose escalation trial. So you would start at a very low dose of a medication and give it to a certain number of patients. And if they tolerate it, you increase the dose for a certain rotation. So their tolerance keeps going up, until all of a sudden the patients don’t seem to be tolerating the medication either because of side effects or lab abnormalities, then you go down the dose. Once you find the dose that the majority of patients seem to tolerate, and it seems to be safe, then you would move to a Phase two. Phase Two is the first time you’re really looking to see if a medication is working. This is usually a larger group of patients, everybody will get the same dose and typically it’s compared to a control arm at standard care, either historically what we know to be the case, or sometimes there would be a control arm getting in the standard of care therapy.

Then you move into the Phase three, which is these randomized control trials. Now, on top of that there are all these other ones that are coming out that we hope are helping not only speed up the process, but give greater access to clinical trials to more patients. So you mentioned basket trials. This would be a trial where it’s not just for brain tumors. It’s for many, many, many different kinds of cancer types. But you all have to have one common feature like one biomarker or EGFR amplification. And so I might have a lung tumor patient and a brain tumor patient. Both of those patients might be eligible to be on that trial, which is somewhat of a novel design. The other one that you mentioned is called an adaptive clinical trial and this is very exciting. We have a clinical trial ongoing in the brain tumor world called AGILE. So an adaptive clinical trial attempts to really speed the process of finding treatments that are efficacious. And so what this allows is that it’s a trial that continually adds new treatments as they come along.

So you add arms over time. So instead of it just being one trial for one drug and being over, it’s an open trial that can stay open for years, where you continuously add new arms over time. Now, if those arms or treatments seem to be working, then you expand that to include more patients. If they don’t seem to be working, they will decrease and close and stop. Additionally, a fascinating feature of the adaptive trial especially for AGILE is that there is an enrichment process. So as time goes on, it seems like a certain population of patients is responding to a specific treatment because of the biomarker they have. The trial will

actually enrich patients with that biomarker into that treatment arm. So again, really trying to speed up the process of finding efficacious treatments, both by allowing for it to be open for a long period time and adding arms, but also kind of targeting the type of patient that we're treating if it looks like it's working for a certain type of patient.

Adam: Terrific, that's great. And we know that timing is of the essence with these tumors and cancer. So that's good to hear about speeding up the time to potentially. I want to shift gears just a little bit for this question. And I also acknowledged that it might be a little bit contentious, so within the neuro-oncology space, but I've become really interested in palliative care. And I know that some folks will say, oh, there's a branding problem with palliative care, and that sometimes, folks that are receiving care for brain tumors don't necessarily have the access to palliative care that maybe other cancer patients from other cancers may they find themselves more engaged in palliative care. So I'm interested just in how it relates to quality of life and just to hear your thoughts on the role that palliative care may have to play in enhancing quality of life.

Dr Nancy Bush: That's an excellent question and something that we feel very passionately about at UCSF. So I do feel like palliative care is a very important part of the care of a patient with a brain tumor. I should say that brain tumors are a little bit different than patients with other kinds of cancers. There is less pain in a lot of ways. There's a less shortness of breath and kind of many of the symptoms that palliative care has focused on in the past, but it's different, we have more neurologic difficulties, so difficulty walking, difficulty seeing, difficulty speaking, which can be very challenging for our patients, and that will progress over time. And so I feel like it's very important for each patient have a very open and honest relationship with their neuro-oncologist to always be able to talk about quality of life, and whether or not treatments make sense and when they don't make sense, and being able to have that two way conversation for both the patient and the end the doctor.

Additionally, I should say that there is an idea to increase palliative care earlier in patient's treatment. And so I know at our institution, we're trying to have patients meet with palliative care within the first few months of their diagnosis of the high grade tumors, just to know that they're there and having another care team member. I think it's somewhat complicated because neuro-oncologists themselves are typically very good at palliative care. But we can't do everything and we're not good at everything. And so it is really important to have that palliative care piece to help patients along the way. And I do think it's important to start discussions early because we do know this is an incurable tumor, and especially for our patients who we know have difficulty speaking and communicating. It's really important that families of patients and doctors can have these conversations about the importance of quality of life and how they would like to have the end of their days early rather than later when all of a sudden they're not able to talk anymore. And so, I do really feel very strongly about bringing palliative care into neuro-oncology.

Adam: Terrific. Thank you so much.

Priya: Thank you, Adam. Next on the panel we have Jeremy. Jeremy advocates for the brain tumor and young adult cancer communities through writing, speaking and fundraising. He is a patient ambassador on palliative care for the EndWell foundation, co-moderates a monthly brain tumor social media Twitter chat, and is a regular contributor for the CURE magazine. Jeremy was originally diagnosed with a brain tumor at the age of 12. He had a recurrent when he was 23. And given the rare molecular makeup of this tumor is now undergoing experimental treatments for the new tumor growth. Jeremy, you're on.

Jeremy Pivor: Thank you Priya. And thank you for having me and Dr. Bush. Thank you for taking the time. And Adam, it's great to hear your voice. So I have a question. We've talked a lot about clinical trials as the path to finding better treatments for brain tumors. And many of these trials have pretty stringent criteria for patients to be able to enter them, which can be emotionally distressing and frustrating for patients and loved ones looking for treatments beyond standard of care options. And so broadly, can you discuss why these criteria exist for trials?

Dr Nancy Bush: Absolutely, Jeremy, it's good to hear your voice. These criteria really exist for patient safety, because these are all experimental therapies. We don't know if they're going to work and we don't know if they're actually going to cause harm. So most of the criteria are very stringent for that reason. Additionally, the criteria really exists for the integrity of the trial at the end of the day. We really want to be able to answer that question, is this treatment efficacious for this kind of brain tumor type? And if we start to involve all sorts of different kinds of brain tumors, and different pathologies, we may really not be able to answer that question at the end of the day. And so that's why we really do have these very stringent inclusion and exclusion criteria.

Jeremy: Thank you that makes a lot of sense and kind of following up on that, with new technology in precision medicine, allowing doctors and patients to get better insight into their tumor's mutation. Some of the molecular makeup of the tumor or life history of the tumor may make the patient ineligible to participate in clinical trials. So for example, I live within an anaplastic oligodendroglioma with an IDH2 mutation but not an IDH1 mutation, which can exclude me from a lot of trials. However, I've been really fortunate to have the privilege and certain insurance and access to academic hospital facilities like UCSF and also Dana Farber, that allows me to experiment with immunotherapy off label. So can you discuss for the audience what options patients have if they are not eligible for clinical trials to access the latest treatments? And how might patients overcome those barriers?

Dr Nancy Bush: Sure, and honestly, it's very difficult. And so typically, we would first just try to prescribe it through your insurance and most insurance companies will deny it because they're not FDA approved medications for the disease type. Then in many cases, we're able to appeal to insurance companies for this treatment off label. So what off label means is that these are medications that are FDA approved for other types of diseases, but not for brain tumors. But we have rationale, why they might work for your tumor. And so we can write letters to the insurance companies and try to appeal showing this is our rationale, this is why we think it's going to work. We don't have any other good options. Sometimes that works. Sometimes it doesn't. And so the other thing that we commonly do is work directly with the drug companies themselves through patient assistant programs. And so many times we are able to work with these large drug companies and say, this is the medication that we want to give. This is why would you be willing to give the medication at a reduced cost to the patient, and many times they are able to reduce costs or and sometimes even free to our patients, which is wonderful, the drug companies, but again, it's not a guarantee. So we go to bat for our patients every time but I do tell people, sometimes it's just out of our hands.

Jeremy: Yeah, it makes sense. I've been fortunate that my insurance has covered it, but I know for a lot of people I've talked to there's been issues where their insurance doesn't cover that or sometimes their doctors actually don't even know of some of the methods or clinical trials that do exist.

Dr Nancy Bush: And for that reason, we do usually recommend getting second opinions at other academic institutions or at an academic institution. Because sometimes, we have a little bit more tricks than a general medical oncologist about how to get these medications off label. So it is worth kind of seeking out one of these big brain tumor centers to see if we can get things off label.

Jeremy: And that's actually a great segue to the final question I wanted to ask you. And so as a patient who has lived with the brain tumor since I've been 12 years old, and with two recurrences since then, I've seen a lot of doctors and received a lot of opinions about treatments, which has been an incredible privilege for me. And sometimes those recommendations have been aligned, but often they're individual or sometimes institutional recommendations differ and with so much information and with the development of new research and trials, the lay of the land is changing so fast, even everything you've mentioned so far during this segment, I've learned a lot of information for myself. And so when patients encounter situations when doctors are providing different recommendations for treatment, how would you advise the patient to work through all of this information and make their decision?

Dr Nancy Bush: So again, I think this is such a difficult question. Because the truth is, many times when we're talking about experimental therapies, we don't know, we don't have the answer. If we knew that

something was going to work, we'd all be aligned on the same page and you'd have a really easy recommendation. I should say that when you're trying to decide between these different treatments, I would really consider quality of life and the side effect profile of the experimental therapies and what makes sense for you. So if there's a clinical trial that you're eligible for, but it's completely across the country, and you're going to have to fly there every week, does that really make sense? If you could do a treatment that may be just as good close to home, and so that's really the things that you have to kind of keep in your mind. Sometimes you're eligible for clinical trial only at first recurrent, it may make sense to do that one now because the other treatments that people are talking about, you could do it second or third or fourth recurrence – another thing to keep in mind.

And then the last thing that I would say is that most patients will have at least one doctor that their primary oncologist who they know really well. And a lot of times those physicians may be the most insightful just because they know you, they know your life, and they might know what treatments may be best for you based on kind of how rigorous it would be and the side effect profile. And so when it comes down to things, it's really easy for me to make recommendations for somebody across the country who I've never met, but the truth is, that might not actually be the right treatment for them. And if I had met them in person and evaluated them clinically, then I might not have said that same treatment. So a lot of times, kind of, your main point person may have the most insight. That's what I'm trying to say.

Jeremy: Yeah, thanks, Dr. Bush. I appreciate your thoughtfulness with all the…

Priya: Thank you Jeremy. Dr. Bush. We are getting some questions from our audience. So we can get into those now. We have a question from a 63 year old who's asking what is the long term results for a 63 year old who has had an aneurysm and now has clips and plugs to stop the bleeding on the brain. The surgery was done in 2011, does it cause neurological disorders and do the coils have to be cleaned out at all?

Dr Nancy Bush: So unfortunately, I'm not a vascular neurologist. The aneurysms are typically abnormalities of the blood vessels of the brain and when they bleed they need to be coiled and that usually those coils would stay in. After the bleeding if it doesn't bleed again, it doesn't usually cause more neurologic damage, but again, I'm not an expert on vascular neurology. I'm more an expert on tumors.

Priya: Thank you, Dr. Bush. The next question is it common place for children who had ALL to develop a glioblastoma as an adult?

Dr Nancy Bush: In the past, treatment of ALL would include radiation to the brain. We do know that radiation to the brain is a risk factor for development of brain tumors later in life. Over the past several years, though, however, children no longer get brain radiation, they get intrathecal chemotherapy, which means chemotherapy that's sent directly into this tube of spinal fluid. And so ever since they switched to that form, then brain tumors are less likely a secondary complication of the treatment of ALL. So only if the child has had radiation, but I'd be worried about development of glioblastoma.

Priya: Thank you, Dr. Bush. Yeah, the next question. I try to follow papers and news of trials and studies related to gliomas and those that I see are predominantly for Astrocytomas and GBM in particular. This is understandable given the aggressive nature, natural history and poor prognosis for those gliomas. My selfish question is, are there any promising novel treatment approaches or trials for oligodendrogliomas?

Dr Nancy Bush: So I would say yes, these trials take much longer to do because they're slow growing tumors, and we don't have results as quickly. I think two very promising avenues for the lower grade tumors like the oligodendrogliomas are the IDH inhibitors. So we spoke a little earlier about the fact that oligodendrogliomas can be defined by an IDH mutation. So there are developing IDH1 and IDH2 inhibitors that inhibit this mutation. And so there are ongoing clinical trials that are looking at both of these combinations is, kind of, a targeted therapy for patients with low grade tumors. Additionally, one very exciting strategy for the lower grade tumors would be vaccine clinical trials. So we and other places have developed vaccines that are targeted against lower grade tumors. And so the idea is that you will get a shot just like you

would for the chickenpox into your leg. And the immune system would see that and say this doesn't really belong there and become activated. And when the immune system is circulating through the entire body, it would see potentially brain tumor cells and be activated to kill this tumor. Now, this is a very exciting strategy for the lower grade tumors because they grow kind of slowly over time, they might wake up and grow and go back to sleep and wake up and grow. And so when it would decide to wake up and grow, the treatment is already in your body, the immune system would be activated to go kill those tumor cells, and hopefully put everything back into hibernation. So I would say both of those are very exciting strategies for the lower grade tumors.

Priya: Thank you Dr Bush. We have another question. What is the electrical scalp device? Can you talk about this and whether this can slow down progression of deadly tumors?

Dr Nancy Bush: And so well, the question is referring to something called tumor treating fields with a device from NovaCure called Optune. And what this is, is it's a completely different way of treating brain tumors. It actually uses electromagnetic waves to disrupt how tumor cells divide. And so it's actually electrodes that you wear on your head. So you shave your head and you put these four electrodes on your head and it's connected to a battery pack that you carry around. And several studies have now shown that using this device after radiation actually improves overall survival for patients with glioblastoma at the high grade tumors. So the studies that they did for the newly diagnosed patient show that if you were this device with your chemotherapy that Temodar, and you have to wear it at least 18 hours a day, that there was a significant overall survival benefit of about four months, when they looked longer term, over twice as many people were alive at five years, so the five year survival rate was 13% versus 5% without the Optune.

Additionally, they did a clinical trial for patients with recurrent brain tumors, recurrent glioblastoma, and either patients wore the Optune or were given whatever chemotherapy their physician thought was most appropriate for them. And what they found is that the Optune was equally as efficacious as a chemotherapy. So it is a nice strategy for patients because it's not like chemo. It doesn't make you feel sick. You don't throw up or have a blood count problem. But you do have to shave your head and wear this device over 18 hours a day. So there is some scalp irritation and some psychological impact of being connected to a battery. But it is a very good option, especially for patients who have something called MGMT unmethylated, which is usually the poor prognostic factor, as well as patients who really weren't able to have kind of full surgery.

Priya: Thank you, Dr. Bush. I have one more question from the audience. I think you did mention about polio virus being used in the treatment of brain cancer. So we have someone very interested in that research. And he asks, recently, a team of investigators from the Duke Cancer Institute in Durham, North Carolina, has discovered that they might be able to use the polio virus in the treatment of a form of brain cancer. Can you talk about this, please?

Dr Nancy Bush: Absolutely. So Duke's developed an engineered polio virus that can be infused into the brain via a catheter, which has been shown to kill tumor cells and also activate the immune system to bring it to the improved survival for patients with glioblastoma. So they published their paper in the New England Journal of Medicine, which was their phase one, looking at this escalation, and they found that about 20% of patients had a very durable response. That means they were alive more than 24 months after their infusion of polio and this is for recurrent patients. So those numbers are quite good. And so now they have moved on to a phase two trial that's involving multiple centers, one of which is UCSF who's participating in that polio trial, where again, it's recurrent patients with glioblastoma. They do not have a surgery but a catheter is placed and poliovirus is infused there. And then we let the polio virus work. It does sometimes cause some inflammation and so we can add things like this other medicine (unclear 42:45) to kind of control the inflammation. But yes, it's an ongoing trial and it has shown definite promise in their phase one studies.

Priya: Thank you, Dr. Bush. I'd like to ask you one more question which I had skipped keeping in mind time and wanted to let the panel ask some questions. So we touched the surface of precision and personalized medicine in brain cancer treatment. So maybe you could explain a little bit more about what are some of the treatments that we are looking at and how precision and personalized medicine is, how they are faring in

brain cancer and what the future holds for this kind of treatment?

Dr Nancy Bush: So I think we can look at personalized medicine in several ways, one of which like we spoke earlier about looking at the actual genetics of the tumor, and then looking at the mutations that each person has, and then coming up with personalized approaches. And now that we have more information, having drug companies develop new drugs targeting some of these mutations, because many of us at this point, we don't actually have medications that can target them with common mutations like the TErc mutations that we do see in glioblastoma. Additionally, there's more personalized medicine approaches with things like MGMT methylation, which I also just glossed over. So MGMT is a DNA repair gene. It fixes broken DNA. When it's our chemo, like we discussed, it works by breaking DNA. So when MGMT is active, it can basically come along and fix the damage that our chemotherapy is done. MGMT is inactive in its methylated state, it's turned off, and so our chemo therapies work better. So in many cases, we're also doing personalized approaches for patients who have MGMT methylation where Temodar seems to work better than patients who have unmethylated and the chemotherapy does not work as well.

Priya: Okay, so just one more before we wrap up, the last question for today's discussion. Of course, we did mention quality of life. Adam asked you about it and I believe it's so very important. So what are some of your suggestions for maintaining quality of life during treatment and Adam and Jeremy, I would like both of you to jump on this as well, so that we can know your advice and from your experience, some of your coping mechanisms that you can share with the audience. Dr. Bush, you go first.

Dr Nancy Bush: Sure. So like I mentioned before, I think it's so important to have an open and honest conversation with your oncologist at all points about when treatments make sense and when they don't make sense. Because I do feel like quality and quantity are both important, but we have to maximize both. And I tell the same five things to all of my patients when they're newly diagnosed. And I think it's good advice for kind of everyone to live by, which is also challenging. The first is just good, healthy diet, everything in moderation. There really aren't any known diets like a low sugar diet or a ketogenic diet that has been proven to be efficacious for patients with brain tumors. So I just say everything in moderation. Be healthy. But that means if you want to have chocolate cake, have chocolate cake, it's not three meals a day. It also goes the same for alcohol, patients always ask if it's okay to have a glass of wine or beer. And absolutely, we want you to live your life.

The second thing that I think helps is good sleep. So we know that deep REM sleep is actually when the toxins are cleaned from everybody's brain. So this is very important for our brain tumor patients, because we know that when they're tired, their deficits come out more. So I recommend good sleep hygiene, which usually means going to bed at the same time, waking up at the same time and napping when you need it. But we don't want people acting like college kids sleeping all afternoon and then staying up all night. Because then they're really not getting that deep REM sleep at night when they need it to clean all the toxins from their brain. Number three might be the most important and that's exercise. We know that physical activity and exercise can actually stimulate the immune system to help fight the tumor. It also helps combat fatigue, especially from some of the treatments that we're putting people through, like with radiation. So I do recommend people getting out of the house and trying to exercise at least three times a day, three times a week and not three times a day.

Number four is joy. The reality is that none of us knows what's going to happen in this world. And each of us truly needs to live our life to our maximum and find joy every day, in the little things that we do, and the big things, so don't wait to take that big trip, if you want to do it, go do it. And then five is different for everyone, I call it the novelty factor. That just means doing something different that stimulates your brain in a new way. So that could be puzzles and Sudoku, it could be reading books, it could be a new hobby, learning an instrument or a language or something like meditation, something that's engaging to your brain that's novel and a little bit challenging for you. We actually think that helps promote healing and new neural pathways. So those are kind of my big five to maximize quality of life.

Priya: Thank you, Dr. Bush. That was really great. Adam, what is your advice to our listeners on this?

Adam: Yeah, terrific. So I think I might answer it just in two parts. I think one by analogy and another by anecdote. The analogy that I'd like to make is that oftentimes we all ask a five year old or a six year old will say, what do you want to be when you grow up? And we know that we shouldn't hold them accountable to that when they're 25 or 30. So the idea being that quality of life will be evolving through the disease trajectory. So we want to have those conversations as Dr. Bush mentioned, with our loved ones and our care teams, but we need to remember that a quality of life conversation is not only checking the box, but it is an evolving and organic conversation as we move along the treatment journey and into survivorship. So that's kind of the analogy there. I think the anecdote, I had an awake craniotomy, an awake brain surgery. And in some ways, although an overwhelming experience, it also provided me the opportunity to, in fact, have some dialogue in the moment. So we reached a point in that surgery, where the surgeon said he could be more aggressive, but that came with the risk of some really significant deficits, or we can conclude with the margins of the surgical cavity not quite as clear. And so we kind of made that decision together and my surgeon said, listen, you've got to make a decision, not on what you think could happen in the future, but based on your quality of life today. So I think that's also important. So I have some long term goals, five years out, 10 years out, but I also make sure that I do something every single day, that at least in some incremental way, we'll get to that goal. So that's kind of how I navigate my own quality of life, did I do something today to help work towards that big goal. So thanks, Priya.

Priya: Adam that surely is very nice to hear. And Jeremy, what has been your experience and do share some of your coping mechanisms?

Jeremy: Yeah, thank you Priya. I think for me it's split into three different ways, especially since my first occurrence in 2014 and being diagnosed at 23 with that recurrence. Society's not built for young adults to have cancer. And so you're kind of chugging along, forming your identity, moving forward with all your friends around you, but then once you're hit with a recurrence, or even the first diagnosis, you're held back into this no man's land. And so for me, I've developed these three different ways of coping, the first being with like, being able to be okay with doing less. Most recently with my second recurrence, I was a medical student. And nine months into medical school when I had my recurrence, I realized I could not keep doing full time Medical School and maintain the five parts of quality of life that Dr. Bush mentioned, which I loved. And so I realized I need to step back to part time or even take some time off at certain points.

And I think that's especially for young adults to kind of step away from constantly moving forward, whether that's with family or career. The second quality of life that I've realized is being willing to ask for help, whether that's during treatment or in survivorship. And that might be help with food or groceries, laundry or even just asking for people to come over and having some social time with friends or family members that you love because at times, going through treatment, and even survivorship can be pretty lonely and having that social experience with others or getting yourself to go out and be with others is really important. And the final thing for me and what's been the hardest since I've been diagnosed in 2004, when I was 12, is really the uncertainty factor. And I think that's, for me, the hardest point emotionally.

And I've really over – I'm trying to count the number of years – I've been going through this. But over that long time period, I've been kind of gaining tools to deal with that uncertainty. I call it my toolbox for uncertainty. And I think one of the greatest tools has been really clarifying and understanding my values, which have been, really focusing my relationships with my family, and then also really using what I've been able to gain through this experience to help others. And I call these tools and those values as my flashlight in a dark room. And that helps me when I have major decisions, whether they're medically related or just life related. I really use the flashlight to guide me when there are two or multiple goals. For me that recently meant moving back from the west coast to the east coast to be closer to my family. And as I keep making those decisions, it's really been helpful for me to be able to be content with all the uncertainty I faced while I go through the treatments I've been doing most recently. And so I think for each person, those values will be different and might change over time. But it really helps deal with all this, these decisions and uncertainty that we face as brain tumor patients.

Priya: Thank you, Jeremy, thank you for sharing that. It's time to conclude today's discussion on brain

tumor. Dr. Bush. It was a pleasure to have you with us. Thank you for your time and all the information you share with us and our audience. Adam and Jeremy, I truly appreciate your participation and of course for those great questions and the suggestions for folks who have brain cancer and how they can cope with their treatment and how the quality of life is actually an evolving concept. That is really great, and how you should go back and accept your values. Connect with your family Jeremy, that's very well taken. Thank you so very much for that. We thank UCSF Helen Diller Family Comprehensive Cancer Center, and the audience for being with us today. The talk will be available on cure talks.com, as well as the UCSF website, so please visit our website for details on upcoming talks. Thank you everybody, and have a great day.