American Brain Tumor Association Webinar

Current and Future Therapeutic Strategies for Glioblastoma

>> Welcome to the American Brain Tumor Association’s webinar series. Thank you for participating in today’s free educational webinar. Today’s webinar is on current and future therapeutic strategies for glioblastoma. It will be presented by Dr. Duane Mitchell, Maryam Rahman and Dr. David Tran. If you have a question you would like to ask, type and submit using the question box in the control panel on the right-hand side of your screen. Dr. Tran, Dr. Mitchell or Dr. Rahman will answer questions at the end of the presentation. Tomorrow you will receive an e-mail asking you to evaluate this webinar. It is a brief survey. Please take a few minutes to share your comments. Your feedback is important as we plan for future webinars. Today’s webinar is being recorded. The report will be posted to the ABTA website shortly. Register participants will receive the webinar link in a follow-up e-mail once the webinar is available. Let’s pause for a moment so we can begin our webinar recording.

>> The American Brain Tumor Association is pleased to welcome you back to our webinar series. Our webinar today will discuss current and future therapeutic strategies for glioblastoma. My name is Mary Lovely, I’m senior advisor at the American Brain Tumor Association. I'm delighted to introduce our speakers today. Dr. Duane Mitchell, M.D., PhD, Dr. Maryam Rahman, M.D., M.S., and Dr. David Tran, M.D., Ph.D. Dr. Tran is the Chief of Division of Neural Oncology, an Associate Director of the Preston A. Wells, Jr. Center for Brain Tumor Therapy at the University of Florida McKnight Brain Institute. He is specialized in treating patients with primary brain cancer and brain metastases. His research interests are focused on understanding the mechanism of cancer cell invasion and developing novel therapies for brain cancer. Dr. Rahman and Dr. Mitchell are faculty within the Department of Neurosurgery at Preston A. Wells, Jr. Center for Brain Tumor Therapy at the University of Florida. Dr. Rahman is a neurosurgeon with specialty interests in the care of patients with malignant brain tumors and leads research into mechanisms of treatment resistant in brain tumors and means to overcome this resistance. Dr. Mitchell is a clinical and translational researcher specializing in the immunologic treatment of malignant brain tumors and serves as Co-Director of the Preston A. Wells, Jr. Center for Brain Tumor Therapy. Recently, Dr. Mitchell and Dr. Rahman collaborated in delivering a presentation on clinical trials for our Tampa partners in our Treatment and Care Meeting.

>> Thank you for joining us Dr. Mitchell, Dr. Rahman and Dr. Tran. You may now begin your presentation.

>> Good afternoon, this is Dr. Mitchell and it’s my pleasure with myself and our colleagues to share with you some information on current and future therapeutic strategies for glioblastoma. So, briefly as an introduction, we should start with just some conflict of interest disclosures for both Dr. Tran and myself. We do have relationships with pharmaceutical companies that are engaged in brain tumor therapeutic,
however these relationships will not impact on the discussion or the material that is covered today. Just by way of brief outline we will first have Dr. Maryam Rahman who would talk about advances in the surgical applications for patients with glioblastoma and then we’ll transition to Dr. David Tran who will discuss standard treatment for glioblastoma as well as the introduction to new treatments and clinical trial options. I will then conclude with some specific discussions about immunotherapy options as well as small molecule inhibitors and then a discussion about participation in clinical trials for patients with brain tumors. With that I would turn the discussion over to Dr. Rahman.

>> Good afternoon. My name is Maryam Rahman and I am a neurosurgeon specializing in brain tumors at the University of Florida. I’m going to cover some recent advances in the surgical treatment of glioblastoma. One of the underlying knowns for glioblastoma is the more tumor you can remove with surgery, the better patients do in terms of survival. There are multiple good studies that have shown this including this important study that came out of the University of California San Francisco where they looked at 500 patients who had newly diagnosed glioblastoma. They found that the residual volume of tumor found on their MRI scan after surgery was about 2.3 cubic centimeters in this equated to about a 96% extent of resection that is what EOR stands for. The median survival for all of these patients was about 12 months and they did find that certain characteristics of these patients predicted a good survival and that was a young age, less than 60, a good performance status which is what KPS stands for meaning that they were independent, that they were able to do things for themselves and having an increased extent of resection- meaning the more tumor you removed at the time of surgery, the longer people survived. This is the survival curve they showed in that paper. On the Y axis is a percent of patients alive. This is survival over time and you can see even with the extent of resection of 90% or greater, you start seeing in increased survival with the more tumor you can remove. The surgeon’s job is to assess the patient in see how much tumor you can remove safely and our goal with surgery is to remove as much tumor as we can based on the patient's MRI scan.

>> This is not always low risk. Obviously if you are trying to be aggressive in surgery, you may increase the risk of causing a neurologic deficit or complication and we know from other studies that looked at 118 patients with malignant glioma that had a resection using an agent called 5-ALA which I will go over in a few minutes, that about half of these patients had some residual tumor fluorescence at the end of surgery meaning they had some residual tumor left and 27 of the patients had no residual tumor left at the end of surgery. They found those who had no residual tumor live longer, but those patients also had a much higher complication rate with surgery of 18.5%. As we become more aggressive with surgery there is also increased risk associated with that for the patient. There are multiple things that we do as surgeons to try to decrease this risk. One of those things is a narrow navigation, which means we take the MRI scan that the patient had an during surgery, we would register that to a special computer and that allows us to use the MRI scan like a GPS system during surgery so we can point a wand at the patient’s head or the tumor and be able to track where that wand is based on their MRI scan. The other thing that we do is for patients who have tumors in important areas of the brain that we call eloquent areas, parts of the brain that are important for speaking or for movement of the body, many times we will wake the patient up during surgery to map out portions of that part of their brain to make sure that we keep that portion of their brain safe during our resection of the tumor. Another option is doing intraoperative MRI scan. You respect the portion of the tumor and then get an MRI scan immediately
and assess how much tumor is left behind to try to obtain the best resection as possible. Other surgeons will advocate doing very early redo surgery, so if we do a resection after surgery and we get an MRI scan that shows some residual tumors, some surgeons will take patients back to the operating room to do an early repeat resection to try to get as much tumor as possible. Finally, another tool relatively new is something called tumor fluorescence and this is where we give the patient a dye right before we start the surgery and during surgery we use the special operating microscope with a special light filter that allows the dye to show up in the tumor cells and the tumor cells primarily take up this dye and normal brain cells do not. So, while we’re operating the tumor cells show up very bright under this special light and the normal brain tissue shows up dark and it helps you distinguish between tumor and normal brain and this will theoretically help with the safety of surgery. I’m going to go into detail about two of these options, one is the tumor fluorescence and the other one is the awake mapping for tumors that are in eloquent areas. For tumor fluorescence there are two main drugs that are used to help light up a tumor during surgery. One of those is called 5-ALA. This is a natural biochemical precursor of hemoglobin and it elicits synthesis of a special product called porphyrins within the malignant glioma. You have to give this drug orally and it is independent of the breakdown of the blood brain barrier. The light we use in the operating room to visualize this fluorescence is Blue 400. There was an important study where they took malignant glioma patients and randomized them to receive the fluorescence, or not receive the fluorescence and they had to stop early because they found that patients who received 5-ALA had much better tumor resection compared to those who did not receive the fluorescent dye. The picture in the corner shows what this looks like under the blue fluorescent light. This is the surface of someone’s tumor and the red here is the tumor and what you see here on the edge that is not red, that is normal brain tissue. They found that those who had the better resection also survived longer. Their progression free survival in six months was 41% compared to those who did not receive the fluorescent dye that progression free survival was 21.1%.

>> There are limitations to using 5-ALA. One, you have to give it orally and it has to be given at least two or three hours before you actually need it, so two to three hours before you begin surgery. It does not have great sensitivity or specificity at the margins of the tumor. Sometimes over time during the course of surgery there can be photobleaching just from the use of the light can make the chemical degrade and it’s not as bright. Postoperatively, the patients have to be kept in the dark for 24-48 hours to avoid skin burns that can be a complication of the 5-ALA being under the skin.

>> Another drug that is starting to be used is called Fluorescein, which is the fluorescent synthetic organic compound. This can be used not just for tumors, but also for vascular leakage or neovascularization or any place where there may be some abnormal blood brain barrier in the brain and it is been prescribed for brain surgery as early as 1948. I would like to inform the audience that in the upcoming slide there may be some surgical videos that may be graphic videos of surgery and if that affects anyone you may want to temporarily turn off the slides until we get through the surgical section. Fluorescein, the nice thing is that it is FDA approved in the U.S. There is no need for any special postoperative care. The patients don't have to be in the dark. The downside of Fluorescein is it does require there to be a breakdown of the blood brain barrier which is very common in glioblastoma, so it’s good for glioblastoma. Right now there is no good data that actually improves the extent of resection or
the ability to remove more tumor. This is a surgical picture taken here. This is the surface of the patient's brain. You can see the tumor that is bright yellow with Fluorescein with a special yellow light. This is an example after partial tumor resection. This tissue is normal brain tissue in this tissue still has tumor in it and that is how we are able to use the Fluorescein to guide the resection.

>> I'm going to begin talking about awake cortical mapping for glioblastoma. The reason to do this is to help guide the surgical resection and it's important for patients with tumors in eloquent areas of the brain, such as the motor part or the speech area. We can map out the sensory part of the brain, the language cortex and motor cortex very easily. The way it works is that we put people to sleep and open up the skull. Once we have the tumor exposed, we wake the patient up and we use a special probe on the surface of the brain to create little electrical stimuli on the surface of the brain. As we do that would test the patient's motor skills and language skills or ability to feel one part of their body and we are able to figure out exactly what part of the brain is important for that function. Once we know that we put a label on the surface of the brain to know this is an important part of the brain and we are not going to go near this during the resection and then we can precede to remove the tumor safely. These are the EEG signals we see during surgery. Before surgery, commonly we will get a functional MRI scan which will also show us where important parts of the brain live. This an example of one where you can see motor function or language function or visual function, based on someone's performance in an MRI scanner. This helps guide us before surgery.

>> I'm going to show a brief video. This is an example of an awake craniotomy. You can see the surgeons are standing behind the patient. We have her brain exposed and we're currently providing a little electrical stimuli on the surface of her brain. She is now awake during surgery and this is the neuropsychologist asking her questions and testing language function and on the phone she is about to show pictures and ask her to name what she sees. This is what the typical operating room looks like during one of these cases.

>> I'm now going to turn the presentation over to Dr. Tran who is going to discuss standard medical treatment for glioblastoma. Thank you.

>> Thank you Dr. Rahman. My name is Dr. David Tran and I'm an oncologist who specializes in the treatment of the tumor of the central nervous system. I'm going to spend the next 10 minutes to talk to you about, first, the standard treatment for glioblastoma and then move on to some of the current and future treatment for this deadly disease.

>> First, I'd like to talk about the standard treatment for newly diagnosed GBM. The current way newly diagnosed GBM is treated as a combination of radiation therapy with the chemo drug called temozolomide. This combination is given at the same time for about six weeks. It is followed by 6 to 12 months of chemotherapy. The standard of care was established based on a clinical trial published in 2005. Five years later there was another publication in the five-year follow-up for the same study published in 2009. Here is a graph of that study which established the combination of radiation and
temozolomide and the standard of care for glioblastoma. Here you can see the yellow line represents a patient randomized who received radiation alone and the blue line represents patients who received a combination of radiation and temozolomide. The vertical axis is the percent of patients who survive and the horizontal axis is the survival time in years. As you can see, the addition of temozolomide to radiation therapy increased the overall survival of 50% for about 2 months from 12 months of radiation alone to about 14.6 months with the addition of temozolomide. The more important parameter I would like you to focus on is the two-year survival rate which is demonstrated here. If you draw a vertical line at the two-year mark where it crosses the two survival curves and you draw two horizontal lines to determine the percentage of patients who survive the two years and you can see that with radiation alone the number of patients who survive at two years is about 10% and that was increased to about 28% with the addition of temozolomide. This is the data that established a combination of radiation and temozolomide as a standard of care for GBM.

Also in this study, the investigator also looked further into some of the molecular genetics of the tumors and tried to understand which patients appeared to benefit from the addition of chemotherapy more than the other patients. What was discovered is there was an enzyme called MGMT, this is a DNA repair enzyme. A normal enzyme present in almost all the cells in your body. It functions to repair DNA damage caused by drugs especially chemotherapy drugs. In theory, when you give the patient a temozolomide-like drug, you don’t want this enzyme to be turned on because you don’t want your body to neutralize the damage that the chemotherapy causes on the cancer cells. This MGMT gene is controlled inside your cells by a region in front of the gene called the promoter. If the cells put a particular mark on the promoter called the methyl group, then gene is off. If methyl group is removed from the promoter, then the gene is on. The two survival graphs our patients who had the MGMT gene on versus when they have MGMT off. If you look at the methylated promoter -- the patients don’t seem to benefit from the addition of chemotherapy. It is because the enzyme is on and therefore it will neutralize any therapeutic effect that chemotherapy has on the cells. If you look on the right-hand side where we have the MGMT off, the patients appeared to benefit significantly from the addition of chemotherapy. If you look at the median survival of patients who received radiation alone have the survival of about 16 months compared to patients who received chemoradiation and survival increased to about 22 months and these are the patients who had the MGMT turned off which is much more significant than the un-methylated promoter. This has been used by a practitioner to stratify patients in terms of whether or not they would recommend temozolomide for the standard of treatment.

The second drug approved by the FDA for the treatment of GBM is called Bevacizumab or Avastin. It is approved by the FDA to treat recurrent GBM. The way Avastin works is it is a biologic agent and works by finding and neutralizing markers called VEGF. VEGF is a substance secreted by many tissues including GBM to make new blood vessels. When VEGF is neutralized by Avastin, the tumors cannot make new blood vessels very effectively and without new blood vessels the tumor does not grow very well. This is just a diagram to depict the actions of VEGF. You can see significant VEGF formations and in the presence of an anti-VEGF you see a reduction. Avastin was then tested in two large trials in newly diagnosed GBM. Unfortunately in these two trials, Avastin was not very effective at prolonging survival. AVAglio was conducted in Europe and RTOG in the U.S. The survival curve for both of these trials, the top panel is the survival percentage of patients and the lower panels depicts the percentage of patients...
who lived without the tumors recurring. In both of these trials, Avastin appeared to improve the progressive free survival as shown in the purple line compared to the blue line. It is consistent between the two trials. However when you look at the percentage of patients who survive, it does not appear to have any difference between the group that received Avastin versus the group that did not and that was consistent in both of these trials. The status and fate of Avastin right now is not clear. The data is being reviewed by the FDA and we are waiting for their final decision in terms of whether or not Avastin should be offered to patients with glioblastoma.

>> I would like to talk more about some of the new treatments and clinical trials ongoing in the field for the treatment of glioblastoma. Some of the emerging treatment strategies for GBM include tumor treating fields. This is an emerging field that uses electric fields to disrupt the way cancer cells divide. The second topic is about cancer immunotherapy. In this approach we basically stimulate the patient’s immune system so the immune system can recognize and kill tumor cells. The third new approach is designing small molecules to target particular growth pathways within the GBM cells and it is called targeted small molecules. We will spend some time to talk about each of these topics.

>> The first treatment that I would like to talk to you about is tumor treating fields. The tumor treating fields is the type of electric fields that are intermediate in frequency. Not too fast to create heat and not too slow to affect normal electrical activities inside normal cells. What this therapy does is it affects the way cancer cells divide. When any cells in the body divide, they have to ensure the genetic content of the cells is divided equally. One of the way the cells accomplish that mission is to create this structure called the spindle structure so they can light up all the genes to make sure the genes are divided equally. It turns out the spindle structure is formed by molecules called tubulin which is the dipole molecule, what that means is that the molecule actually does have an electrical charge and on one end it is positive and the other end it is minus. In normal spindle formation this marker will light up with the plus end connected to the minus end of the next molecule and so on and so forth until you form the spindle structures. If the structures are subjected to an electric field, you can imagine that this field may scramble the whole structure and cause the massive disruption of the spindle formation and that leads to the inability of the cells to divide the genetic content appropriately and the end result is that cells undergo cell death. The TT fields can affect multiple phases of the cell cycle. It may affect when the cells were getting ready to divide the genetic content in the metaphase or it can affect cells that happen to complete pa of the pinching off, the TT fields can also disrupt the final process which is -- where the cells have this hourglass appearance in when you apply an electric field on top of that structure, all of the launch markers inside the cells get pulled into the middle of the cells which cause a massive disruption of all the cell structures and they undergo cell death. In essence, this therapy is considered to be and antimitotic mechanism. This therapy causes cell damage. This technology is currently FDA approved for recurring GBM. It was currently tested in Phase 3 trials and in this trial, the TT fields is delivered to the patients using this device. In this device, patients wear electrodes where their scalp has been shaped so that the electrodes can be flush with the scalp to provide maximal field strength. The field strength is evenly delivered to the brain about 1 to 3 volts per centimeter. There is a computer program the provider can use to map the location of the tumors and with that map, one can actually place the electrodes in a certain configuration to maximize field strength delivery to the region of the brain where the treatment is desired.
In this clinical trial called EF-14, there were 700 patients enrolled in this clinical trial. All the patients were newly diagnosed GBM. They all received standard chemo and radiation. After the end of the chemo and radiation, the patient was then randomized to either receiving the temozolomide chemotherapy in addition to the tumor treating fields or they were randomized to standard chemotherapy alone.

The primary endpoint for this clinical trial is progressive free survival, that is the measurement of the amount of time patients survive without the tumor recurring. With this measurement you can see this is the survival curve for this trial with all 700 patients analyzed. The red curve is represents standard treatment without TT fields and the blue standard treatment with TT fields. The addition of TT fields to the standard treatment for newly diagnosed GBM increased progression free survival by about three months, so about 7.1 months to 4.2 months.

The secondary endpoint for this trial is overall survival. This is a measurement of how long the patients live in general. For this measurement, again, the red line is standard treatment. The blue line is standard treatment with TT fields. In this measurement the survival benefit that was described with TT fields was close to three months, an increase of 16.6 months and the control standard treatment alone to 19.4 months with a combination of standard treatment with TT fields. I mentioned earlier in the standard treatment for temozolomide, the more useful numbers that will allow you to focus on is the two-year survival rate. The two-year survival rate in this trial for the standard treatment of temozolomide which is similar to the regional trial that led to the approval of temozolomide of standard care-- 29% of patients treated with standard treatment survive at two years compared to 43% of patients survive at two years if TT field is added to standard treatment. Right now the trial was terminated early and all the patients on the control arm which is the standard treatment alone were allowed to crossover and receive TT fields. The entire data has been submitted to the FDA for consideration so we are waiting for a final review of the data and a final decision on the part of the FDA in terms of whether or not this will become the new standard of treatment for newly diagnosed GBM.

With that I will pass it over to Dr. Duane Mitchell who will talk to you about immunotherapy as well as targeted chemotherapy.

Thank you Dr. Tran. Continuing our discussion about new and emerging treatments for glioblastoma, one of the areas that has emerged as being a potentially powerful new way of treating difficult to tackle tumors has been immunotherapy or using the immune system to actually respond and recognize cancer cells and lead to their rejection. This is not a new concept, the idea that the immune system can recognize tumors and they to their rejection has been around and explored in the research setting and clinical trials for many years. We are seeing over the last five to ten years enough understanding about how the immune response works and why it fails under normal circumstances to recognize cancer cells and that we have begun to see some successes in being able to trigger immunologic responses against cancer types. This diagram is showing a somewhat simplified picture of the very complex interactions that have to occur for the immune system to recognize and kill the tumor. This is a process that involves several cell types in the body and I will start at the bottom of the diagram. Pictured in the red are tumor...
cells. For the immune system to recognize either a tumor cell or an infected cell, it requires a process by which antigens are released from those cells when they die and are picked up by an important cell type called antigen presenting cells. These cells have the function of traveling to the lymph nodes and talking to the lymphocytes of the immune system to alert the body there is something abnormal occurring and to start the process for which there is an immunologic attack against that pathogen, infection or tumor cell. When they picked up antigens typically in the form of proteins released from dying cells may migrate to lymph nodes where they will engage a cell population called natural killer cells and they can lead to the activation of these NK cells that can traffic back through their mechanisms that NK cells use to recognize and kill tumors that can lead to the destruction of the tumor cell. They also talk to the T cells of the immune system and these are the very specific arm of immunity that recognizes alterations inside cancer cells such as mutated proteins or abnormally expressed proteins. If these T cells are properly activated they will expand, divide and leave the lymph nodes and go back out into circulation and search for other cells that contain the antigen that the cell alerted them to. If they migrate to the tumor microenvironment there is interaction between these T cells and the antigens that are present on those cells that then lead to the destruction through what we call a cytotoxic response. This could be an extraordinarily specific and powerful way of killing a targeted tumor cell or an infected cell and very importantly because of the specificity of this approach these cells will typically lead uninfected or normal cells completely unharmed. As we know in a patient that has developed cancer this process has obviously not occurred at an efficient enough level to prevent the growth of tumor cells, so immunotherapy involves trying to stimulate the immune response in one or several of these steps to get a potent enough response that can lead to the killing of the tumor cell. There are a variety of approaches being explored under this topic of cancer immunotherapy. Several of which have been evaluated in clinical trials in patients with cancer including glioblastoma. Just by way of example, some of the earliest approaches involve what we call cancer vaccines where we are essentially taking a portion of the tumor cells, either antigens specifically identified within tumor cells in glioblastoma or sometimes the whole tumor cells themselves and modifying them in such a way they can be delivered back to the immune system in a form that is more potent at stimulating an immune response. This can be done with dendritic cells that are loaded with tumor antigens and delivered back to the patient or portions of the tumor cells modified in a way that when they are given back to the patient they are able to be picked up by the dendritic cells and lead to the stimulation of an immune response. There is another form of therapy considered to be a type of immunotherapy called oncolytic virus therapy. This is a strategy were viruses have been modified so they replicate within tumor cells and not within normal cells and when these viruses are injected into a GBM or other tumor, they will replicate within the tumor cells and the process of that will kill the tumor cell as they spread to infect other neighboring tumor cells. It turns out in addition to this direct killing mechanism where the virus kills the tumor cells that it has infected, this process can also trigger an immune response and awaken the immune system to both the virus and the cancer such that the immune system becomes more effective at fighting off the tumor cells. There is another strategy called adoptive T cell therapy. Instead of trying to induce the whole immunologic response inside the patient, the patient’s own lymphocytes are harvested from the blood or from the tumor microenvironment and expanded to large numbers outside the patient in a clinical laboratory in such a way they are activated against that patient’s own cancer. These expanded and activated lymphocytes are delivered back to the patient in what we call an adoptive cellular therapy approach. Last on this list is another area that has become an exciting area as well and this is called immune checkpoint blockade. The immune system has a number of checks and balances so with the
immune response is activated there are signals that cause an immune response to be turned off at the appropriate time or prevent that immune response from expanding and spilling over into harming normal tissue. It's important to have these checkpoints to prevent what we would call autoimmune reactions that would otherwise harm the body. It is now understood patients with glioblastoma and other cancers oftentimes have the tumor cells use these checkpoints blockades to essentially evade the immune system by providing a much stronger stop signal to the immune system and preventing the immunologic attack against those tumor cells. There are now antibodies that block these immune checkpoints. They take the foot off the brakes and allow the immune system to proceed without receiving this stop signal. It has been shown if we block these immune checkpoints, the patient's own immune system can start to respond much more effectively and in some cases have a very significant immunologic rejection. All of these approaches at present are being explored in what we would call clinical trials. They are not yet FDA approved treatment for patients with glioblastoma, but there are examples in the early stages of the evaluation of these approaches that certainly hold promise for some of these becoming effective therapies in the not-too-distant future.

>> Another area that has received a lot of attention are targeted small molecule developments. These are drugs to specifically block the growth signals that the tumor cells are using to proliferate. Some of the advantages of these small molecule is that they can often be designed to penetrate the blood brain barrier which can be a significant limitation for delivering drugs to the central nervous system. They are under investigation in several clinical trials for glioblastoma and other cancers. This picture briefly shows an oversimplified diagram of the number of pathways we now know are important for tumor cell to grow and persist and in which targeted therapies and small molecule inhibitors are currently being developed and evaluated for their effectiveness against glioblastoma. These involve pathways to have to do with whether tumor cells can invade and migrate to normal tissues. That involves metalloproteinase and something called matrix degradation. There are inhibitors that stop this process. Dr. Tran talked about the development of blood vessels, what we call angiogenesis, and there are inhibitors under development and investigation for enhancing the ability to prevent tumor cells from developing new blood vessels growth and there are many others which we won’t have time to go into detail. As we learn more about how tumor cells persist and how they grow, that understanding does provide additional targets in which we can try to develop therapies that may prevent the growth of glioblastoma and not inhibit the function of normal tissues.

>> In the last part of this we will talk about how patients get an opportunity or are there opportunities to be exposed to these new treatments, what are the benefits and some of the limitations. Before a drug becomes standard of care, they need to be evaluated a through process of clinical trials. These trials are a FDA regulated research study designed to first determine the safety and then the effectiveness of a new treatment for a disease or condition. There usually three steps or phases to clinical trials any drug must go through before becomes the standard of treatment in the United States. You may have heard what we call Phase 1 trials. These trials are usually when the new treatment is first be evaluated in patients. The primary goal is to determine whether it is safe and to establish the doses of the drug that can be tolerated. If that shows to have a reasonable safety profile this drug can move on to the Phase 2 evaluation. Phase 2 clinical trials involve a larger number of patients and have a safety assessment and an attempt to understand how patients are responding clinically to the drug and

www.abta.org • 1.800.886.ABTA
whether it looks promising. If the Phase 2 study looks worthy of advancement and drugs can go on to
the final stage which we referred to as the Phase 3 clinical trial. This is usually in a multicenter setting
where more than one hospital or clinical setting is involved in treating patients and oftentimes the
comparison to patients enrolled in the trial, but given a standard treatment in comparison to the new
treatment. This is to determine whether the new regimen shows the benefit when compared to
standard treatment for the disease. If benefit is shown at this stage that drug can move on for filing for
FDA approval in which case it can become a new standard of care for treatment. There are several steps
involved in bringing a new treatment forward but this does allow patients to participate in clinical trials
and potentially receive these treatments before they have become widely available. It’s important to
know when you participate in a clinical trial although the treatments are new, they are not at that time
known to be better than the standard of care treatment so all patients have to provide consent to
participate. The risk and potential benefits will be covered with patients as part of the informed consent
process. The potential benefit is you may receive newer treatment that can benefit the treatment of
disease. You may receive increased attentive care and management by the clinical research team and
they contribute to better knowledge that may benefit patients in the future. However newer drugs may
have known and unknown side effects that have not been tested and evaluated. This may require more
frequent visits to a treatment center or additional tests to participate and the benefits of the treatment
are really unknown. If patients are interested in finding out about clinical trials there is a number of
resources they can turn to. One is to talk to their treating oncologist and let them know you’re
interested in clinical trials. There are several public databases that lists clinical trials. There were over
1000 studies listed on the clinicaltrials.gov website. There’s also a cancer.gov/clinical trials site. You may
contact institutions or individual investigators conducting clinical trials for glioblastoma. The American
Brain Tumor Association also maintains a clinical trial matching service where patients can learn about
trials that may be relevant to their disease with respect to their clinical brain tumor.

>> That will conclude the presentation and move to the question and answer period.

>> Thank you so much for your presentations. They were fabulous and we learned a lot. Now it’s time
for questions. If you have a question you would like to ask, please type and submit it using the question
box in the webinar control panel on the right-hand side of your screen. Dr. Mitchell and Dr. Tran will be
available for questions. One question is: As a 10-year glioblastoma survival, what role will drugs like
isotretinoin play in the future of newly diagnosed or recurrent glioblastoma?

>> This drug has been tested in a few clinical trials. The concept is to use this drug to basically change
the stem cell component of glioblastoma to make them no longer stem cells. Whether or not the drug
works we do not know. There has been no Phase 3 clinical trial testing this drug have gone with the
standard of care. We are still waiting for further data to know for sure.

>> Thank you. I have a question, which vaccines or immunology are showing most favorable to GCIMP
subtype glioblastoma? My child is 19, IDH1 positive P53ATRX and other mutations.

>> This is Dr. Mitchell and that's a great question. Obviously the genomic information we learn about
glioblastoma and other cancers is helping us design specific treatments including vaccine approaches.
There are a number of treatment regimens under investigations that are looking at targeting the IDH1 mutation itself and whether that maybe immunogenic and potentially a target for a cancer specific vaccine. The other approaches I described are all at the investigational stage and we don't know which are going to be most effective yet at treating what we would call molecular subtypes of glioblastoma. In some ways the fact there are number of at least promising options on the horizon is encouraging. We still have a lot of information before we actually know for a given patient what approach might be the most effective so I would probably say we don't know yet but we are learning more and there are therapies including immunotherapy that are specifically being developed and others under investigation.

>> Do you have any thoughts on the benefits of garlic for brain tumor treatment after surgery, radiation and chemotherapy? The person who wrote in said “I had good results.”

>> This is Dr. Tran. I have not had any definitive testing with garlic on the treatment of brain tumors so I can't really comment on whether or not it is actually effective.

>> This is Dr. Mitchell, I would echo that. We see a lot of patients who have used supplements of different types as part of their care. Many of these we don't know the actual impact so the important thing is to share that information with their treating oncologist so their physicians are aware of what patients may be taking. Some of these could impact their treatments in unknown ways but it is always helpful if the care team is aware all things patients are taking whether they are prescribed or not. We don't have any information yet about garlic or other supplementation and how they may impact outcomes but I'm glad to hear this patient had a favorable outcome. That is encouraging.

>> Another question: I'm interested in treatments for people with inoperable recurrent glioblastoma who already had first line Avastin therapies.

>> This is Dr. Tran. Avastin refractory GBM is probably the most difficult tumor to treat among the brain tumors. There are very few options that have shown to be effective. Multiple chemotherapies have been tested and none of them have actually shown any survival benefit. The two things we usually look at, one is if it is not operable whether or not some other less invasive minimally invasive approach can be used for example laser ablation can sometimes be applied for tumors very close to the eloquent region of the brain. The second is the TT fields I mentioned in the talk, there are some evidence although not definitive that this device may be particularly effective in patients with Avastin refractory GBM. Whether or not that is actually true, will need to be tested in the clinical trials but the early results we have seen appear to be promising. Short of any definitive treatment that this patient would need, they need to talk to a surgeon or oncologist to see if any minimally invasive approach can be applied and if that is not an option then perhaps TT fields and if that is not an option, then I would seek clinical trials, especially new drugs out there to help with this difficult to treat tumor.

>> Another question: In a young 30-year-old very healthy person, what are some of the longest survival rates with radiation therapy and temozolomide treatments with glioblastoma?

>> The question is –
What are the longest survival rates?

I've seen patients who have survived more than 10 years with the standard treatments. The standard treatment has been around about 10 to 13 years so I have seen patients who live more than 10 years. There have been reports of patients who have survived with multiple recurrence GPM up to 25 years but that is relatively rare.

Thank you very much, does Valacyclovir work for targeting CMV in glioblastoma patients?

This is Dr. Mitchell. There has been one clinical trial that has evaluated the benefit of the addition of Valcyte which is an antiviral agent based on the discovery of human cytomegalovirus often activated or at least genes specific for human CMV are expressed within glioblastoma tumors. That trial looked at patients who received the standard of care or the standard of care plus the addition of Valcyte and in the randomized trial there was not of benefit seen in the addition of Valcyte to the standard of care to those patients. Subsequent to that there was a report of the analysis of patients within that trial that stayed on Valcyte for longer periods or patients that were treated with Valcyte outside the context of the clinical trial that appeared to have a significant overall benefit compared to what would be considered to be the standard treatment. We are left with the trial that didn't show benefit in the head-to-head comparison but left to the suggestion of some activity in patients that may receive the drug in a different context. There needs to be clinical further study to understand if in fact there is a benefit of the information of the drug in this setting. At this time it is not a standard of care and I think something still under investigation as to whether there may or may not be of benefit for whether certain patients.

We have time for two more questions. The first is what do you know about cannabinoids? I believe results on mice are very positive.

This is Dr. Tran. Yes, I'm aware of the publication when an investigator used cannabinoids in a mouse model of brain tumors and showed significant improvement in mice. Over the years we have seen multiple drugs we have tested in mouse models of glioblastoma and it showed significant improvement but when they get translated into human trials, many of these drugs did not show any improvement. Until we see more clear benefits in the clinical trials that involve human patients, my response to that is we don't know for sure whether or not it is actually effective. It definitely had some benefits in the treatment of side effects of chemotherapy, not just chemotherapy for brain tumors but many other cancers. Even for that indication, the data is actually not very extensive and that needs to be investigated further. To use the substance as a primary treatment for brain tumors will need to be looked at and investigated much more before we know for sure.

Thank you. The final question is how can I best support my parents during this very difficult time? My father will begin chemo and radiation and will be part of a clinical trial using immunotherapy.

Is this a newly diagnosed GBM?

It appears to be.
The immediate step this patient would need is a standard treatment, chemo and radiation. It is a very involved and time-consuming process. The patient has to be in the clinic in the hospital almost daily. They have to take chemotherapy and monitored for side effects of both the radiation and chemotherapy. My understanding is most of the vaccine and immunotherapy trails right now do not start until after the patient has finished chemo and radiation. My immediate advice is to provide as much support for the patient as they go through the standard treatment first because that will be the key. The patient has to be able to tolerate the standard treatment and have a reasonable status at the end of radiation therapy before the patient would be considered for any clinical trials after the standard treatment is completed.

This is Dr. Mitchell, I might add to that as well, there are associations like the American Brain Tumor Association that have patient and family support information. Sometimes it means for assistance in things like understanding may be resources for travel. I don’t know the specific needs of the family, but I think connecting with ABTA or other tumor associations and patient support groups for families who have had patients and family members affected with glioblastoma can provide resources in terms of psychosocial support as well as point their way toward resources that may be of assistance to the family. It would also be another great option to work with the medical care team to deal with the actual treatment.

Thank you. I also want to let people know about the American Brain Tumor Association CareLine. (800)886-2282. Anybody, patients and families and caregivers and friends can learn more about brain tumors and resources because you don’t want to be alone and we can optimize quality of life.

That’s all the time we have for today. Thank you for joining us and thanks once again to Dr. Mitchell, Dr. Tran and Dr. Rahman. For more information on the topics discussed today or for more information on brain tumors and the treatment options, our licensed healthcare professionals can provide you with support or help you navigate information available on our website. Call the ABTA CareLine at (800)886-2282. Let’s pause for just a moment to conclude our webinar recording.

We invite you to continue to check back at our website www.ABTA .org for the ABTA library of free on-demand webinars that feature experts addressing the range of brain tumor topics from treatment options and tumor types to diet and coping with the diagnosis. Please join us for ABTA's National Patient and Family Conference coming up July 24th and 25th at the Renaissance Chicago O'Hare Suites Hotel. The conferences are for patients, families and caregivers to come together to learn more about the latest advances in brain tumor research, treatment and care from experts around the country. Patients and caregivers will network with each other and gather the most up-to-date brain tumor information at our exceptional educational programming. This will include treatment updates, symptom management, strategy, tumor breakout sessions, research, updates and much more. To register, please visit www.braintumorconference.org. A discounted hotel room of $105 per night is available, but must be booked by July 10th by calling (773)380-9600. This concludes our webinar. Thank you for joining us and please be sure to complete the evaluation survey you will receive by e-mail tomorrow. You may now disconnect.