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What would I do if diagnosed with a Glioblastoma?

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Get Help: The first thing I would do is join our **patient navigation program.** Go to https://virtualtrials.org/navigation.cfm for details and to register. Our team of experts will evaluate your case and give a personalized list of suggestions to look into.

Surgery:
My first treatment would be **surgery**. It is pretty important to choose an experienced surgeon who has a better chance of removing more of the tumor with less damage. The ABTA has a list of experienced teams at https://www.abta.org/about-brain-tumors/treatments-side-effects/find-a-brain-tumor-center/. I would add the use of **Gleolan** (5-ALA) to increase the chances of a total resection. There is a trial underway (or about to start) to add **photodynamic therapy** at the time of surgery. Too early to tell but sounds good in theory.

Gamma Tiles have been approved for newly diagnosed as well as recurrent Glioblastoma. This is a radioactive implant placed at the time of surgery, allowing a higher dose of radiation to be delivered precisely where it is needed and at the optimal time – immediately after tumor removal, before regrowth begins. It might add on average about 10 months to the progression free survival time! This buys time for other treatments to work. It is worth considering but check if you are thinking about entering a clinical trial if the use of Gamma Tiles may disqualify you from most trials. I would also consider **Gliadel** if Gamma Tiles weren't available.

I would send some of the tumor removed to make a vaccine such as **DC-VAX**. This vaccine is not yet approved in the USA but is available under a special access program in the UK. It is expensive but at least accessible. The rest of the tumor would be sent for **advanced testing**. See https://virtualtrials.org/PDF2024/biomarkers2024.pdf for details.

Scans: Standard MRIs often struggle to differentiate between various tissue types (tumor, necrosis, swelling, normal brain, or scar tissue). Newer techniques can help distinguish these. My current favorite of the easily available ones is called **Fractional Tumor Burden Mapping**, which is better (but not perfect) at telling what is really live tumor. It gives you a number that is the % of the abnormality which is actually tumor. See https://virtualtrials.org/video2022.cfm?video=202204 for details. I would insist on something like that for all of my scans – as comparing them over time is the best way to tell how the

treatment is going. With standard MRIs, sometimes the scan looks worse even if the tumor is not progressing, a phenomenon called pseudo-progression, which could lead to unnecessary changes in treatment.

Radiation:

There are many types of radiation, and it is beyond the scope of this article to specify which type to use in each situation, so this choice should be left to your medical team. Typically, Temozolomide is used concurrently with radiation to enhance its effect. Using **Gamma Tiles** at the time of surgery might allow you to delay standard radiation until after other treatments or possibly replace standard radiation altogether.

Other Approved Treatments:

Temozolomide: This is an FDA-approved standard treatment. A biomarker called MGMT can indicate prognosis. If the pathology report shows MGMT Unmethylated, there's a lower chance of Temozolomide being effective—not zero, just less than if MGMT is Methylated. It is typically continued for an additional 6–12 months after radiation ends. I would probably choose to use Temozolomide if my MGMT was methylated but might avoid it if MGMT unmethylated.

Gliadel: These are biodegradable wafers inserted into the brain during brain tumor surgeries – either at initial surgery or any following surgeries for recurrences, which slowly release Carmustine to the tumor bed. They buy time for other treatments to work and a new trial is starting that combines Gliadel with a checkpoint inhibitor for newly diagnosed Glioblastoma - patients with unmethylated MGMT do not use Temodar, but those with methylated MGMT do use Temodar. (Carmustine is not affected by MGMT methylation status). Preclinical studies on this combination are very promising. Gliadel might make you ineligible for some trials, so you need to plan out your course of treatment before deciding but they offer a known benefit at relatively little side effects or hassles so worth considering.

Gleostine: Also known as CCNU or Lomustine. There is some evidence that adding Gleostine to Temozolomide has better results than Temozolomide alone – especially if MGMT is methylated. However, it also increases the chances of side effects. The combination may be best for younger, stronger patients, and I would consider it for myself, unless I was adding other drugs – and did not want to take the risk of needing to stop all drugs because of side effects

Optune: This is an FDA approved device applied to the skull using adhesive arrays and delivers tumor treating fields to the tumor. See https://virtualtrials.org/optune/NVCR_Clinical_Evidence_Flipbook_June-2024.pdf This has the best reported outcomes of any approved treatments for glioblastomas. The link shows ways to make it work even better. The suggested usage is at least 75% of the time, but if you use it over 90% of the time, the results are much better. Adding a **checkpoint inhibitor** probably increases the effectiveness of **Optune**.

Some doctors do not recommend Optune as they think it is too much of a hassle to use or worry that it makes you ineligible for a clinical trial. However – you should be the one making the decision based on information about the choices and your values. I would definitely try Optune and probably a checkpoint inhibitor. The biggest mistake I see people do is stop too early. The first scan after starting Optune is usually worse due to pseudoprogression. See this article for why: https://virtualtrials.org/optune/Musella/Musella.pdf So I would use the advanced scans mentioned above to make sure that I do not stop too early.

Avastin: This is a VEGF-inhibitor. By itself it did not really improve overall survival, but it does work well to reduce swelling, like a super steroid. Some of the other treatments I mentioned could cause potentially life threatening swelling, so if the swelling gets bad, I would use Avastin to combat it.

Experimental or "off label" treatments: There are many to choose from. Our patient navigation program can help you select the best ones for you. Here are a few of my favorites, and I would choose to use the ones that I could get easiest access to, and follow with advanced imaging and change at first sign of treatment failure.

Onc-201: if the tumor is in the midline structures, especially thalamus or brainstem, or in younger people, consider testing the tumor for H3K27M mutation or a low EGFR level. If either is present, consider **Onc-201**. It is not yet approved but is available in a clinical trial, and possibly on expanded access.

5-ALA: The concept of 5-ALA is elegant. A dye called 5-ALA (approved as oral Gleolan and experimental in an injectable format) is administered to the patient, where it is preferentially absorbed by tumor cells rather than non-tumor cells. When exposed to a special frequency of light, it causes the tumor cells to glow, helping the surgeon identify and remove any remaining tumor tissue during surgery. Additionally, when a laser is applied to the area, the dye-absorbed cells are destroyed. This is the essence of photodynamic therapy.

Photodynamic therapy with 5-ALA has some limitations, as the laser cannot penetrate deeply into the brain or pass through the skull, making the procedure invasive. It is currently experimental, but if the surgeon I choose is willing, I would consider trying it whenever I was having surgery anyway – but I wouldn't have a surgery just to use this.

There is also a non-invasive approach to targeting cells that absorb 5-ALA called **sonodynamic therapy.** In this method, focused ultrasound is directed at the tumor through the skull. When the 5-ALA is excited by the ultrasound, it selectively destroys tumor cells while sparing normal cells. This technique can be repeated as needed, either to treat new areas of growth or even prophylactically in regions where recurrence is anticipated. I would likely opt for sonodynamic therapy once a month for the first year, then as needed thereafter.While sonodynamic therapy for glioblastoma is not yet FDA-approved, it is currently in clinical trials. The components of

this treatment are already approved, which might expedite its pathway to full FDA approval.

Niraparib is a parp inhibitor approved for other types of cancers and should be able to be obtained off label. This stops the cancer calls from repairing damage to the DNA and should make most other treatments we use work better. We do not yet know the best combination but worth considering especially for MGMT unmethylated Glioblastomas.

Gallium Maltolate This is an experimental oral drug that also has an elegant mechanism of action and early promise. See https://virtualtrials.org/video2024.cfm?video=202403 for details. It is available in clinical trials, or if you can not participate in the trial, an expanded access program is available.

MDNA55 is an IL4R targeted toxin with impressive early results.

Survaxm, CeGat, Gliovac, Jaime Leandro Foundation Vaccine, ImVax, Pan American vaccine, CMV Vaccine (and others). I like the concept of vaccines and would choose to use at least one. My choice would be DC-Vax or Gliovac if possible, because they are custom made from my tumor and attacks all of the targets in the tumor, but if not available, I would choose one of the other vaccines. Too early to really tell which is best, so I would get the one that is easiest to get. None of these are approved yet – so it is a challenge and expense to get them.

Car-T cells and Viral Therapies: There is a lot of excitement about Car-T cell therapies. It has cured some other types of cancers, but not yet glioblastoma. Every generation of CAR-T cell gets better and we are getting closer. There are many viral based therapies in development and they show some early promise. Lerapolturev (used to be known as PVSRIPO) shows promise and a new trail recently launched. See https://virtualtrials.org/video2024.cfm?video=202405 for details. **Delytact** is another viral therapy with impressive results and is approved in Japan but not easily accessible for Americans.

Some **antidepressant drugs** are thought to help with the tumor – and depression is common with brain tumors anyway – so may be worth a try. See https://virtualtrials.org/PDF2024/antidepressants.pdf for details.

There are 2 protocols of combining off label drugs that I like: **Care Oncology protocol** https://careoncology.com/the-coc-protocol-in-glioma/ they use a few off label drugs along with Temozolomide to try to hit the tumor from many sides. **CUSP9v3** is another combination https://academic.oup.com/noa/article/3/1/vdab075/6308707#google_vignette . Both of these look good, and are worth considering, but we do not yet know which combination is the best and a subset of CUSP9 might work just as well with less side effects and cost.

Checkpoint Inhibitors: Cancer cells are tricky, and manage to avoid being attacked by the immune system by generating signals called checkpoints that block the immune attack. It is like putting up a "do not disturb" sign on the tumor cells. Checkpoint inhibitors, and many are FDA

approved for other cancers and can easily be used off label, take down that “do not disturb” sign and allow the immune system to attack the tumor. Many trials have shown that checkpoint inhibitors by themselves do not help much (except a small trial showing that if using them before surgery they may help). The reason for this is there are not many immune cells in the area of the tumor to fight the tumor. I feel something needs to be done to trigger an immune response to get the cells in place, then use the checkpoint inhibitor to really unleash the immune system. This can be anything that causes the cells to die which triggers an immune response, such as the vaccines, viral therapies, or even Optune.

I would consider one or more of the above, especially if it were possible to add it to other treatments.

Disclosure: The following companies are or have been sponsors of the Musella Foundation: Novocure Ltd (Optune), GT Medical (Gamma Tiles), Chimerix (Onc-201), Genentech(Avastin)