MEDINT
Medical Intelligence Ltd.

- Confidential -
1409-2872

This report is comprised of relevant and updated findings available. In accordance with the provided personal details, and pre-defined questions we have indicated data and insights taken from various sources of information. These insights aim to inform and enhance future decisions. In no circumstances the information contained in this report or any information given in the process are intended or implied to be a substitute for professional medical advice. It is provided for informative purposes only. We have given careful thought in order to construct the report in a way that suits both patients and physicians. We strongly encourage you to use this report and consult your physician before making any medical decisions.

Serial Number: 1409-2872
Date: 10/02/2019

Methodology

This is a personal health meta-research designed to address specific pre-defined queries. For that purpose, we have conducted an extensive search through relevant medical databases, journals, and other trusted sources. We have also reviewed unofficial platforms such as relevant social media, forums and blogs and extracted insights from similar patients relevant as much as these were relevant to the situation at hand. We have analyzed the data, evaluated the reliability of the sources of information and the relevancy to the specific case. Finally, we have assembled all insights into an actionable report, which has been reviewed by a senior analyst.

Health reports tend to be complicated to read, so in order to ease the process for the patient we have highlighted parts, which we found important. We also added references as endnotes for sources of information that the patient or his/her physician wishes to further explore. Additional information such as patient's testimonials is added in the footnotes.

This report contains:

1. Patient Summary
2. Meta-Research
3. Doctor's Letter

Patient Summary

טיפולים קונבנציונליים

1. טיפול ב-Eflornithine – נמצא במחקרים כמעלה את חציון ההישרדות כאשר ניתן יחד עם כימותרפיה מסוג PCV (Procarbazine, Lomustine and Vincristine, פירוט בהמשך) או לבד. נמצא כרגע בשלב 3 של מחקרים קליניים. בעל תופעות לוואי קלות יחסית לכימותרפיות אחרות הנמצאות בשימוש. התרופה זמינה בשלב זה רק כחלק מהשתתפות במחקר/במתן פרטני על ידי החברה.

2. טיפול ב-PCV – שילוב כימותרפי הניתן בחלק מהמטופלים עם אסצטרוציטומה אנפלסטית. קיימת מחלוקת בקרב חוקרים בנושא האם יש לתרופה יתרון על טיפול בטמודל, בעיקר כיוון שטיפול ב-PCV נמצא ככרוך ביותר תופעות לוואי. כפי הנראה טיפול זה כבר אינו רלוונטי בשלב זה כיוון שכבר ניתנו מספר טיפולים של טמודל.

3. טיפול בקרינה ממוקדת – הליך במסגרתו ניתנת קרינה במינון גבוה באופן ממוקד לאיזור הגידול, במטרה לפגוע בגידול עם פגיעה מינימלית ברקמת המוח הבריאה. יש להדגיש כי קרינה חוזרת אינה טיפול שגרתי במקרים מסוג זה, אך ניתן לשקול קרינה ממוקדת במטופלים מסוימים.

4. טיפול ב- Avastin (Bevacizumab) – טיפול בנוגדן הקושר Vascular endothelial growth factor (VEGF) שמעורב בצמיחה לא תקינה של כלי דם בגליומות. הטיפול מאושר לגליומות חוזרות בדרגה גבוהה, אך קיימות עדויות מעורבות בנוגע ליעילותו במצבים אלו. עם זאת, כן נראה שהוא נוטה להיות יעיל בעיקר בקרב חולים מבוגרים עם אסטרוציטומה אנפלסטית.

קיימת אפשרות לטיפול משולב ב- Avastin המוזרק לכלי דם מוחיים יחד עם טיפול רגיל ב- Avastin באמצעות עירוי תוך ורידי. טיפול זה נמצא בשלבים מוקדמים של ניסויים קליניים.

5. טיפול ב- Optune (נקרא בעבר TTF -Tumor-Treating fields) – התקן נישא המולבש על ראשו של המטופל למשך 18-22 שעות ביום למשך תקופה מינימלית של ארבעה שבועות. קיימות עדויות לשיפור בהישרדות בקרב מטופלים עם גליובלסטומה כאשר ניתן בנוסף לטיפול סטנדרטי. חשוב לציין כי יעילות הטיפול תלויה בהקפדה על הנחיות היצרן. יש לבדוק עם הרופא המטפל האם לדעתו טיפול זה יכול להיות רלוונטי גם במטופלים עם אסטרוציטומה בדרגה 3.

טיפולים נסיוניים

1. טיפול בוירוסים DNX-2401 ו-DNX-2440 – טיפול באמצעות וירוסים המוזרקים לתוך הגידול הממוקדים לתאי הגידול. בניסוי קליני בשלב מוקדם (Phase 1) נראה שיפור בהישרדות בקרב מטופלים עם גליומות חוזרות בדרגה גבוהה. בימים אלו נערך ניסוי קליני בשלב 2 (Phase 2) הבודק את השילוב של טיפול בוירוס DNX-2401 עם טיפול בנוגדן Pembrolizumab עם תוצאות ביניים הנראות מבטיחות. כפי הנראה החוקרים אינם מגייסים מטופלים נוספים בשלב זה, נשלח מייל לחברה המייצרת בנוגע לאפשרות קבלת הטיפול באופן פרטני.

2. טיפול ב- PARP Inhibitors – Olaparib – תרופה המאושרת לשימוש בסרטן השחלות ונמצא כי גליומות מסוג IDH-mutant רגישות אליה במיוחד. התרופה נמצאה יעילה במודלים פרה-קליניים ובטוחה בניסוי קליני בשלב מוקדם (Phase 1). בימים אלו נערך ניסוי קליני בשלב 2 (Phase 2). נשלח מייל לחוקרים העורכים את הניסוי.

3. טיפול ב- Laser Interstitial Thermal Therapy (LITT) – טיפול ממוקד באמצעות לייזר שנועד להרוס את תאי הגידול. הטיפול נמצא כיעיל במחקר קטן על מטופלים עם גליובלסטומה חוזרת. בימים אלו נערך ניסוי קליני בשלב 2 (Phase 2) הבודק את הטיפול בשילוב של LITT וכימותרפיה מסוג לומוסטין במטופלים עם גליומות חוזרות (בפרט אסטרוציטומה אנפלסטית). נשלח מייל לחוקרים העורכים את הניסוי.

טיפולים אלטרנטיביים

1. קנבינואידים – קיימים מחקרים המראים כי קנבינואידים יכולים לעזור בטיפול בסרטן, אולם חשוב לציין כי קיימות גם עדויות לכך שהם עלולים להגביר גדילה של תאים סרטניים. ספציפית בנוגע לגליומות, נראתה יעילות במחקרים על בעלי חיים אולם יש עדיין צורך במחקרים גדולים בבני אדם לצורך הוכחה של יעילות.

Diagnosis Summary

A 54-years old male patient, with a history of back surgeries and pain in the right leg, was diagnosed on July 2018 with grade III anaplastic astrocytoma (IDH1 mutant), following weakness and numbness of the right hand and leg and a vertigo episode.

- Following the diagnosis, the patient went through a subtotal resection of the tumor. The tumor was involving the corpus callosum and the lateral ventricles and was observed as suited in characteristics to both low-grade and high-grade gliomas.
- Histological examination of the tumor revealed infiltrating astrocytoma cells, IDH1 mutant (R132H), grade II-III, with low staining of Ki67 (2-7%), positive for P53, with the focal tumor demonstrating morphology and mitotic activity similar to higher grade tumor.

The patient was treated with:

- 6 weeks of radiation + Temozolomide (Temodal) (high-grade glioma protocol), after which MRI results demonstrated no change from the tumor status after the surgery.
- 2 courses of Temodal (320mg for 5 days every month), after which MRI results demonstrated increase in tumor size.

The patient is expected to start treatment with Avastin, and is also treated with Keppra (1000mg*2) and Vasodip (10mg)

This report addresses the following questions:

1. Which conventional and innovative treatments can be effective for treatment of grade III anaplastic astrocytoma with IDH mutation, after tumor resection and treatment with radiotherapy and chemotherapy (Temodal), worldwide?
2. Which clinical trials are testing treatments that can be relevant for treatment of grade III anaplastic astrocytoma with IDH mutation, after tumor resection and treatment with radiotherapy and chemotherapy (Temodal), worldwide (with a focus on Israel)?
3. Who are the leading experts in the field of astrocytoma worldwide?

Research Information

Thorough research was performed to best address the questions mentioned above. We explored formal medical databases and journals, as wells as unofficial platforms such as personal blogs and forums, in which patients share their knowledge and experience with battling the disease.

Based on the collected information, we contacted numerous experts, services, companies, and researchers in an attempt to gather the most relevant, up-to-date data regarding treatment options for the disease.

All research products are summarized below, including answers provided by services we contacted with.

Conventional treatment options

According to the National Comprehensive Cancer Network (NCCN) recommendations, the current standard of care[1] for grade III anaplastic astrocytoma with IDH mutation include maximal surgical resection followed by combination therapy of radiation and chemotherapy[2]. **Other options include**:

1- Additional systemic chemotherapy options

1.1- Eflornithine

- **What is it?:** Eflornithine is an inhibitor of a key metabolic enzyme that can affect DNA stability and inhibit cell growth and proliferation[80].
- **Efficacy evidence**: Eflornithine showed a clinically meaningful increase in median overall survival[81] in patients with recurrent anaplastic gliomas when used alone and in combination with PCV. The addition of eflornithine led to a median progression-free survival (PFS) of 71.1 versus 37.5 months with PCV alone in patients with anaplastic gliomas and 56.2 versus 22.2 months in patients with anaplastic astrocytoma[82].
- **Stage of development:** The drug is developed by Orbus Therapeutics, Inc. (website), and is being tested in phase 3 clinical trial[83]. It was granted Breakthrough Therapy Designation by the FDA[84], which means it has provided evidence that it can provide a substantial improvement over existing therapies. The drug is already FDA approved to treat African trypanosomiasis, a type of sleeping sickness, and as a topical cream for the removal of unwanted facial hair in women.
- **Side effects:** Eflornithine toxicity is relatively mild in comparison to currently used chemotherapies for gliomas with reversible hearing impairment and tinnitus being the most noticeable. When used as a single agent in high doses, it can also cause granulocytopenia[85] (decrease in granulocytes, immune cells).

- **How to get it?**: The drug is not available yet, but can be obtained by applying for an expanded access program of the company (link). It is also being evaluated in phase 3 clinical trial[86] in combination with lomustine[87] in patients with recurrent anaplastic astrocytoma. **See table below**

1.2- PCV

- **What is it?**: PCV is a chemotherapy combination that includes **Procarbazine, Lomustine** (also called CCNU) and **Vincristine**. You have vincristine as a drip into your bloodstream (intravenously). Lomustine and procarbazine come as capsules that you swallow whole. In the neuro-oncology community, a debate is currently ongoing on whether the PCV and temodal are interchangeable [3].
- **Efficacy evidence**: No significant difference in the efficacy of the treatment was found in a trial comparing temodal and PCV in patients with high-grade gliomas in a study from 2010[4], and there is an ongoing trial[5] comparing the efficacy of the two chemotherapies in patients with anaplastic glioma. However, according to a recent review, PCV treatment can be of benefit[6] for patients with IDH-mutated astrocytoma.
- **Side effects:** PCV is considered to have more side effects compared to temodal, which is why it has been largely replaced[7] by temodal[8].
- **How to get it?**: PCV can be prescribed by your doctor as it is one of the standard treatments for gliomas.

2- Focused non-invasive radiation- Novalis Shaped Beam Surgery

- **What is it?**: Radiosurgery is a radiation procedure that uses a special system to precisely deliver a large radiation dose to the tumor. The goal of this non-invasive procedure is to destroy the target without surgery or harming nearby healthy tissue. It is used to treat brain tumors and other brain disorders. Novalis is an advanced device for radiosurgery, in which the treatment beams are shaped to match the exact structure of the tumor[13] so that even irregularly shaped tumors can receive doses of radiation consistent with what has been prescribed, effectively destroying the tumor and sparing the healthy tissue.
- **Efficacy evidence**: The device was shown to be safe and effective[14] in treating patients with metastatic brain tumors.
- **Side effects:** Novalis can use a specific form of radiation (fractionated stereotactic radiotherapy) that is given in small amounts through several sessions, so that healthy tissue can recover from session to session. Common side effects include headaches and dizziness.
    - It should be mentioned that the standard protocol for your case does not include re-radiation because of the risk of neurotoxicity. However, such focused radiation can be considered.
- **How to get it?**: The treatment can be obtained worldwide, including at Ichilov hospital in Tel Aviv (link).

3- Targeted therapy- Avastin (Bevacizumab)

- **What is it?**: Avastin (anti-VEGF-A) is an antibody that was approved by the FDA in May 2009 as a first-line treatment of recurrent GBM patients[15]. Even though it is commonly used for such states, there is mixed evidence regarding its efficacy:
- **Efficacy evidence**:
  - According to some[16] reviews[17] there is no strong evidence for the benefit of using Avastin for recurrent grade III gliomas.
  - There is evidence for its efficacy[18], specifically for the older patient in anaplastic astrocytoma[19].
  - A retrospective stud[20]y showed that the use of avastin in patients with recurrent anaplastic glioma was not associated with an improvement in progression-free survival, and may be associated with poorer overall survival (when compared to other chemotherapies).
  - Another retrospective study[21] determined that avastin has activity in cases of recurrent high-grade gliomas, but it wasn't a large effect.
  - There are studies claiming that avastin should be used in combination with other drugs[22], or should be given again after its first use[23] to gain a better effect.
- **Side effects**: The most common side-effects of avastin[24] include hypertension (high blood pressure) , fatigue , constipation, diarrhea and abdominal pain , nosebleeds or rectal bleeding , dry or inflamed skin and back pain or headaches.
  - Since you are taking Vasodip, blood pressure should be monitored closely throughout the treatment with avastin.
  - Serious and less common side effects also include severe bleeding and gastrointestinal perforation (hole in the stomach or intestine).
- **How to get it?**: There is a phase 1+2 trial[25] that is currently recruiting patients, which is testing the effect of adding a selective injection of avastin to the tumor along with "regular" IV treatment with avastin to enhance its efficacy. **See table below**
  - This treatment was shown to be safe and effective[26] in a phase 1 trial.
  - Since you fit the trial criteria, if you wish to participate you can contact John Boockvar, MD at the Feinstein Institute for Medical Research (phone: +1212-434-3905 mail: jboockvar@nshs.edu). An email was sent to the trial organizers.

4- Optune (Tumor-Treating fields- TTF)

- **What is it?**: Optune® is a wearable, portable, FDA-approved device for newly diagnosed or recurrent glioblastoma[27], developed by Novocure Ltd. based on the research of Yoram Palti in Israel.
    - It is a portable device worn on the patient's shaved head for 18-22 hours per day (breaks allowed for showers) that delivers electric currents in a non-invasive manner, that interfere with active cell division. Four weeks is considered to be the minimum interval to reverse tumor growth and preliminary trials have studied the use of the device for periods of a year or more.
- **Efficacy evidence**: Clinical evidence showed an increase in overall survival of recurrent glioblastoma patients[28] when using TTF in addition to standard therapy, and also similar efficacy as chemotherapy, with an improved patient-reported quality of life and a lower incidence of serious adverse events.
    - It is important to note that the device's effectiveness is dependent on the adherence to the manufacturer instructions.
    - Even though the main focus of the study around this device is newly diagnosed and recurrent glioblastoma, there is also evidence on testing it for grade III glioma[29] in early stage trials[30].
- **Side effects:** Most common side effects[31] using the device are scalp irritation (redness and itchiness) that can be treated with over-the-counter lotions.
- **How to get it?**: This device is an acceptable treatment option in the US, given in over 600 treatment centers. It is also available internationally, including in Israel, by Prof. Zvi Ram, Tel Aviv Medical Center.

Novel treatment options

DNX-2401 & DNX-2440 Virus therapy

- **What is it?**: These are virus therapies that are developed by the company DNAtrix therapeutics[32] for recurrent glioblastoma, with DNX-2401 at a more advanced stage of development. In virotherapy, viruses are injected into the tumor, specifically target the tumor cells, and kill them. The tumor cells' death stimulates an additional immune response. DNX-2401 has been granted PRIME and Orphan designation by the EMA and Fast Track and Orphan designation by the FDA, which means its approval will be enhanced[33].
- **Efficacy evidence**: In a phase 1 trial with DNX-2401, tumor reduction was observed in 72% of patients[34] (18 of 25), with a median overall survival time of 9.5 months regardless of dose. Five patients (20%) survived for more than 3 years, three of whom had a ≥ 95% reduction in a cross-sectional area of the enhancing tumor.
- **Side effects:** Only two patients in the phase 1 trial experienced adverse events related to DNX-2401, including grade 1 to 2 headaches, nausea, confusion, vomiting, and fever.

- **How to get it?**: A phase 2 clinical trial[35] (active, not recruiting) conducted in multiple centers in the US and Canada evaluated the efficacy and safety of DNX-2401 in combination with pembrolizumab (KEYTRUDA) in patients with recurrent glioblastoma, in collaboration with the pharmaceutical company Merck. Interim results that were published for this trial claim that the combination of the two agents is well tolerated and associated with promising survival[36].
    - According to the trial organizers, they are not recruiting patients anymore. An email was sent to the company to try and obtain the drug through expanded access or compassionate care programs.

Poly-ADP-ribose-polymerase (PARP) inhibitors- Olaparib

- **What is it?**: PARP inhibitors have recently been proposed for the treatment of IDH-mutant tumors, since it was discovered in 2017 that IDH-mutant gliomas appear especially sensitive to PARP inhibitors. They are already FDA approved for the treatment of Ovarian cancer[37]. Olaparib[38] is a PARP inhibitor, which blocks a specific enzyme that supposes to fix DNA damage, and by blocking the ability of DNA repair cause cancer cells to die.
- **Efficacy evidence**: PARP inhibitors, either alone or in combination with Temozolomide, have shown powerful anticancer activity[40] in preclinical [41]models of IDH1 mutated gliomas. A phase 1 clinical trial demonstrated that the combination of Olaparib with temodal is safe and tolerated[42].
- **How to get it?**: There is a phase 2 clinical trial[43] that aims to test Olaparib in patients with glioma with IDH mutation that has progressed despite standard therapy, or for which no effective standard therapy exists. The trial is recruiting in multiple sites in the US and is sponsored by the National Cancer Institute (NCI) . **See table below**
    - Since you fit the trial criteria, if you wish to participate you can contact Patricia LoRusso at Yale University Cancer Center LAO (phone (Site Public Contact): +1-203-785-5702 mail: canceranswers@yale.edu). An email was sent to the trial organizers.

Laser Interstitial Thermal Therapy (LITT)

- **What is it?**: LITT [44]is an emerging technique to treat primary and metastatic brain tumors that can be hard to reach with conventional surgery. In this procedure, a laser catheter is implanted into the tumor using real-time MRI and minimally invasive technique. It typically requires only a 2-millimeter incision in the scalp, and takes only a few minutes to perform. The heat of the laser is then being used to kill the tumor cells.
- **Efficacy evidence**: This technique was shown to be effective in recurrent glioblastoma patients[45]: 5 out of 13 patients with recurrent disease demonstrated response of tumor shrinkage after the treatment.

- **How to get it?**: There is an ongoing phase 2 clinical trial[46] that is recruiting patient to test LITT using the NeuroBlate System in combination with lomustine (both are approved as a single treatment by the FDA) in recurrent glioma patients, specifically in anaplastic astrocytoma patients. **See table below**
    - Since you fit the trial criteria, if you wish to participate you can contact Barbara J. O'Brien, MD at the M.D. Anderson Cancer Center (phone: +1-713-792-2883 mail: bjobrien@mdanderson.org). An email was sent to the trial organizers.
- LITT can be performed in multiple leading brain cancer specialized centers such as MD Anderson Cancer Center, UCSF brain tumor center, and Johns Hopkins. The technique is also used in Israel (Tel Aviv Sourasky Medical Center, Ichilov) for epilepsy ablation surgery.

Toca 511 & Toca FC (combined virotherapy with selective chemotherapy)

- **What is it?**: This treatment combines a virally delivered gene therapy with integrated chemotherapy: the Toca-511 is injected to the tumor, and this virus infects only cancer cells and creates a special protein, that later on creates a chemotherapeutic drug from Toca FC within the tumor cells only. This allows for killing cancer cells with the virus combined with the delivery of a highly selective, tumor-specific dose of chemotherapy to tumor cells only without the systemic toxicity[47].
- **Efficacy evidence**: Pre-clinical studies[48] in glioma mouse models showed tolerability and immunotherapeutic activity[49]. Phase 1 trial[50] demonstrated the safety and possible efficacy[51] of this treatment in recurrent high-grade glioma patients[52]. The patients that responded to the treatment demonstrated multiyear survival, and it was concluded that this treatment might be specifically beneficial for patients with IDH1 mutant and first recurrence of the tumor.
- Following these encouraging results, the FDA has granted Toca 511 & Toca FC Breakthrough Therapy Designation for the treatment of recurrent HGG and the European Medicines Agency (EMA) has granted Toca 511 PRIME (PRIority MEdicines) designation for the treatment of glioma, which means its approval will be enhanced[53].
- **How to get it?**: A phase 2+3[54] randomized trial is currently evaluating the treatment (active but nor recruiting) in patients with recurrent high-grade gliomas. We are trying to find ways to obtain the drug as the trial is no longer recruiting and the company does not provide expanded access or compassionate care programs.

Methylation inhibiting agents

- **What is it?**: Since the main effect of a mutation in the IDH1 gene[55] is the creation of hypermethylation on the DNA, research is also focused on understating the effect of approved drugs that reduce this methylation on glioma patients.
- **Efficacy evidence**: Pre-clinical in-vitro and in-vivo studies have shown that Decitabine[56] and 5-azacitidine[57] inhibit the growth of glioma cells and mouse model tumors, specifically in combination with Temodal in mice models of IDH1 mutated glioma[58]. These 2 drugs are FDA approved and routinely used in myelodysplastic syndrome and are well tolerated.
- **How to get it?**: There is a planned (not yet recruiting) phase 2 clinical trial[59] that will be conducted in Paris to evaluate the efficacy of a treatment by azacitidine in recurrent IDH mutated grade II and III gliomas.
    - An email was sent to the trial organizers to check if this drug can be obtained outside the trial.

IDH-1 Inhibitor FT-2102

- **What is it?**: The mutated IDH1 enzyme contributes to the process of tumor progression, and inhibiting its activity can fight cancer. Forma Therapeutics is developing the IDH-1 inhibitor FT-2102[60], a drug given orally, for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and glioma patients.
- **Efficacy evidence**: In a phase 1 trial, the drug showed to be safe and tolerable[61] and demonstrated anti-leukemic activity[62] (overall response rate- 32%) in patients with IDH1-mutated acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).
- **Side effects:** Severe side effects occurred in ≤5% of the patients[63].
- **How to get it?**: FT-2102 is now being tested in a non-randomized phase 1+2 clinical trial[64] for advanced gliomas. The trial is recruiting at the University of Miami, Sylvester Comprehensive Cancer Center in Florida, US. **See table below**
    - Since you fit the trial criteria, if you wish to participate you can contact Kathryn Lipford, MD from Forma Therapeutics (phone: +1-857-209-2204 mail: klipford@formatherapeutics.com).
    - An email was sent to the trial organizers, and they responded that you indeed fit the trial criteria. They recommended that your physician will contact one of the trial centers. They also mentioned that although the trial is taking place only in the US at the moment, they will be opening centers in Europe (UK, France, and Spain) as well as Asia (South Korea and Australia) in the upcoming months.

Alternative treatment options

Cannabinoids

Research Information

General explanation: There are currently 85 known cannabinoids found in the Cannabis plant, the most prominent of which are Tetrahydrocannabinol (THC) and Cannabidiol (CBD). THC is responsible for the high sensation together with its health-related effects (pain and nausea relieve, anti-inflammatory and anti-oxidant), while CBD exerts many of the same health benefits without creating a "high" sensation. While there's some promising research surrounding the use of cannabis to treat cancer, experts are still a long way from having conclusive evidence about which cannabinoids and strains work best and in which dosage. In addition, some research suggests that THC can actually increase the growth of cancer cells[65]. Specifically for gliomas, several early in-vitro and in-vivo studies showed that:

- THC and CBD increased the effectiveness of radiation[66] against an aggressive type of brain cancer in mice models.
- Cannabinoids inhibited Angiogenesis, Invasion, and Metastasis[67] in glioma cells.
- The combined administration of cannabinoids and temozolomide was very effective in a mouse model[68].

Even though cannabinoids were shown to be highly effective in animal models in terms of tumor reduction, large human studies are needed before cannabis becomes a recommended cancer treatment. Recently, there have been a few early-stage clinical trials[69] involving small numbers of human participants[70] with cancer, specifically recurrent gliomas, demonstrating the safety and possible efficacy of using cannabinoids[71], alone or in combination with chemotherapy. While these studies have shown that cannabinoids are safe to use in cancer patients, they don't fully demonstrate whether cannabinoids can help treat or control cancer[72]. It should be noted that cannabis can have unwanted interactions with other drugs listed here.

Researched cannabinoids option: Sativex- a liquid form of cannabis (Sativa plant) in the form of inhaler spray that contains THC and CBD in a 1:1 ratio, and has been approved in over 25 countries for the treatment of spasticity due to Multiple Sclerosis and neuropathic pain. Pre-clinical results using mouse models of glioma showed anti-tumor effect[73] when Sativex was combined with Temozolomide.

- Preliminary results[74] of phase 1+2 trials[75] showed that Sativex is safe to use and that patients with recurrent Glioblastoma that were treated with Sativax+Temozolomide (38) had higher survival after one year compared to patients treated with Temozolomide alone.
- A previous trial comparing Sativex to placebo in 21 patients with recurrent glioblastoma showed 83% one-year survival rate compared with 53% for patients in the placebo group. The most common adverse events[76] (three patients or more and greater than placebo) were vomiting (75%), dizziness (67%) nausea (58%), headache (33%), and constipation (33%).

- It should be noted that current dosing recommendations for Sativex are based on the approved indications for multiple sclerosis and cancer pain management, not as an actual cancer treatment. Neopharm Ltd is the Sativex manufacturer partner in Israel and therefore any inquiries relating to Sativex® in Israel should be directed to Neopharm.
- *An email was sent to Neopharm, and we received this answer: "*Sativex is approved in Israel for MS patients for pain and spasticity, and for pain associated with cancer, both with physician' reference. Sativex may be purchased from kupat holim for these indications, or purchased privately from the company or from private pharmacies. Feel free to contact us for further information.*" (contact: medinfo@neopharmgroup.com)

Clinical trials that are testing relevant treatments

Clinical Trials

Therapy	Trial description	Therapy description	Phase and placebo	Location, contacts and next steps
Eflornithine With Lomustine link link	The purpose of this study is to compare the efficacy and safety of eflornithine in combination with lomustine, compared to lomustine taken alone, in treating patients whose anaplastic astrocytoma has recurred/progressed after radiation and temozolomide chemotherapy. Patients are randomly assigned to one of the two treatment groups. Treatment lasts up to 12 or 24 months, depending on the treatment group. In order to join the trial, you have to be 6 months after radiation, and you can't start any other systemic treatment.	Eflornithine is an oral novel cytostatic (inhibiting cells growth) drug, which is developed specifically for anaplastic astrocytoma patients by Orbus Therapeutics, Inc. (website). Lomustine [77](CeeNU® or Gleostine®) is a chemotherapy drug affecting cell growth that is used to treat certain types of cancers, including brain cancers. It is often used to treat patients with recurrent anaplastic astrocytoma but it is not specifically licensed for the treatment of it.	Phase 3 No placebo	**Location** : California, USA **Contacts**: +1-6504506634 marietta.franco@orbustherapeutics.com *An email was sent to the trial organized to check for compassionate use option

Research Information

Therapy	Trial description	Therapy description	Phase and placebo	Location, contacts and next steps
Avastin + avastin injection link	The trial is testing the effect of adding a selective injection of avastin to the tumor along with "regular" IV treatment with avastin to enhance its efficacy. This is a non-randomized open-label trial.	Avastin (anti-VEGF-A) is an antibody that was approved by the FDA in May 2009 as a first-line treatment of recurrent GBM patients. The combined treatment with the injection was shown to be safe and effective[78] in a phase 1 trial.	Phase 1+2 No placebo	**Location :** Lenox Hill Brain Tumor Center New York, New York, United States, 10065 **Contacts**: +1-212-434-3905 jboockvar@nshs.edu An email was sent to the trial organizers.
Olaparib link	The trial aims to test Olaparib in patients with glioma with IDH mutation that has progressed despite standard therapy, or for which no effective standard therapy exists. This is a non-randomized open-label trial.	Olaparib[38] is a PARP inhibitor, which blocks a specific enzyme that supposes to fix DNA damage, and by blocking the ability of DNA repair cause cancer cells to die. It is already FDA approved for the treatment of Ovarian cancer and showed safety results in a phase 1 trial.	Phase 2 No placebo	**Location :** Yale University, New Haven, Connecticut, United States, 06520 **Contacts**: +1-203-785-5702 canceranswers@yale.edu An email was sent to the trial organizers.
LITT + Lomustine link	The trial will study the effect of LITT (using the NeuroBlate System) in combination with lomustine (both are approved as a single treatment by the FDA) in recurrent glioma patients, specifically in anaplastic astrocytoma patients. This is a non-randomized open-label trial. In order to join the trial you can't receive prior Avastin treatment.	LITT is an emerging technique to treat primary and metastatic brain tumors that can be hard to reach with conventional surgery. In this procedure, a laser catheter is implanted into the tumor using real time MRI and minimally invasive technique.	Phase 2 No placebo	**Location :** University of Texas MD Anderson Cancer Center, Houston, Texas, United States, 77030 **Contacts**: +1-713-792-2883 bjobrien@mdanderson.org An email was sent to the trial organizers

Research Information

Therapy	Trial description	Therapy description	Phase and placebo	Location, contacts and next steps
IDH-1 Inhibitor FT-2102 link	This Phase 1/2 study will evaluate the safety, efficacy, and optimal dose of FT-2102 as a single agent and in combination with other anti-cancer drugs in patients with advanced solid tumors and gliomas. The study is divided into two parts: single agent FT-2102 followed by combination therapy. This is a non-randomized open-label trial.	Forma Therapeutics is developing the IDH-1 inhibitor FT-2102, a drug given orally, for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and glioma patients.	Phase 1+2 No placebo	**Location :** University of Miami, Sylvester Comprehensive Cancer Center Miami, Florida, United States, 33136 **Contacts**: +1-305-243-0865 txl351@med.miami.edu An email was sent to the trial organizers and they responded that you indeed fit the trial criteria. They recommended that your physician will contact one of the trial centers. They also mentioned that although the trial is taking place only in the US at the moment, they will be opening centers in Europe (UK, France, and Spain) as well as Asia (South Korea and Australia) in the upcoming months.

Experts

Name	Description	Contacts and location
Steven Brem, MD	He serves as the Chief of Neurosurgical Oncology and Co-Director of the Penn Brain Tumor Center at the Hospital of the University of Pennsylvania. His clinical focus is to obtain the best possible outcomes in patients presenting with complex brain tumors, harnessing the current technology of neuroimaging, computer-guided surgery, and brain mapping. He takes part in clinical trials in the field of electrical field therapy, vaccine therapy, anti-angiogenesis therapy, and sophisticated brain mapping. He has vert good reviews from patients and is recognized by "Best Doctors in America" and by "America's Top Doctors".	**Location**: Penn Brain Tumor Center 3400 Spruce Street, 3rd Floor Silverstein Department of Neurosurgery Philadelphia, PA 19104 **Phone**: +1 (215) 662-3487 **Mail**: steven.brem@uphs.upenn.edu Link
Dr. Andrew Kanner	A senior neurosurgeon specialized in complex brain tumors, experienced in tumor removal (both primary and secondary tumor) from difficult locations (specifically speech and movement areas). He was a pioneer in the field of stereotactic radiotherapy in Israel, and is one of the most experienced doctors in Israel with this technique. He is listed in the Forbes best doctors in Israel list.	**Location**: Beilinson hospital (Clalit) and Asuta center **Phone**: 03-7644444 (Asuta) **Mail**: andrewka@clalit.org.il Link

Research Information

Name	Description	Contacts and location
Henry S. Friedman, MD	Dr. Henry S. Friedman is an internationally renowned neuro-oncologist who helps lead The Preston Robert Tisch Brain Tumor Center at Duke University. He is the author of more than 500 peer-reviewed articles, reviews, and book chapters. He is involved in a broad spectrum of approaches including chemotherapy, viral therapy, immunotherapy, stem cell therapy, and vaccine therapy.	**Location**: Duke Cancer Center 20 Duke Medicine Circle Durham, NC 27710 **Phone**: +1 (919) 684-5301 **Mail**: henry.friedman@duke.edu Link
Susan Chang, M.D.	Director, Division of Neuro-Oncology. An internationally recognized leader in the field of neurological malignancies. Dr. Chang's research expertise is in clinical trial design and the development of novel therapies. She is involved in more than 20 active clinical trials that evaluate treatments such as chemotherapy, targeted agents, immunotherapy, and convection-enhanced delivery of novel agents. The neuro-oncology department in USCF is highly recommended, and this blog probably talks about Dr. Chang specifically[39].	**Location**: Brain tumor center, University of California, San Francisco. 400 Parnassus Ave., Eighth Floor, San Francisco, CA 94143, USA **Phone**: +1 (415) 353-2966 **Mail**: ChangS@neurosurg.ucsf.edu Link
The Neurological Surgery, P.C. (NSPC) center	This is a brain tumor center that can provide treatment with a multi-disciplinary team that includes radiation neuro-oncologists, neurophysiologists, neuropsychologists and neurosurgeons. They have medical centers located on Long Island and the New York area, and they offer award-winning doctors to treat the most complex brain conditions with world-class care.	**Location**: Neurological Surgery, P.C. 100 Merrick Road, Suite 128W Rockville Centre, NY 11570, USA **Mail**: info@nspc.com Link
Brain and Spine Center at MD Anderson	The Brain and Spine Center is a multidisciplinary clinical and research unit devoted to the development of improved treatments for brain and spine tumors. It is one of the largest centers of its kind, with 40 physicians and scientists in nine specialty areas. Physicians work closely with scientists, who research anti-cancer drug development and the molecular biology and genetics of tumors of the nervous system.	**Location**: 1515 Holcombe Blvd, Houston, TX 77030 USA **Phone**: +1-713-745-0450 **Mail**: Contact form Link

Additional information

- The Israeli Cancer association runs support groups throughout the country (link).
- The brain tumor forum of the Israeli Cancer association can be accessed through here.
- "Gisha La'haim" is a non-profit organization that promotes the well being of the patient throughout their healing process.

Clinical trial phase definitions:

Research Information

Clinical trials = Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people.

Phase	Description
I	Phase I is the first stage in the clinical development of a medicinal product. It is to ensure a treatment is safe for people to take, rather than to try to treat a condition. These trials are very small, (typically around 30 people), and usually involve healthy volunteers or sometimes patients.
II	Phase II aims to investigate the safety and effectiveness of a potential therapy. Usually between 100 and 300 people will be enlisted to take part with the aim of determining whether the treatment will be safe and effective to treat a condition.
III	If previous trials have indicated a treatment is safe and that it also shows promise in being able to treat a condition, phase III clinical trials begin. These involve large numbers of participants, usually from several hundred to several thousand subjects, and are often spread between different hospitals and countries. If these trials show that a drug is safe and effective, the manufacturers can apply for a marketing authorization.
IV	Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

References

Research Information

1. https://link.springer.com/article/10.1007/s11864-018-0579-0
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5735229/
3. https://www.futuremedicine.com/doi/10.2217/cns.15.36
4. https://www.ncbi.nlm.nih.gov/pubmed/20855843?dopt=Abstract
5. https://clinicaltrials.gov/ct2/show/NCT00887146
6. http://sci-hub.tw/10.1007/s11864-018-0579-0
7. http://ascopubs.org/doi/10.1200/JCO.2009.23.6497
8. http://www.ascopost.com/issues/march-10-2017/low-grade-gliomas-understanding-the-new-treatment-paradigm/
13. http://www.sdradiation.com/novalis-shaped-beam-surgery.php
14. https://www.redjournal.org/article/S0360-3016(08)01480-6/fulltext
15. https://www.ncbi.nlm.nih.gov/pubmed/23868553
16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5404815/#R70
17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3633547
18. https://www.ncbi.nlm.nih.gov/pubmed/18953491
19. http://astrocytomaoptions.com/bevacizumab-avastin/
20. https://academic.oup.com/neuro-oncology/article/15/suppl_3/iii98/1088904
21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494648/
22. http://astrocytomaoptions.com/bevacizumab-avastin/
23. https://academic.oup.com/nop/article/4/1/15/2661725
24. https://www.thebraintumourcharity.org/understanding-brain-tumours/treating-brain-tumours/adult-treatments/bevacizumab-avastin/
25. https://clinicaltrials.gov/ct2/show/record/NCT01269853?term=Phase+I%2FII+Trial+of+Repeated+Super-Selective
26. https://www.northwell.edu/clinical-trials/14-353
27. http://astrocytomaoptions.com/electric-field-therapy-novo-ttf/
28. http://astrocytomaoptions.com/electric-field-therapy-novo-ttf/
29. http://astrocytomaoptions.com/electric-field-therapy-novo-ttf/
30. https://clinicaltrials.gov/ct2/show/record/NCT03128047?term=optune&draw=8&rank=4
31. http://astrocytomaoptions.com/electric-field-therapy-novo-ttf/
32. https://www.dnatrix.com/pipeline/
33. https://www.dnatrix.com/pipeline/#2401

References

34. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6075856/
35. https://clinicaltrials.gov/ct2/show/NCT02798406
36. https://oncozine.com/interim-phase-ii-results-of-dnx-2401-pembrolizumab-for-glioblastoma-shows-remarkable-results/
37. https://www.thebraintumourcharity.org/media-centre/news/research-news/ovarian-cancer-drug-olaparib-to-treat-glioblastoma/
38. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/olaparib
39. https://thelizarmy.com/2017/07/how-i-chose-my-new-neuro-oncologist/
40. https://www.ncbi.nlm.nih.gov/pubmed/28202508
41. https://www.ncbi.nlm.nih.gov/pubmed/28148839
42. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.2022
43. https://clinicaltrials.gov/ct2/show/record/NCT03212274
44. https://www.mdanderson.org/treatment-options/laser-interstitial-thermal-therapy.html
45. https://www.ncbi.nlm.nih.gov/pubmed/27690657
46. https://clinicaltrials.gov/ct2/show/NCT03022578?recrs=a&cond=Anaplastic+Astrocytoma&age=1&phase=123&rank=6
47. https://tocagen.com/product-candidates/#toca_diagram
48. https://academic.oup.com/neuro-oncology/article/18/10/1390/2223004
49. https://www.ncbi.nlm.nih.gov/pubmed/28387849
50. https://clinicaltrials.gov/ct2/show/NCT01470794
51. https://academic.oup.com/neuro-oncology/article/20/10/1383/4995454
52. http://stm.sciencemag.org/content/scitransmed/8/341/341ra75.full.pdf
53. https://www.prnewswire.com/news-releases/tocagens-toca-5-pivotal-phase-3-clinical-trial-in-patients-with-recurrent-brain-cancer-continues-without-modification-at-planned-first-interim-analysis-300701404.html
54. https://clinicaltrials.gov/ct2/show/record/NCT02414165
55. http://astrocytomaoptions.com/idh1-mutation/
56. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858559/
57. https://www.ncbi.nlm.nih.gov/pubmed/29427211
58. https://academic.oup.com/neuro-oncology/advance-article-abstract/doi/10.1093/neuonc/noy146/5089721?redirectedFrom=fulltext
59. https://clinicaltrials.gov/ct2/show/record/NCT03666559
60. https://www.ncbi.nlm.nih.gov/medgen/1389961
61. http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.7009

References

62. https://www.ashclinicalnews.org/on-location/meeting-coverage-on-location/evaluating-ft-2102-idh1-mutated-aml-mds/
63. https://ash.confex.com/ash/2018/webprogram/Paper114263.html
64. https://www.clinicaltrials.gov/ct2/show/record/NCT03684811
65. http://cancerres.aacrjournals.org/content/64/6/1943.long#sec-10
66. https://www.ncbi.nlm.nih.gov/pubmed/25398831
67. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791144/
68. https://www.ncbi.nlm.nih.gov/pubmed/21220494/
69. https://academic.oup.com/nop/article/4/3/151/2918616
70. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5692009/
71. https://meetinglibrary.asco.org/record/153300/abstract
72. https://www.healthline.com/health/rick-simpson-oil-cancer#research
73. https://www.ncbi.nlm.nih.gov/pubmed/30125556
74. https://meetinglibrary.asco.org/record/153300/abstract
75. https://www.clinicaltrials.gov/ct2/show/NCT01812603?term=NCT01812603&rank=1
76. https://www.gwpharm.com/about/news/gw-pharmaceuticals-achieves-positive-results-phase-2-proof-concept-study-glioma
77. https://www.stellarstudy.com/caregiver
78. https://www.northwell.edu/clinical-trials/14-353
79. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5404815/#R70
80. http://www.orbustherapeutics.com/product-candidate/
81. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5977277/
82. https://www.oncnursingnews.com/web-exclusives/new-combo-may-treat-rare-brain-tumor
83. https://clinicaltrials.gov/ct2/show/record/NCT02796261
84. http://www.orbustherapeutics.com/product-candidate/
85. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5977277/
86. https://clinicaltrials.gov/ct2/show/NCT02796261
87. https://www.oncnursingnews.com/web-exclusives/new-combo-may-treat-rare-brain-tumor
88. https://www.futuremedicine.com/doi/10.2217/cns.15.36

Doctor's Letter

Dear Dr.

1. Can **Eflornithine** therapy be a treatment option for this patient?

2. Can **focused Radiation** therapy be a treatment option for this patient?

3. Could **Optune (TTF)** be a treatment option for this patient (even though it was mainly examined for Glioblastoma?)

Novel treatment options

1. Could **Repeated Super-selective Intraarterial Cerebral Infusion of Avastin** be a treatment option for this patient?

"Repeated Super-selective Intraarterial Cerebral Infusion of Bevacizumab (Avastin) for Treatment of Relapsed GBM and AA"

(https://clinicaltrials.gov/ct2/show/record/NCT01269853?term=Phase+I%2FII+Trial+of+Repeated+Super-Selective&view=record)

2. Could **virus therapy with DNX-2401** be a treatment option for this patient?

"Combination Adenovirus + Pembrolizumab to Trigger Immune Virus Effects (CAPTIVE)" (https://clinicaltrials.gov/ct2/show/NCT02798406)

3. Could **PARP inhibitors** be a treatment option for this patient?

"Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations" (https://clinicaltrials.gov/ct2/show/record/NCT03212274)

4. Could **Laser Interstitial Thermal Therapy (LITT)** be a treatment option for this patient?

"Study of Laser Interstitial Thermal Therapy (LITT) in Recurrent Glioblastoma"

(https://clinicaltrials.gov/ct2/show/NCT03022578?recrs=a&cond=Anaplastic+Astrocytoma&age=1&phase=123&rank=6)

Thank you for taking the time to respond.