NCI Community Oncology Research Program – Kansas City (NCORP-KC)

N0577 (CODEL): Phase III Intergroup Study of Radiotherapy with Concomitant and Adjuvant Temozolomide versus Radiotherapy with Adjuvant PCV Chemotherapy in Patients with 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in a research study because you have a newly diagnosed anaplastic glioma or low grade glioma, a type of brain tumor.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research subject. The decision to take part is yours. If you decide to take part, please sign and date at the end of the form. We will give you a copy so that you can refer to it while you are involved in this research study.

If you decide to take part in this research study, you will need to have some tests done to see if you are eligible to be in the research study. These tests are called eligibility tests. The research study has certain requirements that must be met. If the eligibility tests show that you can be in the research study, you will be able to start on the study treatment.

If the tests show that you cannot be in the research study, you will not be able to participate in this research study. If you are not able to participate in the research study, the study doctors will discuss with you other treatment options and/or refer you back to your regular doctor.

We encourage you to take some time to think this over and to discuss it with other people and your doctor and to ask questions now and at any time in the future.

Why is this research study being done?

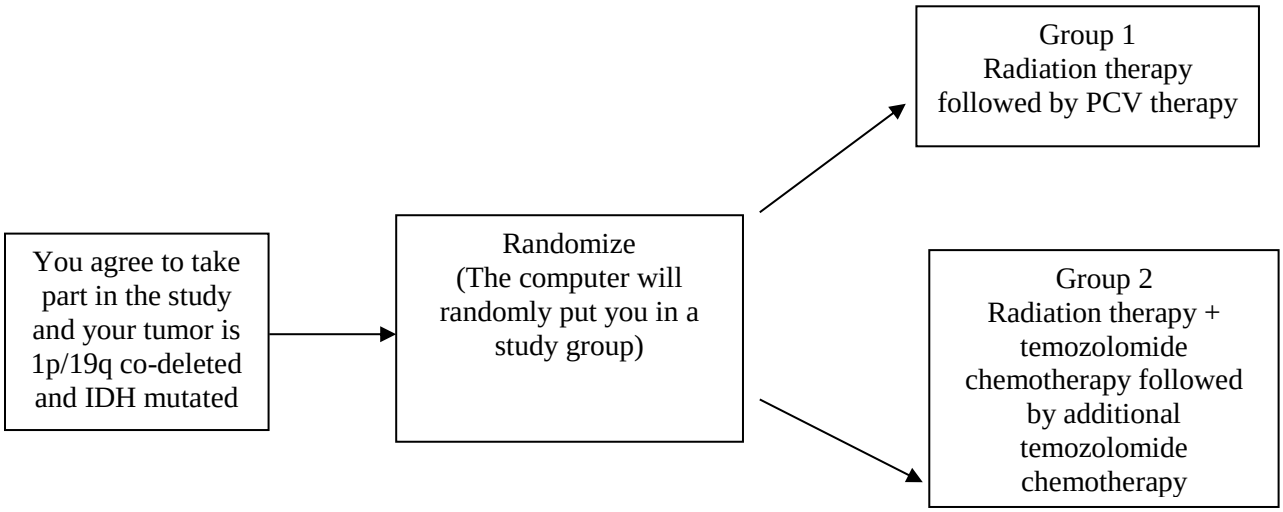
This study has been developed to treat people with anaplastic or low grade glioma brain tumors which are positive for (contain) the 1p/19q co-deletion and IDH tumor markers.

If you are interested in taking part in the treatment research study you are eligible for, your study doctor will discuss with you the treatment research study in more detail.

This treatment research study requires that you have a certain kind of tumor, one that is missing part of both chromosomes 1 and 19. These missing parts of chromosomes are called a “tumor marker” as they make the tumor distinct from other kinds of tumors. This tumor marker is called the 1p/19q co-deletion. Another tumor marker is called "IDH mutation", which is an altered form of a normal gene in the tumor. Tumors with the 1p/19q co-deletion and IDH mutation typically have a more favorable outcome than

other types of anaplastic glioma or low grade glioma.

The purpose of this study is to compare the effectiveness of either 1) radiotherapy (RT, radiation therapy) along with temozolomide chemotherapy followed by additional temozolomide chemotherapy (RT + TMZ → TMZ); or 2) radiotherapy followed by PCV chemotherapy [(RT → PCV); PCV chemotherapy consists of three drugs, Matulane (procarbazine), Lomustine (CCNU) and Oncovin (vincristine)]; in the treatment of anaplastic glioma or low grade glioma with the 1p/19q codeletion. In this study, you will get one of the two possible treatments.



This is considered an 'investigational' or research study. The treatment with TMZ is not yet considered standard treatment for patients with 1p/19q co-deleted / IDH mutated anaplastic gliomas or low grade gliomas.
The main question this research study will answer is:

1. Do patients survive for a longer period of time without the tumor progressing if they are treated with a combination of radiotherapy with temozolomide chemotherapy as compared to radiotherapy with PCV chemotherapy?

This study is conducted by the Alliance / Alliance for Clinical Trials in Oncology, a national collaboration of researchers and physicians with different types of backgrounds and training who work together to plan and conduct clinical trials in cancer that will lead to improved treatment strategies. Alliance members come from major academic medical centers, community hospitals and community practice.

How many people will take part in the research study?

About 396 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study

After signing this consent form, you will be asked to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are likely to be part of regular cancer care and may be done even if you do not take part the research study. If you have had some of these tests

performed recently, they may not need to be repeated; this will be up to your study doctor.

- A medical history (questions about your past and current health, medications and current symptoms).

- A physical examination including height, weight and blood pressure with performance status. Performance status is an assessment by your study doctor of how the cancer affects your daily activities.

- A neurologic history and examination. Your doctor will ask you to perform simple tasks to test consciousness, memory, muscle reflexes, muscle coordination and movement and the senses of vision, hearing, taste, smell and touch.

- Performance status. Your doctor will assess how the cancer affects your daily activities.

- A measurement of your tumor by imaging devices called MRI (magnetic resonance image) and/or CT (computed tomography) scanners. MRI scanners use magnets and radiowaves to produce an image; CT scanners use a series of x-rays or tomographs. MRI and CT scans require an i.v. injection of contrast dye. If you have a metal device (such as a pacemaker), are not comfortable with close spaces or are unable to lie still comfortably, you will not be able to have an MRI and must have a CT scan instead. Most MRI scanners make loud knocking noises during use; you may be asked to wear earplugs to minimize any discomfort fromnoise. You will be getting scans of your tumor as part of your care for this study. As required by this study, your scans will be submitted to a central image library, so that researchers can review and analyze the scans. These images will be stored at the Imaging Radiation Oncology Core Lab University of Heidelberg for studies shared with the European Organisation for Research and Treatment of Cancer (EORTC)."

- Routine blood tests, including chemistry, hematology, and possibly other tests that your doctor may feel are necessary. These tests are done to make sure that there are no problems with your organs or blood. This will require about 1 to 3 tablespoons of blood.

- A serum or urine pregnancy test for women of childbearing potential.

- A mandatory tumor tissue sample. The tissue sample will be sent to laboratories associated with Alliance to confirm the results reported by your local medical center's laboratory review. This review is mandatory. The tissue and the microscope slides that are made from the tissue will be stored and kept by Alliance.

- Questionnaires and simple tests about how cancer has affected your quality of life and mental function. We want to know your view of how your life has been affected by cancer and its treatment. These questionnaires and simple tests look at how you are feeling physically and emotionally during your cancer treatment and how well you are able to carry out your everyday activities. This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer. You will be asked to complete questions in a paper booklet and perform simple language and numbers tests during a clinic visit. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. These questionnaires and tests require about 25 to 35 minutes to complete.

During the research study (treatment)

You will be "randomized" into one of the two treatment groups described below. Randomization means that you are put into a group by chance (as in a roll of the dice). A computer program will place you in one of the treatment groups. Neither you nor your doctor can choose the treatment group you will be in but after the randomization you will know which treatment you will receive. You will have an equal 1 in 2 chance of being placed on either of the two treatment groups. If you are in group 1, you will receive radiotherapy followed by PCV chemotherapy and if you are in group 2, you will receive radiotherapy with temozolomide chemotherapy followed by additional temozolomide chemotherapy.

Group 1: Radiotherapy followed by PCV Chemotherapy (RT →PCV) Treatment with PCV chemotherapy has been associated with an increased risk of certain types of infection. Your doctor may advise you to take antibiotics to prevent these infections while you are taking PCV chemotherapy and for at least one month after your last dose of PCV chemotherapy. The antibiotics most commonly used are Bactrim or pentamidine or dapsone. Your doctor will discuss the medication you might need to take to protect you from these infections.

You will receive radiotherapy five days per week for about 6 to 7 weeks. You will then have a 4 to 6 week treatment break. You will then receive PCV chemotherapy for up to 6 cycles with each cycle lasting six to seven weeks. During each cycle of PCV chemotherapy, you will receive the three medications that compose PCV chemotherapy as follows:

1. Lomustine (also called CCNU) orally on day 1 of each cycle
2. Matulane (also called procarbazine) orally on days 8 through 21 of each cycle
3. Oncovin (also called vincristine) by i.v. on days 8 and 29 of each cycle

Group 2: Radiotherapy with Temozolomide Chemotherapy followed by Additional Temozolomide Chemotherapy (RT + TMZ → TMZ)

Treatment with temozolomide chemotherapy has been associated with an increased risk of certain types of infection. You may be asked by your doctor to take antibiotics to prevent these infections while you are taking temozolomide and for at least one month after your last dose of temozolomide. The antibiotics most commonly used are Bactrim or pentamidine or dapsone. Your doctor will decide with you which medication you will need to take to protect you from these infections.

Temozolomide is taken orally with a full glass (8 ounces or one cup) of water on an empty stomach or one to two hours after food. Because temozolomide can sometimes cause an upset stomach, your study doctors will give you an anti-nausea medication to take before you take the temozolomide. You may be asked to record your dosing with temozolomide in a medication diary every day that you take the medication.

You will receive radiotherapy five days per week and oral temozolomide seven days per week for about 6 to 7 weeks. You will then have a 4 week treatment break. You will then receive oral temozolomide on days 1 through 5 **only** of each cycle, for up to 6-12 cycles, with each lasting 4 weeks.

The following table describes the study activities of each treatment group throughout the study:

Group 1: RT followed by PCV chemotherapy (RT → PCV)

Day(s)	Schedule of Study Activity
Cycle 1 **During RT** for about 6 to 7 weeks total	**Five days per week:** Radiotherapy (RT) **Every other week:** Routine chemistry and hematology blood tests (Blood tests may be more frequent if your study doctor feels it is necessary). **Prior to cycle 1:** Neurocognitive and quality of life questionnaires
Cycle 2	**4 to 6 week rest period; no study activities required**
Cycles 3 through 8 **During PCV chemotherapy** Each cycle is 6 to 7 weeks long for about 36 to 42 weeks total	**PCV chemotherapy with procarbazine and CCNU** **1. Lomustine (CCNU) orally on day 1 of each cycle** **2. Matulane (procarbazine) orally on days 8 through 21 of each cycle** **3. Oncovin (vincristine) by i.v. on days 8 and 29 of each cycle** **Prior to each cycle:** Medical history Physical exam Routine chemistry and hematology blood tests (Blood tests may be more frequent if your study doctor thinks necessary) **Prior to Cycle 3 only:** Chest x-ray Urinalysis Neurocognitive and quality of life questionnaires and simple tests **Prior to every other cycle (ie, cycles 3, 5 and 7):** Neurologic history and exam MRI or CT* (MRI or CT may be more frequent if your study doctor thinks necessary)*

Day(s)	Schedule of Study Activity
Observation period After PCV chemotherapy is complete	**Every 12 weeks for 1 year from completion of treatment, then every 4 months for 2 years, then every 6 months until the cancer progresses or you decide to stop the study or the study is stopped:** Medical history Physical exam Neurological history and exam MRI or CT* (MRT or CT may be more frequent if your study doctor thinks necessary)* **As your study doctor thinks necessary:** Routine chemistry and hematology blood tests **<u>Yearly:</u>** Neurocognitive and quality of life questionnaires and simple tests
Study End and after	**At the time that the cancer progresses or you decide to stop the study or the study is stopped:** Questionnaires and simple tests **At the time the cancer progresses or you decide to stop the study, then yearly:** Neurocognitive and quality of life questionnaires and simple tests

*As required by this study, your MRI (or CT) scans will be submitted to a central image library and will be stored at the Imaging Radiation Oncology Core Lab University of Heidelberg for studies shared with the European Organisation for Research and Treatment of Cancer (EORTC).

Group 2: RT with TMZ chemotherapy followed by TMZ chemotherapy (RT + TMZ →TMZ)

Day(s)	Schedule of Study Activity
Cycle 1 **During RT + TMZ** for about 6 to 7 weeks total	**Five days per week:** Radiotherapy (RT) **Seven days per week:** TMZ chemotherapy **Every other week:** Routine chemistry and hematology blood tests (Blood tests may be more frequent if your study doctor feels it is necessary). **Prior to cycle 1:** Neurocognitive and quality of life questionnaires
Cycle 2	**4 week rest period** **At 10 weeks from start of Cycle 1:** MRI or CT* (MRI or CT may be more frequent if your study doctor thinks necessary)* Simple tests
Cycles 3 through 8* **During TMZ chemotherapy** Each cycle is 4 weeks long for up to 48 weeks total	**Prior to each cycle:** Medical history Physical exam Neurologic history and exam Routine chemistry and hematology blood tests (Blood tests may be more frequent if your study doctor thinks necessary) **During each cycle, days 1 through 5 only:** TMZ chemotherapy **Prior to cycle 3 only:** Urinalysis Neurocognitive and quality of life questionnaires and simple tests **Prior to cycles 5, 8 and 11*:** MRI or CT* (MRI or CT may be more frequent if your study doctor thinks necessary)* *Please note: Your study doctor may advise that you keep taking TMZ for an additional 6 cycles if you are doing well.

This table continues on the next page.

Group 2: RT with TMZ chemotherapy followed by TMZ chemotherapy (RT + TMZ →TMZ)

Day(s)	Schedule of Study Activity
Observation period After TMZ chemotherapy is complete	**Every 12 weeks for 1 year from completion of study treatment, then every 4 months for 2 years, then every 6 months until the cancer progresses or you decide to stop the study or the study is stopped:** Medical history Physical exam Neurologic history and exam MRI or CT* (MRT or CT may be more frequent if your study doctor thinks necessary)* **As your study doctor thinks necessary:** Routine chemistry and hematology blood tests **<u>Yearly:</u>** Questionnaires and simple tests
Study End and after	**At the time that the cancer progresses or you decide to stop the study or the study is stopped , then yearly:** Neurocognitive and quality of life questionnaires and simple tests

*As required by this study, your MRI (or CT) scans will be submitted to a central image library and will be stored at the Imaging Radiation Oncology Core Lab University of Heidelberg for studies shared with the European Organisation for Research and Treatment of Cancer (EORTC).

How long will I be in the research study?

You will be in the treatment part of the study for about 12 to 14 months, depending on which treatment group you are placed in. After you are done with your treatment, the study doctor will ask you to visit the office for follow-up exams unless your disease gets worse. We would also like to keep track of your medical condition. Keeping in touch with you and checking on your condition every 6 months until conclusion of the study helps us look at the long-term effects of the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

There is no radiation associated with an MRI scan which is the standard scanning method for this study., However, if you have a metal device (such as a pacemaker), are not comfortable with close spaces or are unable to lie still comfortably, you may not be able to have an MRI and must have a CT scan instead. Most MRI scanners make loud knocking noises during use; you will be asked to wear earplugs to minimize any discomfort from noise. If you have to have CT scans, you will be exposed to a small amount of radiation. The amount of radiation you will receive has a low risk of harmful effects.

You will be asked to have blood drawn during the study. The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

This study will also use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Reproductive risks: You should not become pregnant or father a baby during this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby during this study and for 6 months after the last dose of medication. It is important you understand that you need to use birth control while on this study and for 6 months after your last dose of medication. Check with your health care provider about what kind of birth control methods to use. Some methods might not be approved for use in this study.

If your or your partner becomes pregnant during this study, tell your study doctor right away. She/he will discuss stopping study treatment with you and any other steps that need to be taken.

If you are a woman who is able to become pregnant, you will have a pregnancy test before you can start

this study. If the pregnancy test is positive, you will not be able to take part in this study.

You should talk to your study doctor about any side effects that you have while taking part in the study.
Risks and side effects related to procarbazine include:

Likely risks of procarbazine ***(Events occurring > 20% of the time)***

- Dizziness
- Fatigue (Drowsiness)
- Pain in the head (Headache)
- Loss of muscle coordination including awkward, unsteady walking (Ataxia)
- Nerve damage, possible numbness, pain, and/or loss of motor function (Peripheral neuropathy)
- Hair loss (Alopecia)
- Feeling sick to the stomach (Nausea)
- Throwing up (Vomiting)
- Dry mouth (Xerostomia)
- Loss of appetite and weight loss (Anorexia)
- Reproductive dysfunction
- Decreased production within the bone marrow that causes decreased production of red cells, white cells, or platelets (Myelosuppression)
- Decreased white blood cells, which are the infection fighting cells, which could put you at risk for infection (Leukopenia)
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding) (Thrombocytopenia)
- Fever, chills, swelling of body, shortness of breath (Allergic reaction)
- Allergic reaction (Hypersensitivity)

Less likely risks of procarbazine ***(Events occurring ≤ to 20% of the time)***

- Cardiovascular swelling (Edema)
- Sudden reddening of the face and/or neck (Flushing)
- Low blood pressure, which may cause dizziness, lightheadedness or fainting (Hypotension)
- Fainting (Syncope)
- Fast heartbeat (Tachycardia)
- Apprehension (Fearfulness)
- A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever (Chills)
- Unconscious state (Coma)
- A disorder characterized by a lack of clear and orderly thought and behavior (confusion)
- Feeling sad or blue (Depression)
- Feeling tired (Fatigue)
- A disorder characterized by elevation of the body's temperature above the upper limit of normal (Fever)
- Seeing things that are not real (Hallucination)
- Difficulty falling or staying asleep (Insomnia)
- Very Sleepy, difficulty arousing (Lethargy)
- Nervousness (Anxiety)

- Nightmares (Bad dreams)
- A disorder characterized by the sensation of marked discomfort, distress or agony (Pain)
- Involuntary changes in body movement or function, sensation, awareness, or behavior (Seizure)
- A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech (Slurred speech)
- Skin irritation, rash (Dermatitis)
- Darkening of the skin (Hyperpigmentation)
- Very small broken blood vessels in skin or lining of the mouth which may result in bleeding (Petechiae and Purpura)
- A disorder characterized by an intense itching sensation (Pruritus)
- Flaking or sloughing of skin (Rash)
- Hives, swollen raised areas on the skin that are intensely itchy (Urticaria)
- Abdominal pain
- Difficulty passing stool (Constipation)
- Loose stools (Diarrhea)
- Difficulty swallowing (Dysphagia)
- Vomiting of blood (Hematemesis)
- Tarry or coffee ground-like blood in the stool (Melena)
- Mouth sores, inflammation of the mouth (Stomatitis)
- Low sperm count (Azoospermia)
- Blood in the urine (Hematuria)
- Urination at night (Nocturia)
- Frequent urination (Polyuria)
- Increase in infection-fighting cells (Eosinophilia)
- Breakdown in red blood cells (Hemolysis (in patients with G6PD deficiency))
- Destruction of red blood cells that leads to anemia (Hemolytic anemia)
- Reduction in the number of red blood cells (which could make you feel tired), white blood cells (which could put you at risk for infection), and platelets (which could put you at risk for bleeding) (Pancytopenia)
- Abnormal liver function (Hepatic dysfunction)
- Yellowing of skin and/or eyes (Jaundice)
- Joint pain (Arthralgia)
- Falling
- Nerve damage-foot/ankle weakness causing abnormal walking (Foot drop)
- Muscle aches (Myalgia)
- Damage to the nerves which can cause numbness or pain, and weakness (Neuropathy)
- Tingling, burning, or prickling sensation (Paresthesia)
- Reflex diminished
- A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts (Tremor)
- Unsteadiness
- Weakness
- Cough
- Bloody nose (Epistaxis)
- Vomiting blood (Hemoptysis)
- A disorder characterized by harsh and raspy voice arising from or spreading to the larynx (Hoarseness)
- Build-up of fluid around the lungs (Pleural effusion)

- Inflammation of the lungs (Pneumonitis)
- Pulmonary toxicity
- Watery blisters in the skin or mucous membranes of the mouth, lips or genitals (herpes)
- Infection
- Secondary malignancies

Rare but serious risks of procarbazine *(Events occurring < 2-3% of the time)*

- Enlarged breasts in males (Gynecomastia)
- Double vision (Diplopia)
- Inability to focus
- Rapid, jerky movements of the eye (Nystagmus)
- Swelling of the eye nerve (Papilledema)
- Eye sensitivity to light (Photophobia)
- Bleeding in the eye (Retinal hemorrhage)
- Hearing loss

Risks and side effects related to the Lomustine/CCNU include:

Likely risks of lomustine/CCNU *(Events occurring > 20% of the time)*

- Nausea
- Vomiting
- Decreased production within the bone marrow that causes decreased production of red cells, which could make you feel tired (Anemia)
- Decreased white blood cells, which are the infection fighting cells, which could put you at risk for infection (Leukopenia)
- Decreased number of platelets that help to clot the blood (which could put you at increased risk of bleeding) (Thrombocytopenia)

Less likely risks of lomustine/CCNU *(Events occurring to ≤ 20% of the time)*

- Loss of appetite
- High level of liver enzymes in the blood
- Mouth sores
- Drowsiness
- Difficulty walking
- Diarrhea
- Loss of fertility (meaning, your ability to conceive or father a child may be affected by lomustine/CCNU)
- Hair loss

Rare but serious risks of lomustine/CCNU *(Events occurring < 2-3% of the time)*

- Lung damage
- Kidney damage
- Visual disturbances
- Pale color to the back of the eye

- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects normal blood cell production) may develop as a result of this treatment; however the chance of this happening is very small

Risks and side effects related to the vincristine include:

Likely risks of vincristine ***(Events occurring > 20% of the time)***

- Loss of body and head hair (alopecia)
- Rash

Less likely risks of vincristine ***(Events occurring ≤ 20% of the time)***

- Blood pressure fluctuation when rising from a seated position (Orthostatic hypotension or hypertension)
- High blood pressure (Hypertension)
- Low blood pressure (Hypotension)
- Central Nervous System (CNS) depression
- Confusion
- Loss of voluntary muscle movement in the face due to nerve damage (Cranial nerve paralysis, Bell's Palsy)
- Fever
- Headache
- Difficulty falling and/or staying asleep (Insomnia)
- Irregular muscle movements (Motor difficulties)
- Involuntary changes in body movement, function, sensation, awareness or behavior (seizure)
- Increased uric acid in the blood (Hyperuricemia)
- Abdominal cramps
- Uncontrolled loss of appetite or not feeling hungry (Anorexia)
- Swelling due to fluid or water (Bloating)
- Difficulty passing stool (Constipation)
- Loose, watery stools (Diarrhea)
- Metallic taste
- Feeling sick to your stomach (Nausea)
- Mouth sores (Oral ulceration)
- Throwing up (Vomiting)
- Weight loss
- Muscular weakness in the bladder (Bladder atony)
- Painful or difficult urination (Dysuria)
- Excessive urination (Polyuria)
- Inability to urinate (Urinary retention)
- Decrease in white blood cells, infection fighting cells, which could put you at risk for infection (Leukopenia)
- Decreased number of platelets, blood cells that help to clot the blood, which could put you at an increased risk of bleeding (Thrombocytopenia)
- Decreased production within the bone marrow that causes decreased production of red cells, white cells or platelets (Myelosuppression)
- Tissue blistering (Vesicant)
- Inflammation of the veins (Phlebitis)

- Skin irritation and skin death if the drug leaks to tissue surrounding the IV (Tissue irritation and necrosis if infiltrated)
- Cramping
- Jaw pain
- Leg pain
- Muscle pain (Myalgia)
- Numbness
- Weakness
- Numbness, tingling or inflammation of the nerves, usually in the hands and feet, which could be painful (Peripheral neuropathy: Frequently the dose-limiting toxicity of vincristine. Manifested as loss of the deep tendon reflexes in the lower extremities, numbness, tingling, pain, tingling, burning or prickling (paresthesia) of the fingers and toes (stocking glove sensation), and "foot drop" or "wrist drop)
- Wasting away of the nerves and structures of the eye (Optic atrophy)
- Inability to tolerate light (Photophobia)

Rare but serious risks of vincristine *(Events occurring < 2-3% of the time)*

- Low blood sodium and concentrated urine (Syndrome of Inappropriate Secretion of Antidiuretic Hormone, SIADH)
- Mouth sores (stomatitis)

Risks and side effects related to the temozolomide include:

Risk Profile for Temozolomide

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Temozolomide, more than 20 and up to 100 may have:

- Constipation, nausea, vomiting, diarrhea
- Dizziness
- Muscle weakness, paralysis, difficulty walking
- Trouble with memory
- Tiredness
- Difficulty sleeping
- Hair loss

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Temozolomide, from 4 to 20 may have:

- Headache, seizure
- Infection, especially when white blood cell count is low
- Anemia which may cause tiredness
- Bruising, bleeding
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require blood transfusions

RARE AND SERIOUS In 100 people receiving Temozolomide, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Cancer of bone marrow caused by chemotherapy • Rash • Severe skin rash with blisters and can involve inside of mouth and other parts of the body • Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

Risks and side effects related to the radiotherapy include:

Likely risks of radiotherapy ***(Events occurring greater than 20% of the time)***

- Short-term reddening and drying of the skin, fatigue, and hair loss within treated area

Less Likely risks of radiotherapy ***(Events occurring less than or equal to 20% of the time)***

- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Headache

Rare but serious risks of radiotherapy

- Seizures
- Coma
- Lower white blood cell and platelet counts raising the risk of infection and bleeding
- Radiation therapy at these dose levels also may cause damage to normal brain, but this is rare
- Specific effects depend upon the location of the area(s) of damage but may be a decrease in judgment, memory, emotions, vision, hearing, sensation, or ability to control movement.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope that the combinations of radiotherapy and temozolomide chemotherapy will be better or as effective as standard radiotherapy with PCV chemotherapy, this is as of yet unproven.

We do know that the information from this study will help doctors learn more about radiotherapy, temozolomide and PCV chemotherapy as treatments for cancer, and whether one treatment or the other is better tolerated. This information could help future brain tumor patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

Getting treatment or care for your cancer without being in a study

- Getting radiotherapy, temozolomide chemotherapy and PCV chemotherapy without being in a study
- Taking part in another study
- Getting no treatment

- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- Alliance for Clinical Trials in Oncology (Alliance)
- European Organisation for Research and Treatment of Cancer (EORTC)
- Other organizations from the National Clinical Trials Network that take part in this study
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- When your scan or blood samples are sent to the researchers, no information identifying you (such as your name) will be sent. Images and samples will be identified by a unique code only.
- The list that links the unique code to your name will be kept separate from your image, sample and health information. Any Biobank and Imaging Core Laboratory staff with access to the list must sign an agreement to keep your identity confidential.
- Researchers to whom the Imaging Core Laboratory sends your images and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
- Information that identifies you will not be given to anyone, unless required by law.
- If research results are published, your name and other personal information will not be used.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____*investigator's name(s),* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *telephone number.*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *name(s)* at _____*telephone number.*

For questions about your rights while taking part in this study, call the Central Institutional Review Board (a group of people who review the research to protect your rights) at 888-657-3711.

About Using Biological Samples for Research

<u>Blood samples (Mandatory)</u>

You will be asked to give a small volume blood sample once before starting the study at the time of your routine blood tests so as not to have an additional blood draw just for this sample. This blood sample is **mandatory** and would require about 1 to 3 tablespoons of blood. Some of your blood samples will be used to help understand how your cancer responds to treatment; the results of these tests would not be given to you or your doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them. Some of your blood will be sent to the University of Heidelberg in Germany for studies shared with the European Organisation for Research and Treatment of Cancer (EORTC). Some of the research will study genes in your blood. Genes carry information about features that are found in you and in people who are related to you.

Tissue Samples (Mandatory)
Previously, a small piece of tumor tissue that was obtained during your prior surgery was sent to laboratories associated with Alliance to confirm the results reported by your local medical center's laboratory review. The tumor tissue sample and the microscope slides that are made from the tissue were stored and kept by Alliance. Additional tumor tissue may be requested from your physician for the research. This would not involve additional surgery but would be obtained from the tissue taken at the time of your prior surgery.

Future Use of Blood and Tissue Samples (Mandatory)

As part of your participation on this study your blood and left-over tumor tissue samples will be stored at the Alliance BioBank and will be used for future research

In the future, people who do research may need to know more about your health. While Alliance may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and left-over tissue samples are used for genetic research (about diseases that are passed on in families). Even if your blood and/or left-over tissue samples are used for this kind of research, the results will not be put in your health records.

Your blood and left-over tumor tissue samples will be used only for research and will not be sold. The research done with your left over tissue and blood may help to develop new products in the future. If this should happen, you will not be paid.

Benefits
The benefits of research using blood and left-over tumor tissue samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks
The greatest risk to you from the use of your samples is the possible release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

This study will also use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in
This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

Optional imaging study

You will be getting regular scans of your tumor as part of your care for this study. As required by this study, your scans will be submitted to a central image library and will be sent to University of Heidelberg. These scans will be saved so that researchers can look back at these scans after the study is over.

NOTE TO INSTITUTIONS: ***The Optional Imaging study section is not to be removed from the consent. Please select one of the following based on whether or not your institution elected to participate in the advanced imaging sub-study:***

☐ Your health care facility has extra MRI testing available, known as "DSC and DWI" MRI. If your facility has this available, researchers would like to use these scans for a related research study to see whether they can predict how well a patient will do following treatment. If you choose to take part in this optional study, your MRI scan is at the same timepoints and same images you normally would receive, but the "DSC and DWI" scans will be sent to the central image library, and then sent on to the University of Heidelberg. You will simply be agreeing to a more specialized type of MRI than you would usually get for additional research. You or your insurance will be billed for the scans no matter what option you choose. Check "yes" or "no" depending on whether or not you want to participate.

☐ Your health care facility does NOT have extra MRI testing available, known as "DSC and DWI" MRI. You will not be able to take part in the optional MRI study, and should check the box for "no" below.

Please place a check before your answer: I choose to take part in the imaging study and allow my routine MRI scans to be analyzed for the optional research study.

☐ YES ☐ NO

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

I permit Alliance to contact me in the future to take part in more research:

☐ Yes ☐ No

Alliance has the right to end storage of the sample(s) without telling you.

Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/
- For NCI's general information about cancer in Spanish, go to http://www.cancer.gov/espanol

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. this may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all 20 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent: _____

Signature of person obtaining informed consent: _____

Date _____