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May 15, 2025

Martha Kruhm, MS, RAC
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Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #6B to protocol **ACNS1831**, *A Phase 3 Randomized Study of Selumetinib (IND # [redacted] versus Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) Associated Low-Grade Glioma (LGG)sociated with BRAFV600E Mutations or Systemic Neurofibromatosis Type 1 (NF1)*

Amendment #6B to ACNS1831 is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. Lorraine Pelosof (lorraine.pelosof@nih.gov), dated May 01, 2025. In this amendment, the revised CAEPR for Selumetinib (Version 2.11, dated February 25, 2025) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised. Revisions to both the protocol and consent documents are detailed in the pages below.

Administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

Natasha Mirt, Protocol Coordinator (for)

Jason Fangusaro, MD, ACNS1831 Study Chair,
Maryam Fouladi, MD, CNS Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

**SUMMARY OF CHANGES: INFORMED CONSENT**

In accordance with the above discussion, the following specific revisions have been made to the consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | General | All | Updated version date of consent to match the current version of the protocol. |
| 2. | Risks of Study | 9 | In response to a Request for Rapid Amendment (RRA) from Dr. Lorraine Pelosof, Dated May 1, 2025, the Selumetinib risk profile has been updated. |
| 3. | Possible Side Effects of Selumetinib | 10-11 | In response to a Request for Rapid Amendment (RRA) from Dr. Lorraine Pelosof, Dated May 1, 2025, the Selumetinib risk insert has been updated as follows:<br>• Added New Risk:<br>  • Occasional: Liver damage which may cause yellowing of eyes and skin, swelling; Swollen or broken skin around the nail which may cause redness (paronychia); Potential liver damage (Alanine aminotransferase increased and Aspartate aminotransferase increased); Muscle pain/muscle breakdown (CPK increased)<br>  • Rare: Cloudiness of the eye, visual disturbances; Glaucoma; Blockage of internal organs which may cause inability to pass stool; Blood infection; Bleeding (increased risk of bleeding given the vitamin E levels in the capsules)<br>• Increase in Risk Attribution:<br>  • Changed to Occasional from Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Change in hair color<br>  • Changed to Rare from Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Seeing spots before eyes; Discomfort from light, visual loss; Damage to muscle which may cause muscle pain, dark red urine; Redness, pain or peeling of palms and soles<br>• Decrease in Risk Attribution:<br>  • Changed to Occasional from Common: Rash<br>  • Changed to Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution from Rare (i.e., removed from the Risk Profile): Damage to lungs which may cause shortness of breath<br>• Deleted Risk:<br>  • Rare: Damage to eye causing blurred vision or blindness; Vision changes; Blood clot in the eye which may cause blurred vision or blindness |

| | | | |
|---|---|---|---|
| | | | Provided Further Clarification:<br>• Belly pain (under Common) is now reported as Pain (under Common) |
| 4. | Possible Side Effects of Selumetinib | 11 | Deleted<br>• "~~in addition to the side effects above, selumetinib may rarely cause visual loss~~" and<br>• "~~some patients may develop a nail disease (also known as paronychia) that is an often tender infection of the hand or foot where the nail and skin meet at the side or the base of a finger or toenail~~".<br><br>These risks are now included in the risk insert tables. |

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions must use the sections of this document that are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

**SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM**

**ACNS1831:**
**A Phase 3 Randomized Study of Selumetinib (IND # 77782) versus Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) associated Low-Grade Glioma (LGG)**

*Study Title for Participants:*
***A Study of the Drugs Selumetinib vs. Carboplatin/Vincristine in Patients with Neurofibromatosis and Low-Grade Glioma***

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

## Overview

You are being asked to take part in this research study because you have been diagnosed with a genetic disorder called Neurofibromatosis type 1 (NF1) and a cancer called low-grade glioma (LGG). Together, this is also called NF1-associated LGG.

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

The overall goals of this study are to see if a drug called selumetinib works just as well as the standard treatment using carboplatin and vincristine (called CV) for subjects with NF1-associated LGG, and to see if selumetinib is better than CV in improving vision in subjects with LGG of the optic pathway.

The treatment involves cancer fighting medicine called chemotherapy.

In this study you will get 1 of 2 treatment plans. The 2 treatment plans are called Arm 1 and Arm 2. The treatment on Arm 1 is CV, which is standard therapy for people with NF1-associated LGG. For subjects getting CV, the treatment on this study takes about 15 months. The treatment on Arm 2 is selumetinib, which is an experimental therapy for people with NF1-associated LGG. For subjects getting selumetinib, the treatment on this study takes about 27 months. In addition to the length of the study treatment, all subjects will complete research tests for about 5 years after they enter this study.

The treatment plan that you receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a

coin, except that it is done by computer. You and your doctor will not pick which treatment you get.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.

Arm 2 of this study uses the investigational drug selumetinib. Common side effects of this drug are diarrhea, nausea, swelling of the body, tiredness, acne, nail infection (also known as paronychia) and rash. Some less common but notable side effects are constipation, vomiting, dry mouth, sores in the mouth, and loss of appetite. The full list of risks for selumetinib are available in the section What side effects or risks can I expect from being in the study?

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the section Are there benefits to taking part in the study?

You have a choice between a standard treatment for NF1-associated LGG and this clinical trial.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

## Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have a genetic disorder called Neurofibromatosis type 1 (NF1) and a cancer called low-grade glioma (LGG). You have also not received any treatment, other than surgery, to treat your NF1-associated LGG.

Cancer cells sometimes clump together to form tumors. The word “glioma” means a tumor that grows in a special type of cell in your brain called a “glial” cell. A low-grade glioma is a type of cancer that grows as a tumor in the brain. Glioma is considered low risk (or low-grade) when it is growing slowly and not spreading quickly to other parts of your brain or body. The term, risk, refers to the chance of the cancer coming back after treatment.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children’s Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part.

You have a choice between a standard treatment for LGG, another therapy as recommended by your doctor, and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

## What is the current standard of treatment for this disease?

Most NF1-associated LGGs do not grow or require treatment. For patients that do require treatment, the standard treatment includes surgery to remove as much of the tumor as possible, but only if the tumor can be removed safely.

Chemotherapy (cancer fighting medicine) can also be given alone if a surgery is not possible or after surgery to get rid of any remaining tumor cells, stop the tumor cells from growing, or shrink the tumor. Carboplatin and vincristine are two chemotherapy drugs that may be used to treat NF1-associated LGG. They are often considered the standard of care chemotherapy for these types of tumors.

## Why is this study being done?

Although most LGGs are treatable and curable, patients with NF1-associated LGG have a higher chance of getting LGG in their optic pathway or brainstem. This can lead to vision loss in one or both eyes or a difficulty in moving certain parts of one's body. Study doctors want to find treatments that will be better at getting rid of or shrinking NF1-associated LGGs and stopping them from coming back. One thing they want to do is try using different anti-cancer drugs. A drug that will be used on this study is called selumetinib. Early studies have shown that selumetinib was successful in treating patients with NF1-associated LGG that came back after a first attempt at treatment.

The standard treatment carboplatin and vincristine for NF1-associated LGG requires frequent visits (weekly for much of the treatment) for almost 15 months. The drugs are given through the veins and have some side effects that may lessen a patient's quality of life. The study doctors want to see if using selumetinib will be just as good as treatment with carboplatin/vincristine (CV) in helping to get rid of or shrink LGGs. They also want to know if selumetinib will be better than CV in improving vision in subjects whose LGG has caused vision problems (subjects are people who agree to take part in this study). Finally, the study doctors want to see if selumetinib improves a subject's quality of life compared to CV.

Selumetinib is a drug that works by blocking proteins (a basic building block of the human body) needed for cell growth and killing cancer cells. The use of selumetinib has been FDA approved for NF1-associated plexiform neurofibromas, however, selumetinib has not been approved in the treatment of previously untreated NF1-associated LGG and is still considered experimental.

**The overall goals of this study are to see if selumetinib works just as well as the standard treatment of CV for subjects with NF1-associated LGG, and to see if selumetinib is better than CV in improving vision in subjects with LGG of the optic pathway.**

Other goals of this study include:

- To compare the effects, good and/or bad, of selumetinib versus CV in subjects with NF1-associated LGG to find out which is better. In this study, you will get either the selumetinib or CV. You will not get both.

In addition to the treatment goals, we would like to answer some other questions about your vision, quality of life, and muscle strength. These research studies are described later in this form.

## What will happen on this study that is research?

The treatment involves cancer fighting medicine called chemotherapy. Subjects will receive either CV or selumetinib.

The CV treatment in this study is considered the standard or regular therapy for people with NF1-associated LGG. Treatment that is standard for NF1-associated LGG is described in **Attachment 1**.

Some parts of the treatment on this study are different from standard therapy. The selumetinib treatment in this study is experimental.

**Summary of Study Treatments**
In this study you will get 1 of 2 treatment plans. The 2 treatment plans are called Arm 1 and Arm 2, as follows:

- **Arm 1: Carboplatin/Vincristine (CV) – This is standard therapy**

  For subjects taking CV, the treatment on this study takes about 15 months total. It is divided into 2 stages called Induction and Maintenance.
  - Induction: Induction will last about 12 weeks, including a rest period where you won't receive any chemotherapy.
  - Maintenance: Maintenance will last about 48 weeks (12 months). During Maintenance, you will receive treatment in "cycles." Each cycle of Maintenance lasts 42 days (6 weeks). You will receive 8 cycles of Maintenance therapy.

- **Arm 2: Selumetinib – This is experimental therapy**

  For subjects taking selumetinib, the treatment on this study takes about 27 months. Treatment will be given in "cycles." Each cycle of selumetinib lasts 28 days (4 weeks). You will receive 27 cycles of selumetinib.

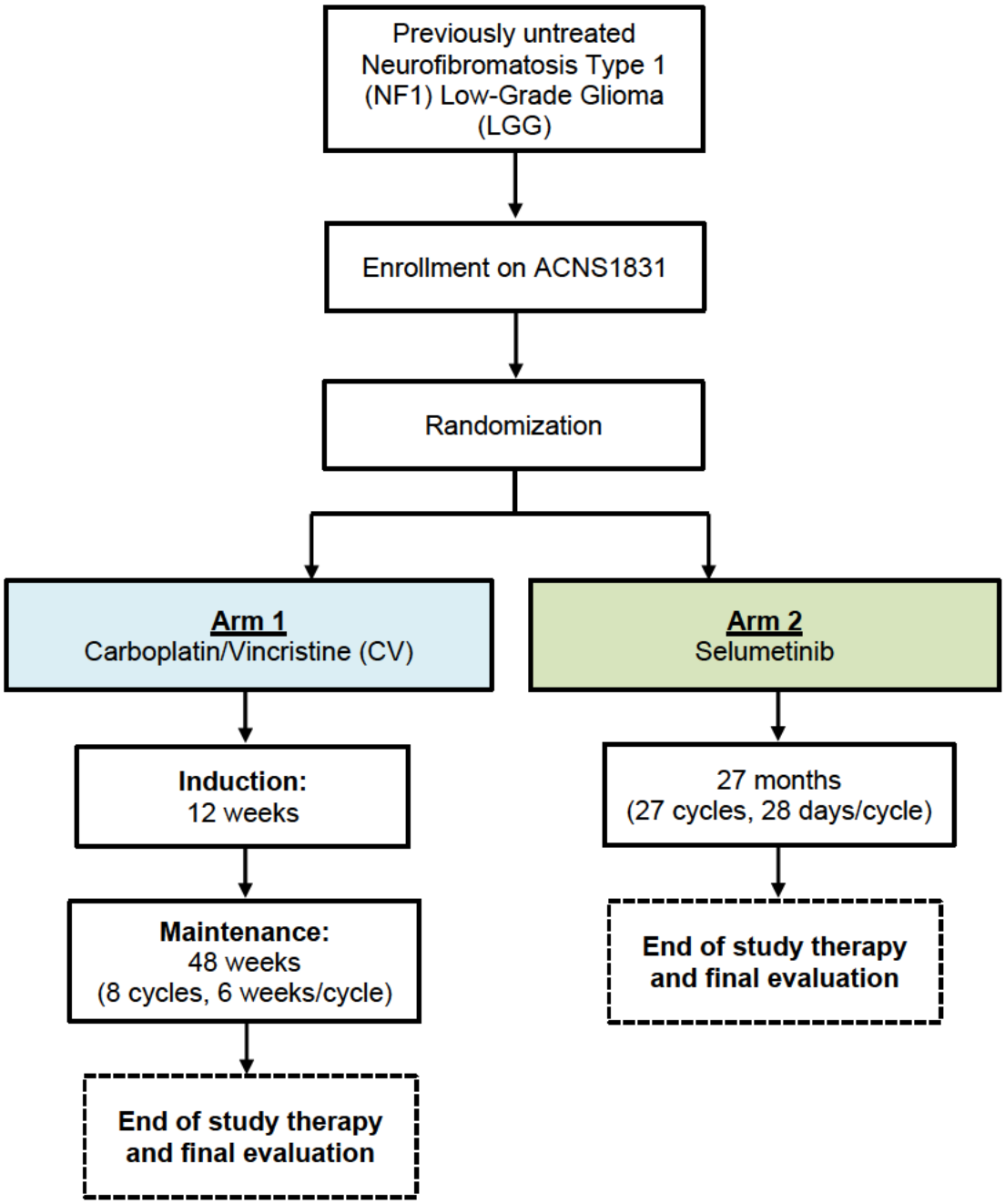
**Random Assignment**
You will receive 1 of 2 different treatment plans. The treatment plan that you receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick which treatment you get. The randomization process is described in the COG Family Handbook for Children with Cancer.

Subjects will be randomized 2:1 to selumetinib or CV following enrollment. This means that twice as many subjects will be assigned to receive selumetinib as CV. This will help the study

doctors learn more about selumetinib in the treatment of LGG since it is considered experimental and there is already a lot of understanding about CV from previous studies.

**Diagram of Treatment**

This chart shows the treatments on this study.




During treatment, you will have evaluations. If you get worse, you may stop study therapy and your doctor will discuss other options with you.

**Treatment that is Research**

Various methods will be used to give drugs:

- **PO** (oral) - Drug is given by capsule swallowed through the mouth.
- **IV** (intravenous) - Drug is given using a needle or tubing inserted into a vein.

**Treatment for subjects who are on Arm 1 (CV)**

This arm does not involve experimental therapy. Subjects randomized to this arm will receive standard therapy. This therapy is described in **Attachment 1**.

**Treatment for subjects who are on Arm 2 (Selumetinib)**

On this study, you will take selumetinib for 27 cycles. Each cycle of treatment is 28 days.

| Drug | How the drug will be given | Days |
|---|---|---|
| Selumetinib | PO twice daily | 1–28 |

You will take selumetinib twice a day with or without food. The capsules cannot be broken or chewed and must be swallowed whole with only water. If you vomit within 15 minutes of taking selumetinib, you may repeat the dose once.

You will be given a Patient Medication Diary for each cycle of selumetinib. Use the diary to record the date and time you take the drug, the number of capsules taken, side effects you experience, and any other medications you are taking. The completed diary should be returned to the clinic at your next scheduled clinic visit. This will help us to know how much of the drug you take and how it made you feel.

You will have regular clinic visits to monitor the disease and your response to treatment. You will have clinic visits every month for the first 9 cycles of treatment and then every 3 months for the rest of treatment.

**Research Study Tests and Procedures**

The following tests will be done because you are part of this study. If you were not in the study you may not have all these tests done. The results from these tests will not be returned to you unless otherwise stated below.

Copies of the scans used to diagnose the cancer will be sent to a central review center as part of COG quality control. The results of these reviews will not be returned to you.

Procedures that are common to all patients with NF1-associated LGG are described in **Attachment 1**.

**Required Research Study Tests**

- Motor Function Test: (for subjects who have problems with movement, called motor function deficits)

  At the beginning of this study, your doctor will check to see if you have any problems with muscle movement or strength. If he/she finds that you have motor function deficits, you will take part in research tests to see how your motor function changes over time

while you are on this study. These tests will be done before you receive any study treatment and at 48 weeks (about 11 months) after you start treatment. You and your parent/guardian will be contacted by phone to answer a questionnaire that will take about 30 minutes to complete.

- Neurocognitive and Quality of Life (QOL) Tests: (for all patients)

  The study doctors would like to learn more about the effects of treatment for subjects on this study. Cancer treatment can affect functions of the brain that relate to how we learn and remember new things, and even how we solve problems and tasks (also called "neurocognitive function"). Your participation in these tests will help us better understand how your brain function may be affected by cancer and its treatments. The neurocognitive study looks at several things that measure brain function.

  You will be tested at 5 different times while you are on this study: (1) before treatment; (2) 9–12 months after you start treatment; (3) 24 months after you start treatment; (4) 30 months after you start treatment; and (5) 60 months after you start treatment. You will be asked to complete some short tests of attention and memory on the computer, lasting about 20–30 minutes. For parents, we will also ask you to fill out a questionnaire about your child's everyday thinking and learning and a questionnaire about quality of life. It takes about 15 minutes to fill out the parent questionnaire. You and your child will complete the questionnaire and computer test during your child's clinic visits.

  Parents filling out the questionnaire about their child's every day thinking and learning can feel worry. If any questions make you feel uncomfortable, please speak with the psychologist or a study team member.

  If the neurocognitive tests suggest that there may be a problem, your doctor will share these results with you and discuss whether or not additional tests are needed. Remember that these tests are only a small part of the evaluation that should be done if you feel that your child is having problems with thinking or learning. Since these tests are short and focused, there is the possibility that the test results will not fully describe your child's complete level of functioning. If you believe your child is having trouble learning, talk to your doctor.

**Optional Research Study Tests**

- Neuropsychological Tests:

  Similar to the neurocognitive tests described above, this set of tests will allow the study doctors to get more information about how your brain function might be affected by cancer and its treatments. You will be given a set of tests called neuropsychological tests. While the subject is taking these tests, the subject's parent or guardian will fill in answers to a set of written questions. These questions will be used to learn more about the subject, for example, about his/her social skills, emotional well-being, behavior, and quality of life.

  There are 3 testing sessions which will be done: (1) 9–12 months after you start treatment; (2) 30 months after you start treatment; and (3) 60 months after you start treatment. Each session lasts about 1-2 hours. You will get these tests done at separately scheduled visits.

The information learned from the tests will not change the way you are treated. The results may be given to your doctor.

- Retina Thickness Test: (for patients with a certain type of tumor called an optic pathway tumor)

  The study doctors are interested in finding new ways to detect vision loss without the need to perform vision tests on patients. This is important because loss of vision is a key reason for why doctors might start cancer treatment for patients with optic pathway tumors. Normal methods of vision testing are sometimes hard to perform on all patients, like those who are very young. For this research test, a special camera will take images of the back of your eye to measure the thickness of your retina. This measure might be able to predict vision function in people with optic pathway tumors. The camera is a non-invasive, non-contact camera. This test will be performed 3 times while you are on this study during your clinic visits. They will take about 5 minutes to complete. The name of the test is called Optical Coherence Tomography (OCT).

- Research Study on MRIs: (for patients with a certain type of tumor called an optic pathway tumor)

  MRI scans will be done as part of your routine care to check how your cancer is responding to treatment. This research study will look at data from those MRI scans for research purposes. We want to find out if information from the scans can help us learn more about how patients might respond to treatment and how the treatment might affect vision. It will not require you to undergo any extra procedures.

- Banking:
  If you have any surgery while on this study, we would like to take some of your tumor and blood for future research. This is called “specimen banking” or “tissue banking.” A tissue bank is a lab where specimens (such as tumor, blood, or bone marrow) are kept for use in future research studies. The research that may be done with these samples is not designed to help you during your current treatment. The research might help people who have cancer and other diseases in the future. On this study, we will take about 1 teaspoon of blood for each tumor sample that is collected.

  Research on the banked specimens is **very unlikely** to discover results that are important to your current or future health. However, if it does, COG will try to contact your doctor about what the research tests might mean. Only the doctor will be notified and the information will not become part of your medical record. Your doctor will decide whether to discuss the results with you. Your doctor may recommend repeat testing, meeting with a genetic counselor, or no further action.

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

**Treatment Risks**

**All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.**

The risks of the individual drugs given as standard treatment are listed in **Attachment 2**.

**Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.**

**Side effects can be increased when chemotherapy drugs are combined.**

**The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency**. Low blood counts are described in the COG Family Handbook for Children with Cancer. Parents will be taught more about caring for their child when his or her blood counts are low.

**Risks of Study**

The use of selumetinib instead of carboplatin/vincristine may cause different complications.

The selumetinib treatment that is being studied could be less effective than the current standard treatment.

You may lose time at school, work, or home and spend more time in the hospital or doctor's office than usual. You may be asked sensitive or private questions which you normally do not discuss.

While most children enjoy the one-to-one interactions during the neuropsychological tests, some find the testing to be boring or tiring or frustrating. Rarely, the testing may remind you about other problems. If the results of your testing show that you have problems that are concerning to the study doctors, you may be given further assessments or referrals for other care. Further assessments or referrals are not part of this study and will be up to the study doctors. In this case, you will have to give up more of your time for the extra testing.

The chemotherapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

If you choose to take part in this study, there is a risk that the selumetinib (AZD6244 hydrogen sulfate) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The selumetinib (AZD6244 hydrogen sulfate) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

**Possible Side Effects of Selumetinib (AZD6244 hydrogen sulfate)**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving Selumetinib (AZD6244 hydrogen sulfate), more than 20 and up to 100 may have: |
|---|
| • **Diarrhea, nausea**<br>• **Swelling of the body**<br>• **Tiredness**<br>• **Acne** |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving Selumetinib (AZD6244 hydrogen sulfate), from 4 to 20 may have: |
|---|
| • **Anemia which may require blood transfusion**<br>• **Blurred vision**<br>• **Swelling of the eye**<br>• **Pain**<br>• **Constipation, vomiting**<br>• **Dry mouth, skin**<br>• **Sores in the mouth which may cause difficulty swallowing**<br>• **Fever**<br>• **Liver damage which may cause yellowing of eyes and skin, swelling**<br>• **Swollen or broken skin around the nail which may cause redness (paronychia)**<br>• **Potential liver damage (Alanine aminotransferase increased and Aspartate aminotransferase increased)**<br>• **Muscle pain/muscle breakdown (CPK increased)**<br>• **Infection, especially when white blood cell count is low**<br>• **Loss of appetite**<br>• **Dizziness, headache** |

- **Cough, shortness of breath**
- **Change in hair color**
- **Itching, rash**
- **High blood pressure which may cause headaches, dizziness, blurred vision**

**RARE, AND SERIOUS**

In 100 people receiving Selumetinib (AZD6244 hydrogen sulfate), 3 or fewer may have:

- **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness**
- **Cloudiness of the eye, visual disturbances**
- **Glaucoma**
- **Seeing spots before eyes**
- **Discomfort from light, visual loss**
- **Blockage of internal organs which may cause inability to pass stool**
- **Blood infection**
- **Change in heart function**
- **In children and adolescents: decreased height**
- **Damage to muscle which may cause muscle pain, dark red urine**
- **Redness, pain or peeling of palms and soles**
- **Bleeding (increased risk of bleeding given the vitamin E levels in the capsules)**

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

**Reproductive risks**

**Women should not become pregnant and men should not father a baby while on this study and for 12 weeks after stopping study therapy because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).**

## Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include:

- getting rid of your cancer for a long time or for the rest of your life,
- fewer side effects,
- fewer long term side effects (for example, being less likely to develop problems with the heart, lungs, kidneys; being less likely to have learning problems, or, less risk of getting another cancer later as a result of treatment),
- better vision or less vision loss for patients with optic pathway tumors

- the potential benefits of taking part in the neuropsychological tests are that the testing may find thinking, learning, remembering, or other problems that perhaps would otherwise not have been found.

With any cancer treatment, sometimes treatment does not make the cancer go away. Or, sometimes treatment makes the cancer go away for a while but the cancer comes back later.

We expect that the information learned from this study will benefit other patients in the future.

## What other options are there?

Instead of being in this study, you have these options:

- **Current standard therapy even if you do not take part in a study. Standard therapy is described in Attachment 1. It is Arm 1 of this study.**

- **Taking part in another study.**

Please talk to your doctor about these and other options.

## How many people will take part in the study?

The total number of people enrolled on this study is expected to be 165.

## How long is the study?

People in this clinical trial are expected to receive treatment on this study for about 1–2 years. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health every year for about 10 years after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if you become pregnant
- if you begin breastfeeding
- if new information becomes available that shows that another treatment would be better for you

## What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Children's Oncology Group has 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 Children's Oncology Group will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute (NCI)**
- **The study sponsor and any drug company supporting the study or their designated reviewers.**
- **The company that owns the test used for the neurocognitive study (CogState)**

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

## What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The NCI will supply selumetinib at no charge while you take part in this study. The NCI does not cover the cost of getting the selumetinib ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the selumetinib to the NCI for some reason. If this does happen, other possible options are:

- You might be able to get the selumetinib from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no selumetinib available at all, no one will be able to get more and the study would close.

If a problem with getting selumetinib occurs, your study doctor will talk to you about these options.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

## Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing optional specimens to the researcher, there are no plans for you to profit from any new product developed from research done on your specimens.

## What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if

changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/)*. To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all people on the study is completed, and not only when you complete treatment.

## Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* IRB Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

## Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

## Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide now that your specimens can be used for research and banking, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

1) Neuropsychological Tests:
   Check YES if you agree to the neuropsychological tests. Check NO if you do not want to take part in these tests.

   Yes _____ No _____ _____ / _____
   Initials Date

2) Retina Thickness Test:
   Check YES if you agree to the retina thickness test. Check NO if you do not want to take part in this test.

   Yes _____ No _____ _____ / _____
   Initials Date

3) Research Study on MRIs:
   Check YES if you agree to the research study on MRIs. Check NO if you do not want to take part in this test.

   Yes _____ No _____ _____ / _____
   Initials Date

If you agree to Biobanking, your sample will be stored *in the Biopathology Center at Nationwide Children's Hospital, in a locked freezer*. The samples *will be kept until they are used up*, unless you request that they be destroyed. Some information from your medical record will also be kept in secure databases at the Biobank and updated from time to time. The information and samples will be kept under a code, not your name.

This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. Qualified researchers can submit a request to use the materials stored in the Biobank. The research may be about your type of cancer, about other cancers, or even about conditions unrelated to cancer. A science committee at the Children's Oncology Group, and/or the National Cancer Institute, will review each request. Researchers will not be given your name or any other information that could directly identify you. Your sample will not be sold to third parties. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples, unless something is discovered that could directly affect your health. If that happens your study doctor will be notified and will decide whether and how to contact you.

Right now, we don't know what research may be done in the future using your samples. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue (including blood cells) and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

Some of your genetic and health information may be placed in central databases that may be made available to qualified researchers, along with information from many other people. Information that could directly identify you will not be included.

Even without your name or other identifiers, your genetic information is unique to you. If you agree to Biobanking, there is a risk of a data security breach and that someone could trace the genetic information in a central database back to you. Although this has never happened in real life and we have many safeguards in place to prevent it from happening, the risk may change in the future as people come up with new ways of tracing information. There are laws against the misuse of genetic information, but they may not give full protection. In some cases, misuse of the information could be used to make it harder for you to get or keep a job or insurance.

There can also be risks in learning about your own genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. Sometimes this is upsetting to families or they wish they didn't know the information. We encourage you to discuss this study with your relatives before you decide whether to participate in the Biobanking part.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called “Providing Your Tissue For Research: What You Need To Know.” This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue.

Please read the information below and think about your choices. After making your decisions, check “Yes” or “No”, then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB’s phone number included in this consent.

1) Banking:
   Check YES if you agree to have tissue and/or blood sample kept (banked) for use in research to learn about, prevent, or treat cancer or other health problems (for example: diabetes, Alzheimer's disease, or heart disease). Check NO if you do not want any new samples banked.

Yes _____ No _____ _____ / _____
Initials Date

## Signature

**I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.**

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

# Attachment 1

## Treatment and Procedures Common to all Patients with Low-Grade Glioma

### Methods for Giving Drugs

Various methods will be used to give drugs:

- **PO** (oral) - Drug is given by capsule swallowed through the mouth.
- **IV** (intravenous) - Drug is given using a needle or tubing inserted into a vein.

### Chemotherapy

Chemotherapy is anti-cancer drugs. Chemotherapy is considered the standard treatment for patients with NF1-associated LGGs who require therapy.

### Treatment on Chemotherapy

The treatment described below is standard treatment for patients with NF1-associated LGG. In this study, patients on Arm 1 will receive this treatment. The treatment is divided into 2 stages, called Induction and Maintenance.

Induction lasts about 12 weeks (84 days). The treatment during Induction is described in the table below.

| Drug | How the drug will be given | Days |
|---|---|---|
| Carboplatin | IV | 1, 8, 15, 22, 43, 50, 57, and 64 |
| Vincristine | IV | 1, 8, 15, 22, 29, 36, 43, 50, 57, and 64 |

Maintenance lasts about 48 weeks. Participants will receive 8 cycles of therapy; each cycle is 6 weeks (42 days). The table below describes 1 cycle of Maintenance.

| Drug | How the drug will be given | Days |
|---|---|---|
| Carboplatin | IV | 1, 8, 15, and 22 |
| Vincristine | IV | 1, 8, and 15 |

### Standard Tests and Procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- Frequent labs to monitor your blood counts, blood chemistries, and liver or kidney functions.
- Frequent physical exams
- Pregnancy test for females of childbearing age before treatment begins.
- MRI scans to monitor your response to treatment.
- Tests to monitor your heart and lung function.
- Tests to monitor your vision (if you have a type of cancer called an optic pathway tumor)

# Attachment 2

## Risks of Chemotherapy Drugs Used to Treat NF1-associated LGG

**Possible Side Effects of Carboplatin, Vincristine**

| **COMMON, SOME MAY BE SERIOUS**<br>In 100 people receiving Carboplatin, Vincristine, more than 20 and up to 100 may have: |
|---|
| • Infection, especially when white blood cell count is low<br>• Bruising, bleeding<br>• Anemia which may cause tiredness, or may require blood transfusions<br>• Vomiting, nausea, diarrhea, or constipation, which may be severe, as a result of bowel blockage<br>• Headache, jaw pain and/or muscle pain<br>• Numbness and tingling of fingers or toes<br>• Swelling of lower legs<br>• Muscle weakness and difficulty walking<br>• Swelling, pain, or redness at the site of the medication injection<br>• Hair loss |

| **OCCASIONAL, SOME MAY BE SERIOUS**<br>In 100 people receiving Carboplatin, Vincristine, from 4 to 20 may have: |
|---|
| • High or low blood pressure<br>• Swelling that may be accompanied by confusion, and dizziness<br>• Paralysis, weakness<br>• Difficulty with balance and hearing<br>• Belly pain<br>• Loss of appetite, weight loss<br>• Difficulty emptying the bladder or urinating, excessive, frequent, or painful urination<br>• Changes in taste<br>• Hoarseness<br>• Drooping eyelids, abnormal eye movement |

| **RARE, AND SERIOUS**<br>In 100 people receiving Carboplatin, Vincristine, 3 or fewer may have: |
|---|
| • Seizure<br>• Coma<br>• Visual loss with a chance of blindness<br>• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat |

# Attachment 3

## Certificate of Confidentiality

**The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.**

**The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.**