Title: A Phase II Trial of Poly-ICLC in the Management of Recurrent or Progressive Pediatric Low Grade Gliomas
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Rady Children's Hospital – San Diego and University of California, San Diego

Consent to Participate in Research

A Phase II Trial of Poly-ICLC in the Management of Recurrent or Progressive Pediatric Low Grade Gliomas

You are being asked to take part in a research study. A research study is a way that doctors look at something different, such as an additional treatment or a different combination of treatments to see how well it works. Research studies include only people who choose to take part. People who choose to take part in research are called "subjects" rather than "patients." You are being asked to take part in this study because you have a recurrent or progressive low grade glioma.

This study is being done in collaboration with the doctors at the University of California, San Diego and Rady Children's Hospital - San Diego.

STUDY INVESTIGATORS:

Principal Investigator: Donald L. Durden, MD,PhD

Co-Investigators: John Crawford, MD, MS
Lisa R. Hartman, MD

WHY IS THIS STUDY BEING DONE?

You have a tumor called a low grade glioma of the central nervous system (brain and spinal cord). Your tumor has grown despite attempts to control it with chemotherapy, radiation, and/or surgery. Low grade gliomas are a group of tumors that tend to grow slowly and could be cured if every bit of the tumor were surgically removed. These tumors are either Grade I or II, and their pathologic names include:

- juvenile pilocytic astrocytoma (JPA)
- pleomorphic JPA
- diffuse astrocytoma (fibrillary, gemistocytic, giant cell, or pleomorphic xanthoastrocytoma)
- subependymal giant cell astrocytoma (SEGA)
- low grade oligoastrocytoma
- low grade oligodendroglioma
- pilomyxoid astrocytoma
- low grade glioma not otherwise specified

These tumors often grow in parts of the brain that prevent total removal without devastating neurologic complications or death. Although some low grade gliomas never grow, most will and are treated with either chemotherapy or radiation. There is good data showing that the growth of most low grade gliomas can be controlled with chemotherapy or radiation. However, some low grade gliomas in children and young adults grow despite these treatments.

Poly-ICLC is an investigational drug that works on brain tumors by stimulating the immune system (cells in your body that fight infection). An investigational drug is a drug that has not yet been approved by the U.S. Food and Drug Administration (FDA) for use by prescription. Investigational drugs are only available in research studies. This drug has been used safely in children and adults with different types of brain tumors in other research studies like this one. Earlier studies showed that this drug worked better for children and young adults with low grade gliomas than for children with more aggressive brain tumors. The main purpose of this study is to use Poly-ICLC treatment in a larger number of patients with low grade gliomas to see how well it works and how many side effects occur in these patients.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 15 subjects per year will take part in this study over the next two years. This study will be done at Rady Children's Hospital – San Diego and Children's Healthcare of Atlanta/Emory University.

HOW LONG IS THE STUDY?

Treatment will last for about 2 years. You may stay on treatment for longer than 2 years if:

- the tumor shrinks in response to the injections
- doctors in charge of the study think it is safe
- you want to remain on the treatment
- if the medication is available

Researchers may decide to take you off the study if:

- the tumor gets worse
- you have side effects from the treatment that are considered too severe
- the doctor thinks it is in your best interest to leave the study

As part of this study, we would like to follow you every 3 months for the first year, every 4 months for the second year, every 6 months for the third year. We will collect information about how you are doing from your regular doctor visits. You will still be followed by your doctor for your regular care.

You can stop your participation in the study at any time. However, if you decide to stop your participation in the study, please talk to your doctor first.

WHAT WILL HAPPEN?

Surgery

To be in this study, you will already have had surgery to try and remove the tumor and identify the type of tumor. No surgery will be done specifically for this study.

Clinical Review

Prior to any treatment in this study. information about your tumor and treatment will be reviewed by the doctors at the UCSD and Rady Children's Hospital. This information will include pathology reports, radiology scans (MRI), and treatment history.

Standard Medical Tests

Before you start this study and while you are getting treatment on this study, you will have medical tests done. These tests would be done even if you decided not to be on this study.

Medical Tests Before Treatment :

- **Complete physical and neurological exam**
- **Blood tests** - About a teaspoon of blood will be drawn from your vein. We will look at kidney function, liver function, blood clotting tests, and blood counts.
- **Urine tests** – We will take a small sample of your urine to check for damage, bleeding, or infection in the kidneys or bladder.
- **Pregnancy test** – If you are female, you will have a pregnancy test before any treatment begins.
- **Scans of brain and spine (MRI)** – MRI is an imaging study that allows us to see the main tumor and to see if there are other tumors elsewhere in the body. It uses magnetic waves to measure the size of the tumor and to see how the treatment is working. It requires an injection of contrast (gadolinium). Contrast is given through a small needle placed into a vein. While you are getting the contrast, you may feel the contrast being injected.
- **Spinal fluid analysis from a lumbar puncture** – A needle will be inserted into your spinal canal and a small amount of fluid will be taken out. This allows us to see if the tumor cells have shed into the fluid that bathes the brain and spine. There is a slight risk of infection, nerve damage or headache. You will get medication to numb the pain and blur the memory before the test, since it can be painful. The pain is usually brief, but may occasionally last. You will be asked to review and sign a separate clinical consent form that fully explains the risks of this test.

Some patients need to be fully sedated for spinal taps. If you need sedation, you will be asked to review and sign a separate clinical consent form that explains the risks of sedation.

Medical Tests Given During Treatment

- **Complete physical and neurological exam** will be done every 2 weeks for the first month, then every 4 weeks.
- **Blood tests** will be done every 2 weeks for the first month, then every 4 weeks if the results are stable.
- **MRI of the brain** will be done every 3 months. You have had this test done several times before.
- **MRI of the spine** will be done every 3 months, but only if there was tumor seen on the MRI of the spine that was done before treatment
- **Spinal fluid analysis from a lumbar puncture** will be done every 3 months, but only if there were tumor cells seen in the spinal fluid examined before treatment

Medical Tests Given After Therapy Ends

- **Complete physical and neurological exam**
- **Blood tests**
- **MRI of the brain and spine**
- **Spinal fluid analysis from a lumbar puncture** (only if there were tumor cells in the spinal fluid examined before treatment).

Research Tests:

- **Blood tests** – About 3 tablespoons (15ml) of blood will be taken from a vein in your arm before treatment starts and again after 2 weeks of treatment (Day 15). This will be used to study how Poly-ICLC impacts proteins in the blood. You will not receive any results from these research tests.

Optional Research Tests

The following tests will be done only if you agree. You can choose be in this study without taking part in these additional research tests. These tests are not part of standard care. Results of these tests will not be given to you. Treatment decisions will not be based on these tests. You (or your insurance company) will not be charged for these research tests. Please review the information about these research tests and make your choice regarding whether or not you want to take part in these extra research tests.

- **Spinal fluid analysis** – All subjects will have spinal fluid examined before starting therapy. About 1 teaspoon of this fluid will be collected and examined for tumor cells as part of your regular care. With your consent, a little more than ½ a teaspoon (3ml)

of extra fluid will be collected and frozen for this study. Proteins in this fluid will be examined and identified. These proteins may help us understand why low grade gliomas grow despite common tumor treatments, and may identify new targets to kill these and other brain tumor cells. Additional spinal fluid will only be collected during procedures done for your regular care. Additional spinal taps will not be done solely for the study.

_____ Yes, the additional CSF fluid can be collected during your regular
Initial care spinal tap (lumbar puncture) for these research studies.

OR

_____ No, the additional CSF fluid cannot be collected during your regular
Initial care spinal tap (lumbar puncture) for these research studies.

▪ **Tumor tissue analysis –** You had surgery to determine the type of tumor you have, before beginning this study. As part of this study, we would like to use any left-over tissue from that surgery for this study. The tissue will be analyzed by a pathologist at UCSD to look for certain markers and genetic traits found in these tumors. If you have another surgery while on this study, we would also like to use any left-over tissue from that surgery as well. Additional surgeries will not be done solely for the study. This is a request to use any left-over tissue that has been stored by the Hospital that was not used for evaluation of your disease.

_____ Yes, the leftover tissue can be used for these research studies.
Initial

OR

_____ No, the leftover tissue cannot be used for these research studies.
Initial

Study Treatment with Poly-ICLC

You will get injections of Poly-ICLC into muscle two times weekly. The first treatments will be given in the clinic so nurses and doctors can make sure you do not have any (allergic) reactions to the injection. They will also teach you or a care giver how to safely give the injections. If you tolerate the injections and do not have a severe reaction, then the rest of the injections will be given at home.

The medicine will be supplied in vials. You will be shown how to draw up the correct amount of the study drug in a syringe and how to give the injection. The study drug should be kept in the refrigerator, but not frozen. It can be left at room temperature for up to 3 days without losing effectiveness

While you are receiving Poly-ICLC, you will be asked to keep a temperature log, noting your temperature before your receive the Poly-ICLC, then 2-4 hours and 12 hours after the dose. Temperature may be taken orally, under the arm, or in the ear. Your doctor will review the log with you. This will be done with every dose of Poly-ICLC and you will need to bring this log with you each time you come to the clinic.

You will also be asked to keep a medication diary, noting the date, time, site and any problems you had when taking the Poly-ICLC. This will be done with every dose of Poly-ICLC and you will need to bring this diary with you each time you come to the clinic.

While you are on this study information about how you are doing will also be collected. This will include what medications you are taking, any side effects that happen and the status of your disease.

WHAT ARE THE RISKS OF THE STUDY?

All medications have side effects. Poly-ICLC has been used safely in children and adults at this dose and at higher doses in other research studies. Frequently seen side effects include irritation of the skin where the injection is made and mild flu-like symptoms. These are usually relieved or avoided by use of over-the-counter medicines like acetaminophen (Tylenol).

Side effects of Poly-ICLC include:

	Common (21-100 patients per 100)	**Occasional (5 to 20 patients per 100)**	**Rare (1 to 4 patients per 100)**
Immediate (within 1 to 2 days of receiving the drug)	Muscle soreness and redness where the drug is injected.		
Prompt (within 2 to 3 weeks)		Fatigue Muscle aches Fever	Decreased number of white blood cells (transient)
Delayed (anytime later during therapy)			Increased liver enzymes and BUN (reflects kidney function) levels in the blood
Late (anytime after completion of therapy			

Blood Draw Risks
Risks associate with needle sticks for drawing blood are slight, but some possible risks include bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Sedation Risks
If you need sedation for any procedure, you will get a separate clinical consent form that explains the risks of sedation. Depending on the type of sedation required, there may be one or more of the following side effects: nausea, vomiting, air passage obstruction, breathing problems or heart irregularity. Sedation would only be used for your regular procedures, which are not part of this study

Lumbar Puncture Risks
Lumbar punctures (spinal taps) can be painful and may cause headaches. The skin at the site of needle insertion is usually numbed with an anesthetic cream or lidocaine. You will be given another clinical consent form that covers the risks associated with this procedure. Lumbar punctures would only be done as part of your regular care. Additional lumbar punctures will not be done solely for the study.

Reproductive Risks
Treatment may cause temporary or permanent loss of reproductive function in males and females. In males, treatment may cause low sperm counts or sterility (being unable to produce viable sperm). Males may be candidates for sperm banking, which can be discussed with your doctor. In females, treatment may damage eggs, stop monthly periods, or cause infertility (being unable to produce viable eggs). Treatment may harm a fetus or breast-fed child. Pregnant and/or breast-feeding women cannot participate in this study. Females will have a pregnancy test before treatment. If you are sexually active, you must take measures to prevent pregnancy. You and your doctor will discuss effective methods of birth control. If you suspect that you or your partner have become pregnant during the study, you must notify your doctor immediately. If you become pregnant you will be withdrawn from this study.

Other Risks
In addition to the risks described, there may be unanticipated and unknown risks associated with being in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may be no direct benefit to you for taking part in this study. It is hoped however that the use of Poly ICLC will control your disease, but this cannot be guaranteed. We also hope that information learned from this study will help other patients who have resistant and recurrent low grade gliomas in the future.

WHAT OTHER OPTIONS ARE THERE?

Alternatives to this therapy include:

- use of drugs or other therapies that have been previously tried in the treatment of this disease
- no anti-tumor therapy at this time
- palliative care, which treats the symptoms and quality of life, rather than the disease.

Your doctor can provide detailed information about your disease and the benefits of the various available treatments. Please discuss the disease and future outlook with your doctor.

You will still be treated at this Hospital, even if you decide to not take part in the study.

Please talk to your doctor about these and any other options.

WHAT ABOUT CONFIDENTIALITY?

Every reasonable effort will be made to keep your records confidential. We will keep your records in locked files in the Oncology research center and only the treatment and study staff will have immediate access to them. Your medical information, which may include reports and lab results, and research specimens (e.g., blood and spinal fluid), will be sent to Dr. Durden's laboratory at UCSD. Dr. Durden and his study team will receive your medical information, but you will only be identified by a study number.

While you are in this study all related records may be made available to:

- Oncovir Ribopharm Inc (supplier of Poly-ICLC) and its authorized representatives
- The Moores Cancer Center Data and Safety Monitoring Board (DSMB) at UCSD
- The UCSD Institutional Review Board (IRB)
- The National Cancer Institute (NCI)
- The U.S. Food and Drug Administration (FDA)
- Other U.S. governmental regulatory agencies involved in keeping research safe for people

A copy of this form and the HIPAA authorization form that you sign will be placed in your medical record. Your records and information will not be released without your consent unless required by law. If the study results are published or presented, you will not be identified.

WHAT ARE THE COSTS?

You or your insurance company will be charged for continuing medical care, including but not limited to standard procedures, lab and imaging tests,,and/or hospitalization. The study drug, Poly ICLC, will be provided by Oncovir Rhibopharm Inc., at no cost to you or your insurance company. The research specific tests (blood, spinal fluid, tissue) will also be paid for by the study.

WHAT IF YOU ARE INJURED IN THE STUDY?

If you are injured or become ill as a direct result of participation in this research study, Rady Children's Hospital – San Diego or the University of California will provide any medical care needed to treat those injuries. Neither Rady Children's Hospital-San Diego nor the University will provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 455-5050 for more information about this, to inquire about your rights as a research subject or to report research-related problems..

WILL YOU BE COMPENSATED?

There are no plans to compensate you for taking part in this study.

Specimen samples, including blood, spinal fluid, and tissue may be used during this study for analysis. During the analysis of the samples from all subjects in this study, new diagnostic tools or treatments may be developed. There are no plans to compensate you if such developments occur.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions about the study or a research-related injury, you may contact Dr. Durden, Dr. Crawford or Dr. Hartman at (858) 966-5811. During weekends or after hours, please call (858) 576-1700 and ask the operator to page the Oncologist on call.

WHAT ARE YOUR RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is voluntary. You may choose not to take part or you may choose to leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled, including the quality of care you receive. No matter your decision the doctors and hospital personnel will still take care of you.

If you have questions about your rights or to report a research related concern you may call the UCSD Human Research Protections Program at (858) 657-5100. This is a group of people who review the research to protect your rights.

You will be told about any new information that may affect your health, welfare, and willingness to stay in this study.

CONSENT TO BE IN THE STUDY:

Your signature below means that you have read the above information about the Poly ICLC study and have had a chance to ask questions to help you understand what you will do in this study and how the information will be used.

You have been told that you can change your mind later if you want to. You will be given a copy of this form and a copy of the Subject's Bill of Rights. By signing this form you are not giving up any of your legal rights.

You consent to be in this study.

_____	_____
PRINTED NAME OF SUBJECT	AGE
_____	_____
SIGNATURE OF SUBJECT	DATE
_____	
PRINTED NAME OF PERSON EXPLAINING THIS FORM	
_____	_____
SIGNATURE OF PERSON EXPLAINING THIS FORM	DATE

SUBJECT'S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. As a participant in research, you have the right to:

1. Be informed of the nature and purpose of the research.

2. Be given an explanation of all procedures to be followed and of any drug or device to be used.

3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.

4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.

5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.

6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.

7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.

8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.

9. Be given a copy of this signed and dated written form.

10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your rights as a research subject, please contact the researcher or the UCSD Human Research Protections Program at (858) 455-5050.