

SAMPLE INFORMED CONSENT

Modulation of Intensive Melphalan (L-PAM) By Buthionine Sulfoximine (BSO) With Autologous Stem Cell Support for Resistant/Recurrent High-Risk Neuroblastoma NANT (99-02)

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial (a type of research study using human patients). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

You are being asked to participate in this study because you have neuroblastoma which is not responding or has relapsed after having standard treatment.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest dose of melphalan that can be given with BSO without causing severe side effects.
- To measure blood levels of melphalan and BSO during treatment.
- To determine if your tumor responds (gets smaller) after receiving treatment.

The research is being done because:

Currently there is no treatment for your neuroblastoma which is known to be able to cure your cancer.

This study uses a combination of two anticancer drugs: Buthionine Sulfoximine (BSO) and melphalan. Melphalan has anti-cancer effects in neuroblastoma and other childhood solid tumors. Buthionine Sulfoximine (BSO) is an experimental drug that removes an important chemical called glutathione from both normal and tumor cells. Glutathione protects tumor cells from the anti-cancer effects of melphalan. Adding BSO has been shown in the laboratory to increase the killing of cancer cells by melphalan.

In a pilot study testing BSO/melphalan in 32 children with neuroblastoma, some tumors got smaller, however, 2 children died from decreased function of the kidneys combined with brain swelling. After a careful examination of these cases, the exact reason for these fatal side effects is not known. It is possible that antibiotic use or having tumor in the brain may have increased the side effects of the BSO/melphalan. This Phase I study requires that patients do not have any tumor in the brain, and does not allow the use of certain antibiotics during the BSO/melphalan therapy. The two deaths occurred using the same dose of BSO and lower doses of melphalan than will be used during this study. Although there is a risk of fatal toxicity, you are being offered this Phase I treatment because of laboratory data suggesting that BSO/melphalan may kill neuroblastoma cells that are highly resistant to standard therapy.

Laboratory studies in some adult tumors and in neuroblastoma have shown that sometimes BSO needs to be combined with higher doses of melphalan to kill more cancer cells. These higher doses of melphalan have been given to children and are known to be tolerated when given alone. When the combination of BSO and melphalan was given together to the 32 children in the previous pilot study, all patients had a decrease in the number of normal blood cells. It is possible to give blood forming cells (called stem cells) to patients to help the normal blood cells to recover faster. That is why all patients treated on this study will get their own stem cells given back after the BSO/melphalan to decrease the side effects on the blood cells.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 18 to 36 people will take part in this study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study, you will need to have the following exams, tests, or procedures done to find out if you can be in the study. These are part of regular cancer care and may be done even if you do not join the study.

• **Stem Cell Collection**

Before you can get treatment on this study, stem cells must be stored from your bone marrow or peripheral blood. If you need to have stem cells collected, you will be given a separate consent form to sign. If you have stem cells already stored and they meet the study requirements, then they may be used for this study. If you do not have enough stem cells stored you will not be able to participate in this study.

• **Exams/Tests/Procedures -- Before the Study Starts**

Physical Exam	Various scans ²
Blood tests	Tests of kidney function
Bone marrow tests ¹	Tests of heart and lung function
Pregnancy test	
Urine tests	

¹ Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is the soft tissue inside the bone that makes blood cells, for study and diagnosis.

²Various scans are done to see how the tumor responds to the treatment including CT/MRI scans and MIBG scans.

• **Exams/Tests/Procedures – During the Study**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

Physical Exam including a neurological exam
Blood tests
Urine tests

Because you are in this study, physical exams, neurological exams, blood and urine tests that are part of your regular cancer care will be done more often.

- Physical exams will be done at least once a week.
- Neurological exams will be done daily at the start of treatment and then decrease to weekly by 4 weeks after treatment.
- Blood and urine tests will be done daily at the start of treatment and then decrease to weekly by 4 weeks after treatment

You will be asked if you want to participate in research tests that are done to see how the study is affecting your body. **This part of the study is voluntary.** You can decide not to let the doctors do these tests and still be able to be treated with BSO/melphalan as part of this clinical study. The test results do not affect your treatment with BSO/melphalan and will not be told to your doctor or become part of your medical record. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these voluntary studies.

Determining the blood levels of BSO and Melphalan (called pharmacokinetics)

Part of the research goal for this study is to look at blood levels of BSO and melphalan. For these tests, 3 ml of blood (about ½ teaspoon) will be drawn from a vein at 18 different times (total 54ml or 11 teaspoons) over several days while you are (your child) is in the hospital getting the treatment. You may need a blood transfusion after having all these samples drawn. These drug levels must be drawn from an IV that is different from the one where the BSO and melphalan are being given.

Determining the level of glutathione (GSH) in the blood

Ten ml of blood will be drawn from a vein twice (total 4 teaspoons) to learn more about the effects of BSO on glutathione levels in the blood.

- **When I am finished taking BSO/melphalan:**

You will have an evaluation to see how your neuroblastoma responded to this treatment. You will repeat all the same tests you had done when you were preparing to enter on the study.

- **Protocol Treatment with BSO / melphalan:**

BSO and melphalan are given by IV. Both drugs may be given through a central line.

See diagram of treatment below: Only one course of this treatment will be given. On the first day BSO is given by IV over 30 minutes followed by a continuous infusion of BSO for 3 days. Melphalan is given IV over 20 minutes on 2 days. The stem cells will be infused into the central line, 24 hours after the infusion of BSO has finished. Four hours after the stem cell infusion, G-CSF (a medicine to help the growth of white blood cells), will be given either as an injection under the skin or by IV every day until enough white blood cells are present in the blood to fight infection.

Day -4	Day -3	Day -2	Day -1	Day 0
BSO	BSO	BSO	BSO	Stem cell infusion and G-CSF
BSO IV over 30 minutes (Day 1) then continuously x 3 days (Day-4 to Day -1)				
	Melphalan	Melphalan		

- **Dose escalation of BSO/melphalan**

The dose of BSO will be the same for all patients. The dose of melphalan will be increased in groups of 3 patients at a time until the highest dose that can be given without causing serious side effects is found. This study will start at dose levels of melphalan that are known to be safe without stem cell support and will increase the dose of melphalan until other kinds of side effects are seen. Doses are not increased within groups of patients.

To prevent severe effects to the liver by BSO: NO ACETAMINOPHEN (Tylenol®) or acetaminophen containing products may be taken beginning 7 days (1 week) before starting the drug BSO until 14 days after the BSO infusion has finished. Your doctor will talk about other medicines that can be used instead of acetaminophen during this time.

To possibly prevent severe side effects to the kidney:

No antibiotics of any kind may be taken beginning 7 days before starting the drug BSO.

Also specifically NO CEPHALOSPORIN ANTIBIOTICS may be taken beginning 7 days before starting the drug BSO until 14 days after the BSO infusion has finished. Your doctor will talk about other medicines which can be used during this time.

HOW LONG WILL I BE ON THIS STUDY?

You will only get one treatment with BSO/melphalan. You will stay on this study for 84 days or for as long as it takes for your stem cells to regrow and make enough normal blood cells and for you to recover medically from any side effects. You will have an evaluation done to see how your neuroblastoma responded to this treatment. We would like to follow and observe you after the therapy is finished. You will continue to have tests and scans done to assess the status of your tumor. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about about your disease until the cancer comes back or you get other treatment. Information will be collected for a lifetime about whether you are still alive, whether you have developed any side effects from the treatment or any additional cancer. This information may be gotten from your oncologist or family doctor at regular intervals.

Possible side effects of Melphalan:

- Mouth sores, mouth swelling and damage to the Gastrointestinal (GI) system Common
- Diarrhea Common
- Loss of appetite Common
- Abnormal liver function tests Occasional
- Abnormal kidney function tests Occasional
- Tingling or numbness in of the hands and feet (known as paresthesias) Rare
- Mucositis (irritation of mucous membranes) Common
- Allergic reaction (may cause hives, and/or difficulty breathing, and/or lowered blood pressure. Symptoms of an allergic reaction can be treated with anti-allergy medicines.) Rare
- Effects on the peripheral nerves (abdominal pain, constipation, clumsiness, or poor coordination, or abnormal sensations) Occasional
- Lung scarring known as stiff lungs or pulmonary fibrosis Rare
- Irritation of the bladder Occasional
- Hair loss Common
- Difficulty breathing Rare
- Production of a hormone that decreases urination and lowers blood levels of salts Rare

Possible side effects of BSO in combination with Melphalan + Stem Cell Infusion:

- Nausea and vomiting Common
- Lowering of the number of blood cells Common
Some of the blood cells will be damaged or destroyed in all patients who get this treatment. At higher doses of melphalan this might be fatal if you was not “rescued” by the stem cell infusion. Stem cells make white blood cells, red blood cells and platelets which are needed for you to live. Until the new stem cells begin making enough of the new blood cells, you will have side effects from having low blood cells. Side effects of low blood cells may include infection, bruising and /or bleeding, pale color, and/or fatigue
- Skin Damage Red skin is common. Blistering or peeling skin is not as common.
- Kidney damage Rare
- Venocclusive disease of the liver Rare
Venocclusive (VOD) is a scarring of the small blood vessels in the liver. When this happens, fluid collects in the abdomen or lungs, weight increases, yellow jaundice may occur, and an increased tendency for bleeding may happen. The risk for VOD may increase using BSO and melphalan together since they both have effects on the liver.
- Multiple organ system failure Rare
- Bone marrow dysfunction Rare
Treatment with BSO + Melphalan can affect the body such that the new stem cells may not be able to grow and make blood cells or that the blood cells would grow but not return to normal levels. If this happens, back-up stem cells may be used if they are available or growth factors also may be given to try to improve stem cell growth.

Possible side effects of Granulocyte Colony Stimulating Factor (G-CSF):

G-CSF is not an anti-cancer medicine. It helps the growth of white blood cells, which fight infection.

- Fever, chills, nausea, headache, malaise = flu-like symptoms Common
- Bone pain Common
- Low blood pressure Rare
- Shortness of breath Rare
- Enlargement of spleen Rare

Possible side effects associated with stem cells:

- ANYTIME BEFORE STEM CELL INFUSION: The freezer where PBSC are stored could malfunction, the container holding them could break and the stem cells could be damaged so they could not be used. This is expected to be an extremely rare event, however, if it occurs, another stem cell collection may be attempted or the back-up stem cells (if available) may be used if they were not damaged.
- Shipping of stem cells: If your stem cells need to be shipped, there is a small risk they could be lost or damaged in the shipping process such that they could not be used. This is expected to be an extremely rare event. If this occurs, another stem cell collection may be attempted or the back-up stem cells, if available, may be used.
- PURGED STEM CELLS ONLY: Purging may injure the normal stem cells so they will not grow to make a normal working bone marrow after they are infused. This is expected to be an extremely rare event, but could be fatal if it happened. There would be the option to give medicine(s) to stimulate bone marrow growth, or infuse additional back-up stem cells, if they are available.

Possible side effects of stem cell infusion:

- | | |
|----------------------------|--------|
| • Fever and chills | Common |
| • Allergic reaction | Rare |
| • Increased blood pressure | Rare |
| • Infection | Rare |
| • Infusion of tumor cells | Rare |
- Tumor cells may still be present in the harvested stem cells and they could regrow in the patient receiving them.

Possible long term side effects of this treatment:

- Recurrence of the tumor
- Infection
- Sterility and / or delayed onset of sexual maturity
- Increased risk of having a second cancer different from the kind of cancer you have now.

Reproductive Risks:

You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. We hope the information learned from this study will benefit other patients with pediatric solid tumors.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

There are other options for treatment. You may get other therapy even if you do not take part in the study. Instead of being in this study, you have these options:

- Treatment with a different chemotherapy regimen using stem cell support.
- Treatment with combinations of anti-cancer medicines in lower doses that do not need stem cell support.
- Other experimental agents that are available
- No therapy at this time with care to help you feel more comfortable.

Please talk about these options with your doctor as well as other trusted personal and family advisors.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

You may read your record. We will do our best to make sure that the personal information in your medical record will be kept private. However we cannot guarantee total privacy. Your personal information will be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- New Approaches To Neuroblastoma Therapy (NANT) Consortium at Childrens Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you (your child) by a number.
- Independent auditor to monitor quality assurance for the NANT Consortium
- The Investigational New Drug Sponsor (the supplier) of BSO, Dr. C. Patrick Reynolds, MD PhD, Texas Tech University Health Sciences Center.
- The Federal Government – National Cancer Institute (NCI) and the Food and Drug Administration (FDA) may examine records of patients participating in this study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

C. Patrick Reynolds, MD PhD of Texas Tech University Health Sciences Center as the Investigational New Agent (IND) sponsor will supply the NANT Consortium with the investigational agent BSO free of charge for this study. If during the study BSO becomes commercially available, you may have to pay for the amount of drug needed to complete the study.

Melphalan is commercially available. You will pay for the amount of drug you need to complete this study. This cost is normally covered by your insurance company.

The tests for BSO/melphalan pharmacokinetics and GSH in the blood will be done at no extra cost to you if you agree to participate in these voluntary tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw the blood samples from you.

Your insurance company will be charged for continuing medical care and / or hospitalization. Taking part in this study may lead to added costs to your insurance company. Please ask about any expected added costs or insurance problems.

You will receive no payment for taking part in this study.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, carfare, parking, and baby sitter fees.

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 Web site.

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 STUDY?

It is important that you tell your study doctor, _____, 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 _____.

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 due to injury while being on this study.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS 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, 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 for our institution.

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

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

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ at _____.

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

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at **1-800-4-CANCER (1-800-422-6237)** or **TTY: 1-800-332-8615**

You may visit the NCI at <http://cancer.gov/>

1. For NCI's clinical trials information, go to <http://cancer.gov/clinicaltrials/>
2. For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

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

CONSENT FOR EXTRA STUDIES FOR RESEARCH

- **Blood Levels of BSO and Melphalan (Pharmacokinetics)**

#1 Circle YES, if you agree to let researchers take up to 54ml of blood (11 teaspoons) to test blood levels of BSO and melphalan. This will be done in 18 extra blood draws. This blood must be taken from an IV different from the one used for the bso + melphalan treatment. You may need to have another iv started to get these samples. The results of these tests will be confidential and not made available to you or your treating doctor.

Circle NO if you do not want researchers to take extra blood samples for BSO + Melphalan pharmacokinetics.

#1 **YES** **NO**

Signature Participant: _____

DATE: _____

- **Blood Levels of GSH (glutathione)**

#2 Circle YES, if you agree to let researchers take 20 ml of blood (4 teaspoons) to test blood levels of GSH. This will be done in 2 extra blood draws. This blood must be taken from an IV different from the one used for the bso + melphalan treatment. The results of these tests will be confidential and not made available to you or your treating doctor.

STATEMENT OF CONSENT

I have been given a copy of all _____ 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.

Patient Name

Signature of Parent or Guardian

____/____/____
Date

Signature of Parent or Guardian

____/____/____
Date

Signature of Patient (If ≥ 7 years old)

____/____/____
Date

**Signature of Physician or
Responsible Investigator**

____/____/____
Date

Signature of Witness

____/____/____
Date

**Signature of Translator
(If applicable)**

____/____/____
Date

CONSENT ADDENDUM

A blank box means the test is not done at that time point in the study.

Tests that will be done on this study.

STUDIES TO BE OBTAINED	Pre-Study	Day -4 through Day 0	Day 0 through Day +28	Day +28 through Day +84	Off Protocol Therapy
Physical Exam	X	X	Weekly	Weekly until normal	X
Neurological exam			Twice a week x 2 weeks then weekly if normal	Weekly until normal	X
Blood and/or urine tests	X	Day 0, 6, 13	Range from daily to 1x/week for different tests		X
Kidney test	X				X
Test of lung function only if necessary	X				X
Heart test (echocardiogram/MUGA and EKG)	X				X
Chest X-Ray	X				
Head Imaging (CT/MRI)	X				
Tumor Imaging with CT/MRI and MIBG scans	X				X
Urine test (VMA/HVA)	X				X
Bilateral bone marrow aspirate and biopsy for routine morphology	X				X
Tests below this line would only be done if you gave permission for them to be done.					
Blood levels of BSO and Melphalan (OPTIONAL)		X			
Blood levels of GSH (Optional)		Day-4 and Day -2			