15.0 SAMPLE INFORMED CONSENT AND ASSENT

NANT 2013-02 A Phase I Study of Sorafenib and Cyclophosphamide and Topotecan in Patients with Relapsed and Refractory Neuroblastoma.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your study doctor.

You are being asked to participate in this study because you have been diagnosed with neuroblastoma. Your cancer has either grown back (relapsed) or has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest doses of sorafenib given together with cyclophosphamide and topotecan that can be given to children with refractory or recurrent neuroblastoma without causing severe side effects
- To learn about the side effects of giving of sorafenib together with cyclophosphamide and topotecan
- To determine if your tumor gets smaller after treatment with sorafenib, cyclophosphamide and topotecan
- To learn how sorafenib changes immune cells in tumor cells.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called TLDA) that has been found to be more sensitive.

The research is being done because:

Currently there is no known effective treatment for your type of cancer. This study will combine three drugs: sorafenib, cyclophosphamide and topotecan. You may have taken 1 or all of these medicines before (but not all three together) for treatment of your neuroblastoma.

This study involves the use of an experimental drug, called sorafenib. Sorafenib blocks the function of a protein that is important in the growth of cancer cells. This drug has been tested by itself (as a single-agent) in children with relapsed solid tumors, including patients with neuroblastoma. In the laboratory, sorafenib appears to make neuroblastoma tumors smaller, and can help immune cells to be more active in attacking tumors and blocks other harmful immune cells from promoting tumor growth and function. Sorafenib also helps to block tumor cells from developing blood vessels used to "feed" to tumor. Sorafenib is an FDA-approved drug currently widely used for adults with specific types of liver and kidney cancer.

Cyclophosphamide and topotecan are both FDA-approved chemotherapy drugs. These drugs are approved for the treatment of certain adult cancers, but have also been used to treat children with cancer. These drugs have been used in combination in many people with neuroblastoma. In some neuroblastoma patients, this combination has reduced the amount of tumor present.

Adding sorafenib to cyclophosphamide and topotecan may increase the effectiveness of this combination. We first need to find out the highest dose of sorafenib that can be given safely together with cyclophosphamide and topotecan. This is the first study to test giving these three drugs together and will help determine the highest dose of sorafenib that can safely be given together with cyclophosphamide and topotecan to patients with resistant/relapsed neuroblastoma.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 4 and 18 people will take part in this study.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Medical Tests Before You Begin the Study

You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Physical exam, including a blood pressure check	Bone marrow tests[#]
Blood tests	Various scans*
Pregnancy test**	Echocardiogram/MUGA and EKG to check the heart function
Urine tests	

[#] Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans**.**

[**] If you are a female at least 10 years old or who could have children, you must have a pregnancy test done by the doctor the week prior to starting treatment. If there is ANY chance that you can get pregnant, you must either agree to practice abstinence from heterosexual intercourse or begin an effective method of birth control.

You will also be expected to join a companion biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. Your study doctor will talk with you in detail about this study and have you sign a separate consent form.

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 during the study. Many are part of regular cancer care.

Physical exam, including a blood pressure check	Bone marrow tests[#]
Blood and urine tests	Various scans*

[#] Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans**.**

Treatment Plan

A map of treatment course 1 and all subsequent courses is shown below. Course 1 is 35 days because of the 1 week of sorafenib given before starting the cyclophosphamide/topotecan combination. Course 2 and subsequent courses are 28 days. You may receive up to 12 courses of therapy as long you are benefiting from treatment and continue to meet the criteria to continue safely on this study.

COURSE ONE:		
Day -6 to 0	**Day 1-5**	**Day 6-28**
Sorafenib	Sorafenib	Sorafenib
	Cyclophosphamide/Topotecan	Myeloid Growth factor – Filgrastim or Pegfilgrastim

COURSE TWO AND ALL SUBSEQUENT COURSES:	
Day 1-5	**Day 6-28**
Sorafenib	Sorafenib
Cyclophosphamide/Topotecan	Myeloid growth factor – Filgrastim or Pegfilgrastim

You will receive sorafenib by mouth twice a day without a break between treatment courses.. Sorafenib may be taken either as a tablet or as a liquid. Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for administering this medication. You will need to avoid grapefruit and grapefruit juice during drug administration to maximize intestinal drug absorption. It is preferable that Sorafenib is taken on an empty stomach (for example at least 1 hour before you eat a meal or at least 2 hours after eating a meal) but if you take sorafenib with food, it should be taken with a moderate to low fat meal.

You will be asked to keep a written record of when you are taking sorafenib and return it to your nurse/doctor at the end of each course of treatment.

You will receive cyclophosphamide into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 30 minutes on days 1-5. This medicine is typically given in the outpatient clinic.

You will receive topotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 30 minutes on days 1-5 immediately following the infusion of cyclophosphamide. This medicine is typically given in the outpatient clinic.

You will also receive a drug to boost the white blood cell count (called myeloid growth factor -- filgrastim or pegfilgrastim). This drug will be started on day 6 of each course of treatment. Filgrastim is a shot given into the

skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of filgrastim that is given as a shot into the skin just once per course. Your study doctor will talk with you about which of these drugs you will receive.

When you join the study, you will be assigned a certain sorafenib dose. This study will test up to three sorafenib doses in groups of 3-6 patients. The starting sorafenib dose for the first group of patients is about 40% lower than what was given to patients who received sorafenib alone without bad side effects. If this is tolerated without serious side effects, then the sorafenib dose will be increased ("dose escalation") in groups of 3-6 patients until serious side effects are seen. At that point, investigators will have found the highest dose of sorafenib that can be given along with topotecan and cyclophosphamide without bad side effects.

The doses of cyclophosphamide and topotecan are not increased during this study. The doses used are typical doses used to treat patients with relapsed neuroblastoma.

You can receive up to 12 courses of treatment (approximately 49 weeks or about 1 year) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may receive a different dose of sorafenib, your assigned dose of sorafenib will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of sorafenib.

When you have finished treatment with sorafenib, topotecan and cyclophosphamide

After you stop treatmenton this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, they will be repeated monthly until the test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Bone marrow tests[#]
Blood tests	Various scans*
Urine tests	Echocardiogram/MUGA and EKG to check the heart function

[#] Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans**.**

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent.

Additional Tests in this Study – REQUIRED

There are 3 required tests that are being done to see how the study drugs are affecting your body**.** The results of these tests will not be told to you or your doctor or become part of your medical record. These results also willnot be used to make decisions about your care while enrolled on this study. The total amount of blood taken to perform these additional tests will be limited to the amount set by the human subjects protection committee at your institution.

- **Test 1: Sorafenib Pharmacokinetics**

Part of the research goal for this study is to look at the effects the different doses of sorafenib have on your cells, and how much of the drug is in your blood. These will be measured in the first course of therapy only. For this test, 2 ml of blood (less than 1 teaspoon) will be taken 4 times. You will need one extra clinic visit for this part of the study. The total amount of blood drawn for testing will be about 8 mL (almost 2 teaspoons) over 35 days. The blood will be drawn or taken from your central line (or port). **This amount of blood is considered safe to donate. Samples will be sent to the University of Southern California.**

- **Test 2: Immune Modulation**

Part of the research goal for this study is to look at changes in your immune function by looking at your cells before and during the first treatment course of this study**.** We will also be looking at the way sorafenib acts in your body (including testing genes that are connected to the way sorafenib works). For this test, 2 mL of blood (about half of 1 tablespoon) will be taken 4 times for all patients. You will need one extra clinic visit for this part of the study. The total amount of blood drawn for testing will be 8 mls (almost 2 teaspoons) over 35 days. The blood will be drawn or taken from your central **line (or port). This amount of blood is considered safe to donate. Samples will be sent to Children's Hospital Los Angeles.**

- **Test 3: Protein Activation (Bone Marrow)**

Part of the research goal of this study is to look for changes in a protein that helps tumor cells to grow and whether the treatment will stop the effect of this protein on tumor growth. Tests will be done on bone marrow biopsy material obtained as part of clinical disease evaluations done before entering on study and after completing 2 treatment courses. Part of your bone marrow biopsy that is not needed for clinical care will be sent to Childrens Hospital Los Angeles. No extra bone marrow biopsy material will be obtained for these tests.

HOW LONG WILL I BE ON THIS STUDY?

You will receive up to twelve courses of treatment on this study. Each course is twenty eight days, with the exception of course 1 which is 35 days. It will take about 12 months to complete the twelve courses.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

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

WHAT ARE THE RISKS OF THE STUDY?

This is a Phase I study. A Phase I study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase I study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase I study.

In this study, researchers will be looking at side effects seen in patients taking different doses of Sorafenib together with cyclophosphamide and topotecan. Since subjects will be assigned to different dose levels of Sorafenib, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed on the following pages:

Possible Risks of Sorafenib

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare but Serious** (happens to < 5 children out every 100 children)
• Diarrhea • Abdominal Pain • Anorexia • Nausea • Hair loss • Inflammation of the skin on the palms of the hands or soles of the feet • Fatigue or tiredness • Increased blood liver enzymes (AST/ALT) • Increased blood level of a liver pigment (bilirubin) often a sign of liver problems • Increased blood level of fat-digesting enzyme (lipase) • Increased blood level of a digestive enzyme level (amylase) • Decreased number of a type of white blood cell (lymphocyte) • Decreased number of a type of blood cell that help to clot blood (platelet) • Increased blood level of sodium • Decreased blood level of calcium • Low levels of a blood protein called albumin • Decreased blood level of phopsphorus • Weight loss • Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	• Mucositis • High Blood pressure • Blood clots that travel from the location they originally formed to another part of the body (ie: clots in the legs that travel to the lungs) • Fever and/or Fever associated with dangerously low levels of a type of white blood cell (neutrophils) • Chest pain not heart-related • Infection • Itching • Inflammation of the skin or rash • Decreased number of a type of white blood cell that helps fight infection (neutrophil/granulocyte) • Either a decreased or an increase of the blood level of potassium. • An increased level of uric acid in the blood • Decreased blood sugar level • Decreased bicarbonate • Constipation • Edema: Swelling of the extremities (arms and/or legs) • Fluid collection in the abdomen • Joint pain • Back pain • Bone pain • Muscle and extremity pain • A problem with the functioning of the nerves outside the spinal cord. Symptoms of peripheral neuropathy may include numbness, weakness, burning pain (especially at night), and loss of reflexes. • Injury to the kidneys Acute renal injury • Blood in the urine • Dry Skin	• Acute Coronary Syndrome Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart. Left Ventricular Systolic Function : Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole) • Bleeding in the brain • Gastrointestinal Perforation: Hole in a part(s) of the digestive tract • Erythema Multiforme: Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue • Stevens-Johnson Syndrome: Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer) • Anaphyaxis: Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness • Reversible posterior leukoencephalopathy syndrome: Collection of symptoms including headache, confusion, seizures, and vision loss associated with imaging findings (MRI, CT Scan)

Possible side effects of Cyclophosphamide

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)

• Loss of appetite
• Nausea
• Vomiting
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells may make it easier to get infections.
• Hair loss
• Decreased ability of the body to fight infection
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
	• Abdominal pain
	• Diarrhea
	• Fewer red blood cells and platelets in the blood
	  ○ A low number of red blood cells may make you feel tired and weak.
	  ○ A low number of platelets may cause you to bruise and bleed more easily.
	• Bleeding and inflammation of the urinary bladder
	• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Temporary blurred vision
		• Nasal stuffiness with fast IV infusions
		• Irregular heart rate with fast IV infusions
		• Skin rash
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• Abnormal hormone function which may lower the level of salt in the blood
		• Heart muscle damage which may occur with very high doses and which may be fatal
		• Darkening of areas of the skin and finger nails
		• Fingernail changes
		• Slow healing of wounds
		• Infection
		• Infertility which is the inability to have children
		• Damage and scarring of lung tissue which may make you short of breath
		• A new cancer or leukemia resulting from this treatment.
		• Damage or scarring of urinary bladder tissue

Possible side effects of Topotecan

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)

• Diarrhea
• Nausea
• Vomiting
• Constipation
• Fewer white blood cells, red blood cells and platelets in the blood.
  o A low number of white blood cells can make it easier to get infections
  o A low number of red blood cells can make you feel tired and weak
  o A low number of platelets causes you to bruise and bleed more easily
• Fever including fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
• Pain which may be in your abdomen, back or bones
• A feeling of weakness and/or tiredness
• Temporary hair loss
	• Loss of appetite
	• Headache
	• Lack of muscle strength or weakness
	• Rash, hives, itching or a red bumpy rash
	• A mild lowering of the blood pressure which usually does not require treatment
	• Shortness of breath
	• Inflammation and/or sores in the mouth, throat and/or esophagus
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• An infection in the blood which will require admission to the hospital and treatment with antibiotics
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath.
		• Chest pain
		• Shaking chills
		• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
		• Numbness and tingling in the fingers and toes
		• Muscle or joint aches and pains
		• Bleeding into the tumor which may cause damage depending on the location of the tumor
		• Small amount of blood and/or protein in the urine or an elevation in blood creatinine which may indicate mild kidney damage

Possible side effects of G-CSF (such as Neupogen, filgrastim Or Neulasta, Pegfilgrastim)

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

Neulasta (Pegfilgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood which may make you bruise and bleed more easily	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Resiratory Distress Syndrome)

Unknown frequency and timing: It is unknown whether pegfilgrastim produces birth defects or other serious abnormalities in the unborn child in humans as there is conflicting data from animal studies. It is also unknown whether this drug is excreted in breast milk.

Neupogen (Filgrastim) Toxicity :

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Skin rashes, hives and facial swelling • Wheezing or shortness of breath • Low blood pressure and/or increased heart rate • Low fever • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. Or rupture of the spleen. • Worsening of existing skin rashes • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Higher than normal white blood count. • Inflammation of blood vessels leading to a raised purple rash and bruising • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by the growth factor, travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome) • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug.

Possible risks to unborn child

Patients who agree to participate in this study should not become pregnant while on this study. This study and the medicines used in this study may be hazardous to an unborn child. Patients and their sexual partners should avoid sex and /or use an effective method(s) of contraception that is medically appropriate based on your personal doctor's recommendation at that time.

Possible long term side effects of this treatment

- Development of another cancer that is different from the one you have now.
- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity

Possible risks from having blood drawn

The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown risks

The treatment combinations may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

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

Yes there are other options for treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma therapy at this time, with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

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 may 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 medical records for research, quality assurance and data analysis include:

- NANT Consortium
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Pharmaceutical company which makes Sorafenib

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

All the drugs being used on this study are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

The required studies and other optional studies will be done at no cost to if you agree to participate in this voluntary study. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

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, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this 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, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

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

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from 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. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

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

In case of injury resulting from this study, you do not lose any of you 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 _____ *[name(s)]* at _____ *[telephone number].*

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

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 Web sites at http://cancer.gov/
For NCI's clinical trials information, go to **http://cancer.gov/clinicaltrials/**
For NCI's general information about cancer, go to **http://cancer.gov/cancerinfo/**

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

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

SIGNATURE OF RESEARCH SUBJECT

Your signature below indicates

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You consent/assent to your participation in this research study; and

_____
Name of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF PARENT(S)/LEGAL GUARDIAN(S) (If the subject is a minor)

Your signature(s) below indicates

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to your child's participation in this research study; and

_____ _____
Name(s) of Parent(s)/Legal Guardian(s)

_____ _____
Signature of Parent/Legal Guardian Date

_____ _____
Signature of Parent/Legal Guardian Date

SIGNATURE OF INVESTIGATOR/PERSON OBTAINING CONSENT

I have explained the research to the subject and/or the subject's parent(s)/legal guardian(s) and have answered all of their questions. I believe that they understand all of the information described in this document and freely give assent/consent/permission to participate.

_____
Name of Investigator/Person obtaining consent

_____ _____
Signature of Investigator/Person obtaining consent Date

SIGNATURE OF WITNESS (if applicable)

My signature as Witness indicates that the subject and/or the subject's parent(s)/legal guardian(s) voluntarily signed this assent/consent/permission form in my presence.

_____
Name of Witness

_____ _____
Signature of Witness Date

SIGNATURE OF INTERPRETER (if applicable)

_____
Name of Interpreter

_____ _____
Signature of Interpreter Date

Complete if applicable:

Please check appropriate box and sign below.

☐Investigator/person obtaining consent's statement of certification for subjects less than seven years of age (assent):

The undersigned, _____, hereby certifies that he/she has discussed all the information contained in the study consent to the subject, and has explained all the information in the study consent to the participant/patient, including any risks that may reasonably be expected to occur. The undersigned further certifies that the subject was encouraged to ask questions, that all questions were answered, and that assent was obtained.

☐ Assent was not obtained for a subject under 18 years of age. *(Please state the reason. Examples include: child is an infant; child is comatose; child lacks cognitive abilities to understand the information.)*

_____

_____

Date:_____

Time:_____

Signature_____

Consent Addendum I: Tests that will be done on this study.

Observation	Before Entry	Course 1	Subsequent Courses	End of Therapy
Physical exam	X	Day 1	At start of each course	X
Blood pressure check	X	Weekly	Day 1 and Day 5	
Blood tests	X	Weekly for other tests and twice weekly for blood counts	At start of each course then twice weekly for blood counts	X
Urine test	X		At start of each course	
Pregnancy test	X			
Heart tests Echocardiogram and EKG	X			X
Blood samples for correlative studies (REQUIRED)		Day -6, Day 1, Day 14, Day 28		
Bone marrow sample for correlative studies (Required)	X		Course 2	
Disease Evaluation Tests[#]				
Bone marrow aspirate and biopsy	X		Done at the end of course 2, 4, and 8	X
CT/MRI scans and/or MIBG/PET scans	X		Done at the end of course 2, 4, and 8	X
Urine catecholamines	X		Done at the end of course 2, 4, and 8	X

Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 for more information.

Consent Addendum 2

Certificate of Confidentiality Information

NANT 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.

SAMPLE ASSENT FORM

NANT 2013-02 A Phase I Study of Sorafenib and Cyclophosphamide and Topotecan in Patients with Relapsed and Refractory Neuroblastoma.

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____is doing a research study about using other medicines to get rid of Neuroblastoma.

2. We have been talking to you about your **Neuroblastoma** that has either grown back or has never gone away after treatment. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using three medicines called **sorafenib, cyclophosphamide and topotecan and** to see what effects (both good and bad) these medicines have on patients and their cancer. Sorafenib is a medicine that is given by mouth, either as a pill (tablet) or liquid. Cyclophosphamide and topotecan are medicines that are given into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm). The doctors think that giving these three drugs together may help get rid of neuroblastoma cancer cells.

3. If you agree to be in this study this is what will happen:

   The medicines will be given in courses that each last 28 days, except for the first course which lasts 35 days... Your doctor will explain to you and your parents the schedule for each course. You can continue to get this treatment for up to 12 courses (about 1 year) unless you have bad side effects or your tumor gets worse. These medicines work differently than some of the other medicines you have received in the past to treat your neuroblastoma. They help your body attack and kill the cancer cells.

   Sorafenib:

   You will take Sorafenib by mouth twice a day every day of the course without a break between courses.

   Cyclophosphamide and topotecan:
   You will take the cyclophosphamide and topotecan by I.V. once a day for 5 days of every course. You will be in the clinic on those days. You do not need to be in the hospital to get these chemotherapy medicines.

   Other medicines (not chemotherapy):

   You will need to take

   Neupogen (given once a

   day as an injection) or Neulasta (give each cycle as an injection) that are given to help your normal blood cells get better after getting chemotherapy medicines like cyclophosphamide and topotecan.

   Coming to See the Doctors:
   During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;
   - Blood tests (we will do this twice each week to start with, and then less often)
   - MRI, CT, and MIBG Scans (special pictures of your tumor)
   - Bone marrow test (to look for tumor in your bone marrow)

- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.

When you are in a research study, sometimes good things and bad things can happen

4. Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks'. Some of the risks of this study are:
    - You may feel sick to your stomach and you may throw up.
    - You may feel tired.
    - You may have a bad appetite.
    - You might get a fever, have a hard time breathing and get a rash on your skin.
    - You might have problems with your heart.
    - You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection. You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
    - You may get sores in your mouth that makes it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
    - You may get diarrhea.
    - The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing.
    - You could get a different kind of cancer, this doesn't happen often, but can happen years later.
    - It is possible that you could die from the treatment or cancer.

Not all of these things may happen to you. None of these things may happen. Or things may happen that the doctors don't know about yet.

5. Will we do everything possible to keep your information private.

6. Things that happen to children in research studies that are good are called "benefits." Some of the good things for this research study could be: this treatment might make your neuroblastoma tumor stay the same size or get smaller for some time. We hope to learn more about this new treatment which could help other children with neuroblastoma.

7. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

8. Being in this study is up to you. You do not have to be in this study if you don't want to. You may stop being in this study at any time.

9. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time. Study doctor's phone number: _____.

10. Special study tests :

    You will need to have some special blood tests done to measure the amount of medicine in your blood and measure the effects of the medicine on immune cells. We will draw 4 blood samples (almost 2 teaspoons) on days -6, 1, 14 and 28 of first course of your treatment. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

11. Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Subject: _____

_____ _____
Signature of Subject: **Date**

_____ _____
Signature of Investigator **Date**

_____ _____
Signature of Person Conducting Discussion **Date**