Informed Consent for Research

NEUROBLASTOMA PROTOCOL 2012: THERAPY FOR CHILDREN WITH ADVANCED STAGE HIGH-RISK NEUROBLASTOMA

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

1. Why am I being asked to take part in this research study?

You are invited to take part in this study because you have high risk neuroblastoma. Neuroblastoma is a type of cancer. Neuroblastoma shows up as a lump or mass in the belly or around the nerves in the chest, neck, or pelvis. Neuroblastoma is a cancer of nerve cells. It develops in nerve cells that are outside of the brain. It often spreads to bone, liver, lymph nodes and bone marrow, which is the soft tissue in the center of bones where blood cells are made. You have the type of neuroblastoma that is called high-risk because your tumor has spread from where it started or because your type of tumor is harder to treat.

This consent form gives you information about the study which will be discussed with you. Please take your time making a decision and feel free to discuss it with your friends, family and St. Jude staff. Before agreeing to take part in this research study, it is important that you read this consent form that describes the study. After you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

2. What are my rights in this study?

Before you learn about the study, it is important that you know the following:

- Whether or not you take part in this study is entirely up to you.
- If you choose not to be in the study or to leave the study at any time, you are still eligible for medical care at St. Jude. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.
- This study is being sponsored by St. Jude Children's Research Hospital.
- St. Jude has applied for licensing rights for the drug being tested and may be paid if the drug works well.

- The principal investigator (researcher) in charge of this study is Dr. Wayne Furman, who may be reached by phone at 901-595-3300, if you have any questions or concerns about this research.

3. What is the current standard of treatment for this disease?

The treatment for neuroblastoma includes 3 parts (phases) of therapy called Induction, Consolidation and Maintenance. During Induction therapy, anti-cancer drugs (chemotherapy) and surgery are used to kill and remove as much tumor as possible. Blood stem cells are collected during the Induction phase of therapy. After collection the blood stem cells are frozen and stored to be used during the Consolidation (also called intensification) phase of treatment. Blood stem cells are the cells that create new blood cells, such as red blood cells, white blood cells, and platelets. Blood stem cells can be collected from the blood by using a machine that can separate out the part of blood that has stem cells and then return the remaining blood back to the patient.

During the consolidation phase of treatment, extremely high doses of chemotherapy are given to kill any remaining neuroblastoma cells. The extremely high doses of chemotherapy destroy healthy bone marrow. Bone marrow is the soft tissue in the hollow of flat bones of the body that produces new blood cells. The peripheral blood stem cells that were stored during the Induction phase of treatment are given back to the person after the high dose chemotherapy. These stems cells allow the bone marrow to return to normal so that new blood cells can be made. This type of therapy is called a "hematopoietic stem cell transplant or rescue".

Once the person has healed from the effects of high doses of chemotherapy, radiation therapy is given to the first place the tumor was found and to any additional places where the tumor was found after Induction therapy.

The third phase of treatment is called Maintenance. During this phase, an oral drug, called isotretinoin (13-cis-retinoic acid, Accutane®) is given, usually for about 6 months. A recently published study showed that the addition of a new treatment [a 3-drug combination using a new drug called ch14.18 monoclonal antibody together with 2 other drugs (IL-2 and GM-CSF)] to isotretinoin improved the chance of cure compared to treatment with isotretinoin alone. The ch14.18 monoclonal antibody was recently approved by the FDA and is now available under the trade name Unituxin™ (also called dinutuximab).

4. What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to other combinations of therapies including chemotherapy with or without stem cell transplant using different agents, and/or surgery and radiation treatments without being on a study
- you could take part in another research study, if one is available
- or you could decide not to be treated

5. Why is this study being done?

This study is being done because more than half of children with high risk neuroblastoma will not be cured of their disease and better treatment strategies are needed. The main purpose of this research study is to find out if the addition of an investigational drug called hu14.18K322A to two initial cycles of induction chemotherapy will result in better tumor responses than the standard induction therapy with chemotherapy only. Hu14.18K322A is in a class of drugs called "monoclonal antibodies or mAbs". Monoclonal antibodies will be explained in more detail later in this consent.

With this research study, we also plan to meet the following goals:

- To find out if it is feasible (possible, practical) to give hu14.18K322A mAb during the Induction phase of treatment
- To learn more about the effects (good and bad) of giving a type of radiation therapy called "intensity modulated radiation therapy" to participants with neuroblastoma in the abdomen (belly)
- To learn more about the effects (good and bad) of hu14.18K322A mAb in combination with chemotherapy.
- To find out if giving hu14.18K322A mAb during maintenance therapy will be a safe and effective treatment to keep the neuroblastoma from coming back
- To learn more about the biology of neuroblastoma and how the different treatments given during this study effects participants' tumor and normal cells/tissues by studying tumor specimens, bone marrow samples, and blood samples for research studies. Specifically, we will study:
    - how certain genes (genes direct activities of cells) affect how you respond to treatment,
    - whether your immune system (blood cells that help fight infection) can produce cells that will find and kill the neuroblastoma cells, and
    - whether new tests can be used to find small amounts of neuroblastoma cells
- To learn more about the effects of hu14.18K322A mAb on the immune system (the immune system is a system of biological structures and processes within a person's body that protects them from disease)

- To learn more about imaging studies commonly used to evaluate neuroblastoma tumors and if there are factors that can be used to predict how children with neuroblastoma tumors will respond to treatment
- To compare side effects experienced in participants who treated with different techniques for giving radiation treatment (photon IMRT techniques and proton beam radiation)
- To learn more about how the body processes a drug called busulfan (given during the Intensification phase of the study) and the effects busulfan has on the body

Up to 70 children will take part in this study at St. Jude only.

6. How long will I be in the study?

The total length of treatment will be about 18 months. At the end of treatment, you will have follow-up tests for at least 5 years to monitor for side effects of the treatment and to watch for relapse of the neuroblastoma. After you finish the study drugs, your doctor will continue to watch you for side effects and follow your condition for at least 5 years. At the end of the follow-up visits, you will be invited to take part in the St. Jude Long-Term Follow-up Study. This study will help researchers learn about the health and quality of life of those who took part in the study in the years after they complete cancer therapy.

7. What will be done in this study?

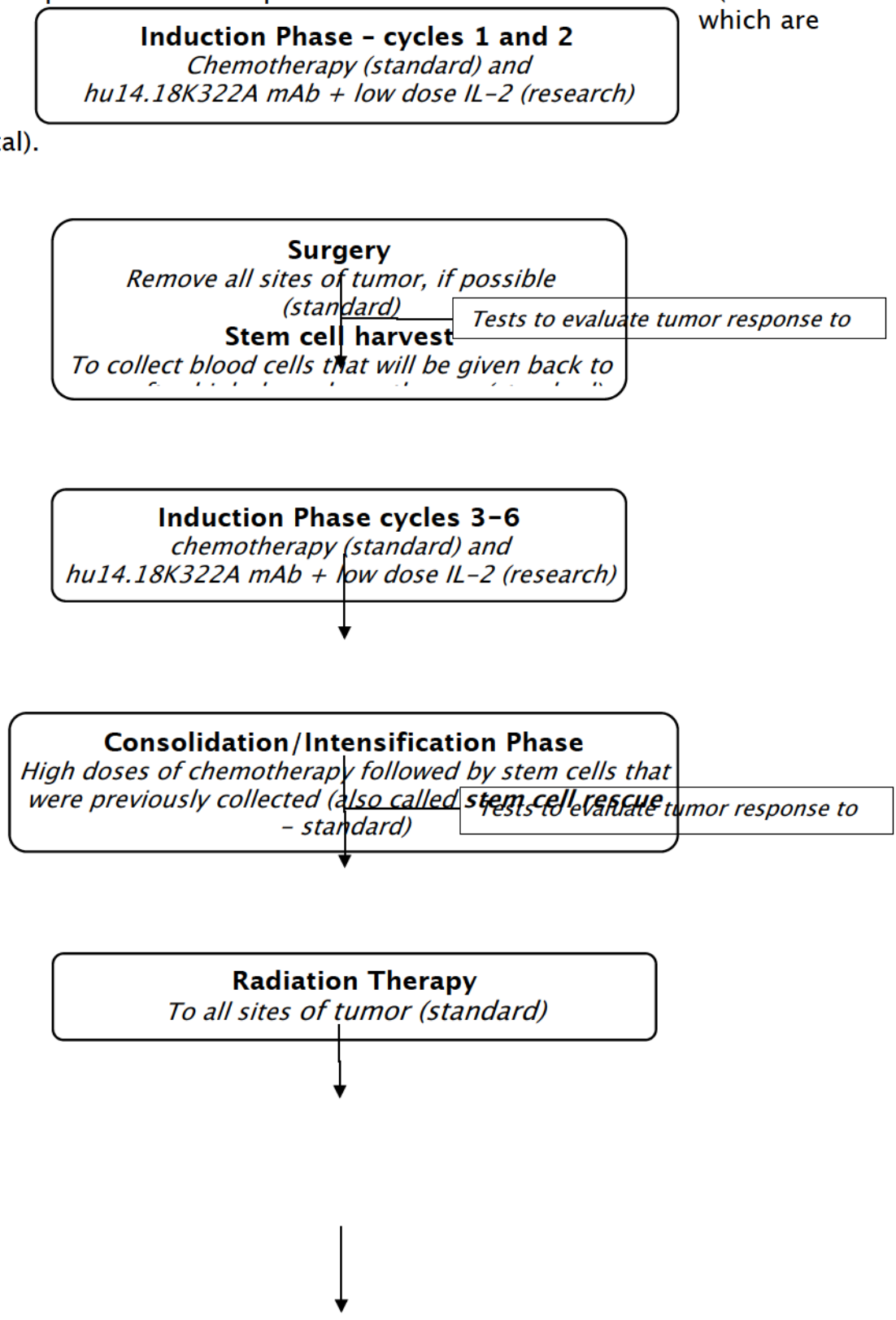
The parts of the study are listed below:

1. Induction phase – includes chemotherapy + hu14.18K322A mAb for 6 cycles. You will also have surgery during this part of the study to remove as much tumor as possible

2. Consolidation/Intensification phase – includes high doses of chemotherapy and blood stem cell transplant. You will also get radiation treatment to all sites of the tumor(s) after you recover from the stem cell transplant

3. Maintenance/MRD treatment phase – with immune therapy in addition to the standard treatment with the drug isotretinoin. MRD means "minimal residual disease. This will be explained in more detail later in this consent.

Overview of treatment plan: This diagram gives an overview of the treatment on this study, and points out which parts of the treatment are standard (usual care), and which are research (experimental).



Maintenance/MRD Treatment Phase
isotretinoin (standard) and immune therapy (research) with mAb+GM-CSF+IL-2

Tests to evaluate final response to protocol treatment, then long-term follow-up

INDUCTION PHASE

Placement of a central line

Your doctor will recommend the placement of a tube, or catheter, into a large vein in the chest or neck during a short operation as the standard way to give chemotherapy into a vein. This tube is called a central line. You will be given medication to help you sleep during this procedure and pain medication afterwards to help you stay comfortable. The central line is used to give chemotherapy drugs and to take small amounts of blood for testing during treatment. A central line will be used to give chemotherapy even if you do not participate in this study. The risks associated with central lines will be explained to you by your surgeon. You will be given a separate informed consent form to read and sign prior to having a central line inserted.

Chemotherapy (standard)

This treatment uses chemotherapy to make the tumor(s) as small as possible, hopefully allowing the primary tumor to be completely removed with surgery. All participants will begin treatment with the Induction phase of chemotherapy, which is divided into six 3-week cycles. There are three different drug combinations used during the six cycles. Cycles 1 and 2 will use cyclophosphamide and topotecan. Cycles 3 and 5 use the anti-cancer drugs etoposide and cisplatin. Cycles 4 and 6 use the anti-cancer drugs vincristine, cyclophosphamide, and doxorubicin, as well as the drug MESNA. MESNA is given to help protect the bladder from potential damaging effects of cyclophosphamide. The chemotherapy drugs used in cycles 1-6 are all standard drugs used for the treatment of high risk neuroblastoma. Cycles of chemotherapy will be given approximately every 21 days. An additional drug, which is a growth factor for white blood cells called GM-CSF, is given after the chemotherapy. It helps with the production of white blood cells (infection fighting cells) and will help your body recover from treatment.

hu14.18K322A mAb (research)

An experimental new drug, hu.14.18K322A monoclonal antibody (mAb) will be added to all six cycles of induction treatment. Antibodies are part of the body's normal immune (defense) system that help to look for and attack certain cells that it sees as "different" and harmful such as bacteria, viruses, and cancer cells. Hu14.18K322A is "monoclonal antibody." Monoclonal antibodies are proteins made in laboratories, and are designed to seek out and attach (bind) themselves to specific molecules or antigens on cancer cells. Hu14.18K322A was designed to bind to cancer cells that contain or "express" a certain protein called GD2 antigen. Almost all neuroblastoma cells express the GD2 antigen. When hu14.18K322A mAb binds to these types of cancer cells, it is hoped that the body's immune

system will be stimulated (activated) to attack and kill the cancer cells without destroying nearby healthy cells.

Earlier studies using similar monoclonal antibodies (such as chimeric 14.18 – also called ch14.18) in children with neuroblastoma have shown promising results. However, these results were limited because the monoclonal antibodies used in those studies were obtained from mice. One difficulty with mouse antibodies is that in some cases the people's immune system senses these as different, causing the immune system to attack and reject the antibodies as soon as they enter the body. For this reason, researchers at St. Jude have produced a "humanized" monoclonal antibody, hu14.18K322A, which the human body will see as "similar," and therefore, be less likely to reject. A very small part of this antibody is from mouse antibody, but most of it is human antibody. The end product of this mouse-human monoclonal antibody looks more like a normal human antibody, so there is a better chance that it will not be destroyed and rejected by the human immune system. Because the humanized monoclonal antibody is less likely to be rejected, we hope it may cause fewer side effects.

Schedule and methods of giving drugs

Schedules of how and when the drugs will be given during the Induction phase of therapy are shown in the tables on the next 2 pages.

Different methods will be used to give drugs during all phases of the study treatment:

- PO – drug is given by tablet or liquid swallowed through the mouth (PO)
- IV – drug is given using a needle or tubing inserted into a vein. Most IV drugs can be given into your central line
- SubQ – drug is given by injecting a needle into the tissue just under the skin (SubQ shot)

Cycles 1 and 2 of Induction

Drug	*How the drug will be given*	*Days*
Cyclophosphamide	Into the vein (IV) x 5 days	Days 1-5
Topotecan	Into the vein (IV) x 5 days	Days 1-5
hu14.18K322A mAb	Into the vein (IV) over 4-8 hours x 4 days	Days 2-5
Low dose IL-2	SubQ (a shot under the skin)	Days 6, 8, 10, 12, 14 and 16 (6 doses)

GM-CSF	SubQ	Days 7-21 (until white blood cells recover)
G-CSF (given during stem cell collections)	SubQ	Start on day 7 and continue until enough stem cells are collected

Each cycle lasts about 3 weeks. You will start cycle 2 about 21 days (or 3 weeks) after the start of cycle 1.

Response evaluation: After the first 2 cycles, you will have imaging scans (CT or MRI and MIBG or bone scan) as well as bone marrow, blood and urine tests to see how your neuroblastoma responded to the treatment and to watch for side effects of treatment.

Surgery: After the second cycle of Induction, you will have surgery to remove as much remaining tumor as possible. If you cannot have the surgery after cycle 2 of induction, you will have it after additional cycles of induction treatment, when your surgeon thinks it possible. The surgeon will talk to you about your surgery and any possible risks involved with the surgery and you will need to sign a separate consent form for your surgical procedure.

Stem cell harvest: After the second cycle of Induction is finished, your stem cells will be collected using a procedure called apheresis. During apheresis, your blood is collected into a machine that filters out the stem cells and the filtered blood is returned to your body. This procedure may need to be done several times to collect enough stem cells for the next phase of therapy – Intensification. The stem cells will be frozen and stored until they are needed for the Intensification phase of therapy. Stem cell collection will happen after cycle 2 for most participants, but may need to be repeated or delayed for medical reasons.

Cycles 3 and 5 of Induction (CiE)

Drug	*How the drug will be given*	*Days*
Cisplatin	Into the vein (IV) daily x 4	1, 2, 3 and 4
Etoposide	Into the vein (IV) daily x 3	1, 2 and 3
hu14.18322K mAb	Into the vein (IV) over 4 hours daily	Days 2-5
Low dose IL-2	SubQ	Days 6, 8, 10, 12, 14 and 16 (6 doses)
GM-CSF	SubQ	Days 7-21 (or until white blood cells recover)

Cycles 4 and 6 of Induction (CAV)

Drug	*How the drug will be given*	*Days*
Cyclophosphamide	Into the vein (IV) daily x 2	1 and 2
Doxorubicin (**A**driamycin)	Into the vein (IV) by a continuous infusion over 3 days	1 – 3
Vincristine	Into the vein (IV) daily x 3	Days 1, 2 and 3
hu14.18K322A mAb	Into the vein (IV) over 4 hours x 4 days	Days 2–5
Low dose IL–2	SubQ	Days 6, 8, 10, 12, 14 and 16 (6 doses)
GM–CSF	SubQ (a shot under the skin)	Days 7–21 (or until white blood cells recover)

You will start each cycle about 3–4 weeks after the previous cycle, depending on how quickly you recover. If your neuroblastoma gets worse at any time during induction, you will skip the second cycle of that treatment combination and get the next treatment combination instead (for example, if your neuroblastoma gets worse during cycle 1 of cyclophosphamide and topotecan, you will skip cycle 2 and move to cycle 3 of cisplatin and etoposide (CiE). Similarly, if your neuroblastoma gets worse during cycle 3 CiE, you will continue to cycle 4 and get CAV instead.

The entire Induction phase will last about 6–7 months.

Response evaluation

You will have imaging scans (CT or MRI and MIBG or bone scan) as well as bone marrow, blood and urine tests to see how your neuroblastoma responded to Induction treatment and to watch for side effects of treatment.

Additional medicines and supportive care

You may get some extra medications, like antibiotics, to help fight and/or prevent infection(s). Other medications may be given to lessen the side effects of chemotherapy. These medicines are part of standard care.

CONSOLIDATION/INTENSIFICATION PHASE

After you finish induction therapy, you will get one cycle of very high dose chemotherapy and a hematopoietic stem cell transplant (also called stem cell rescue). The transplant will begin with very high doses of the chemotherapy drugs busulfan and melphalan, along with another drug called levetiracetam, which is given to prevent seizures with the high doses of chemotherapy.

Following the chemotherapy, you will get your stem cells that were previously collected and stored.

High dose chemotherapy and stem cell rescue (standard)

Busulfan is given into the vein (central line) every 6 hours for 4 consecutive days. The drug melphalan is given into the vein as a daily dose for 2 days. After the high dose chemotherapy treatment, your stored stem cells will be given IV (through the central line). These stem cells were collected from you during the Induction phase of therapy and frozen. This is called a "hematopoietic stem cell transplant or stem cell rescue". You will get filgrastim (G-CSF) to help your blood counts recover after transplant.

Consolidation/Intensification treatment table

Drug/agent	*How given*	*Days*	*How many doses*
Levetiracetam	By mouth or IV every 6 hours on first day, then every 12 hours	-7, -6, -5, -4, -3, -2, -1 (every day for 7 days *before* stem cell rescue)	Depends on your blood levels of this drug
Busulfan	Into the vein (IV) every 6 hours	-6, -5, -4, -3 (every day for 4 days *before* stem cell rescue)	Depends on your blood levels of this drug
Melphalan	Into the vein (IV) once daily	-2, -1 (every day for 2 days *before* stem cell rescue)	2 doses
Stem cell rescue infusion of *your* stem cells into the vein (IV) on **Day 0**			
Filgrastim (G-SCF)	As a shot just under the skin (subcutaneous or SubQ)	Starting on day +6 and continuing daily	Until your blood counts recover to a safe level

Additional medicines and supportive care

You will get extra medications and other supportive care (such as antibiotics, pain medicine, nutritional support and anti-nausea drugs) to help fight infection and to manage the side effects of treatment. You will also get blood and platelet transfusions when you need them. These treatments are part of standard care after high dose chemotherapy and stem cell rescue. If you develop a fever while

your blood cell counts are now, you will need to be hospitalized for treatment of possible infection.

Radiation therapy

It is standard to give radiation treatment to the area of the main tumor and to areas that still show signs of active disease at the end of Induction phase of treatment. Radiation therapy will begin after you recover better from the immediate side effects of the high doses of chemotherapy and stem cell rescue. Radiation therapy usually starts about a month after the stem cell rescue. The radiation therapy doctors will discuss this with you in more detail. The radiation is given in one short session each day, for a period of about 3-4 weeks.

You will get a higher dose of radiation treatment if imaging scans done at the end of Induction treatment still show tumor (a lump). The higher dose of radiation will only be given to the area where tumor is present and lower dose to the normal tissues around the tumor to lessen side effects of radiation. We are studying whether this higher dose of radiation will decrease the risk of the tumor(s) growing back.

Response evaluation

You will have imaging scans (CT or MRI and MIBG or bone scan) as well as blood and urine tests to see how your neuroblastoma responded to Intensification treatment and radiation therapy, and to watch for side effects of treatment. This will be done before you start the Maintenance/MRD treatment phase

MAINTENANCE/MRD TREATMENT PHASE

Maintenance therapy will begin after you have recovered from effects of the Consolidation/Intensification treatment and radiation therapy. Maintenance therapy is given in the hopes of destroying any neuroblastoma cells that may be so small that we cannot detect it with current technology. This phase is also called "MRD Treatment" because the intent of this treatment is to destroy any minimal residual disease (MRD) that may still be present.

During Maintenance/MRD treatment, you will receive an additional 5 cycles of treatment with hu14.18K322A mAb, GM-CSF, and IL-2 (experimental) in combination with isotretinoin (standard). You will receive a 6th course of treatment with isotretinoin (standard) only.

Because we do not yet know the best dose of the anti-GD2 mAb to give when it is given with maintenance therapy, the first 10 participants on this study will get a lower dose of the mAb. If the first 10 participants have significant side

effects, the subsequent participants will get a lower dose the mAb. If there are significant side effects, the dose will be lowered.

Maintenance cycles 1, 3 and 5

Drug/agent	*How given*	*Days*
hu14.18K322A mAb	Into the vein over 4 hours	3, 4, 5 and 6 (once daily for 4 days)
GM-CSF	SubQ or IV	0-13 (once daily for 14 days)
Isotretinoin	By mouth for 14 days	Cycle 1 – start on Day 10 or 11 and continue for 14 days. Cycles 3 and 5, start Day 1 and continue for 14 (twice daily for 14 days)

Maintenance cycles 2 and 4

Drug/agent	*How given*	*Days*
hu14.18K322A mAb	Into the vein over 4 hours for 4 days	7-10
Interleukin-2 (IL-2)	By continuous infusion over 4 days for the first week, and then again for 4 days starting on day 7	1-4 and 7-10
Isotretinoin	By mouth	1-14 (twice daily for 14 days)

Maintenance cycle 6

Drug/agent	*How given*	*Days*
Isotretinoin	By mouth	1-14 (twice daily for 14 days)

Option for receiving treatment with the Unituxin™ (dinutuximab)

The ch14.18 mAb was recently approved by the FDA and is now available under the trade name Unituxin™ (also called dinutuximab). You have the option of receiving ch14.18 mAb, IL-2 and GM-CSF in combination with isotretinoin for 6 months, instead of the maintenance/MRD treatment on this study with hu14.18K322A mAb.

8. What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra research studies that you will need to have if you take part in this study. This research is required in

order for you to take part in this study because the research on the sample is an important part of the study.

Required antibody research studies

These research tests are required. If you choose to not take part in these research studies, you cannot take part in this study. Researchers will test your blood samples to learn more about how hu14.18K322A mAb affects your immune system, and to see if differences in your genes affect how your body responds to the antibody. Your blood will also be tested to measure the amount of the antibody in your blood over time (this kind of study is called "pharmacokinetics"). For these tests, about ½ teaspoon of blood will be drawn before and after the first dose of hu14.18K322A mAb is given in each cycle of treatment during the Induction and Maintenance/MRD phases of treatment. These studies may help us learn more about hu14.18K322A mAb, and may help children and young adults who get this drug in the future.

Required NK cell research studies

These research tests are required. If you choose to not take part in these research studies, you cannot take part in this study. We will monitor cells in your blood and perform tests to see how your body's immune system reacts to this treatment. For this research, about ½ teaspoon of blood will be collected several times during the Induction and Intensification phases of the study. Blood will be drawn for this research at the same time it will be collected for routine care. These studies may help us learn more about this treatment for neuroblastoma, and may help children and young adults in the future.

Routine tests

You will have physical exams, blood and urine tests, chest X-rays, and heart tests during treatment to check your health. You also may have bone marrow tests done. The researcher may order other tests during treatment. All of these tests are routine and would be done even if you were not in this study. Tests that will be done while you are receiving treatment include:

- Physical exam
- Blood tests
- Bone marrow tests
- Tests of vision and hearing
- Urine tests
- Imaging scans (imaging scans and x-rays to see how the tumor(s) are responding to treatment)
- Tests of kidney function

- EKG/echocardiogram to test heart function
- Dental exams

9. What about returning home during treatment?

It may be possible for you to return home to your local doctor to receive some treatment on this study. This would only involve parts of the treatment that are not considered experimental. If your study doctor agrees that it would be medically possible for you to receive some care outside of St. Jude, we will request and receive copies of your medical records from your local doctor, including documentation that protocol-related treatment was given. We may also request and receive results of clinic visits, hospitalizations, and laboratory, imaging, or other tests done to evaluate your disease or to monitor for side effects of treatment. Although this information is obtained as part of standard care for your disease, some or all of the information may also be included in the research record. By signing this informed consent, you agree to allow your local doctor to release this information to us.

10. What risks can I expect if I take part in this study?

If you choose to take part in this study, there is a risk that you may:

- Lose time at school, work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss

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

There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The study doctor may adjust the study drugs to try to reduce side effects.

Risks of the study

The main risk of this study is that you will not be eligible to take part in other clinical trials using the ch14.18 mAb. Getting the hu14.18K322A mAb will make you ineligible for other research studies using the ch14.18 mAb. As stated at the beginning of this consent, ch14.18 mAb has already been shown to improve the chance of cure for neuroblastoma patients who received this drug (with IL-2 and GM-CSF) after stem cell transplant/rescue.

Researchers at St. Jude think that the hu14.18K322A will also be an effective treatment to improve the chance of cure, and that this antibody will have fewer side effects than ch14.18 mAb, but this has not been proven. The hu14.18K322A mAb may turn out to be less effective and have the same or more side effects as ch14.18 mAb.

Risks of anti-cancer treatment (chemotherapy, transplant, radiation)

Drug treatment for cancer (chemotherapy) has side effects that can be mild or severe. Common side effects of chemotherapy include nausea, vomiting, hair loss, mouth sores, stomach ulcers, and low blood counts. Low blood counts can mean that you are more likely to have infection, bleeding, and anemia (weakness and pale skin). This may lead to a need for blood transfusions. Whenever you take medicine, you might have an allergic reaction to the drugs you get in this study. This reaction may be mild, such as a skin rash, or you may have more severe symptoms like throat tightness, low blood pressure, and it may be hard to breathe. In rare cases, a severe reaction could cause death. If you need emergency information about an adverse reaction to a drug, you may contact your study doctor at 901-595-3300.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. The high doses of chemotherapy used during the intensification phase of treatment will cause very severe lowering of the blood cell numbers. You will be at risk to develop a life-threatening infection and bleeding following the very high doses of chemotherapy. To limit the risk of infection, you will remain in a special hospital room until your blood counts return to safe levels. Your stem cells that were previously collected and stored will be used to help your body make new blood cells.

It is possible that it will take a very long time for your blood cells to be made. This can happen if the stem cells were injured in your body even before they were removed or if the stem cells are injured during the collection, freezing or thawing processes. If this happens, you will have a high chance that you will develop a severe infection and/or bleeding. This is very unlikely to happen, but would almost certainly be fatal. Even after your body makes blood cells after the transplant, your ability to fight infection will be low for weeks to months after the transplant is complete. You will be more likely to develop an infection in the months after transplant, especially from viruses.

There is also a small risk of severe organ damage, especially to liver and kidney, with an even smaller risk to the heart and lungs. Though rare, the kidney damage can be severe enough to require dialysis. The liver damage can also be severe, resulting in jaundice and, occasionally, complete failure of the liver to function. This damage may be reversible or irreversible, and if irreversible, the liver failure would be fatal.

Risk of HLH / MAS after stem cell transplantation

Three participants treated on this study experienced a severe side effect called Hemaphagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS). HLH / MAS occurs when the immune system is excessively activated such as with some infections or after very intensive chemotherapy, such as that used with a stem cell transplant. It causes fevers, enlarged liver with liver damage, increased iron in the blood and bleeding. This is a known side effect after stem cell transplantation, but we think that it has occurred more than it should in patients on this study (in 2 out of 42 patients after stem cell transplant treated so far). An additional patient developed HLH during the Induction chemotherapy, with an infection, which also is known to cause this. HLH / MAS is a rare but very serious complication and can result in death even when treated. Because of these two patients we are changing the treatment during Consolidation to stop giving the extra course of the antibody (called hu14.18K322A) with the medicines interleukin-2 and GM-CSF and the NK cells from a parent. These were to be given to participants in the week after stem cell rescue and was called 'Experimental MRD treatment' in the original consent form you signed. This extra 'Experimental MRD treatment' may have contributed to the development of HLH / MAS in these two participants. We will also need for you to sign a new consent form in which this potential new risk is included and the change in treatment plan following stem cell rescue is explained.

We will continue to watch all participants closely after transplantation for this rare, but serious side effect.

There is a small chance that the stem cells may contain tumor cells. These cells could result in the tumor coming back.

These problems alone or in combination may be severe enough to be life-threatening. The purpose of using stem cells is to decrease the chance that these problems will happen. Your doctor will also give you antibiotics and blood transfusions to decrease risk for infection or bleeding.

Months or years after treatment other side effects may appear.

- We know that the chemotherapy drugs cyclophosphamide, melphalan and etoposide can cause leukemia later in life
- Radiation therapy may cause bone cancers or other kinds of sarcomas later in life
- Cyclophosphamide and melphalan will cause damage to the sexual glands. As a result, if you are a boy, you will almost certainly not be able to have biologically related children. If you are girl, you are likely to need hormones or other interventions to have children

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

Possible risks and side effects of hu14.18K322A mAb include:

COMMON, SOME MAY BE SERIOUS	
· Pain, which may be in the back, abdomen (belly) as cramping, joints, arms, legs and other body parts and will require pain relieving medications during the infusion · Numbness and tingling in the fingers and toes · A slight drop or rise in blood pressure	· A fast heartbeat, which may cause chest pain · Itching and hives · Fever · Nausea · Low level of salt in the blood · Cough · Feeling of tiredness

OCCASIONAL, SOME MAY BE SERIOUS	
· A moderate drop or rise in blood pressure, which may require treatment · Vomiting · Diarrhea · Low level of chemistry levels in the blood (salts or potassium), which	· Increased levels of a chemical (creatinine) in the blood, which may mean kidney damage · Elevation in the blood of certain enzymes found in the liver · Fewer platelets in the blood, which can cause the body to bruise and

OCCASIONAL, SOME MAY BE SERIOUS	
may require treatment · A low level of albumin in the blood · Feeling of sleepiness, inability to stay awake or aware or be aroused by someone · Weight loss · An allergic reaction, which causes fever, aches/pains in the joints, skin rash and swollen lymph glands · Anemia, which may cause tiredness, or may require blood transfusion · Difficulty emptying bladder, which may require catheterization during therapy, and in rare cases may be required after discharge from the hospital	bleed more easily · A problem in nerve function, which may cause pain, numbness, tingling, and muscle weakness in various parts of the body · Drooping of the eyelids, blurred vision or inability of the eye to react to bright or dim light, increased sensitivity to bright light · Clotting of the central catheter (the line in the vein in the chest)

RARE, AND SERIOUS	
· Severe allergic reactions, which can be life threatening with shortness of breath or wheezing, low oxygen levels in the blood, 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, making it difficult to breath · Irritation of the small airways of your lungs, which can make you cough and wheeze · Seizures · A rapid heartbeat, which could be life-threatening · Chest pain, which may mean heart damage · Reaction during or following infusion of the drug, which may cause fever, chills, rash, low blood pressure · Anemia and kidney problems, which may cause swelling, or may	· Vascular leak syndrome, which is a condition in which fluid and proteins leak out of tiny blood vessels and flow into surrounding tissues, resulting in dangerously low blood pressure. Vascular or capillary leak syndrome may lead to multiple organ failure such as kidney, heart or liver failure and shock · Severe rashes, which can result in loss of skin and damage to mucous membranes and may be life-threatening · Swelling in the back of the eye caused by an increase in pressure in the brain · Damage to the optic nerve (nerve from brain to eye) leading to decreased vision · Vision changes, which may include changes in the pupils of the eye · Excess fluid between the two tissue layers of the heart's lining (pericardial effusion), which may

require dialysis · A sudden stopping of the heart or breathing	require a procedure in which a needle is inserted between the ribs to remove the fluid around the heart

Risks and side effects of hu14.18K322A mAb in children treated on another St. Jude study:

In another study done at St. Jude, the hu14.18K322A antibody was given to 39 children every day for 4 days every 28 days, with no other chemotherapy drugs. The most common side effects were pain and fever. Some children also had cough, blurry vision requiring prescription glasses, increase in liver enzymes, low levels of salt in the blood, decreased appetite, sensitive skin and feeling of tiredness. One child treated on Part A of the study had a side effect called "serum sickness". Serum sickness is a type of allergic reaction with rash, fever, and achiness in the joints that begins one to two weeks after a drug is given. The same child also had increased blood pressure that was difficult to control, but did eventually resolve with medical management.

Possible risks and side effects of CYCLOPHOSPHAMIDE include:

COMMON, SOME MAY BE SERIOUS	
· Loss of appetite · Nausea · Vomiting · Fewer white blood cells in the blood, which 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 and may decrease the ability to have children

OCCASIONAL, SOME MAY BE SERIOUS	
· Abnormal hormone function, which may lower the level of salt in the blood · Abdominal pain · Diarrhea · Fewer red blood cells and platelets in the blood, which can make you feel tired and weak and may cause you to bruise and bleed more easily · Bleeding and inflammation of the urinary bladder	· Absent or decreased monthly periods, which may be temporary or permanent and may decrease the ability to have children · Temporary blurred vision · Nasal stuffiness with IV infusions · Skin rash · Darkening of areas of the skin and finger nails · Slow healing of wounds · Infections

RARE, AND SERIOUS	
· Heart muscle damage, which may occur with very high doses and may be fatal · Abnormal heart rhythms	· Damage or scarring of urinary bladder tissue · Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure, rapid

· Damage and scarring of lung tissue, which may make you short of breath · A new cancer or leukemia resulting from this treatment	heart rate, chills and fever · Infertility or the inability to have children

Possible risks and side effects of TOPOTECAN include:

COMMON, SOME MAY BE SERIOUS	
· Diarrhea · Nausea · Vomiting · Fewer white blood cells, red blood cells and platelets in the blood ○ a low number of white blood cells can make it easier to get infections o a low number of red blood cells can make one feel tired and weak ○ a low number of platelets can cause you to bruise and bleed more easily and may lead to a need for transfusions	· Constipation · Fever including fever with a low white blood cell count, which could indicate infection. This may require hospitalization and treatment with antibiotics, and rarely could be fatal · Pain that may be in the abdomen, back or bones · A feeling of weakness and/or tiredness · Temporary hair loss

OCCASIONAL, SOME MAY BE SERIOUS	
· Loss of appetite · Elevation in the blood of certain enzymes or bilirubin found in the liver · Headache · Rash, hives, itching or a red bumpy rash · A mild lowering of the blood pressure, which usually does not require treatment · Inflammation and/or sores in the mouth, throat and/or esophagus · An infection in the blood, which could require admission to the hospital and treatment with antibiotics	· Numbness and tingling in the fingers and toes · Small amount of blood and/or protein in the urine or an elevation in blood creatinine, which may mean mild kidney damage · Shortness of breath · Muscle or joint aches and pains · Chest pain · Shaking chills

RARE, AND SERIOUS
· 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, making it difficult to breathe

Possible risks and side effects of INTERLEUKIN-2 (IL-2) include:

COMMON, SOME MAY BE SERIOUS	
· Fever and chills · Nausea, vomiting, and diarrhea · Decrease in blood pressure · Rash, skin itching · Muscle and/or joint pain · Rapid heart rate · Headache	· A feeling of weakness and/or tiredness · A low number of red blood cells can make you feel tired and weak · An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions

OCCASIONAL, SOME MAY BE SERIOUS	
· A low number of white blood cells, which can make it easier to get infections · A low number of platelets can cause you to bruise and bleed more easily · Abnormal blood clotting, which can use up the factors in the blood that help your blood to clot normally · A decrease in your ability to concentrate, confusion, changes in mood, depression · Difficulty breathing or shortness of breath · Fluid build-up in the lungs, which can make you feel short of breath · Skin redness or flushing · Inflammation and sores in the mouth, which may be painful · Development of antibodies (a type of protein produced by the body's immune system), which may have no effect or may lead to rashes or other allergic reactions	· A decrease in urine, which may mean kidney damage or difficulty emptying the bladder · Severe blood infections that will need to be treated and may be life threatening · Decreased appetite · Low level of phosphate (a salt) in the blood, which may require replacement · High levels of sugar in the blood, which may require treatment · Lower than normal levels of protein in the blood, which may cause fluid build-up in the tissues usually in the lower legs · Fluid build-up in the tissues, which may cause weight gain · A decrease in kidney function

RARE, AND SERIOUS	
· Weight loss · Decrease in blood sugar, which may make you feel faint or weak · Protein in urine, which may mean kidney damage	· Numbness in the fingers and toes · Dry mouth · Blurred vision · Changes in taste · Scaling or peeling of skin

· High blood pressure · Slow or irregular heart rate · Heart attack · Increased sensitivity to touch or pain	· A sudden stoppage of the heart or breathing · Coma · Death

Possible risks and side effects of SARGRAMOSTIN (GM-CSF) include:

COMMON, SOME MAY BE SERIOUS
· None

OCCASIONAL, SOME MAY BE SERIOUS	
· Fever	· Nausea
· Chills	· Sudden redness of the face
· Headache	· Vomiting
· Muscle pain	· Diarrhea
· Rash	· Excessive perspiration (sweating)
· Bone pain	· Inflammation of a vein
· Stomach cramps	· Reaction at the injection site
· Weakness	· Itching
· Loss of appetite	

RARE, AND SERIOUS	
· Life-threatening allergic reaction	· Leakage of fluid into the lungs resulting in severe difficulty with breathing
· Fluid build-up in the tissues	· Inflammation of the lungs
· Abnormal heart beat or rhythm	· Inflammation of the sac covering the heart
· Blockage of a vein or artery from a blood clot	

Possible risks and side effects of MESNA include:

COMMON, SOME MAY BE SERIOUS
· Bad taste when taken by mouth

OCCASIONAL, SOME MAY BE SERIOUS	
· Nausea and vomiting	· Fever
· Stomach pain	· Facial flushing with red cheeks
· Headache	· Nervousness
· Pain in arms, legs and joints	· Dizziness
· Tired feeling	· Confusion
· Rash	· Swelling around the eyes
· Temporary low blood pressure	· Coughing
· Diarrhea	· Rapid heart rate

RARE, AND SERIOUS
· Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever

Mesna is given to prevent bladder side effects of cyclophosphamide.

Possible risks and side effects of FILGRASTIM (G-CSF) include:

COMMON, SOME MAY BE SERIOUS
· Aching or pain in the bones

OCCASIONAL, SOME MAY BE SERIOUS	
· Local irritation at the site of the injection · Headache · Higher than normal levels of liver enzymes and uric acid in the blood, which may mean liver irritation or damage · A low number of platelets in the blood, which can cause you to bruise and bleed more easily	· Low fever · Enlargement of the spleen, which may cause pain in the abdomen or left shoulder · Worsening of skin rashes · Inflammation of blood vessel in the skin leading to a raised purple rash and bruising · Higher than normal white blood count

RARE, AND SERIOUS	
· Allergic reactions, which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling. This reaction is very rare and has been associated mainly with intravenous administration · If you are known to have sickle cell disease, filgrastim may cause a sickle cell crisis · Severe damage to the spleen (an organ in the abdomen/belly that stores blood cells), which could lead to pain and loss of blood into the abdomen (belly) and may be life threatening	· Difficulty breathing and lung damage, which may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected · A blood disorder or leukemia, which has only been seen in patients with certain immune disorders who are treated for a very long time

G-CSF is given after chemotherapy to help your white blood cell count recover faster.

Possible risks and side effects of DOXORUBICIN (AdriamycinÒ) include:

COMMON, SOME MAY BE SERIOUS

COMMON, SOME MAY BE SERIOUS	
· Nausea · Vomiting · Temporary hair loss · Pink or red color to urine, sweat, tears, saliva · Fewer white blood cells, red blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak ○ a low number of white blood cells can make it easier to get infections ○ a low number of platelets can cause you to bruise and bleed more easily	· Slight damage to the heart muscle, which is unlikely to have any noticeable effects on your heart function

OCCASIONAL, SOME MAY BE SERIOUS	
· Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach), which may make swallowing difficult and are painful (painful mouth sores) · Damage to the heart muscle, which may make you tired, weak, feel short of breath, and retain fluid · Facial flushing · Fever/chills · Hives · High levels of uric acid in the blood, which could damage the kidneys · Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed	· Damage to the skin if the medication leaks from a vein · Thickening and hardening of the veins where the medication is given · Reddening reaction of the vein where the drug is given · Elevation in the blood of certain enzymes found in the liver · Tearing and inflammation of the eyes · Loss of appetite · Redness and burning at sites that have received radiation in the past · Diarrhea

RARE, AND SERIOUS
· Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate · Ulceration of the lower intestinal tract · An irregular heartbeat, which can be life-threatening · Severe damage to the heart muscle, which may lead to severe heart failure

- A new cancer or leukemia resulting from this treatment

Possible risks and side effects of VINCRISTINE (OncovinÒ) include:

COMMON, SOME MAY BE SERIOUS	
· Hair loss · Reversible nerve problem, which may affect the way you walk or the feelings in your fingers or toes	· Constipation

OCCASIONAL, SOME MAY BE SERIOUS	
· Jaw pain · Headache · Muscle weakness · Pain and bloating in your abdomen · Numbness and tingling · Wrist or foot drop · Drooping eyelids · Double vision, difficulty seeing at night · Abnormal walk with foot slapping · Difficulty with urination or increase desire to urinate · Dizziness	· Abnormal hormone function, which may lower the level of salt in the blood · Seizures · A mild drop in white blood cells, red blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of white blood cells can make it easier to get infections o a low number of platelets can cause you to bruise and bleed more easily

RARE, AND SERIOUS	
· Complete stoppage of your intestinal activity, which can result in intestinal blockage · If the drug leaks out of the vein when being administered it will cause damage to nearby tissue · Seizures · Vocal cord paralysis · Difficulty breathing	· Inability to walk · Decreased ability to hear clearly · Damage to the nerve to the eye (optic nerve) leading to decreased vision and possible blindness · In combination with other chemotherapy drugs, damage to the liver, which can lead to inflammation and/or scarring and could lead to a yellow appearing skin and fluid collection in the abdomen (belly) making it look larger

Possible risks and side effects of ETOPOSIDE (VP-16) (VepesidÒ) include:

COMMON, SOME MAY BE SERIOUS

- Nausea and vomiting
- Hair loss
- A feeling of weakness or tiredness
- Fewer red and white blood cells and platelets in the blood
  - a low number of red blood cells can make you feel tired and weak
  - a low number of white blood cells can make it easier to get infections
  - a low number of platelets can cause you to bruise and bleed more easily

OCCASIONAL, SOME MAY BE SERIOUS	
· Loss of appetite · Decreased blood pressure during the infusion, which may require treatment · Rashes · Diarrhea · Pain in the abdomen · Mouth sores	· Tingling sensation or loss of sensation in fingers or toes · A feeling of extreme tiredness or weakness · The finger or toe nails may loosen from their nail beds · Inflammation of the vein where the medication was given · Chest pain
RARE, AND SERIOUS	
· Damage to the liver · Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever · A new cancer or leukemia resulting from this treatment	· Severe rashes, which can result in loss of skin and damage to mucous membranes · Absent or decreased monthly periods, which may be temporary or permanent and may decrease the ability to have children · Damage to the heart muscle, which may make you feel tired, weak, feel short of breath, and retain fluid

Possible risks and side effects of CISPLATIN (Platinol®) include:

COMMON, SOME MAY BE SERIOUS	
· Nausea · Vomiting · Loss of appetite · Low level of magnesium salts in the blood	· Permanent hearing loss (high sounds) · Damage to kidney tissue · Decrease in the number of red and white blood cells and platelets made in the bone marrow

OCCASIONAL, SOME MAY BE SERIOUS	
· Metallic taste · Abnormal levels of certain salts in	· Permanent hearing loss in the normal range

the body like sodium and potassium

RARE, AND SERIOUS	
· Life-threatening allergic reaction	· Seizure
· Numbness, tingling, clumsiness	· Damage to the liver
· Ringing in the ears	· A new cancer or leukemia resulting from this treatment

Possible risks and side effects of intravenous BUSULFAN INJECTION include:

COMMON, SOME MAY BE SERIOUS	
· Nausea and vomiting	· Loss of appetite
· Fever	· A fast heart beat that may cause pain in the chest
· Headache	· Shortness of breath
· Bloody nose	· Fluid build-up in the tissues usually of the lower legs
· Fewer red and white blood cells and platelets in the blood	· Inflammation and/or sores in the mouth, throat and/or esophagus
o a low number of red blood cells can make you feel tired and weak	· Absence or decrease in the number of sperm and/or damage to the testis that may be temporary or permanent and may decrease the ability to have children in the future
o a low number of white blood cells can make it easier to get infections	· Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have children in the future
o a low number of platelets can cause you to bruise and bleed more easily	· Lower levels of certain salts in the blood such as calcium, magnesium, phosphate and sodium
· Dizziness	· High blood sugar that may require treatment
· Difficulty sleeping	· Elevation in the blood of bilirubin found in the liver
· Mood changes including depression and anxiety	· A feeling of discomfort or not feeling well and/or tiredness
· Rash with itching and/or hives	
· Pain and inflammation in the vein through which the drug is given	
· Back pain or pain in the abdomen	
· Diarrhea or constipation	
· Rectal pain or discomfort	

OCCASIONAL, SOME MAY BE SERIOUS	
· Weight gain	· Damage to the bladder that can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also scarring of the
· Confusion	
· Temporary hair loss or thinning	
· Aches and pains in the muscles and	

OCCASIONAL, SOME MAY BE SERIOUS	
joints · Increased levels of creatinine in the blood that could mean kidney damage · Darkening of the skin · Increase in the blood of certain enzymes that could mean liver irritation or damage · Inflammation or damage to the liver that can be severe and life-threatening and may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen, making it look larger	bladder · Elevation in uric acid in the blood · Redness and burning at sites that have received radiation in the past · Cataracts later in life · Enlargement of the breast

RARE, AND SERIOUS	
· Convulsions even though you will be treated with drugs to prevent convulsions · Vomiting blood · Bleeding into the lungs · A new cancer or leukemia resulting from this treatment · Abnormal heart rate · Damage to the adrenal glands, which may affect the hormones that maintain blood pressure and prevent shock in stressful situations	· Damage to the lungs, which can lead to fluid in the lungs and/or scarring of the lung tissue, cough, and affect your ability to breathe and the levels of oxygen in your blood · Scarring of the heart muscle, which could lead to heart failure · Damage to the bone, which could lead to arthritis pain and weakness of the bone

Possible risks and side effects of LEVETIRACETAM (KEPPRA®) include:

COMMON, SOME MAY BE SERIOUS	
· Dizziness · Sleepiness, drowsiness	· Incoordination

OCCASIONAL, SOME MAY BE SERIOUS	
· Incoordination · Headache · Infection	· Changes in mood · Inflammation in nose, throat, sinuses

· Pain	· Cough
· Loss of appetite	· Double vision
· Depression	· Increase in blood pressure
· Nervousness	· Diarrhea
RARE, AND SERIOUS	
· Suicidal ideas and behavior	· Decrease in red blood cell count
· Serious skin reactions	· Decrease in white blood cell count

Possible risks and side effects of MELPHALAN (Alkeran®) include:

COMMON, SOME MAY BE SERIOUS	
· Loss of appetite	· Temporary hair loss
· Nausea and/or vomiting	· 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 can cause you to bruise and bleed more easily
· Low levels of salt in the blood, which may need to be treated (usually associated with high doses)	
· Diarrhea	
· Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach), which may make swallowing difficult and are painful (painful mouth sores)	

OCCASIONAL, SOME MAY BE SERIOUS	
· Absence of menstrual cycles (periods) and damage to the ovaries, which may decrease the ability to have children in the future	· Low blood pressure
· Absence or decrease in the number of sperm, which may be temporary or permanent and may decrease the ability to have children	· Abnormal heart rate (usually associated with high doses)
· Inability to have children (infertility)	· Damage to the skin if the medication leaks from the vein
· Sweating	· Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products), which could mean liver irritation or damage
· Itching	

RARE, AND SERIOUS	
· Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever	· Sudden damage to the red blood cells (hemolytic anemia), which could cause a rapid decrease in the number of red blood cells such that you would be tired and weak and
· Seizures	

· Damage to the liver, which can lead to inflammation and/or scarring leading to a yellow appearing skin, and fluid collection in the abdomen (belly), making it look larger · Severe damage to the bone marrow, which could be permanent	feel short of breath and may need blood transfusions · Inflammation and/or scarring of the lungs, which can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood making you feel short of breath · A new cancer or leukemia resulting from this treatment

Possible risks and side effects of ISOTRETINOIN (13-cis-retinoic acid, Accutane®) include:

COMMON, SOME MAY BE SERIOUS	
· Dryness of your skin and mucous membranes · Dry, cracked and bleeding lips · An increased tendency to sun burn · Bloody nose from dry membranes of the nose · Aches and pains in the joints	· Back pain · Elevation of the fats in your blood · Increase in calcium in your blood, which may require decreasing the dose · An increase in a laboratory test on your blood, which may measure some non-specified inflammation that may or may not be medically important

OCCASIONAL, SOME MAY BE SERIOUS	
· Rash and itching · Headache · Increase in cholesterol and a decrease in the good fat in the blood · Red eyes · Elevation in the blood of certain enzymes found in the liver, which may mean liver irritation or damage · Fewer red blood cells and white blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of white blood cells can make it easier to get infections	· Dizziness · Difficulty falling asleep or staying asleep and strange dreams · A feeling of tiredness or not feeling well · Nervousness · Numbness and tingling in the fingers and toes · Difficulty hearing clearly or a ringing in the ears · Changes in vision including more difficulty seeing at night, blurred vision, changes in color vision, pain or squinting in bright light, and cataracts formation · Fluid retention · Chest pain

OCCASIONAL, SOME MAY BE SERIOUS	
o a low number of platelets can cause you to bruise and bleed more easily · Too many platelets in the blood · Loss or thinning of hair · Appetite disturbances causing you not to feel hungry or to feel unusually hungry · Weight loss · Increase in blood sugar levels · A darkening or lightening of your skin · Finger and toe nail changes including breaking or splitting more easily · The sudden appearance of little yellow raised bumps on the skin usually because the cholesterol in the blood is too high (xanthomas)	· Inflammation of the gums · A dry throat, which could cause voice changes and more throat infections · Slowed growth · Irregular periods · Mild kidney damage, which could cause blood or protein in the urine or kidney stones · Extra bone growth along the spine and a tendency for calcium deposits in the tendons and ligaments where they attach to the bone, causing pain or stiffness, and inflammation of the bone/tendons (arthritis and tendonitis)

RARE, AND SERIOUS	
· Severe allergic reaction, which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever · Irritation of the small airways in your lungs, which can make you cough and wheeze · An allergic reaction in the blood vessels of the skin, which can turn the skin red, inflamed and bumpy and may lead to skin breakdown · A severe lowering of the white blood count, which can make you very susceptible to infections that could be life threatening · Convulsions · Brain swelling, which can give you symptoms of severe headache, nausea and vomiting, and changes to your vision including blurriness and pressure behind the eyes · Life threatening or fatal changes in	· Thinning of the bone (osteoporosis), which could lead to weakness of the bone, bone fractures or delay in healing of fractures · Inflammation of the pancreas, which can cause severe abdominal pain and in some very rare cases, can cause death · Damage to the muscle, which can result in release of a protein that can cause severe kidney damage · Inflammation of the intestinal tract, which can cause diarrhea and bleeding · Serious skin reactions, which can range from red bumpy rash to severe rash with blistering of the skin. The rash may spread and can result in loss of skin and damage to mucous membranes and may be life-threatening · This drug can cause severe birth

RARE, AND SERIOUS	
moods have occurred including severe depression or feelings of suicide and feelings of aggressiveness and violent behavior	defects in a developing fetus

Risks of stem cell collection and reinfusion

These procedures are usually safe. Side effects that can occur during PBSC collection include nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, flushing (redness and warmness of the skin, usually the face), blood loss, and infection. Tingling of the lips, muscle cramping and, very rarely, changes in the heart rhythm can occur. These can be prevented or made milder by giving calcium supplements, either by mouth or IV. Very rarely, (less than 1 in 1,000 procedures), clotting may occur in the apheresis machine or in a patient and is potentially life-threatening. To reduce the risk of clotting, you will be given a drug called ACD (acid-citrate-dextrose). This drug may increase the risk of bleeding and may cause temporary tingling of the lips and limbs, muscle cramping, seizures, or changes in the heart rhythm.

The risks associated with infusing the cells back into your body include dark urine, nausea, vomiting, fever, chills, and high blood pressure. All of these are temporary and go away after the infusion is done. As with any procedure, there may be side effects we do not expect.

Risks of radiation therapy

The risks of radiation therapy depend on the parts of the body being treated. Some possible risks are described below, but you should talk to your child's doctor to see which apply to your child. Radiation therapy can cause nausea, vomiting, diarrhea, red or dry skin, low blood counts, hair loss (permanent or temporary), jaw pain and swelling, temporary weakness or loss of sensation. Some patients have a week or two of low grade fever and sleepiness can occur six to eight weeks after radiation therapy is done. Damage to body organs such as the brain, eyes, heart, lung, liver, and kidneys can occur. Radiation therapy can also cause abnormal bone growth. There is also a small chance that radiation can cause another type of tumor years later.

Risks of surgery to remove tumor

Your surgeon will discuss the risks of the surgery when you sign the consent for the procedure. In general, surgery may result in one or more of the following side effects: bleeding, infection, problems with wound healing, pain, scar, adhesions, loss of nerve or organ function, or blood vessel damage.

Depending on the type of anesthesia required, there may be one or more of the following side effects: nausea, vomiting, air passage obstruction, breathing problems, or heart irregularity. In rare instances death may occur during or after surgery.

Risks of study procedures

X-rays and scans: MRI, CT, X-ray, Ultrasound, and Nuclear Medicine Scans are common standard imaging tests used in the diagnosis and monitoring of many diseases. Although these tests have been in use for many years, their long-term effects on the body are still being learned. The most common discomfort is the length of time a subject must lay still or flat while an X-ray or scan is being performed. Uncommonly, some subjects may have allergic reactions to dyes injected for some of these tests. Uncommon allergic reactions may result in rash, difficulty breathing, low blood pressure or other severe complications. Please let your doctor or nurse know if you have previously had an allergic reaction. If your imaging scan has "research sequences or series" you will be in the scanner for 4-30 minutes so that the research part of the scan can be done.

EKG and echocardiogram: These procedures are associated with very little discomfort. Some subjects with sensitive skin may develop rashes where the EKG wires are taped on their skin.

Bone marrow aspiration/biopsy: Pain or discomfort may occur during and after the biopsy, even with the use of local anesthetics. There may be some mild burning sensation when the numbing medicine is injected into the skin. There may be bleeding from the biopsy site, which requires putting pressure on it to stop the bleeding. Rarely, infections can occur at the biopsy site. This can be treated with antibiotics. It is possible but very uncommon to have severe bleeding, infection, nerve damage or other life-threatening complications from a biopsy.

Blood tests: Most of the time, blood can be drawn from your central venous catheter. This is associated with a small chance of infection that could require treatment with antibiotics or, rarely, removal of the line. If blood needs to be drawn from a vein in your arm, this will cause some pain and may result in bruising at the site of the needle stick. If a bruise does form at the end of the needle puncture site, it will generally go away on its own without any treatment.

Eye examination: If eye drops are placed in your eyes so that the pupils dilate (become enlarged), your vision may be temporarily blurry and very sensitive to light. We will give you dark glasses to wear.

Other risks of the study

Unknown risks: The combinations of treatments on this study are experimental and still being tested. There may be other risks, including death, which are not known now.

Risks of second cancers: A possible late side effect of cancer treatment is that a second cancer or leukemia may occur. We do not know the exact risk of a second cancer starting with this treatment.

Loss of privacy: Very rarely, personal information from your records could be given out by accident. This might make you upset, embarrass you, or affect your ability to get insurance. To stop this from happening, we:

- Store records behind locked doors, with only study staff having access
- Only allow members of the study team to see the records
- Store electronic data only on computers protected with a password and encryption software
- Report study results on the whole group and never identify one single person in any reports

Risks for unborn children: The treatments on this study can be bad for an unborn or nursing child. **The use of isotretinoin (cis-retinoic acid) can cause birth defects to unborn children if taken during pregnancy**. Females in the study must not be pregnant or nursing when they start the study and must not get pregnant during the study. If you think you may have become pregnant during the study, you must tell the researcher right away. If you become pregnant, you will be taken out of the study.

Males in the study must not father a child during the study. The treatment on this study can damage sperm. Male participants of reproductive potential should talk to the researcher about the option of freezing sperm before taking part in this study.

Participants in this study must use effective forms of birth control. The researcher can tell you about the best birth control methods to use during this study. Effective forms of birth control may include birth control pills taken by mouth, condoms, and not having sex. Birth control methods should be continued for 6 months after treatment to avoid pregnancy. We also do not know if there may be unknown long-term effects to your children.

If you are capable of becoming pregnant or if you are of child bearing age, you must practice 2 forms of reliable birth control, sign the Patient Information/Informed Consent form(s), have regular pregnancy tests while taking isotretinoin, be able to keep appointments, and agree to follow the iPLEDGE program steps (a special program required by the manufacturers and

approved by the Food and Drug Administration (FDA) that your doctor will explain to you).

Your doctors and nurses will be checking closely to see if any of these side effects are occurring. Routine physical exams and laboratory tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is completed.

11. Will my tissue be stored for future research?

Tissue comes from your body, like blood, bone marrow, skin, hair, nails, and urine. After a patient has a biopsy, surgery, or blood sample taken, and all lab tests have been done, some tissue may be left over. This tissue is usually thrown away because it is not needed to care for you. However, you can agree to have your tissue saved for future research. We would like to keep this tissue in a "bank" called the St. Jude Biorepository. These samples are kept by people trained to handle human tissue and to protect patient privacy. The tissue is coded and the key to the code is not given to researchers without the approval of St. Jude Institutional Review Board (IRB), a group that reviews the ethics and safety of research studies. Researchers will help collect leftover tissue from people in the study who agree to have it saved for research. You do not have to agree to have your tissue saved to be in this study. The National Institutes of Health and National Cancer Institute (NIH/NCI) have developed a useful brochure (in English and Spanish) about tissue research: http://www.cancer.gov/clinicaltrials/resources/providingtissue

12. What are the possible benefits of the study?

This experimental treatment may have benefits. This experimental treatment may turn out to be better at treating neuroblastoma than treatments we have used in the past. Unfortunately, there is no guarantee. We may find out that this treatment is not better. It is hoped that the information learned from this study may help future patients with high-risk neuroblastoma.

13. Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor

14. Will I be paid for my time or expenses?

You will not be paid to take part in this study.

15. How will I find out the results of this study?

The researcher will give you information about the overall results of this study. Whether you will know your personal test results will be discussed in another part of this document. St. Jude researchers share information with people in studies in many ways, including:

- articles on *www.stjude.org*
- in newsletters
- in medical or scientific journals
- in the media

Published research results will only describe groups of people who took part in the study. Information that points out a single person will not be in research journals or other reports.

16. Who will see my research records and medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law.
There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- St. Jude study staff members, clinical research monitors, and internal monitoring committee members.
- Federal agencies such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), and
- St. Jude Children's Research Hospital Institutional Review Board (IRB)

17. Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

OPTIONAL RESEARCH TESTS

You will not get health benefits from any of these optional studies. These research studies will not benefit you directly but may help us understand neuroblastoma better and help improve treatment in the future. If you have questions about this study, please talk to the researcher.

The results will not be added to your medical records, nor will you or your study doctor know the results. You can still take part in the main study even if you say 'no' to any or all of these optional studies. If you sign up for but cannot complete any of these optional studies for any reason, you can still take part in the main study.

Your blood and bone marrow samples will be studied in the lab. The information will only be used for research. This information may be shared with other researchers at St. Jude or other researchers from other institutions; however, any shared information will not include your name or other personal identifiers.

1. Optional minimal residual disease (MRD) studies

Very small amounts of neuroblastoma can be present that are too small to be detected by a microscope. These small amounts of neuroblastoma are called "minimal residual disease", or "MRD", for short. Special tests are available that can detect MRD in the blood and bone marrow. If you agree, we would like to collect about 2 teaspoons of bone marrow and 2 teaspoons of blood at these times:

- Pre-treatment
- Before you start course 3 of Induction
- End of Induction (after cycle 6)
- Before starting Maintenance/MRD phase
- End of Maintenance/MRD phase (after cycle 6)
- Every 4 months first year after completing treatment

These samples will be collected at the same time you are having a bone marrow procedure for routine care. They will be sent to a research lab for special studies to measure MRD and assess the effects of treatment.

Please circle your answer: I agree to receive the experimental MRD treatment during Intensification phase after my stem cell rescue

YES **NO**

2. Optional blood sample for plasma catecholamine metabolites

About 90% of children with neuroblastoma will have increased levels of substances called “catecholamines”. Researchers on this study want to find out if measuring these levels in the blood can be another tool that doctors use to measure the effect of treatment, and possibly replace some diagnostic imaging studies for future patients with neuroblastoma. If you agree to take part in this research, about ½ teaspoon of blood will be drawn through your central line 7 times. This blood will be collected at the same time you are having MIBG scans to evaluate your neuroblastoma:

- Pre-treatment
- At the completion of the first two cycles of induction chemotherapy
- At the end of induction (cycle 6)
- Before you start maintenance/MRD treatment
- After cycle 3 of maintenance/MRD treatment
- After completion of therapy

Please circle your answer: I agree to have my blood samples used for plasma catecholamine metabolite research studies

YES **NO**

3. Optional biology research studies on tumor tissue

There is some evidence that the presence of certain proteins and genes in the body can be used to predict how a tumor will respond to treatment. We would like to study your tumor tissue to look for these gene and protein “markers” that may help us predict how neuroblastoma tumors will respond to treatment. This research may help children with neuroblastoma in the future.

As part of your regular care at the time of diagnosis, your surgeon removed some tumor tissue. If any of this tissue is left over and is no longer needed for your medical care, we would like to use it for these gene and protein expression research studies. Also, when you have surgery as part of your medical care while you are on this study, we would also like to keep any leftover tissue that is not needed for your medical care.

Please circle your answer: I agree to have my tumor tissue used for biology research studies

YES **NO**

SUMMARY OF RESEARCH AND PRIVACY RIGHTS

The following statements describe your rights as a research participant in this study:

1) You may refuse to be in this research study or stop at any time. This decision will not affect your care or your relationship with your doctor or St. Jude. If available, you may receive routine medical care at St. Jude Children's Research Hospital.

2) If you have insurance, TennCare or Medicaid, or other health care coverage such as an employer-sponsored benefit plan, they will be billed for many of the services we provide. However, we do not bill patients or their families for the cost of medical care not covered by their health plans. This includes research costs.

3) Your samples and information may be used to develop a new product or medical test, which may be sold. If this happens, you will not receive any payments for these new products.

4) If you have any questions about this study or if you are injured as a result of this study, contact Dr. Wayne Furman, at 901-595-3300 immediately. If you are injured from being in this research study, St. Jude will provide reasonable and necessary care for that injury. If you need more care than St. Jude can provide, we will help you find medical care somewhere else. It is not the hospital's policy to provide payment if you are injured from being in this study; however, you are not giving up any of your rights by signing this consent form.

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

6) A decision to take part in this research means that you agree to let the research team use and share with other researchers your health information, also called protected health information (PHI), for the study explained above. This information will be kept indefinitely. You have the right to see, copy, and ask for changes to your protected health information that will be used or given out. However, research information may not be seen until the end of the study.

7) When you first registered at St. Jude, you received a copy of the St. Jude Notice of Privacy Practices. It tells how your PHI may be used or given to someone outside the hospital. You have the right to read the Notice of

Privacy Practices before you sign this form. It may have changed since you were first registered at St. Jude. You can find it at the bottom of every page on the St. Jude Internet website: *www.stjude.org*.

8) Federal agencies such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), and St. Jude Children's Research Hospital Institutional Review Board (IRB), your insurance company or other health benefits plan (if charges are billed to these plans), as well as other regulatory agencies, committees, or persons involved in overseeing research studies may review your research and medical record.

9) Information about you that may be given out includes your complete medical records, including details about diagnosis, illness, treatment, and information that may be recorded about past diagnosis or treatment and information taken as a part of this research study as explained in this informed consent.

10) After your records are given to or used by others, St. Jude Children's Research Hospital cannot promise that information will not be given out again. Also, the information given out may no longer be protected by federal privacy laws.

11) St. Jude uses reasonable safeguards and means to protect your private information. However, St. Jude cannot guarantee the security and confidentiality of e-mail, text messages, fax communications or mail.

12) Researchers and study staff are required by law to report suspected child abuse, threat of harm to self or others, and certain diseases that spread from person to person.

13) Your permission to use and give out your child's protected health information will end when your child turns 18 years of age. At that time, we may contact your child for his or her permission to continue using it.

14) You may take back permission for your records to be used or given out at any time, for any reason, except when that information has already been given out or used for the study based on your permission. To take back your permission, please fill out a form called a Revocation of Release of Authorization. You may ask for this form by calling the St. Jude Privacy Officer at 901-595-6141. You must mail the form or hand it to:

HIPAA Privacy Officer
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 280

Memphis, TN 38105

15) You can get more details about your rights as a research participant by calling the St. Jude Institutional Review Board at 901-595-4357 or the Research Participant Advocate at 901-595-4644. If you are outside of the Memphis area, please call toll-free 1-866-583-3472 (1-866-JUDE IRB).

16) The St. Jude Research Participant Advocate is an individual who is not part of the research study team and is available to you to discuss problems, concerns, and questions. The Advocate can help you obtain information and can relay any input you may have concerning the research to the research study team. You can reach the Advocate by calling 901-595-4644, or if you are outside of the Memphis area, call toll free at 1-866-583-3472 (1-866-JUDE-IRB).

17) You will be given a copy of this signed consent form.

PARENT/GUARDIAN STATEMENT (Required for participants younger than 18 years):
I have read this document or it was read to me. I have been encouraged to ask questions and all my questions have been answered. I give permission for my child to be in this research study and any additional studies where I circled 'yes'.

_____ _____ _____ AM/PM
Parent/Legal Guardian Signature (circle one) Date Time

ASSENT DISCUSSION (Required for participants 7-13 years old):

☐ The research was explained to the minor participant in age-appropriate terms and the minor verbally agreed to take part in the study.

☐ Minor declined to take part in the study. The minor declined for the following reason(s):

_____

☐ An assent discussion was not initiated with the minor for the following reason(s):
- ☐ Minor is under 7 years of age.
- ☐ Minor is incapacitated.
- ☐ Minor refused to take part in the discussion.
- ☐ Other_____

RESEARCH PARTICIPANT STATEMENT (14-17 years old and Adult Participants 18 years and older): I have read this document or it was read to me. I have been encouraged to ask questions and all my questions were answered. I agree to take part in this research study and any additional studies where I circled 'yes'.

_____ _____ _____ AM/PM
Research Participant Signature Date Time (circle one)

RESEARCHER/DESIGNEE STATEMENT: I have explained the research to the participant and his/her parent(s) or legal guardian(s). The research participant and parent(s)/guardian(s) were encouraged to ask questions and all questions

were answered to their satisfaction. A copy of this form has been given to the participant or his/her representative.

_____	_____	_____ AM/PM
Researcher/Designee Signature (circle one)	Date	Time

_____
Print Name

RESEARCH PARTICIPANT ADVOCATE STATEMENT: I observed the informed consent process. The research study, intervention/observation, risks, benefits, and alternatives were presented to the research participant and/or legal guardian(s). They were encouraged to ask questions, and research team members answered all their questions. The participant /parent(s) indicated that they: 1) understood the information presented; and 2) voluntarily consented /agreed to take part in the research.

_____	_____	_____ AM/PM	
Research Participant Advocate	Date	Time	(circle one)

_____	_____	_____ AM/PM
Interpreter (if needed) (circle one)	Date	Time

PLEASE FAX CONSENT FORM TO PROTOCOL OFFICE #6265