15.0 SAMPLE INFORMED CONSENT

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NANT N2011-04
A Phase I Study Of Lenalidomide And
Anti-GD2 Mab ch14.18 +/- 13-Cis-Retinoic Acid in Patients With Refractory/Recurrent Neuroblastoma.
A New Approaches To Neuroblastoma Therapy (NANT) Treatment Protocol.

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 lenalidomide in combination with fixed doses of ch14.18 and 13-cis-retinoic acid 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 lenalidomide together with ch14.18 and 13-cis-retinoic acid and compare those side effects to those experienced on other studies that used ch14.18.
- To learn about the differences in immune function when giving different doses of lenalidomide given with ch14.18 and 13-cis-retinoic acid.
- To measure the levels of lenalidomide, ch14.18 and 13-cis-retinoic acid in the blood at different dose levels
- To determine if your tumor gets smaller after treatment with lenalidomide, ch14.18 and 13-cis-retinoic acid.
- To determine if specific gene changes makes you respond better to the combination of lenalidomide, ch14.18 and 13-cis-retinoic acid.
- To describe the amount of neuroblastoma tumor amounts in the blood and bone marrow by testing samples for 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; lenalidomide, ch14.18 and 13-cis-retinoic acid. 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 ch14.18. Ch14.18 is a monoclonal antibody. Monoclonal antibodies are proteins made in the lab, designed to attach to specific targets on cancer cells. Ch14.18 was designed to attach to neuroblastoma cells and other cancer cells that have GD-2 on their cells. When ch14.18 attaches to the neuroblastoma cells, the body's immune system is stimulated to attack and kill the neuroblastoma cells. Ch14.18 represents a new kind of cancer therapy that, unlike chemotherapy and radiation, targets the killing of cancer cells without destroying nearby healthy cells.

Isotretinoin (Accutane®, or 13 cis retinoic acid) is a commercially available drug closely related to vitamin A and has been shown to help change the remaining neuroblastoma (cancer) cells into normal nerve cells. Its beneficial role in neuroblastoma therapy has been established in previous studies.

A recently completed study that compared the immunotherapy regimen of ch14.18 with 2 other medications called cytokines (medicines used to stimulate the immune system) to isotretinoin alone showed that the experimental treatment worked better than standard treatment to help remove any remaining neuroblastoma cells.

In this study, Lenalidomide is being given instead of the other two cytokines to see if the side effects will be less than on the prior studies. We are also trying to see if this combination will work on the immune system in the same or better way than the other combinations that have been used.

Lenalidomide is an oral medication that has been approved by the Food and Drug Administration (FDA) for the treatment of other cancers, including multiple myeloma. We are using Lenalidomide because it seems to work against cancer in test tubes and animals and has been used and safely given to children with solid tumors. It affects some of the ways the immune system functions and recognizes tumor, and appears to work by slowing or stopping the growth of new cancer cells. The use of, Lenalidomide in this protocol is considered experimental.

This is the first study to test giving these three drugs together and will help determine the highest doses of lenalidomide that can safely be given together with ch14.18 and 13-cis-retinoic acid to patients with resistant/relapsed neuroblastoma.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 6 and 62 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
- Blood tests
- Pregnancy test**
- Urine tests
- Bone marrow tests#
- Various scans*
- 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**.**

**** If you are a woman who could have children you must have a pregnancy test done by the doctor at least 7 days before you start taking Lenalidomide and then another one within 24 hours before you start taking Lenalidomide. If you are pregnant, you cannot take Lenalidomide. Only if you have had your uterus removed (hysterectomy) or no menstrual periods for at least 24 consecutive months or you are too young to get pregnant (you have not shown any signs of menses or ovulation) (i.e. you are a woman who could not have children), you will not be required to have these pregnancy tests.**

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	Bone marrow tests[#]
Blood tests	Various scans*
Pregnancy test**	
Urine tests	

******Pregnancy Tests and Birth Control***

If you are a female who has had her uterus removed (hysterectomy) or no menstrual period for at least 24 consecutive months or you are too young to get pregnant (you have not shown any signs of menses and ovulation) (i.e. you are a woman who could not have children) you will not be required to follow the guidelines listed below.

If you are a woman who could have children, you must have a pregnancy test done by the doctor every week during the first 4 weeks of treatment. You will then have a pregnancy test every 4 weeks if your menstrual cycles are regular or every 2 weeks if your menstrual cycles are irregular. You may also need to have a pregnancy test if you miss your period or have unusual menstrual bleeding.

If there is ANY chance that you can get pregnant, you must either agree to practice abstinence from heterosexual intercourse or begin TWO methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME. Barrier methods alone (i.e. condoms) are not sufficient. These birth control methods must be used for at least 4 weeks before starting treatment with LENALIDOMIDE, during treatment with LENALIDOMIDE, and for at least 4 weeks after LENALIDOMIDE therapy has stopped. The following methods are considered acceptable birth control methods:

Highly Effective Methods	**Additional Effective Methods**
Intrauterine device (IUD)	**Latex condom**
Hormonal (birth control pills, injections, implants)	**Diaphragm**
Tubal ligation	**Cervical cap**
Partner's vasectomy	

Remember: You must use at least one highly effective method and one additional effective method AT THE SAME TIME. However, for medical reasons, the doctor may recommend that you use two barrier methods. You MUST talk to the doctor before changing any birth control methods.

If you have sex without birth control or if for any reason you think you may be pregnant, you must IMMEDIATELY tell the doctor.

If you are a man, and even if you have had a successful vasectomy, you must agree to use latex condoms every time you have sex with a woman while you are taking LENALIDOMIDE and for 4 weeks after you stop taking LENALIDOMIDE. You must tell a doctor if you have sex with a woman without using a latex condom, or if you think for any reason that your partner may be pregnant. You must not be a sperm or blood donor while being treated with LENALIDOMIDE.

You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (or other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

Treatment Plan

Not all patients will get the same doses of lenalidomide. All patients will receive the same dose of Ch14.18. At the beginning of the study, a few patients will be treated with a lower doses of lenalidomide and standard dose ch 14.18. The first patients on this study will not receive 13-cis-retinoic acid. If these doses do not cause bad side effects, the lenalidomide doses will slowly be made higher, and 13-cis-retinoic acid will be added. Once 13-cis-retinoic acid is added, all patients will receive the same dose of that drug. Your physician will tell you what dose you are assigned to.

A map of one treatment course is shown here. Each treatment course is 28 days. You may receive up to 6 courses of therapy as long you are benefiting from treatment and continue to meet the criteria to continue safely on this study.

DAY OF COURSE:				
Days 1-7	Days 8-11	Days 12-14	Days 15-21	Days 22-28
Lenalidomide	Lenalidomide	Lenalidomide	Lenalidomide (Levels 1-6 only)**	Rest
	ch14.18			
			13-cis-retinoic acid* (Levels 2-6 only)	13-cis-retinoic acid* (Levels 2-6 only)

**Most patients will receive Lenalidomide by mouth once a day as intact capsules on Days 1-21. Some will receive Lenalidomide by mouth only on Days 1-14. Your doctor will explain your schedule to you. You must be able to swallow the Lenalidomide capsule whole to participate in this study.

Ch14.18 will be given IV on Days 8-11 of each course. The infusion of ch14.18 may last up to 20 hours each day. Each patient will receive the same dose of ch14.18 on this study.

*13-cis-retinoic acid will be given by mouth twice daily on Days 15-28 of each course. Patients who receive the lowest doses of lenalidomide will not receive 13-cis-retinoic acid. Your doctor will tell you your schedule.

If you have to stop taking 13-cis-retinoic acid due to bad side effects caused by that medicine, you may continue to receive lenalidomide and Ch14.18. If you have to stop either lenalidomide or ch14.18 due to bad side effects, you will have to come off protocol therapy

After the highest dose of lenalidomide that can be given safely with ch14.18 and 13-cis-retinoic acid has been determined, 20 additional patients may be treated to obtain further information on the side effects of these drugs given together and their effects on neuroblastoma tumors.

You will be asked to keep a written record of when you have taken the lenalidomide and 13-cis-retinoic acid. The ch14.18 will be administered in the hospital.

All Patients:

You must **NEVER** share lenalidomide (or other study drugs) with someone else. You must **NEVER** donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study.

Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

Females of childbearing potential that might be caring for you should wear gloves when handling 13-cis-retinoic acid capsules unless the capsules are intact.

When you have finished treatment with lenalidomide, ch14.18 and 13-cis-retinoic acid:

After you stop treatment on your assigned treatment arm, 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, tests will be repeated monthly until 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
Pregnancy test**	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

You will be asked if you want to participate in the following tests that are being done to see how the study drugs are affecting your body. There are 7 tests; **5 are required and 2 are optional.** The results of these tests would not be told to you or your doctor or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

The required studies are listed below. You may not participate in this study if you do not agree to the following tests.

- **Tests 1 and 2: Evaluation of Immune Function and Genotyping**

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 two treatment course of this study**.** We will also be looking at the way ch14.18 acts in your body (including analyses of DNA relevant to the way ch14.18 work). For this test, 10mL of blood (less than 1 tablespoon) will be taken 6 times for all patients. Patients receiving treatment at Children's Hospital Los Angeles (CHLA) only will have an extra 5mL drawn at 2 of those times. This is because the sample is needed to be fresh for immediate processing. You will not need separate clinic visits for this part of the study. The total amount of blood drawn for testing will be 60mL (or 70mLs for CHLA patients) (no more than 5 tablespoons) over 2 months. 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: Lenalidomide Pharmacokinetic Studies (Determining The Amount of Lenalidomide in Your Blood)**

Part of the research goal for this study is to look at the effects the different doses of lenalidomide 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, 3ml of blood (less than 1 teaspoon) will be taken 8 times. You will not need separate clinic visits for this part of the study. The total amount of blood drawn for testing will be about 24mL (about 5 teaspoons) over 28 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 Celgene, the supplier of Lenalidamide.

- **Test 4 and 5: ch14.18 PK/HACA (Determining The Amount of Humanized Antibody in Your Blood)**

Part of the research goal for this study is to look at how much of the ch14.18 is in your blood. These will be measured in the first, second, fourth, sixth and ninth courses, as well as when you complete protocol therapy. For this test, 3ml of blood (less than 1 teaspoon) will be taken up to 12 times times. You will not need separate clinic visits to participate in this part of the study. The total amount of blood drawn for testing will be about 36mL (about 8 teaspoons) over 4 to 12 months. 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.

The optional studies are listed below. You can decide not to let the doctors do these tests and still be able to be treated as part of this clinical study. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these voluntary studies.

- **Test 6: 13-cis-retinoic acid Pharmacokinetic Studies (Determining The Amount of 13-cis-retinoic acid in Your Blood)**

Part of the research goal for this study is to look at how much 13-cis-retinoic acid is in your blood**.** For this test, 5 mL of blood (about 1 teaspoon) will be taken once to measure the amount of 13-cis-retinoic acid in the blood. This testing will be done on the last day of the 13-cis-retinoic acid treatment on course 1, or on

the first day of Course 2. Your doctor will tell you your treatment schedule. You will not need an additional clinic visit to participate in this part of the study. The total amount of blood drawn for testing will be 5 mL (about 1 teaspoons) obtained on 1 day. This amount of blood is considered safe to donate. The blood will be drawn or taken from your central line (or port). If you do not have a central line then you will need to be poked for these blood draws. Samples will be sent to the Texas Tech University in Lubbock, Texas for analysis.

- **Test 7: Tumor CellQuantification (Blood and Bone Marrow)**

Part of the research goal for this study is to evaluate a new test for blood and bone marrow specimens to find tumor cells. The results of this new test, called 5-gene TaqMan® Low Density Array or TLDA, may be more sensitive than the standard testing available. For this test, 16 mL of blood (about 3 teaspoons) will be taken at study entry and at each disease evaluation. Bone marrow aspirations will also be performed when you have disease evaluations and if you consent, an extra 5ml (about 1 teaspoon) will be taken from each side of where the bone marrow is performed for testing, usually the hip bone. This amount of blood is considered safe to donate. Samples will be sent to the Children's Hospital Los Angeles.

If there are restrictions to the amount of blood that can be done for research purposes based on your weight, you will be advised by your physician and research team, that you cannot participate in the optional studies, or the amount of blood for the required testing may be modified.

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. 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 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.

If you, or your physician decide that you need to stop therapy on this study, you will need to still use acceptable birth control methods for at least 4 weeks after LENALIDOMIDE therapy has 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 and tumor responses seen in patients. Since subjects will be assigned to different dose levels, subjects will have different tumor responses and side effects. The goal of this study is to see which treatment arm has the best response for your neuroblastoma while comparing the side effects of the different treatments.

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 Lenalidomide

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)
• Lack of enough red blood cells (anemia) • Constipation • Diarrhea • Fatigue or tiredness • Decreased number of a type of white blood cell (neutrophil/granulocyte) • Decreased number of a type of blood cell that helps to clot blood (platelet)	• Abnormally low level of thyroid gland hormone • Nausea or the urge to vomit • Vomiting • Chills • Swelling of the arms and/or legs • Fever • Infection • Decreased number of a type of white blood cell (lymphocyte) • Weight loss • Decrease in the total number of white blood cells (leukocytes) • Loss of appetite • Joint pain • Back pain • Muscle cramps/spasms • Muscle pain • Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness) • Headache or head pain • Difficulty sleeping or falling asleep • Cough • Shortness of breath • Excess sweating • Itching	• Inflammation (swelling and redness) of the pancreas • Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness. • Increased blood level of fat-digesting enzyme (lipase) • Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure • A blood disease (leukemia) caused by chemotherapy • Decreased production of blood cells by the bone marrow • Temporary growth in tumor or worsening of tumor related problems • Development of a new cancer resulting from treatment of an earlier cancer

	• Skin rash with the presence of macules (flat discolored area) and papules (raised bump) • A chronic, inflammatory skin condition with sores covering the skin • Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung	• Progressive necrosis (tissue death) of a part (the white matter) of the brain without inflammation (swelling and redness) • Sudden decrease of kidney function • Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue • 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) • Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

<u>Possible side effects of Chimeric MOAB 14.18</u> (Ch14.18 antibody)

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)
• Pain which may be in the back, abdomen (belly) as cramping, arms, legs, head, nerve, headache and other parts of the body and will require administration of pain relieving medications during the infusion • An abnormal level of a protein called c-reactive protein in the blood which signals the presence of inflammation • Fever • Cough • Skin rash with the presence of macules (flat discolored area) and papules (raised bump) .	• Abdominal blood clotting and/or bleeding • Fast heart, regular rhythm • Belly pain • Diarrhea • Nausea or the urge to vomit • Vomiting • Swelling caused by fluid build-up in the tissue of the face, arms and legs • Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. • Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat,	• The heart stops pumping blood

	difficulty breathing, and loss of consciousness. • Allergic reaction to certain medications, injected proteins, or antisera (blood procdcuts) used to treat certain medical conditions (such as an infections or poisonous substance) • Infection • Increased blood level of a liver enzyme (ALT/SGPT) liver which may indicate liver irritation or damage • Increased blood level of a liver enzyme (AST/SGOT) liver which may indicate liver irritation or damage • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Decreased number of a white blood cell (lymphocyte) • Decreased number of a typr of blood cell that helps to clot blood (platelet) • Loss of appetite • A low level of a blood protein called albumin in the blood. • Decreased blood levels of potassium • Back pain • Nerve pain • Inflammation (sweeling and redness) or degeneration of the peripheral nerves (those nerves outside of the brain and spinal cord) causing numbness, tingling, burning • Presence of excessive protein in the urine which may indicate kidney damage • Blockage of the brochus (an air tube from the windpipe to the lungs) • Shortness of breath • Decrease in the oxygen supply to tissues • Abnormal, high-pitched, musical breathing sound caused by a blockage in the throat or voice box • Itching • Hives • Increased in the number and size of the pores in the	

	capillaries (small blood vessels) which causes leakage of fluid from the blood to the tissue spaces, resulting in dangerously low blood pressure, swelling and multiple organ failure • High Blood pressure • Low blood pressure	

Possible side effects of 13-cis-retinoic acid

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)
• 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 that may measure some non specified inflammation which may or may not be of any importance	• Rash • Nausea and Vomiting • Headache • Increase in cholesterol and a a decrease in the good fat in the blood • Red eyes • Elevation in the blood certain enzymes found in the liver which may mean liver irritation or damage. • Fewer red blood cells which can make you feel tired and weak • Extra bone growth along the spine and a tendency for calcium deposits in the tendons and ligaments where they attach to the bone which can lead to pain or stiffness and arthritis of the back and tendonitis.	• 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 that can make you cough and wheeze • Loss or thinning of hair • Appetite disturbances causing you not to feel hungry or to feel unusually hungry • 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) • Convulsions • Dizziness • Brain swelling that 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 moods have occurred including severe depression or feelings of suicide and feelings of aggressiveness and violent behavior • 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 • Weight loss • A severe lowering of the white blood count which can make you very susceptible to infections which could be life-threatening • Increase in the number of a type of blood cell that help the blood to clot • Agranulocytosis • Allergic vasculitis • Chest pain • 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 cataract formation • Fluid retention • Inflammation of the gums • A dry throat which could lead to a change in your voice and more throat infections • Respiratory infections • An allergic reaction in the blood vessels of the skin which turn the skin red, inflamed and bumpy and which may lead to skin breakdown, called erythema

		multiforme • 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) • Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer) • 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 lead to severe abdominal pain and in some very rare cases can be fatal • Damage to the muscle which can release a protein that can cause severe damage to the kidneys • Inflammation of the intestinal tract which can result in diarrhea and bleeding • Mild kidney damage which could lead to blood or protein in the urine or renal stones. • Slowed growth • Irregular periods • This drug can cause severe birth defects in a developing fetus, if you are capable of becoming pregnant or of child bearing age, you mustpractice 2 forms of reliable birth control, sign the PatientInformation/Informed Consent form(s), have regular pregnancy tests, be able to keep appointments and agree to follow the iPLEDGE program steps (a special program required by the manufacturers approved by the Food and Drug Administration (FDA) which

		your doctor will explain to you.

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

- Recurrence of tumor
- Infection

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 and your child 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.
- CTEP (Cancer Therapy Evaluation Program)
- Pharmaceutical company which makes Lenalidomide
- Pharmaceutical company which makes Chimeric MOAB 14.18

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.

The study agent Ch14.18 will be provided free of charge by the Cancer Therapy Evaluation Program, NCI while you are taking part in this study. The NCI does not cover the cost of getting Ch14.18 ready and giving it to you, so you or your insurance company may have to pay for this. Even though it is unlikely, there is a possibility that at some point the supply of Ch14.18 may run out. If this happens, your study doctor will talk with you. You may have to be taken off study.

Lenalidomide will be provided by the pharmaceutical company that makes this drug, and distributed by CTEPwhile you are taking part in this study. However they do not cover the cost of getting Lenalidomide ready and giving it to you, so you or your insurance company may have to pay for this.

The 13-cis-retinoic acid is a commercially available agent. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

The required and 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 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.

CONSENTS FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional. You may still participate in the study even if you do not agree to these tests.

13-cis-retinoic acid Pharmacokinetics:

Circle YES, if you agree to let researchers take blood to evaluate blood levels of 13-cis-retinoic acid. These are extra blood draws. The results of these tests will be confidential and not made available to you or your treating physician.

Circle NO, if you do not want researchers to take extra blood samples to evaluate blood evaluate blood levels of 13-cis-retinoic acid

YES NO

Signature

Participant: _____ Date: _____

Tumor Cell Quantification (Blood and Bone Marrow):

Circle YES, if you agree to let researchers take extra blood to evaluate a new test for blood (16mls) and bone marrow specimens (5ml from each side) to find tumor cells. The results of this new test, called 5-gene TaqMan® Low Density Array or TLDA.

Circle NO, if you do not want to let extra blood to evaluate a new test for blood and bone marrow specimens to find tumor cells.

YES NO

Signature

Participant: _____ Date: _____

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** days 1-7, 13-21	**Days 8-12 any course**	**Subsequent Courses**	**Off Therapy**
Physical Exam	X	Weekly	Daily	day 1, day 15	X
Blood Tests	X	Twice weekly	Daily	day 1, 15, 22	X
Urine tests (including Urine Catecholamines)	X	X (Day 15)		X (Day 15)	X
Pregnancy test	X	Weekly	Weekly (course 1 only)	X (may be done every 14 days)	X
Heart tests (echocardiogram and EKG)	X				X
Bone Marrow Aspirate/biopsy	X			X (disease evaluations end of course 2, 4, 6, 9 and 12/end of therapy)	X
CT, MRI and/or MIBG, PET scans	X			X (disease evaluations end of course 2, 4, 6, 9 and 12/end of therapy)	X
Blood Samples for Correlative Studies (required)		X		X (Course 2,4, 9 and 12/end of therapy))	X
Blood Samples for Correlative Studies (optional)		X		X	X
Bone Marrow Samples for Correlative Studies (optional)	X			X (disease evaluations end of course 2, 4, 6, 9 and 12/end of therapy)	X

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.

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16.0 SAMPLE ASSENT FORM

NANT N2011-04 : A Phase I Study of Lenalidomide and Anti-GD2 Mab Ch14.18 +/- Isotretinoin in Patients with Refractory/Recurrent Neuroblastoma. **NCI Protocol #**

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 **Lenalidomide, ch14.18 and 13-*cis*-retinoic acid (cisRA)** to see what effects (both good and bad) these medicines have on patients and their cancer. Lenalidomide is a medicine that is given by mouth as a pill (tablet). Ch14.18 is a medicine that is given into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm). **13-*cis*-retinoic acid (cisRA)** is a medicine that is given by mouth, usually as a pill (capsule) though it can be given a different way if you cannot swallow capsules. 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 cycles that each lasts 28 days. You will continue to receive cycles of this treatment for up to 12 courses (12 months) unless you have bad side effects or your tumor gets worse. These medicines work differently than some of the other medicines you have received. They help your body attack and kill the cancer cells.

   Lenalidomide:
   You will take Lenalidomide by mouth once a day for the first 21 days of every 28 day cycle. Some children will only take the Lenalidomide for 14 days. Your doctor will talk to you about when you take the medicine.

   Ch14.18:
   You will take the Ch14.18 by I.V. once a day on days 8-11 of every 28 day schedule. You will be in the hospital on those days.

   13-*cis*-retinoic acid (cisRA):
   You will take 13-*cis*-retinoic acid (cisRA) by mouth twice a day for the last 14 days of each 28 day cycle.

   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.
- To measure the amount of medicine in your blood, we will draw up to 21blood samples (about 15 tablespoons total) on days 1, 2, 7, 8, 11 and 22 first cycle of your treatment, and on days 1 and 11 on course 2, 4, 6, and 9. You may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples. If you have a central line, your doctor will be able to tell you if that can be used to draw these blood samples.

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 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.
   - 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. <u>Special study blood tests</u> :

    There is a request for extra special tests in this study. These are done solely for research purposes only. Neither you nor your doctor will know the results.

    #1 One blood sample (1-2 teaspoons) is needed on the last day of the first cycle of your treatment.

    - _____ Yes, it is okay to take an extra blood sample

- _____ No, it is not okay to take an extra blood sample

#2 Extra bone marrow (about one teaspoon) and extra blood samples(about 3 teaspoons) each time you have to have a bone marrow procedure to check on your neuroblastoma.

- _____ Yes, it is okay to take extra bone marrow and blood for research
- _____ No, it is not it is okay to take extra bone marrow and blood for research

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**