SAMPLE INFORMED CONSENT AND ASSENT DOCUMENTS

SAMPLE INFORMED CONSENT: PHASE I

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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

CONSENT FORM FOR PHASE I PORTION OF STUDY

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 invited 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 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 MLN8237, that can be given with irinotecan, and temozolomide without causing severe side effects.

To find out the side effects seen by giving MLN8237 at different dose levels with irinotecan, and temozolomide.

To measure the levels of MLN8237 and irinotecan in the blood at different dose levels

To determine if your tumor gets smaller after treatment with MLN8237, irinotecan, and temozolomide

To determine if specific gene changes makes you more prone to side effects from and/or response to the combination of MLN8237, irinotecan, and temozolomide

To determine if the amount of something in your tumor called MYCN or Aurora A makes you more likely to have a good response to the combination of MLN8237, irinotecan, and temozolomide

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

This study will combine an oral drug called MLN8237 with two chemotherapy medicines called irinotecan and temozolomide.
MLN8237 is an investigational drug that is not approved by the FDA. MLN8237 blocks the function of a protein that is important in the growth of cancer cells. This drug has been tested as a single-agent in children with relapsed solid tumors, including patients with neuroblastoma. In the laboratory, MLN8237 appears to make neuroblastoma tumors smaller. This effect is even greater when MLN8237 is combined with the chemotherapy drugs, irinotecan and temozolomide.

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

Giving MLN8237 together with irinotecan and temozolomide may increase the effectiveness of this combination. We first need to find out the highest dose of MLN8237 that can be given safely together with irinotecan and temozolomide. This study will be the first study to test giving MLN8237 together with irinotecan and temozolomide. Once we have found out the highest dose of MLN8237 that can be given with irinotecan and temozolomide, we will treat more patients with this combination to determine how effective it is.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 17 and 44 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 receive the treatment 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.

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>Bone marrow tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>Various scans*</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td></td>
</tr>
<tr>
<td>Urine tests</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

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. They are part of regular cancer care.

<table>
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Treatment Plan

The treatment will be given in cycles that each last 21 days. A diagram of one cycle is shown in the following figure.
You will receive irinotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 1 hour on days 1-5. This medicine is typically given in the clinic.

You will receive temozolomide by mouth once a day on days 1-5. The medicine is most commonly given as a capsule. If you have a hard time swallowing capsules, the medicine can also taken out of the capsule and swallowed with applesauce or apple juice. This medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive MLN8237 by mouth once a day on days 1-7. The medicine can only be given as a tablet. On days 1-5, this medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

When you join the study, you will be assigned a certain MLN8237 dose. This study will test up to four MLN8237 doses in groups of 3-6 patients. The starting MLN8237 dose for the first group of patients is about 40% lower than what is currently being given to patients receiving MLN8237 alone without bad side effects. If this is tolerated without serious side effects, then the MLN8237 dose will be increased ("dose escalation") in groups of 3-6 patients until serious side effects are seen. At that point, investigators will have found the highest dose of MLN8237 that can be given along with irinotecan and temozolomide without bad side effects. This part of the study is called the Phase I part of the study.

The doses of irinotecan and temozolomide are not increased during this study. The doses used are typical doses used to treat patients with neuroblastoma.

After the highest dose of MLN8237 that can be given with irinotecan and temozolomide has been found, another group of 8-20 patients will be treated with that highest dose to help determine how effective this combination is in treating neuroblastoma. This part of the study is called the Phase II part of the study.

You will only participate in the Phase I part of the study.

Depending on the side effects you have and/or the side effects other patients have had on this study, you may need to receive two other types of medicines to decrease the side effects of MLN8237, irinotecan, and temozolomide. The first type of medicine helps to boost your white blood cell count. White blood cells help fight infection and having low white blood cells can increase your risk of developing an infection. This type of medicine is called filgrastim or GCSF and is given once a day as a shot under the skin until the white blood cell count has increased to a safe level. This usually takes about 10 days for each cycle of chemotherapy. If your hospital uses a related medicine called pegfilgrastim, then you may need just one shot under the skin for each cycle of chemotherapy. The second type of medicine helps to prevent diarrhea. These medicines are antibiotics that you would take by mouth for about 10 days during each cycle. Your study doctor will pick between one medicine called cefixime which is given once a day and another medicine called cefpodoxime which is given twice a day.

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may
receive a different dose of MLN8237, your assigned dose of MLN8237 will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of MLN8237.

When you have finished treatment with MLN8237, irinotecan, and temozolomide

After you stop treatment with MLN8237, irinotecan and temozolomide, 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

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

Determining blood levels of MLN8237 and irinotecan

One of the main research goals of this study is to find out the amount of MLN8237 and irinotecan in the blood during this treatment. Since this is one of the main goals of the study you are required to submit extra blood samples in order to participate in the overall study.

On the first day of the first cycle of treatment, a small amount of blood (5 mL, or about a teaspoon) will be drawn. If you have a central line (such as a port or a Broviac), this sample can be drawn through that line. Otherwise, you will need to have blood drawn through a vein.

On the fourth day of the first cycle of treatment, a total of 36 mL (or a little more than 7 teaspoons) will be drawn over 24 hours. This schedule of blood draws is typically done as an outpatient. If you have a central line with only one lumen or tube and that lumen or tube is being used to give you the irinotecan, then you will need to have at least 6 of these blood samples drawn through a vein. Your study doctor may recommend placing an IV catheter or tube in one of your veins through which the blood can be drawn. This may reduce the number of pokes needed for this part of the study. If you have a central line with more than one lumen or tube, you may be able to have these blood samples drawn through one of the lumens or tubes that is not being used to give you the irinotecan. Your study doctor can tell you whether you will need some pokes or an IV catheter placed or whether your type of central line can be used to draw these samples.

This amount of blood is considered safe to donate over this amount of time. Samples will be sent to the Children's Hospital of Philadelphia in Philadelphia, PA and to the Mayo Clinic in Rochester, MN for testing.

Other Research Tests in this Study

You will be asked if you want to participate in optional research tests. This part of the study is 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. 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 optional studies.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

One part of the research goal is to look for genetic changes in normal blood cells of patients to see if these are related to how the liver handles MLN8237 and irinotecan, or whether you will have bad side effects after taking these drugs. We may also look to see if other genetic changes impact how likely a person is to respond to this drug combination. These tests are done on one sample of blood (one-two teaspoons, 5-10 mL) taken from your central line (or port) at the start of the first cycle of therapy. This
amount of blood is considered safe to donate. The blood will be sent to the Mayo Clinic in Rochester, MN for testing.

**Looking at Aurora A in neuroblastoma tumors**
MLN8237 blocks the action of a protein called Aurora A. Another research goal is to look at the amount of Aurora A in neuroblastoma tumors to find out if the amount of Aurora A impacts whether tumors respond to the combination of MLN8237, irinotecan, and temozolomide. These tests are done on stored neuroblastoma tissue from your previous tumor biopsies or surgeries. If you agree to participate in this optional part of the study, we will request that your hospital send us some of your stored neuroblastoma tissue. You will not need to have an extra biopsy or surgery to participate in this part of the study. The tissue will be sent to the University of California in San Francisco, CA.

**HOW LONG WILL I BE ON THIS STUDY?**

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse.

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. Researchers will be in contact with your primary care doctor to see how you are doing; 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 the 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.

**WHAT ARE THE RISKS OF THE STUDY?**

You will participate in the Phase 1 part of the 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.

In this study, researchers will be looking at side effects seen in patients taking different doses of MLN8237 together with irinotecan and temozolomide. Since subjects will be assigned to different doses of MLN8237, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many side effects go away soon after you stop taking MLN8237, irinotecan, and temozolomide, 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. Because this combination has never been given to children before, there may 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 side effects of MLN8237**

There is limited experience using MLN8237 in humans. The risks and side effects listed here and their frequencies are anticipated or predicted based on tests in animals and some experience in people. It is expected that MLN8237 toxicities will be reversible, however it is possible that MLN8237 will have their toxicities that have not been observed in or predicted from its evaluation in animal studies and the few studies in adults that have been conducted to date.
The frequency provided in the following table is approximate:

**Risks and side effects related to MLN8237 include those which are:**

<table>
<thead>
<tr>
<th>Likely (Anticipated in 21-100 children out of every 100)</th>
<th>Less Likely (Anticipated in 5 -20 children out of every 100)</th>
<th>Rare but Serious (Anticipated in &lt;5 children out of every 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fewer red blood cells in the blood*</td>
<td>• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics*</td>
<td>• Severe rash with redness and pain of the skin on the palms of the hands and soles of the feet.</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Pain in the abdomen (belly)</td>
<td>• Blistering of the skin.</td>
</tr>
<tr>
<td>• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)</td>
<td>• Constipation</td>
<td></td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Mouth pain</td>
<td></td>
</tr>
<tr>
<td>• Vomiting</td>
<td>• Chills</td>
<td></td>
</tr>
<tr>
<td>• A feeling of extreme tiredness not relieved by sleep</td>
<td>• Swelling caused by fluid build-up in the tissues of the arms and legs</td>
<td></td>
</tr>
<tr>
<td>• Low numbers of white blood cells* called lymphocytes and neutrophils/ granulocytes that may make it easier to get infections which may be life threatening</td>
<td>• Fever</td>
<td></td>
</tr>
<tr>
<td>• Fewer platelets in the blood*</td>
<td>• Infections including those caused by bacteria, virus, and fungus</td>
<td></td>
</tr>
<tr>
<td>• Loss of appetite</td>
<td>• Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage</td>
<td></td>
</tr>
<tr>
<td>• Sleepiness</td>
<td>• Increased levels of a chemical (creatinine) in the blood which could mean kidney damage</td>
<td></td>
</tr>
<tr>
<td>• Hair loss</td>
<td>• Excessive loss of water from the body</td>
<td></td>
</tr>
</tbody>
</table>

* If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

MLN8237 has a chemical structure that is similar to a group of drugs called benzodiazepines. These drugs may cause dependence and withdrawal symptoms. Therefore, there is a theoretical risk that MLN8237 could cause dependence and withdrawal symptoms, as well. It is possible that while taking this drug, you will feel changes in your mood such as a sense of euphoria (joy) or a feeling of unhappiness that could lead to depression and thoughts of hurting yourself. When stopping the drug, withdrawal
Symptoms could include: anxiety, restlessness, difficulty sleeping, tremors, rapid heart-beat, nausea and vomiting.

Since there is a possibility that this drug may cause sedation (or sleepiness), you should not drink alcoholic beverages, since alcohol can also cause sleepiness. If you feel sleepy while you are on this study, you should avoid driving or doing anything that may need your full alertness, such as operating dangerous tools or machinery. This drug may also cause sleepiness if you are currently taking an opiate such as morphine, dilaudid, or fentanyl.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

For more information about risks and side effects, ask your study doctor.

### Possible side effects of Temozolomide

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5 - 20 children out of 100)</th>
<th>Rare but serious (happens to &lt; 5 children out of 100)</th>
</tr>
</thead>
</table>
| • Fewer red and white blood cells and platelets in the blood.  
• Nausea  
• Vomiting  
• Constipation  
• Loss of appetite | • Diarrhea  
• Headache  
• Tiredness  
• Rash  
• Itching  
• Increased need to urinate  
• Urinary Tract Infections  
• Mouth sores  
• Fluid buildup in legs and arms  
• Hair loss  
• Elevation in the blood of certain enzymes found in the liver  
• Pain in the abdomen | • Convulsions  
• Difficulty swallowing  
• Dizziness  
• Anxiety or depression  
• Difficulty sleeping  
• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever  
• Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening  
• Partial paralysis or weakness of one side of the body  
• Loss of memory  
• Blood clots which may be life-threatening  
• Visual disturbances that may cause double vision  
• Forgetfulness or confusion  
• Aches and pains in muscles  
• A new cancer or leukemia resulting from this treatment |

### Possible side effects of Irinotecan

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5 - 20 children out of 100)</th>
<th>Rare but serious (happens to &lt; 5 children out of 100)</th>
</tr>
</thead>
</table>
| • Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, | • Fewer red blood cells and platelets in the blood.  
• Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which | • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate  
• Severe loss of water from the body (dehydration) which if untreated may |
flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light. Loss of body water
• Nausea and Vomiting
• Loss of appetite
• Fewer white blood cells
• Fever
• A feeling of weakness and tiredness
• Temporary hair loss
• Elevation of liver and bone enzymes in the blood and of bilirubin (yellow pigment formed in the liver)
• An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions.

could cause excessive loss of water and salts from the body
• Constipation
• Pain at the injection site
• A slow heart beat
• Low blood pressure
• Shortness of breath with cough
• Rash
• Inflammation and/or sores in the mouth, throat and/or esophagus
• Headache
• An upset stomach
• Confusion or Sleepiness
• Infections

cause low blood pressure and severe loss of salts such as and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening
• Inflammation of the lungs which could lead to chest pain and shortness of breath and which may be life-threatening
• Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain
• Blood clots which may be in rare cases life threatening*

• Skin inflammation
• Trembling
• Blood in the urine
• Mildly increased level of protein and glucose in the urine
• Low amount of protein in the blood
• Mouth sores
• Sensation of warmth on face.
• Risk to the unborn child in pregnant patients.**

* This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

** Birth defects and other serious abnormalities in the unborn baby have been noted with irinotecan in animal studies at doses similar to or less than those used in humans. The timing and frequency of these effects is as yet unknown. These may include multiple birth defects and abnormalities of bone formation, small size of baby at birth and increased risk of death of the unborn baby. Irinotecan is excreted in rat milk but this is unknown for humans.

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

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

### Neupogen (Filgrastim) Toxicity :

<table>
<thead>
<tr>
<th>Likely</th>
<th>Less Likely</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>(happens to 21-100 children out every 100 children)</td>
<td>(happens to 5-20 children out every 100 children)</td>
<td>(happens to &lt; 5 children out every 100 children)</td>
</tr>
</tbody>
</table>

- Aching or pain in bones.
- Local irritation at the site of the injection.
- Headache
- Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage.

- Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration.
- If you are known to have sickle cell disease, this drug may
• A low number of platelets in the blood.
• Low fever
• Enlargement of the spleen which may cause pain in the abdomen or left shoulder.
• Worsening of skin rashes
• Inflammation of a blood vessel in the skin leading to a raised purple rash and bruising.
• Higher than normal white blood count.

Neulasta (Pegfilgrastim) Toxicity:

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

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

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5-20 children out of 100)</th>
<th>Rare (happens to less than 5 children out of 100)</th>
</tr>
</thead>
</table>
| • Diarrhea  
• Belly pain  
• Nausea  
• Vomiting  
• Indigestion | • Headache  
• Dizziness  
• Seizures  
• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate  
• Low number of white blood cells in the blood  
• Increase in the blood of a type of white blood cells called eosinophils, which are sometimes associated with allergic reactions  
• Decrease in platelets which may make you bruise or bleed easily.  
• Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,  
• High blood tests of kidney and liver function  
• Hepatitis, yellowing of skin and whites of eyes  
• Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin | |

### Possible side effects of Cefpodoxime (Vantin-R)

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5-20 children out of 100)</th>
<th>Rare (happens to less than 5 children out of 100)</th>
</tr>
</thead>
</table>
| • Diarrhea  
• Diaper rash | • Belly pain  
• Nausea and vomiting,  
• Headache  
• Seizures  
• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate  
• Chest pain  
• Decrease in white blood cells, platelets and red blood cells:  
• Increase in the blood of a type of white blood cells called eosinophils, which are sometimes associated with allergic reactions  
• Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,  
• High blood tests for liver and kidney function  
• Hepatitis, yellowing of skin and whites of eyes  
• Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin  
• Change in blood tests showing decreased ability of the blood to form a clot.  
• Vaginal infection  
• Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin | |
Possible risks to unborn child and nursing child
Patients who agree to participate in this study should not become pregnant or breast feed 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 use abstinence and/or an effective method of contraception that is medically appropriate based on your personal doctor’s recommendation at that time. Male subjects must agree to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of MLN8237.

If you or your partner becomes pregnant while you are participating in this study, please notify your study doctor immediately. For more information about risks and side effects, ask your study doctor.

Possible long term side effects of this treatment
- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

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. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

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 chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No 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:
- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Childrens Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- 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.
- Millennium Pharmaceuticals (supplier of MLN8237)

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/clinic charges, and doctors’ fees related to your participation in this study. Irinotecan and temozolomide are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

MLN8237 will be provided by Millennium Pharmaceuticals, the company that makes this drug. They will provide the drug at no cost to you. A continuing supply of the drug cannot be guaranteed. If there is a problem getting MLN8237, your study doctor will talk with you about possible options. If, during the study, MLN8237 becomes approved for use in your cancer, you and/or your health plan may have to pay for MLN8237 needed to complete this study.

The pharmacokinetic studies will be done at no cost to you. The optional tests looking at tumor Aurora A and at gene changes involved in breaking down MLN8237 and irinotecan will be done at no cost to you if you agree to participate in these optional tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw 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/clinic, car fare, travel to and from the hospital/clinic, parking, and babysitter fees.

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/

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 test is required during the phase I portion of this study. You may not participate in this portion of the study if you do not agree to these tests.

Determining blood levels of MLN8237 and irinotecan

Initial next to YES if you agree to let researchers take blood to study blood levels of MLN8237 and irinotecan. These are extra blood draws that may require blood draws (pokes) or intravenous (IV) catheter placement. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO if you do not want researchers to take extra blood samples to study blood levels of MLN8237 and irinotecan. You will not be able to participate in this portion of the study.

Patient    _______YES  ______NO
Parent/Legal Guardian  _______YES  ______NO

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

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan. This is one extra blood sample and it can be taken from a central line (such as port or Broviac). The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take an extra blood sample to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan.

Patient    _______YES  ______NO
Parent/Legal Guardian  _______YES  ______NO
The following test is optional. You may still participate in the study even if you do not agree to these tests.

**Looking at Aurora A in neuroblastoma tumors**

Initial next to YES, if you agree to let researchers request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor.

Patient    _____YES    _____NO

Parent/Legal Guardian    _____YES    _____NO

**STATEMENT OF CONSENT**

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____________________________________
Patient Name

_____________________________________
Signature of Parent or Guardian      Date

_____________________________________
Signature of Parent or Guardian      Date

_____________________________________
Signature of Patient (If > 7 years old)      Date

_____________________________________
Signature of Physician or
Responsible Investigator

_____________________________________
Signature of Witness      Date

_____________________________________
Signature of Translator
(If applicable)      Date
Consent Addendum 1: Tests that will be done on this study.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Before Entry</th>
<th>Cycle 1</th>
<th>Cycles 2-34</th>
<th>End of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td>Weekly</td>
<td>Start of each cycle</td>
<td>X</td>
</tr>
<tr>
<td>Blood tests</td>
<td>X</td>
<td>Twice weekly</td>
<td>Weekly</td>
<td>X</td>
</tr>
<tr>
<td>Urine tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bone marrow tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor scans (CT scan, MRI scan, and/or MIBG scan)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood for drug level tests</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submission of stored tumor tissue*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood to check for gene change involved in breaking down MLN8237 and irinotecan*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Optional

Consent Addendum #2

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.
SAMPLE ASSENT FORM-PHASE I

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR
[Insert Name of Investigator]
[Insert Name of Institution]
[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. My name is ____________________________.

2. You have a kind of cancer called 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 MLN8237, irinotecan, and temozolomide to see what effects (both good and bad) these medicines have on patients and their cancer. MLN8237 is a medicine that is given by mouth as a pill (tablet). Irinotecan 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). Temozolomide 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 21 days. You will only get the medicine during the first 7 days of each cycle. You will continue to receive cycles of this treatment for up to 2 years unless you have bad side effects or your tumor gets worse.

   **MLN8237:**
   You will take MLN8237 by mouth once a day for the first 7 days every 21-day cycle.

   **Irinotecan:**
   You will take Irinotecan by I.V. once a day for the first 5 days every 21 day cycle.

   **Temozolomide:**
   You will take Temozolomide by mouth once a day for the first 5 days every 21-day cycle.

   **Other medicines (not chemotherapy):**
   You may need to take other medicines to help you with side effects of the three chemotherapy medicines above. These medicines may include Neupogen (given once a day as an injection) or Neulasta (give each cycle as an injection) to help your normal blood cells get better after chemotherapy. To help with diarrhea, you may also take either Cefixime (once per day) or Cefpodoxime (twice each day) by mouth for ten days during each cycle of chemotherapy.

   **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 may have to come to the clinic to have blood and platelet transfusions when the blood counts are low or stay in the hospital if you have a fever with low blood counts.
• 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 9 blood samples (about 8 teaspoons total) on day 1 and day 4 during the first cycle of your treatment. 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 bloods.

**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 have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection. You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
   • You may get sores in your mouth that make it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
   • You may get diarrhea.
   • The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing.
   • You could get a different kind of cancer, this doesn't happen often, but can happen years later.
   • It is possible that you could die from the treatment or cancer.

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

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

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

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

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

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

10. **Special study blood tests:**
    There are 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 day 1 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** Your stored neuroblastoma tissue sample will be used for research purposes in this study.
• ______ Yes, it is okay to use my stored neuroblastoma tissue sample
• ______ No, it is not okay to use my stored neuroblastoma tissue sample

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.
SAMPLE INFORMED CONSENT: PHASE II

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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

CONSENT FORM FOR PHASE II PORTION OF STUDY

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 invited 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 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 continue to look at the side effects seen by giving MLN8237 with irinotecan, and temozolomide.
To determine if your tumor gets smaller after treatment with MLN8237, irinotecan, and temozolomide.
To measure the levels of MLN8237 and irinotecan in the blood at different dose levels.
To determine if specific gene changes makes you more prone to side effects from and/or response to the combination of MLN8237, irinotecan, and temozolomide.
To determine if the amount of something in your tumor called MYCN or Aurora A makes you more likely to have a good response to the combination of MLN8237, irinotecan, and temozolomide.

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

This study will combine an oral drug called MLN8237 with two chemotherapy medicines called irinotecan and temozolomide.

MLN8237 is an investigational drug that is not approved by the FDA. MLN8237 blocks the function of a protein that is important in the growth of cancer cells. This drug has been tested as a single-agent in children with relapsed solid tumors, including patients with neuroblastoma. In the laboratory, MLN8237 appears to make neuroblastoma tumors smaller. This effect is even greater when MLN8237 is combined with the chemotherapy drugs, irinotecan and temozolomide.

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

Giving MLN8237 together with irinotecan and temozolomide may increase the effectiveness of this combination.
HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 17 and 44 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 receive the treatment 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.

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>Bone marrow tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>Various scans*</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td></td>
</tr>
<tr>
<td>Urine tests</td>
<td></td>
</tr>
</tbody>
</table>

# 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.

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. They are part of regular cancer care.

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>Bone marrow tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
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</tr>
<tr>
<td>Pregnancy test</td>
<td></td>
</tr>
<tr>
<td>Urine tests</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Plan
The treatment will be given in cycles that each last 21 days. A diagram of one cycle is shown in the following figure.

<table>
<thead>
<tr>
<th>Day: 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 → 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ir</td>
<td>Ir</td>
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<td>M</td>
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<td>M</td>
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<td>M</td>
<td></td>
</tr>
</tbody>
</table>

Ir = Irinotecan given into the bloodstream on days 1-5
T = Temozolomide given by mouth on days 1-5
M = MLN8237 given by mouth on days 1-7

Disease evaluation after cycles 2, 4, 8, and then every 4 cycles

You will receive irinotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 1 hour on days 1-5. This medicine is typically given in the clinic.
You will receive temozolomide by mouth once a day on days 1-5. The medicine is most commonly given as a capsule. If you have a hard time swallowing capsules, the medicine can also taken out of the capsule and swallowed with applesauce or apple juice. This medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive MLN8237 by mouth once a day on days 1-7. The medicine can only be given as a tablet. On days 1-5, this medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

When you join the study, you will be assigned a certain MLN8237 dose. This dose will be given to all patients entering this part of the study, as it was determined in the first part of the study (phase I portion) to be the highest dose of MLN8237 that can be given along with irinotecan and temozolomide without bad side effects. This part of the study is called the Phase II part of the study.

The doses of irinotecan and temozolomide are not increased during this study. The doses used are typical doses used to treat patients with neuroblastoma.

Depending on the side effects you have and/or the side effects other patients have had on this study, you may need to receive two other types of medicines to decrease the side effects of MLN8237, irinotecan, and temozolomide. The first type of medicine helps to boost your white blood cell count. White blood cells help fight infection and having low white blood cells can increase your risk of developing an infection. This type of medicine is called filgrastim or GCSF and is given once a day as a shot under the skin until the white blood cell count has increased to a safe level. This usually takes about 10 days for each cycle of chemotherapy. If your hospital uses a related medicine called pegfilgrastim, then you may need just one shot under the skin for each cycle of chemotherapy. The second type of medicine helps to prevent diarrhea. These medicines are antibiotics that you would take by mouth for about 10 days during each cycle. Your study doctor will pick between one medicine called cefixime which is given once a day and another medicine called cefpodoxime which is given twice a day.

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may have received a different dose of MLN8237, your assigned dose of MLN8237 will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of MLN8237.

When you have finished treatment with MLN8237, irinotecan, and temozolomide

After you stop treatment with MLN8237, irinotecan and temozolomide, 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

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

Optional Research Studies
You will be asked if you want to participate in optional research tests. This part of the study is 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. 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 optional studies.
Determining blood levels of MLN8237 and irinotecan

One of the research goals of this study is to find out the amount of MLN8237 and irinotecan in the blood during this treatment. Participating in this portion of the study is optional for patients in this phase II part of the study.

On the first day of the first cycle of treatment, a small amount of blood (5 mL, or about a teaspoon) will be drawn. If you have a central line (such as a port or a Broviac), this sample can be drawn through that line. Otherwise, you will need to have blood drawn through a vein.

On the fourth day of the first cycle of treatment, a total of 36 mL (or a little more than 7 teaspoons) will be drawn over 24 hours. This schedule of blood draws is typically done as an outpatient. If you have a central line with only one lumen or tube and that lumen or tube is being used to give you the irinotecan, then you will need to have at least 6 of these blood samples drawn through a vein. Your study doctor may recommend placing an IV catheter or tube in one of your veins through which the blood can be drawn. This may reduce the number of pokes needed for this part of the study. If you have a central line with more than one lumen or tube, you may be able to have these blood samples drawn through one of the lumens or tubes that is not being used to give you the irinotecan. Your study doctor can tell you whether you will need some pokes or an IV catheter placed or whether your type of central line can be used to draw these samples.

This amount of blood is considered safe to donate over this amount of time. Samples will be sent to the Children’s Hospital of Philadelphia in Philadelphia, PA and to the Mayo Clinic in Rochester, MN for testing.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Another research goal is to look for genetic changes in normal blood cells of patients to see if these are related to how the liver handles MLN8237 and irinotecan, or whether you will have bad side effects after taking these drugs. We may also look to see if other genetic changes impact how likely a person is to respond to this drug combination. These tests are done on one sample of blood (one-two teaspoons, 5-10 mL) taken from your central line (or port) at the start of the first cycle of therapy. This amount of blood is considered safe to donate. The blood will be sent to the Mayo Clinic in Rochester, MN for testing.

Looking at Aurora A in neuroblastoma tumors

MLN8237 blocks the action of a protein called Aurora A. Another research goal is to look at the amount of Aurora A in neuroblastoma tumors to find out if the amount of Aurora A impacts whether tumors respond to the combination of MLN8237, irinotecan, and temozolomide. These tests are done on stored neuroblastoma tissue from your previous tumor biopsies or surgeries. If you agree to participate in this optional part of the study, we will request that your hospital send us some of your stored neuroblastoma tissue. You will not need to have an extra biopsy or surgery to participate in this part of the study. The tissue will be sent to the University of California in San Francisco, CA.

HOW LONG WILL I BE ON THIS STUDY?

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse.

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. Researchers will be in contact with your primary care doctor to see how you are doing; 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 the 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.

WHAT ARE THE RISKS OF THE STUDY?

You may have side effects while on the study. 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 and some patients may have very serious side effects and could die as a result of these side effects.

In the first part of this study, researchers looked at side effects seen in patients taking different doses of MLN8237 together with irinotecan and temozolomide. The dose of MLN you will receive was based on the experience of the first portion of the study that has already been shown to be tolerated without bad side effects in several children with neuroblastoma. Your dose will not change with later courses of treatment, unless it needs to be decreased due to side effects.

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 MLN8237, irinotecan, and temozolomide, 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. Although this combination has been given to children in the first part of this study, there may 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 side effects of MLN8237

There is limited experience using MLN8237 in humans. The risks and side effects listed here and their frequencies are anticipated or predicted based on tests in animals and some experience in people. It is expected that MLN8237 toxicities will be reversible, however it is possible that MLN8237 will have their toxicities that have not been observed in or predicted from its evaluation in animal studies and the few studies in adults that have been conducted to date.

The frequency provided in the following table is approximate:

### Risks and side effects related to MLN8237 include those which are:

<table>
<thead>
<tr>
<th>Likely (Anticipated in 21-100 children out of every 100)</th>
<th>Less Likely (Anticipated in 5-20 children out of every 100)</th>
<th>Rare but Serious (Anticipated in &lt;5 children out of every 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fewer red blood cells in the blood*</td>
<td>• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics*</td>
<td>• Severe rash with redness and pain of the skin on the palms of the hands and soles of the feet.</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Pain in the abdomen (belly)</td>
<td>• Blistering of the skin.</td>
</tr>
<tr>
<td>• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)</td>
<td>• Constipation</td>
<td></td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Mouth pain</td>
<td></td>
</tr>
<tr>
<td>• Vomiting</td>
<td>• Chills</td>
<td></td>
</tr>
<tr>
<td>• A feeling of extreme tiredness not relieved by</td>
<td>• Swelling caused by fluid build-up in the tissues of the arms and legs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fever</td>
<td></td>
</tr>
</tbody>
</table>
sleep
- Low numbers of white blood cells* called lymphocytes and neutrophils/granulocytes that may make it easier to get infections which may be life threatening
- Fewer platelets in the blood*
- Loss of appetite
- Sleepiness
- Hair loss

Infections including those caused by bacteria, virus, and fungus
- Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage
- Increased levels of a chemical (creatinine) in the blood which could mean kidney damage
- Excessive loss of water from the body
- Back pain
- Dizziness
- Cough
- Shortness of breath
- Low blood pressure

* If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

MLN8237 has a chemical structure that is similar to a group of drugs called benzodiazepines. These drugs may cause dependence and withdrawal symptoms. Therefore, there is a theoretical risk that MLN8237 could cause dependence and withdrawal symptoms, as well. It is possible that while taking this drug, you will feel changes in your mood such as a sense of euphoria (joy) or a feeling of unhappiness that could lead to depression and thoughts of hurting yourself. When stopping the drug, withdrawal symptoms could include: anxiety, restlessness, difficulty sleeping, tremors, rapid heart-beat, nausea and vomiting.

Since there is a possibility that this drug may cause sedation (or sleepiness), you should not drink alcoholic beverages, since alcohol can also cause sleepiness. If you feel sleepy while you are on this study, you should avoid driving or doing anything that may need your full alertness, such as operating dangerous tools or machinery. This drug may also cause sleepiness if you are currently taking an opiate such as morphine, dilaudid, or fentanyl.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

For more information about risks and side effects, ask your study doctor.
### Possible side effects of Temozolomide

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5 - 20 children out of 100)</th>
<th>Rare but serious (happens to &lt; 5 children out of 100)</th>
</tr>
</thead>
</table>
| • Fewer red and white blood cells and platelets in the blood.  
• Nausea  
• Vomiting  
• Constipation  
• Loss of appetite | • Diarrhea  
• Headache  
• Tiredness  
• Rash  
• Itching  
• Increased need to urinate  
• Urinary Tract Infections  
• Mouth sores  
• Fluid buildup in legs and arms  
• Hair loss  
• Elevation in the blood of certain enzymes found in the liver  
• Pain in the abdomen | • Convulsions  
• Difficulty swallowing  
• Dizziness  
• Anxiety or depression  
• Difficulty sleeping  
• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills, and fever  
• Low numbers of white blood cells that may last a long time and make it easier to get infections which may be life-threatening  
• Partial paralysis or weakness of one side of the body  
• Loss of memory  
• Blood clots which may be life-threatening  
• Visual disturbances that may cause double vision  
• Forgetfulness or confusion  
• Aches and pains in muscles  
• A new cancer or leukemia resulting from this treatment |

### Possible side effects of Irinotecan

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5 - 20 children out of 100)</th>
<th>Rare but serious (happens to &lt; 5 children out of 100)</th>
</tr>
</thead>
</table>
| • Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light.  
Loss of body water  
• Nausea and Vomiting  
• Loss of appetite  
• Fewer white blood cells  
• Fever  
• A feeling of weakness and tiredness  
• Temporary hair loss  
• Elevation of liver and bone | • Fewer red blood cells and platelets in the blood.  
• Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body  
• Constipation  
• Pain at the injection site  
• A slow heart beat  
• Low blood pressure  
• Shortness of breath with cough  
• Rash  
• Inflammation and/or sores in the mouth, throat and/or esophagus  
• Headache | • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate  
• Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening  
• Inflammation of the lungs which could lead to chest pain and shortness of breath  
• Inflammation and/or sores in the mouth, throat and/or esophagus  
• Headache  
• Difficulty swallowing  
• Dizziness  
• Anxiety or depression  
• Difficulty sleeping  
• Low numbers of white blood cells that may last a long time and make it easier to get infections which may be life-threatening  
• Partial paralysis or weakness of one side of the body  
• Loss of memory  
• Blood clots which may be life-threatening  
• Visual disturbances that may cause double vision  
• Forgetfulness or confusion  
• Aches and pains in muscles  
• A new cancer or leukemia resulting from this treatment |
<table>
<thead>
<tr>
<th>Enzymes in the blood and of bilirubin (yellow pigment formed in the liver)</th>
<th>An upset stomach</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions.</td>
<td>• An upset stomach</td>
<td>• Confusion or Sleepiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infections</td>
</tr>
</tbody>
</table>

- Skin inflammation
- Trembling
- Blood in the urine
- Mildly increased level of protein and glucose in the urine
- Low amount of protein in the blood
  - Mouth sores
  - Sensation of warmth on face.
  - Risk to the unborn child in pregnant patients.

* This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

** Birth defects and other serious abnormalities in the unborn baby have been noted with irinotecan in animal studies at doses similar to or less than those used in humans. The timing and frequency of these effects is as yet unknown. These may include multiple birth defects and abnormalities of bone formation, small size of baby at birth and increased risk of death of the unborn baby. Irinotecan is excreted in rat milk but this is unknown for humans.
**Possible side effects of G-CSF (such as Neupogen, filgrastim or Neulasta, Pegfilgrastim)**

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

**Neupogen (Filgrastim) Toxicity:**

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


### Neulasta (Pegfilgrastim) Toxicity:

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out every 100 children)</th>
<th>Less Likely (happens to 5-20 children out every 100 children)</th>
<th>Rare (happens to &lt; 5 children out every 100 children)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aching or pain in bones.</td>
<td>• Local irritation at the site of the injection.</td>
<td>• Low grade fever</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
<td>• Allergic reactions which can be life threatening</td>
</tr>
<tr>
<td></td>
<td>• Higher than normal levels in the blood of uric acid and</td>
<td>with shortness of breath, low blood pressure, rapid</td>
</tr>
<tr>
<td></td>
<td>liver enzymes which may indicate liver irritation or</td>
<td>heart rate, hives, facial swelling. This reaction is</td>
</tr>
<tr>
<td></td>
<td>damage.</td>
<td>very rare and has been associated mainly with</td>
</tr>
<tr>
<td></td>
<td>• A low number of platelets in the blood.</td>
<td>intravenous administration.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5-20 children out of 100)</th>
<th>Rare (happens to less than 5 children out of 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diarrhea</td>
<td>• Headache</td>
<td>• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate</td>
</tr>
<tr>
<td>• Belly pain</td>
<td>• Dizziness</td>
<td>• Low number of white blood cells in the blood</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Seizures</td>
<td>• Increase in the blood of a type of white blood cells called eosinophils, which are sometimes associated with allergic reactions</td>
</tr>
<tr>
<td>• vomiting</td>
<td></td>
<td>• Decrease in platelets which may make you bruise or bleed easily.</td>
</tr>
<tr>
<td>• Indigestion</td>
<td></td>
<td>• Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High blood tests of kidney and liver function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatitis, yellowing of skin and whites of eyes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin</td>
</tr>
</tbody>
</table>
**Possible side effects of Cefpodoxime (Vantin-R)**

<table>
<thead>
<tr>
<th>Likely (happens to 21-100 children out of 100)</th>
<th>Less Likely (happens to 5-20 children out of 100)</th>
<th>Rare (happens to less than 5 children out of 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diarrhea</td>
<td>• Belly pain</td>
<td>• Diaper rash</td>
</tr>
<tr>
<td>• Diaper rash</td>
<td>• Nausea and vomiting,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chest pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Decrease in white blood cells, platelets and red blood cells:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase in the blood of a type of white blood cells called eosinophils, which are sometimes associated with allergic reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High blood tests for liver and kidney function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hepatitis, yellowing of skin and whites of eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Change in blood tests showing decreased ability of the blood to form a clot.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vaginal infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin</td>
<td></td>
</tr>
</tbody>
</table>

**Possible risks to unborn child and nursing child**

Patients who agree to participate in this study should not become pregnant or breast feed 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 use abstinence and/or an effective method of contraception that is medically appropriate based on your personal doctor’s recommendation at that time. Male subjects must agree to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of MLN8237.
If you or your partner becomes pregnant while you are participating in this study, please notify your study doctor immediately. For more information about risks and side effects, ask your study doctor.

Possible long term side effects of this treatment
- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

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. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

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 chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No 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:
- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Childrens Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- 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.
- Millennium Pharmaceuticals (supplier of MLN8237)

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/clinic charges, and doctors’ fees related to your participation in this study.
Irinotecan and temozolomide are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

MLN8237 will be provided by Millennium Pharmaceuticals, the company that makes this drug. They will provide the drug at no cost to you. A continuing supply of the drug cannot be guaranteed. If there is a problem getting MLN8237, your study doctor will talk with you about possible options. If, during the study,
MLN8237 becomes approved for use in your cancer, you and/or your health plan may have to pay for MLN8237 needed to complete this study.

The pharmacokinetic studies will be done at no cost to you. The optional tests looking at tumor Aurora A and at gene changes involved in breaking down MLN8237 and irinotecan will be done at no cost to you if you agree to participate in these optional tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw 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/clinic, car fare, travel to and from the hospital/clinic, parking, and baby sitter fees.

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 your legal rights to seek payment by signing this form.

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

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [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/

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 test is optional. You may still participate in the study even if you do not agree to these tests.

Determining blood levels of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study blood levels of MLN8237 and irinotecan. These are extra blood draws that may require blood draws (pokes) or intravenous (IV) catheter placement. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take extra blood samples to study blood levels of MLN8237 and irinotecan.

Patient _______YES _______NO
Parent/Legal Guardian _______YES _______NO

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

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan. This is one extra blood sample and it can be taken from a central line (such as port or Broviac). The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take an extra blood sample to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan.

Patient _______YES _______NO
Parent/Legal Guardian _______YES _______NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.
Looking at Aurora A in neuroblastoma tumors

Initial next to YES, if you agree to let researchers request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor.

Patient    ______YES    ______NO

Parent/Legal Guardian    ______YES    ______NO

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____________________________
Patient Name

_____________________________          /   /   
Signature of Parent or Guardian   Date

_____________________________          /   /   
Signature of Parent or Guardian   Date

_____________________________          /   /   
Signature of Patient (If > 7 years old)   Date

_____________________________          /   /   
Signature of Physician or Responsible Investigator   Date

_____________________________          /   /   
Signature of Witness   Date

_____________________________          /   /   
Signature of Translator (If applicable)   Date
**Consent Addendum 1: Tests that will be done on this study.**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Before Entry</th>
<th>Cycle 1</th>
<th>Cycles 2-34</th>
<th>End of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td>Weekly</td>
<td>Start of each cycle</td>
<td>X</td>
</tr>
<tr>
<td>Blood tests</td>
<td>X</td>
<td>Twice weekly</td>
<td>Weekly</td>
<td>X</td>
</tr>
<tr>
<td>Urine tests</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bone marrow tests</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor scans (CT scan, MRI scan, and/or MIBG scan)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood for drug level tests*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submission of stored tumor tissue*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood to check for gene change involved in breaking down MLN8237 and irinotecan*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Optional

**CONSENT ADDENDUM #2**

**Certificate of Confidentiality Information**

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.
SAMPLE ASSENT FORM-Phase II

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

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

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

1. My name is ____________________________.

2. You have a kind of cancer called **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 **MLN8237**, **irinotecan**, and **temozolomide** to see what effects (both good and bad) these medicines have on patients and their cancer. MLN8237 is a medicine that is given by mouth as a pill (tablet). Irinotecan 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). Temozolomide 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 21 days. You will only get the medicine during the first 7 days of each cycle. You will continue to receive cycles of this treatment for up to 2 years unless you have bad side effects or your tumor gets worse.

   **MLN8237:**
   You will take MLN8237 by mouth once a day for the first 7 days every 21-day cycle.

   **Irinotecan:**
   You will take Irinotecan by I.V. once a day for the first 5 days every 21 day cycle.

   **Temozolomide:**
   You will take Temozolomide by mouth once a day for the first 5 days every 21-day cycle.

   **Other medicines (not chemotherapy):**
   You may need to take other medicines to help you with side effects of the three chemotherapy medicines above. These medicines may include Neupogen (given once a day as an injection) or Neulasta (give each cycle as an injection) to help your normal blood cells get better after chemotherapy. To help with diarrhea, you may also take either Cefixime (once per day) or Cefpodoxime (twice each day) by mouth for ten days during each cycle of chemotherapy.

   **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 may have to come to the clinic to have blood and platelet transfusions when the blood counts are low or stay in the hospital if you have a fever with low blood counts.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.

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

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

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

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

1. 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.

2. 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.

3. 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.

4. 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: ____________________.

5. **Special study blood tests:**

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

   **#1** Nine blood samples (about 8 teaspoons total) on day 1 and day 4 during the first cycle of your treatment.
   - ______ Yes, it is okay to take an extra blood samples
   - ______ No, it is not okay to take an extra blood samples

   **#2** One blood sample (1-2 teaspoons) is needed on day 1 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

#3 Your stored neuroblastoma tissue sample will be used for research purposes in this study.
•  ________ Yes, it is okay to use my stored neuroblastoma tissue sample
•  ________ No, it is not okay to use my stored neuroblastoma tissue sample

6. 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