Study: NANT 2015-01

Neuroblastoma Precision Trial

Protocol Title:
Neuroblastoma Precision Trial

Study Chair: Shahab Asgharzadeh, MD Childrens Hospital Los Angeles
Study Vice-Chair: Kelly Goldsmith, MD Children's Healthcare of Atlanta

What is this study about:

This is a biology research study where research is performed on tumor cells and normal cells in samples that are collected from you. This research study will test for genetic and immunologic changes (called biomarkers) in tissues of your body where relapsed or refractory neuroblastoma tumors are present. Learning more about these genetic and immunologic changes in relapsed or refractory neuroblastoma tumors may help doctors use or tailor current therapies based on these changes as well as develop better therapies for neuroblastoma in the future. Tumor tissue obtained after relapse along with a sample of your blood will be used to identify specific genetic and immunologic changes that may be present in your tumor. Reports of the changes found in your tumor will be provided to you and your doctor. In some cases, this information may help you plan a cancer treatment that may potentially be more effective for your tumor. It is not the intent of this study to tell you what drugs you should take based on the reported findings but to provide information about the clinical trials available that may match certain genetic and immunologic changes in your tumor. The final decision whether to use this information in treatment planning is for you and your doctor to make. The main purpose of this study is to gather information about the genetic and immunologic make-up of relapsed or refractory neuroblastoma tumors and to understand the best ways to obtain tumor tissue for such evaluations. While the study attempts to provide this information back to you, we may not always be successful if the tissue samples do not have enough tumor cells or don't meet the quality requirements established for successful testing.

Why is this study being done:

- To perform genetic mutation and immunologic biomarker analyses on neuroblastoma tumor cells from tumor tissue, or bone or bone marrow and blood and count how many times these analyses can be performed successfully.

- To determine how often these tests can identify genetic and immunological changes in tumors of patients with relapsed or refractory neuroblastoma that fall into 4 sub-groups of known changes seen in neuroblastoma tumors.

- To determine how often this testing identifies genetic and immunological changes where a drug is available in the clinic that can act on that change (known as an actionable target).

- To evaluate if the researchers can obtain genetic testing results from very small amounts of tumor found in the bone marrow aspirate (liquid part of marrow) after isolating tumor cells; a process called enrichment.

- To evaluate how the relapsed tumor cells are different from tumor that was obtained at diagnosis or prior to relapse and, if applicable, to evaluate for differences in genetic changes of relapsed/refractory tumors obtained from different body sites (soft tissue, bone or bone marrow).

- To evaluate if the small amount of tumor genetic material floating in the blood can identify the same genetic changes that we identify in your tumor tissue sent for analysis.

- To document any treatments you receive for one year after the NANT Precision report is created and given to you and your doctor.

Criteria that need to be met to participate in this study:

- Patients must be at least 12 months old and ≤ 30 years of age.

- Patients must have high risk neuroblastoma and have a response to prior therapy that fits into at least one of the following categories:
    - Relapsed or progressive disease at any time before study enrollment.
    - Refractory disease: patients had "no response" and still have persistent sites of disease after receiving a minimum of 4 cycles of induction treatment and have never had a disease relapse or progression.
    - Persistent disease: patients had a "partial response" and still have persistent sites of disease after receiving a minimum of 4 cycles of induction treatment and have never had a disease relapse or progression.

- Patients must be willing undergo a clinically indicated biopsy and meet at least one of the following criteria:
    - For bone biopsy: MIBG avid or FDG-PET avid (if MIBG non-avid tumor) bone site WITH corresponding anatomical imaging on CT or MRI consistent with a bone metastasis at that site.
    - For soft tissue biopsy: Measurable soft tissue lesion on CT or MRI with MIBG or FDG-PET that is MIBG or FDG-PET avid.
    - For Bone Marrow Biopsy: Suspected bone marrow disease.

- Patients enrolling on study with Refractory or Relapsed disease may submit previously collected tumor specimens if they were obtained after the patient was confirmed to have relapsed/refractory disease and the specimen is confirmed to contain at least 30% tumor by the pathologist. Bone and Bone marrow specimens must have been obtained at a NANT institution and used correct decalcification procedures.
    - Patients enrolling with Persistent Disease are required to have a tumor biopsy.

- Patients must not receive any other anti-cancer agents or radiotherapy during the interval starting from the earliest date of performing scans and ending when the biopsy procedure is done.

- If the first biopsy attempt is not successful and no NANT Precision Report is generated, re-enrollment for additional biopsy attempts are allowed after consultation with the study chairperson.

Patients cannot participate in the study if:

- Patients with disease of any major organ system that would prevent them from being able tolerate having a tumor biopsy done of soft tissue mass, bone or bone marrow.

- Patient who enroll and successfully receive a NANT Precision Report may not re-enroll at a future time.

- Patient declines participation in NANT 2004-05, the NANT Biology Study

Study procedures:

To participate in this study you must agree to let doctors send biopsy material where relapsed/refractory tumor cells may be present along with a blood sample for genetic testing. Tumor tissue or tumor cells could come from soft tissues either at your primary tumor site or another site of relapse, from a bone site or from bone marrow. If you previously had a tumor tissue biopsy after relapse of your neuroblastoma that has been stored properly and you and your doctor are interested in submitting that sample for analysis instead, you will not have to have an another procedure done to obtain more tissue.

All tumor and blood will be sent to the central laboratory at Childrens Hospital Los Angeles. This laboratory will examine the tissue submitted for numbers of tumor cells. If there are enough tumor cells

present, your tumor sample and blood sample will be sent for genetic testing at an outside laboratory. The analysis will include any changes in the genetic make-up of the tumor that are different from those changes found in your normal genetic material obtained from your blood sample. A report will be created that describes these changes will be sent to the CHLA central laboratory. This report will be given to you and your doctor.

The NANT Precision Study Committee will review the genetic report issued by the gene testing laboratory as well any results from tests done by the CHLA central laboratory and create a comprehensive study report (called NANT Precision Report) that will be returned to you through your doctor.

This report will include the genetic report prepared by the genetic testing laboratory that details specific genetic changes found in your tumor and whether or not there are potential drugs that may target those changes. In addition, the report will also show if your tumor belongs to any of the four neuroblastoma specific classification groups the researchers associated with NANT Precision are studying. For patients who submit a soft tissue sample, the report will also include the results from the special stains performed on your tumor.

The NANT Precision Report will include a link to a regularly updated webpage on the NANT Consortium website that will provide a list of open pediatric clinical trials in the NANT Consortium, Children's Oncology Group, and non-NANT clinical trials being conducted in NANT participating institutions. These trials are selected based on current available data matching the clinical trial's drug/s to genetic or immunologic alterations seen in one of the 4 groups. Your decision to enroll in any one of the clinical trials presented on the NANT website or other therapy recommended by your doctor should be made in discussion with your doctor. The NANT Precision Committee will collect data on what treatments you receive for one year after getting the NANT Precision report.

Your doctor will be informed if the CHLA central laboratory determines there are not enough tumor cells identified in your tumor sample to send it to the outside lab for genetic testing, If there are any left over specimens at your institution your doctor may elect to send another sample for analysis. It is possible that despite the biopsy, no specimen will be found to have enough tumor cells for genetic testing. In this case, you and your doctor will have to decide whether to have another biopsy procedure done.

- 4 weeks to Study Registration (Time 0)	**Time 0**	**Time 0 thru + 4 weeks[#]**	**+4 weeks thru +10 weeks**
Radiographic Imaging of tumor lesions performed (CT/MRI/MIBG/FDG-PET)	**Study Registration**	• Blood obtained (any time prior to and up to the day of biopsy) • Biopsy Performed (soft tissue, bone, bone marrow) • Specimen material sent to NANT Central Laboratory	• Specimens tumor content ≥30% sent for genetic +/- IHC analysis. • NANT Precision Report generation or QNS[**] & no report can be generated
No anti-cancer treatment is given during the interval between performing scans and performing biopsy procedure. Therapy can be started after biopsy procedure(s) have been performed and physician deems it is clinically appropriate to proceed.			QNS[**]: Patient may re-enroll for another attempt after consultation with study chair/vice-chair

#:Subjects will be offered participation in optional studies collecting blood and bone marrow at the time of clinically indicated blood collection and bone marrow procedures are being done.

**QNS; Quantity/Quality of tissue insufficient

For more information, please contact nantops@chla.usc.edu.