Clinical Trials

Study: NANT 2015-02

Lorlatinib for patients with Relapsed or Refractory Neuroblastoma

Protocol Title: NANT 2015-02: Phase 1 Study of Lorlatinib (PF-06463922), an Oral Small Molecule Inhibitor of ALK/ROS1, for Patients with ALK-Driven Relapsed or Refractory Neuroblastoma

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WHAT IS THIS STUDY ABOUT?

This study involves the use of an experimental drug called lorlatinib. Lorlatinib works by inhibiting the Anaplastic Lymphoma Kinase (ALK) oncogene. Lorlatinib has demonstrated an ability to target ALK mutations in the laboratory which other drugs have been ineffective at targeting. Neuroblastoma is a cancer that may benefit from a therapy which utilizes lorlatinib because ALK mutations can often be found in neuroblastoma patients.

Lorlatinib has not been approved by the United States Food and Drug Administration (FDA). Lorlatinib has been used only in a small number of adults and has an adult dose identified but there is still more information to learn about it. Lorlatinib has not previously been used in children and adolescents.

This study is a phase 1 study because the goal is to find the highest dose of lorlatinib that can be safely given in children and adolescents. Once we have found out the highest dose of lorlatinib that can be given safely, we will treat more children and adolescents with neuroblastoma with this lorlatinib dose and in combination with chemotherapy (cyclophosphamide and topotecan).

WHY IS THIS STUDY BEING DONE?

- To find the highest safe dose of lorlatinib that can be given to children and adolescents with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib given at different dose levels to children and adolescents 1-18 years of age.
- To measure the levels of lorlatinib in the blood at different dose levels.
- To determine neuroblastoma tumors get smaller after treatment with lorlatinib.

OTHER THINGS WE ARE TRYING TO LEARN DURING THIS STUDY

- To look at genetic changes in tumor DNA found in the blood during treatment with lorlatinib.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.

- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

CRITERIA THAT NEED TO BE MET TO PARTICIPATE IN THIS STUDY

- Patients must have a diagnosis of neuroblastoma either by histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines

- Patients are required to have an activating ALK aberration in their tumor detected by certified assay (i.e. CLIA in the US.) prior to registration. The report from this test is required to be submitted for eligibility. Patients with at least one of the following genetic features in their tumor will be considered to have an activating ALK aberration:

    1. An ALK activating mutation;
    2. ALK amplification (> 10 signals of the ALK gene);
    3. Presence of any ALK fusion protein that arises from a chromosomal translocation.

- Patients must have high risk neuroblastoma according to COG risk classification at the time of study registration. Patients who were initially considered low or intermediate risk, but then reclassified as high risk are also eligible.

- Patients must have at least ONE of the following: 1) Recurrent/progressive disease at any time prior to study enrollment, 2) Refractory disease, 3) Persistent disease.

- Patients must have at least ONE of the following: 1) Bone disease, 2) Any amount of neuroblastoma tumor cells in the bone marrow, 3) At least one soft tissue lesion that meets criteria for a TARGET lesion, 4) At least one non-target soft tissue lesion that is not measurable, but had a biopsy positive for neuroblastoma and/or ganglioneuroblastoma at any time prior to enrollment or is MIBG avid.

- Patients must have a Lansky (≤16 years) or Karnofsky (> 16 years) score of at least 50.

- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

- Patients must not have been previously treated with lorlatinib.

- Patients must not have received any of the specified therapies as stated in the protocol in the time period prior to registration.

- Patients must not be receiving any other anti-cancer agents or radiotherapy at the time of study entry or while on study.

- Patients must not be receiving other investigational medications (covered under another IND) within 30 days of study entry or while on study.

- Patients must not be receiving chronic systemic corticosteroids at doses greater than physiologic dosing (inhaled corticosteroids acceptable).

- Patient must meet the organ function and system function requirements as stated in the protocol.

CRITERIA THAT WOULD MAKE PATIENTS INELIGIBLE TO PARTICIPATE IN THIS STUDY

- Pregnancy, breast feeding, or unwillingness to use effective contraception during the study.

- Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

- Patients with disease of any major organ system that would compromise their ability to withstand therapy.

- Patients who have received prior allogeneic stem cell transplant.

- Patients who are on hemodialysis.

- Patients with an active or uncontrolled infection.

- Known history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C.

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

STUDY SCHEDULE

There are 4 cohorts in this study.

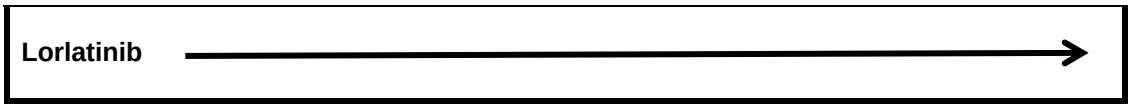
In A1 (dose escalation cohort), lorlatinib will be given orally once daily continuously for 28 days. The dose level of lorlatinib will be assigned at the time of study registration.

Cohort B1 (limited expansion cohort) will start when A1 is complete and the dose level identified.

Cohort A2 is for adult (18 years and older) and larger adolescents. Lorlatinib will be given at the adult recommended phase 2 dose orally once daily continuously for 28 days.

In cohort B2 (combination with conventional chemotherapy), lorlatinib will be given orally once daily continuously for 28 days at the dose level defined by cohort A1. This will be given together with cyclophosphamide and topotecan.

Cohorts A1, A2, B1 Treatment Course			
Week 1	Week 2	Week 3	Week 4*
Days 1 - 7	Days 8 - 14	Days 15 - 21	Days 22 - 28



Cohort B2 Treatment Course									
Week 1							Week 2	Week 3	Week 4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8-14	Days 15 -21	Days 22-28
Lorlatinib →									
CPM	CPM	CPM	CPM	CPM					
TOPO	TOPO	TOPO	TOPO	TOPO	MGF				

CPM: Cyclophosphamide
TOPO: Topotecan
MGF: Myeloid growth factor

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