CALGB-10603

A Phase III Randomized, Double-Blind Study of Induction (Daunorubicin/Cytarabine) and Consolidation (High-Dose Cytarabine) Chemotherapy + Midostaurin (PKC412) (IND #101261) or Placebo in Newly Diagnosed Patients < 60 Years of Age With FLT3 Mutated Acute Myeloid Leukemia (AML)

ClinicalTrial.gov Identifier: NCT00651261

Study Background

Trial Description

The purpose of this study is to compare the effects, good and/or bad, of a standard chemotherapy regimen for AML that includes the drugs daunorubicin and cytarabine combined with or without midostaurin (also known as PKC412), to find out which is better. This research is being done because it is unknown whether the addition of midostaurin to chemotherapy treatment is better than chemotherapy treatment alone. Midostaurin has been tested in over 400 patients and is being studied in a number of illnesses, including AML, colon cancer, and lung cancer. Midostaurin blocks an enzyme, produced by a gene known as FLT3, that may have a role in the survival and growth of AML cells. Not all leukemia cells will have the abnormal FLT3 gene. This study will focus only on patients with leukemia cells with the abnormal FLT3 gene.

Arms:

Induction and consolidation chemotherapy plus midostaurin: (Experimental): Patients will receive a standard combination of chemotherapy drugs during remission induction therapy that includes cytarabine, daunorubicin, and the experimental drug midostaurin. Depending on the outcome of remission induction treatment, there may be a decision to discontinue the study treatment or a second remission induction cycle may be given. If remission induction therapy is successfully completed, patients will receive four courses of high-dose cytarabine consolidation chemotherapy plus dexamethasone together with the experimental drug midostaurin. All patients will undergo a bone marrow aspiration (and perhaps a biopsy) after the final course of remission consolidation chemotherapy. If the patient continues to respond to the treatment, the patient will receive continuation therapy with midostaurin for twelve (12) months.

Induction and consolidation chemotherapy plus placebo: (Active Comparator): Patients will receive a standard combination of chemotherapy drugs during remission induction therapy that includes cytarabine, daunorubicin, and placebo. Depending on the outcome of remission induction treatment, there may be a decision to discontinue the study treatment or a second remission induction cycle may be given. If remission induction therapy is successfully completed, patients will receive four courses of high-dose cytarabine consolidation chemotherapy plus dexamethasone together with placebo. All patients will undergo a bone marrow aspiration (and perhaps a biopsy) after the final course of remission consolidation chemotherapy. If the patient continues to respond to the treatment, the patient will receive continuation therapy with placebo for twelve (12) months.

Objectives:

- In this study, patients will receive either the experimental agent (midostaurin) or placebo combined with chemotherapy treatment. Patients are stratified according to FLT3 mutation status (internal tandem duplication [ITD] allelic ratio < 0.7 vs ITD allelic ratio ≥ 0.7 vs tandem kinase domain [TKD]). There are three parts to the study treatment: remission induction therapy, remission consolidation therapy and continuation therapy.
- Remission Induction Therapy:
  - Cytarabine 200 mg/m2/day by continuous intravenous infusion on days 1-7
  - Daunorubicin 60 mg/m2/day by intravenous push or short infusion on days 1-3
  - Midostaurin 50 mg (two 25 mg capsules) or placebo for midostaurin (2 capsules) twice a day by mouth on days 8-21
  - A bone marrow aspiration will be performed in all patients on Day 21 to determine the need for a second induction cycle.
- Remission Consolidation (Four Remission Consolidation Cycles):
  - High dose cytarabine 3000 mg/m2 will be given by intravenous infusion over 3 hours every 12 hours on days 1, 3 and 5. Serial neurologic evaluation will be performed before and following the infusion of high-dose cytarabine.
  - Dexamethasone 0.1% or other corticosteroid ophthalmic solution 2 drops to each eye once daily to begin 6-12 hours prior to the initiation of the cytarabine infusion and to continue for at least 24 hours after the last cytarabine dose.
  - Midostaurin 50 mg (two 25 mg capsules) or placebo for midostaurin (2 capsules) twice a day by mouth on days 8-21
- Midostaurin/Placebo Continuation Therapy:
  - Midostaurin 50 mg (two 25 mg capsules) or placebo for midostaurin (2 capsules) by mouth twice a day for 28 days. Each cycle will be 28 days in length. Continuation therapy with midostaurin/placebo will continue until relapse or for 12 cycles maximum.
- The primary and secondary objectives of this study are:

- Primary objective:

  - To determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improves overall survival (OS) in both the mutant FLT3-ITD and FLT3-TKD AML patients
- Secondary objectives:
  - To compare the overall survival (OS) in the two groups using an analysis in which patients who receive a stem cell transplant are censored at the time of transplant
  - To compare the complete response (CR) rate between the two treatment groups
  - To compare the event-free survival (EFS) between the two treatment groups
  - To compare the disease free survival (DFS) of the two treatment groups
  - To compare the disease free survival rate one year after completion of the continuation phase of the two groups
  - To assess the toxicity of the experimental combination
  - To describe the interaction between treatment outcome and pretreatment characteristics such as age, performance status, white blood cell (WBC) count, morphology, cytogenetics, and molecular and pharmacodynamic features
  - To assess the population pharmacokinetics (pop PK) of midostaurin and its two major metabolites (CGP52421 and CGP62221). The potential association(s) between PK exposure and FLT3 status, OS, EFS and clinical response will be explored
- There is a pharmacokinetic sub-study (CALGB 60706) within CALGB 10603. This embedded companion study must be offered to all patients enrolled on CALGB 10603, although patients may opt not to participate in CALGB 60706.
- After study entry, patients are followed periodically for up to 10 years.

Study Milestones:

Start date: April 2008

Primary Completion Date: July 2016

Publication Information:

Analysis Type: Primary

Pubmed ID: 28644114

Citation: N Engl J Med. 2017 Aug 3;377(5):454-464. doi: 10.1056/NEJMoa1614359. Epub 2017 Jun 23

Associated Datasets: NCT00651261-D1-Dataset.csv (baseline), NCT00651261-D2-Dataset.csv (screen_pts), NCT00651261-D3-Dataset.csv (consort), NCT00651261-D4-Dataset.csv (outcome), NCT00651261-D5-Dataset.csv (cytox)

Dataset Information:

Dataset Name: NCT00651261-D1-Dataset.csv (baseline)

Description: Dataset NCT00651261-D1-Dataset.csv (baseline) is one of 5 datasets associated with PubMed ID 28644114. This dataset contains information that will allow you to reproduce the baseline characteristics table.

NCT00651261-D1-Dataset.csv (baseline) Data Dictionary:

*Missing values correspond to data not available.

LABEL	NAME	elements	comments
Patient ID	patid		Patient Identifier (this ID is also used on any NCTN Navigator submissions)
Age at start of treatment	agestart		Age in Years
Treatment text	TREAT_TEXT	Midostaurin, Placebo	Treatment
Stratum group text	STRATUM_GRP_TEXT	ITD Allelic ratio =>0.7 (+/- FLT3 TKD), ITD Allelic ratio <0.7 (+/- FLT3 TKD), FLT3 TKD (No ITD)	FLT3 type
PLT (x1000/ microliters)	PLT		Platelet Count
WBC (x1000/ microliters)	WBC		White Blood Cell Count
ANC (g/dL)	anc		Absolute Neutrophil count-manuscript has 55.9; our data has 128.7 for placebo arm. Previous stat reports agree with 128.7, I believe there is a typo.
Modified ELN Classification	ELNclass	Intermediate-II, Normal, Adverse,	ELN Classification

		Favorable	
Sex	sex	Female, Male	Gender
Race	race	White, Other	Race