# A phase 3 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)

Published: 20-11-2008
Last updated: 06-05-2024

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 FLT-3 TKD AML patients.

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Leukaemias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON32771

**Source**
ToetsingOnline

**Brief title**
CALGB 10603 / PKC412 / FLT3 AML

## Condition

- Leukaemias

**Synonym**
Acute Myeloid Leukemia, cancer of the bone marrow

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Novartis
**Source(s) of monetary or material Support:** farmaceutische industrie

## Intervention

**Keyword:** Acute Myeloid Leukemia, FLT3 mutation, Induction and consolidation chemotherapy, Midostaurin

## Outcome measures

### Primary outcome

Overall survival (OS) in the mutant AML FLT3-ITD and the FLT3-TKD patients is

the primary endpoint. The OS time is the period from the date of registration

in the study until death by any cause.

### Secondary outcome

Four secondary endpoints will be analyzed in this study:

1) Complete response (CR) rate in the remission induction stage of the study

2) event- free survival (EFS)

3) disease- free survival (DFS)

4) the DFS rate one year after completing the planned continuation phase

# Study description

## Background summary

Previously untreated patients with AML under 60 years of age overall are treated with inductionchemotherapy with an anthracycline and cytarabine, followed by consolidation therapy with high-dose cytarabine (HiDAC). In this age group, an overall complete response (CR) rate of 65% to 80% can be expected. However, presence of the FLT3 mutation in AML patients (of any age) is poor prognostic factor. In these patients an equivalent CR rate is achieved, however the relapse rate, disease free survival (DFS), event free survival (EFS) en overall survival (OS) at 5 years are significantly worse.
Midostaurin (PKC412) blocks an enzyme, produced by a gene known as FLT3, that may have a role in the survival and growth of AML cells. The addition of a targeted agent against FLT3 offers the possibility for significant therapeutic advantage in AML patients expressing FLT3.

## Study 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 FLT-3 TKD AML patients.

## Study design

A phase III randomized, double blind study

## Intervention

Patients will be randomly assigned to one of the two treatment groups:
Treatment 1)
A standard combination of chemotherapy drugs during remission induction chemotherapy that includes cytarabine (or ara-C, for short), daunorubicin, and the experimental drug midostaurin. After successfully completing remission induction, patients will receive four courses of high-dose ara-C consolidation chemotherapy together with the experimental drug midostaurin. Finally, after completing remission consolidation therapy, the patients will receive continuation therapy with midostaurin for twelve (12) months.

Treatment 2)
As of treatment 1, however instead of midostaurin the patients will receive a placebo.

## Study burden and risks

Total duration of the treatment is 18 months. Patients are followed for a maximum of 10 years after completion of the treatment. During induction and

consolidation therapy the patient will be folowed intensively by the physician. During continuation therapy the patient will be seen monthly. During the post treatment follow-up the frequency of hospital visits varies between once every 2 months (year 1 and 2) to once every quarter (year 3 and 4) and yearly (other years).

Women of childbearing potential must either commit to continued abstinence from heterosexual intercourse or commit to two acceptable methods of birth control (one highly effective and one additional effective method) at the same time. This should be commenced before receiving midostaurin/placebo therapy and continue for 12 weeks after completion of all midostaurin therapy.
Men must agree not to father a child and must use a latex condom during any sexual contact with women of childbearing potential while taking midostaurin/placebo and for 12 weeks after therapy is stopped, even if they have undergone a successful vasectomy.

The following most common side effects with the use of Midostaurin have been reported up to now:
Lowered white blood cell count/ platelet count / red blood cells
Nausea, vomiting, headache, changes in liver function tests, loss of appetite, fever, rash, hair loss, fatigue

Risks and side effects related to bone marrow aspirations (biopsies): pain or discomfort at the site where the needle is inserted as well as possible bleeding, bruising or swelling. There is also a very small chance that you could develop an infection at the site of the procedure.

A number of chemotherapy agents have a risk of causing another cancer (second malignancy). Cytarabine, daunorubicin, and midostaurin are not known to increase the risk of second malignancies, but may be shown at a later time to result in the development of these second malignancies.

# Contacts

**Public**
Novartis

Raapopseweg 1
6824 DP Arnhem
NL
**Scientific**
Novartis

Raapopseweg 1

6824 DP Arnhem
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

*Unequivocal diagnosis of AML (>20% blasts in the bone marrow based on the WHO classification), excluding M3 (acute promyelocytic leukemia).
*Documented FLT3 mutation (ITD or point mutation), determined by analysis in a protocol-designed FLT3 screening laboratory.
*Age greater than or equal to 18 years and less than 60 years.
*AML patients with a history of antecedent myelodyspasia (MDS) remain eligible for treatment on this trial, but must not have had prior cytotoxic therapy (e.g. azacitidine or decitabine).
*Bilirubin < 2.5 times upper limit of normal.

## Exclusion criteria

*No prior chemotherapy for leukemia or myelodysplasia with the following exceptions:
i. emergency leukapheresis
ii. emergency treatment for hyperleukocytosis with hydroxyurea for less than or equal to 5 days
iii. cranial RT for CNS leukostasis (one dose only)
iv. growth factor/cytokine support
*Patients who have developed therapy related AML after prior RT or chemotherapy for another cancer or disorder are not eligible.
*Patients with symptomatic congestive heart failure are not eligible.
*Pregnant or nursing patients may not be enrolled

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 22-05-2008 |
| Enrollment: | 12 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | - |
| Generic name: | Cytarabine |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | - |
| Generic name: | Daunorubicin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | - |
| Generic name: | Midostaurin |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 20-11-2008 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 19-03-2009 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-05-2009 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 19-03-2010 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 28-01-2011 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 08-05-2012 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 11-05-2012 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 15-10-2012 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 21-02-2013 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 02-08-2013 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 13-03-2014 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 17-03-2014 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 03-08-2015 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 10-08-2015 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 01-08-2016 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 12-08-2016 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 28-02-2017 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 06-03-2017 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-09-2017 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 04-10-2017 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 27-12-2017 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 28-12-2017 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 30-07-2018 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 11-09-2018 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 12-09-2018 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 07-05-2020 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 12-05-2020 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 12-05-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 04-10-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 10-10-2021 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 23-07-2022 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2006-006852-37-NL |
| CCMO | NL24604.091.08 |