

# Vyxeos® and Clofarabine in relapsed/refractory pediatric AML

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A safe RP2D of Vyxeos®/CPX-351 in combination with clofarabine can be identified in this phase 1b study.

<b>Ethische beoordeling</b>	Positief advies
<b>Status</b>	Werving gestart
<b>Type aandoening</b>	-
<b>Onderzoekstype</b>	Interventie onderzoek

## Samenvatting

### ID

NL-OMON20809

### Bron

NTR

### Verkorte titel

VyClo study

### Aandoening

relapsed/refractory AML (pediatric)

## Ondersteuning

**Primaire sponsor:** Princess Máxima Center for pediatric oncology

**Overige ondersteuning:** Jazz Pharmaceuticals, Princess Máxima Center for pediatric oncology

## Onderzoeksproduct en/of interventie

## Uitkomstmaten

### Primaire uitkomstmaten

To establish the recommended phase 2 dose of Vyxeos®/CPX-351 in combination with clofarabine in children with relapsed/refractory AML

# Toelichting onderzoek

## Achtergrond van het onderzoek

Treatment with intensive chemotherapy in AML results in approximately 70% survival in newly diagnosed patients. Prognosis at relapse is worse and is in the 30-40% range. Relapse treatment generally consists of one course of fludarabine, cytarabine and liposomal daunorubicin (FLAG-DNX), followed by a fludarabine and cytarabine course and subsequent stem-cell transplantation. Cytarabine has been used in combination with fludarabine and cladribine, with the aim to induce synergism by increasing Ara-CTP (active cytotoxic metabolite from ara-C) accumulation, which can be seen as a surrogate marker for cytarabine induced cell-kill. Synergy with cytarabine can also be achieved with clofarabine, which is a potent inhibitor of ribonucleotide reductase, leading to a depletion of normal deoxynucleotides and subsequently to increased Ara-CTP levels. The phase IB trial ITCC020/I-BFM 2009-02 recently reported that clofarabine, replacing fludarabine in the standardly used fludarabine, cytarabine and liposomal daunorubicin (FLAG-DNX) combination regimen, showed high response rates (Overall Response Rate - ORR 68% and 80% at the recommended phase 2 dose - RP2D) in patients with refractory/relapsed AML, and was generally tolerable, with infectious complications as the main side-effect due to the immunosuppressive properties of clofarabine.

Currently DNX is unavailable in Europe, which urges the need to develop other treatment blocks. The liposomal formulation of Vyxeos®/CPX-351 may be a suitable replacement for DNX, considering the long-term side effect of cardiotoxicity due to anthracyclines which is of primary importance in younger heavily pre-treated patients. Preliminary results in pediatric and young adult patients with relapsed/refractory AML in a COG study using Vyxeos®/CPX-351 at a RP2D of 135 U/m<sup>2</sup> (AAML1421) showed encouraging ORR (80%), with 70% of patients reaching CR/CRi as best response after single agent-treatment with Vyxeos®/CPX-351. Preclinical data have also assessed an increased Ara-CTP accumulation and cytotoxicity in immortalized cell lines, and confirmed by tests in ex-vivo blasts from a cohort of AML patients (n=5), when cells were exposed to Vyxeos®/CPX-351 after 4 hours of incubation with fludarabine.

In this study we therefore evaluate Vyxeos®/CPX-351 in combination with clofarabine in a phase 1b study with the aim to establish the RP2D of this combination.

## Doel van het onderzoek

A safe RP2D of Vyxeos®/CPX-351 in combination with clofarabine can be identified in this phase 1b study.

## Onderzoeksopzet

C1D1, C2D1, 4 weeks after C2D28 (EOT)

## Onderzoeksproduct en/of interventie

Combination treatment is allowed only for Course 1: An adapted regimen is used to combine Vyxeos®/CPX-351 given at day 1, 3, 5 with clofarabine given at day 2-6.

- Vyxeos®/CPX-351 will be infused on day 1, 3 and 5 only, 3 hours after the end of clofarabine (if on the same day).
- Clofarabine infusion will be given daily on day 2-6.
- CNS prophylaxis (recommended) on day +6.

Patients may repeat one course of Vyxeos®/CPX-351 as single agent in Course 2, in the absence of significant safety concerns or progressive disease:

- Vyxeos®/CPX-351 will be administered alone, at the same dose level and with the same infusion schedule of Course 1
- CNS prophylaxis IT therapy, is recommended and scheduled at day 1 of course 2.

## Contactpersonen

### Publiek

Prinses Máxima Centrum voor kinderoncologie  
Miriam Stumpf

+31 650006609

### Wetenschappelijk

Prinses Máxima Centrum voor kinderoncologie  
Miriam Stumpf

+31 650006609

## Deelname eisen

### Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

We will include pediatric patients  $\geq 1$  year and  $< 21$  years with:

- Any  $\geq 2$ nd relapse of AML
- Refractory AML (defined as  $\geq 20\%$  blasts in the bone marrow after standard induction therapy)

- Early 1st relapse (defined as relapse within one year from initial diagnosis) of AML
- Any relapse of AML after prior allogeneic HSCT
- Any relapse of AML with high risk cytogenetic characteristics (as defined in protocol Appendix V)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Initial work-up:

- Complete initial work-up within 7 days prior to study entry, including bone-marrow aspiration, lumbar puncture (without intrathecal therapy)

General conditions:

- Lansky play score  $\geq 60$ ; or Karnofsky performance status  $\geq 60$
- Life expectancy  $> 6$  weeks
- The patient must have a radioisotope GFR  $\geq 70\text{mL/min/1.73 m}^2$ .
- Liver function: serum bilirubin  $\leq 3 \times$  upper limit of normal (ULN) and aspartate transaminase (AST)/alanine transaminase (ALT)  $\leq 5 \times \text{ULN}$
- Adequate cardiac function (defined as shortening fraction  $\geq 28\%$  or ejection fraction  $\geq 50\%$ )
- No evidence of a currently uncontrolled bacterial, viral or parasitic infection
- No evidence of a fungal infection, defined as either:
  - Pulmonary infiltrates suggestive of a fungal infection at HR-CT (within 3 weeks prior to enrollment)
  - Positive Aspergillus serum test (galactomannan), according to local laboratory practice (within 3 weeks prior to enrollment)
- No evidence of isolated extramedullary relapse, including isolated CNS-relapse
- No evidence of CNS3 or symptomatic CNS leukemia
- No presence of Down Syndrome
- No evidence of relapsed/refractory acute promyelocytic leukemia (APL)
- No use of any anticancer therapy within 2 weeks before study entry. The patient must have recovered from all acute toxicities from any previous therapy (note: hematological toxicities do not need to be considered since the patient has overt leukemia)
- No history of prior veno-occlusive disease (VOD)
- No known hypersensitivity to cytarabine, clofarabine or liposomal daunorubicin

Other:

- For female patients with childbearing potential, a negative test for pregnancy is to be performed before entry on study.
- Male and female patients must use a highly effective contraceptive method during the study and for a minimum of 6 months after study treatment.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule is required; those conditions should be discussed with the patient before registration in the trial.
- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

Concomitant treatments:

- Concomitant administration of any other experimental drug under investigation, or concurrent treatment with any other anti-cancer therapy other than specified in the protocol is not allowed.
- GCSF will not be used for priming and no routine GCSF support is allowed during the 1st

course, except for life-threatening infections.

Additional criteria:

- At least 6 patients must be enrolled with an M3 or a WBC count  $>10 \times 10^9/L$  with blasts

## **Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)**

see inclusion criteria

## **Onderzoeksopzet**

### **Opzet**

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blinding:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

### **Deelname**

Nederland	
Status:	Werving gestart
(Verwachte) startdatum:	06-11-2020
Aantal proefpersonen:	25
Type:	Verwachte startdatum

## **Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)**

**Wordt de data na het onderzoek gedeeld:** Nog niet bepaald

## **Ethische beoordeling**

Positief advies	
Datum:	31-10-2019
Soort:	Eerste indiening

## Registraties

### Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

### Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

### In overige registers

Register	ID
NTR-new	NL8134
Ander register	METC Utrecht : not known yet

## Resultaten