# CHIP-AML22 MASTER PROTOCOL: AN OPEN-LABEL CLINICAL TRIAL IN NEWLY DIAGNOSED PEDIATRIC DE NOVO ACUTE MYELOID LEUKEMIA PATIENTS INCLUDING A LINKED PHASE II TRIAL WITH QUIZARTINIB IN *FLT3*-ITD/*NPM1*WT PATIENTS – A STUDY BY THE NOPHO-DB-SHIP CONSORTIUM

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## INTRODUCTION

- Outcomes for pediatric AML have significantly improved over the past decades with current event-free survival (EFS) and overall survival (OS) rates of 50-60% and 70-80%, respectively.[1]
- However, patients with relapsed or refractory disease, and patients with adverse AML genetics and/or poor treatment response, still have a dismal prognosis.[2]
- The addition of new treatment elements to the current chemotherapy backbone, such as the *FLT3*-inhibitor quizartinib (Vanflyta®) and the antibody-drug conjugate gemtuzumab ozogamicin (GO, Mylotarg®), holds promise to further improve EFS. [3,4]
- At the same time, not all patients seem to benefit from a 5th chemotherapy course.[5]

## AIM

The overarching objective of the CHIP-AML22 is to improve EFS in children and adolescents with newly diagnosed AML, as compared to NOPHO-DBH AML-2012, by:

1) a phase II, single arm, open-label study on the safety, efficacy, pharmacokinetics and -dynamics of quizartinib in combination with chemotherapy, and as single-agent after allo-SCT, in *FLT3*-ITD/*NPM1*wt AML (study CHIP-AML22/Quizartinib);
2) a phase III, open-label randomization with GO added to induction course 1 (MEC: mitoxantrone, etoposide and cytarabine) for newly diagnosed pediatric CD33-positive AML patients (study Ri);
3) a phase III, open-label randomization with three (standard of care) versus two (investigational) courses of consolidation chemotherapy for standard-risk patients as non-inferiority trial (study Rc);
4) refining risk-group adapted treatment, as shown in Figure 1;
5) recommending dexrazoxane to all patients before receiving daunorubicin or mitoxantrone.

## STUDY DESIGN

### MASTER PROTOCOL

- **Inclusion criteria**: newly diagnosed de novo AML patients aged ≥1 day to ≤18 years.
- **Exclusion criteria** (among other things): secondary AML, therapy-related AML, acute promyelocytic leukemia.
- **Estimated total study duration**: 12-13 years (approximately 905 patients needed).

### QUIZARTINIB STUDY

**Additional inclusion criteria:** *FLT3*-ITD/*NPM1*wt in bone marrow or peripheral blood, Age: 1 month to ≤ 18 years, adequate liver and renal function, life expectancy > 6 weeks.

**Additional exclusion criteria:** Patients with extramedullary AML, uncontrolled/significant cardiovascular disease.

**Dose:** dosing is depending on the dose cohort (safety run-in), and the patients' weight.

| PRIMARY OBJECTIVES | PRIMARY ENDPOINTS |
|---|---|
| Efficacy: to assess the clinical benefit of quizartinib by the MRD-negativity rate (< 0.1% flow cytometry) after up to 2 courses of conventional chemotherapy plus quizartinib. | The percentage of patients with MRD-negativity after up to two courses, as measured in the bone marrow (BM) using multiparameter flow cytometry. |
| Safety: during the safety run-in, the co-primary objective will be to determine the recommended phase 2 dose of quizartinib, based on the safety and tolerability of quizartinib observed at dose levels. | Incidence of Dose-Limiting Toxicities(DLTs) assessed during induction course 1 and 2 (until day 56 of each course) for the DLTs evaluable patients. |

**Sample size calculation for the primary efficacy endpoint:** Based on historical controls (MRD negativity rate of 39% at end of induction 2) and with the planned sample size of 60 evaluable patients and a true MRD negativity rate of 59%, the study will have at least 85% power to detect the 20% absolute improvement.

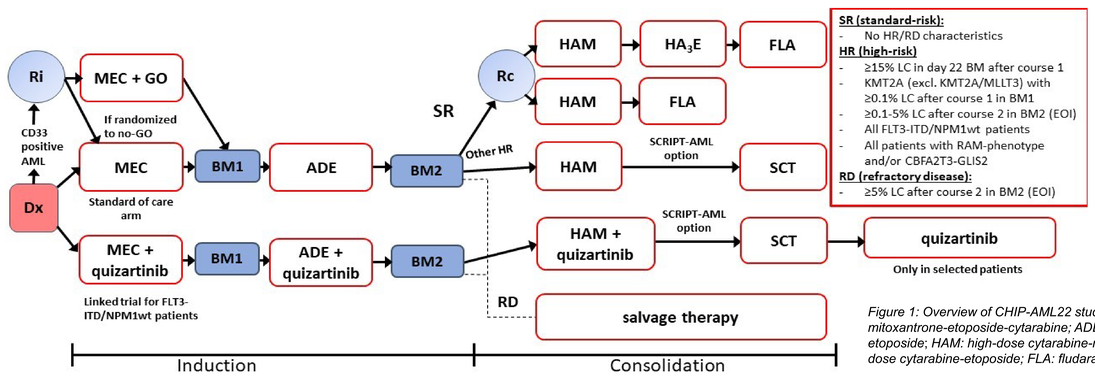



*Figure 1: Overview of CHIP-AML22 study design. MEC: mitoxantrone-etoposide-cytarabine; ADE: cytarabine-daunorubicin-etoposide; HAM: high-dose cytarabine-mitoxantrone; HA3E: high-dose cytarabine-etoposide; FLA: fludarabine-cytarabine.*

### RI: GO ADDED TO INDUCTION CHEMOTHERAPY STUDY

**Additional inclusion criteria:** CD33+ AML blasts measured by flow cytometry at diagnosis.

**Additional exclusion criteria:** Hypersensitivity to active substance of GO, participation in the quizartinib trial, elevated bilirubin ≥ grade 3.

**Dose:** GO twice during induction with MEC at a dose of 3 mg/m$^2$ (max. 5mg/dose)

| PRIMARY OBJECTIVE | PRIMARY ENDPOINT |
|---|---|
| To assess if adding GO to induction course 1 results in better early anti-leukemic efficacy in CD33+ AML patients compared to no-GO. | MRD <0.1% leukemic cells in the BM, as defined by flow cytometry, shortly before start of induction course 2 (BM1). |

**Sample size calculation for the primary endpoint:** Based on historical controls (MRD < 0.1% rate of 62% at day 1 of induction course 2), a treatment effect of 15% (resulting in 77% MRD < 0.1% in the experimental group) and 80% power, the required sample size is 300 patients (150 in each group). One interim analysis will be performed once 75% of the sample size has been randomized and has outcome data available.

### RC: CONSOLIDATION RANDOMIZATION STUDY

**Additional inclusion criteria:** standard-risk patients.

**Additional exclusion criteria:** none.

**Intervention:** HA3E is omitted in the experimental arm (Figure 1).

| PRIMARY OBJECTIVE | PRIMARY ENDPOINT |
|---|---|
| To demonstrate non-inferiority in disease-free survival of two courses of consolidation therapy, by omitting HA3E, as compared to three courses, in the SR group eligible for this randomization. | Disease-free survival. |

**Sample size calculation primary endpoint:** 610 patients are needed (305 per arm) for 80% probability of showing non-inferiority (up to 10% worse EFS accepted, HR 1.45). An interim analysis will be performed once 50% of the required number of events has been observed.

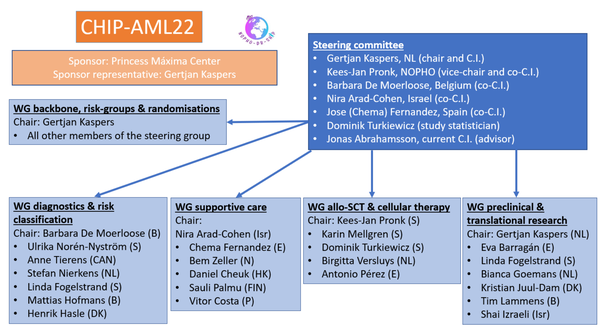
## REGULATORY FRAMEWORK

CHIP-AML22 is a master protocol comprising a complex clinical trial with a stratification approach to allocate patients to randomized studies in the master protocol, or linked trials; relevant biomarkers (e.g. *FLT3*-ITD/*NPM1*wt alterations, CD33-expression, response to treatment) will determine allocation to these randomized studies or linked trials, whereas other detailed inclusion and exclusion criteria are defined in the related sections of the protocol.

The quizartinib study is part of an agreed Pediatric Investigational Plan (PIP) between the MA holder and the European Medicines Agency. Other randomizations and linked trials with novel agents such as BCL-2 inhibitors (e.g., venetoclax) and menin-inhibitors may be added at later time points by amendment as well.

The CHIP-AML master protocol (EU CT no: 2023-504999-25-00) has been approved under the European Clinical Trial Regulation. The linked quizartinib trial (EU CT no: 2023-505000-27-00) has been approved under the European Clinical Trial Directive.

## TRIAL COMMITTEES

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