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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Chip-AML22 Master Protocol: An Open-Label Clinical Trial in Newly Diagnosed Pediatric De Novo Acute Myeloid Leukemia (AML) 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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Background and Significance Pediatric AML is a heterogeneous disease with current rates for event-free survival (EFS) of 50-60% and for overall survival (OS) of 70-80%, for newly diagnosed patients. In patients with refractory and relapsed disease, and in subsets as defined by AML biology and treatment response, prognosis is dismal. To further improve EFS, the NOPHO-DB-SHIP consortium has initiated trial CHIP-AML22. Building on the successes achieved by the recent trial from this consortium (NOPHO-DBH AML-2012, preliminary data as per June 2023, n=878: 5-years pEFS 63%, 5-years pOS 78%), CHIP-AML22 will incorporate innovative elements, mainly the *FLT3*-inhibitor quizartinib (Vanflyta®) that was recently approved by the FDA and PMDA in combination with chemotherapy for the treatment of newly diagnosed adult AML patients with *FLT3*-ITD mutations, and gemtuzumab ozogamicin (GO, Mylotarg ®) that improved outcome in adult and pediatric AML when added to chemotherapy. CHIP-AML22 will maintain the approach of treatment-response driven risk-adapted treatment, intensified induction treatment for patients with ≥5% AML cells in the bone marrow (BM) after course 1, and consolidation with allogeneic stem cell transplantation (allo-SCT) for high-risk patients after the first consolidation course HAM.

Study Design and Methods This clinical trial will enroll newly diagnosed *de novo* patients aged ≥1 day to ≤18 years to 2 randomized studies in the Master protocol, to the linked quizartinib trial, or the standard arm of the Master (Figure 1). Innovations include: (1) a phase II, single arm, open-label study on the safety, efficacy, pharmaco-kinetics and -dynamics of quizartinib in combination with chemotherapy, and as single-agent after allo-SCT, in *FLT3*-ITD/ *NPM1*wt AML; All patients will receive quizartinib monotherapy for 6 months post-SCT, except those that were negative for measurable residual disease determined with multiparameter flow cytometry (MFC-MRD) in BM1 and remained negative (study CHIP-AML22/Quizartinib); (2) a phase III, open-label randomization with gemtuzumab ozogamicin (GO; Mylotarg®) added to induction therapy MEC for pediatric CD33-positive newly diagnosed AML patients aimed at improved outcome (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), and (4) refining risk-group adapted treatment, aimed at improved outcome. Novel high-risk categories are patients with RAM-phenotype and/or *CBFA2T3::GLIS2*, and patients with *KMT2A*-rearranged AML (excluding *KMT2A::MLLT3*) with ≥0.1% AML cells after course 1 in BM1. Patients with ≥15% AML cells on day 22 BM after course 1, or ≥0.1-5% AML cells by MFC-MRD after course 2 in BM2 (end-of-induction), or those with *FLT3-ITD/NPM1wt* remain to be high-risk, similar to AML-2012. Further, dexrazoxane is recommended to all patients before receiving daunorubicin or mitoxantrone, aiming to prevent late-onset cardiotoxicity.

The quizartinib trial includes a safety run-in with a modified rolling-6 design and two dose levels with 6 evaluable patients per dose level. In study Ri, patients assigned to the experimental GO-arm will receive GO twice during induction with MEC at a dose of 3 mg/m ^{2} (max 5 mg) with an interim-analysis for superiority of any of these two arms. The investigational arm of the Rc randomization will omit HA $_3$E. Both the quizartinib trial and each randomization will also be compared to historical controls from the AML-2012 trial.

CHIP-AML22 expects to enroll 130-140 patients per year and it will take 7-8 years to reach the total number of 905 patients needed to answer all study questions. Patients will be followed-up for at least 5 years from diagnosis and thus, the total study duration is expected to be 12-13 years.

The Master protocol (EU CT: 2023-504999-25) and linked quizartinib trial (EU CT: 2023-505000-27-00) were approved by the Dutch Ethical Review Authority and as of July 2023, enrollment in the Master protocol including study Rc has started in The Netherlands. Study Ri and the linked quizartinib trial are expected to open in Q4 2023. At least 15 other countries with nearly 60 sites will participate in CHIP-AML22: Belgium, Denmark, Estonia, Finland, Hong Kong, Iceland, Israel, Latvia, Lithuania, Norway, Portugal, Spain, Sweden, Switzerland and Uruguay.

Disclosures Zwaan: *Abbvie:* Research Funding; *Sanofi:* Other: Advisory role; *BMS:* Consultancy; *Gilead:* Consultancy; *Syndax:* Research Funding; *Abbvie:* Research Funding; *Kura Oncology:* Consultancy; *Novartis:* Consultancy, Other: Advisory role; *Incyte:* Consultancy; *Takeda:* Research Funding; *Pfizer:* Consultancy, Research Funding; *Jazz Pharmaceutical:* Research Funding; *ITCC Hem Malignancies Committee:* Membership on an entity's Board of Directors or advisory committees. **Biserna:** *Daiichi Sankyo:* Current equity holder in publicly-traded company; *Daiichi Sankyo Inc.:* Current Employment; *BMS:* Current equity holder in publicly-traded company. **Kamel:** *Daiichi Sankyo Inc.:* Consultancy, Other. **Tierens:** *BD Biosciences:* Honoraria, Speakers Bureau.

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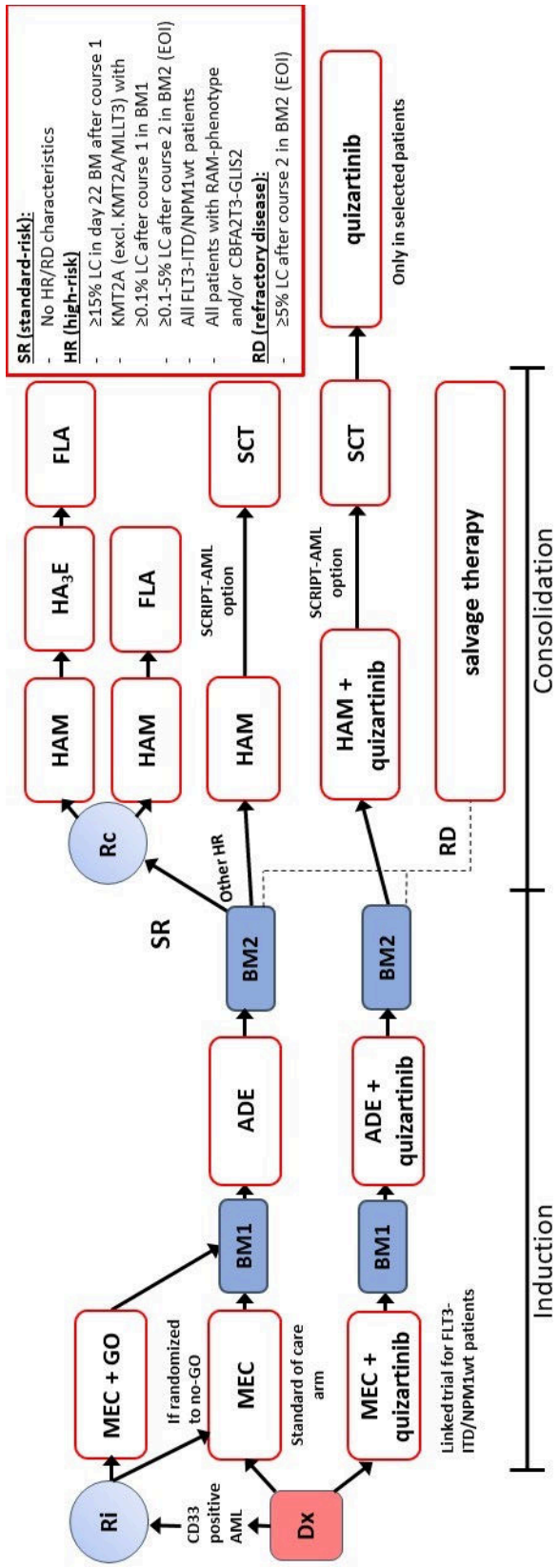

Figure 1

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