# Acute myeloid leukemia: negative prognostic impact of early blast persistence can be in part overcome by a later remission prior to post-induction therapy

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# SUPPLEMENTARY APPENDIX

## Acute myeloid leukemia: negative prognostic impact of early blast persistence can be in part overcome by a later remission prior to post-induction therapy

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## SUPPLEMENTARY METHODS

### 1. Treatment

### 1.1 Induction and consolidation chemotherapy

Standard first-line induction therapy consisted of Cytarabine-/Daunorubicin-based chemotherapy according to the "7+3" regimen (Cytarabine i.v. at a dosage of 100-200 mg/m$^2$ on 7 days, Daunorubicin 60 mg/m² i.v. on 3 days). 8/1008 patients received Idarubicin 10-12 mg/m² on 3 days, Cytarabine 100 mg/m$^2$ for 7 days and Etoposide 100 mg/m2 on 3 days intravenously (ICE regimen). TAD9 (oral Thioguanine 2 x 100 mg/m$^2$ on 7 days, Cytarabine 100 mg/m$^2$ continuously on days 1+2, Cytarabine 2 x 100 mg/m$^2$ on days 3-8 and Daunorubicin 60 mg/m² on 3 days) was administered in 183/1008 patients. As a part of the induction chemotherapy, 176 patients were treated with HAM (Cytarabine 2x 1-3 g/m$^2$ on 3 days and Mitoxantrone 10 mg/m$^2$ on 3 days). A few patients (10/1008) received induction chemotherapy with 5-Azacytidine at 100 mg/m$^2$ subcutaneously on 5 consecutive days (instead of Cytarabine) together with Idarubicin 12 mg/m² and Etoposide 100 mg/m$^2$ on 3 days in the experimental arm of a clinical trial protocol. Within particular clinical trials, targeted therapies were applied in addition to a "7+3"-based regimen: Midostaurin in FLT3-mutated AML (19/1008), Gemtuzumab-Ozogamicin in NPM1-mutated AML (7/1008) and Dasatinib in core-binding factor AML (4/1008).

Consolidation chemotherapy was performed with intermediate to high-dose Cytarabine-based therapy (HD-AraC 2 x 1-3 g/m$^2$ on 3 days) +/- Mitoxantrone (10 mg/m$^2$). TAD9 (see above) was used as consolidation chemotherapy within clinical trials in 180 patients. A small number of patients (10/1008) received an autologous stem cell transplantation (auto-HSCT) as consolidation chemotherapy as a part of a clinical trial protocol. Auto-HSCT was considered as chemotherapy consolidation in our analysis. Therefore, patients with auto-HSCT were included into the group of non-allo-HSCT patients. After consolidation chemotherapy, some of the patients in complete remission (CR) or complete remission with incomplete hematological recovery (CRi) who had

been treated within TAD9-based protocols (40/1008) were scheduled for maintenance therapy with alternating cycles of Cytarabine/Daunorubicin, Cytarabine/Thioguanine and Cytarabine/Cyclophosphamide over 3 years.

### 1.2 Allogeneic hematopoietic stem cell transplantation

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) following either myeloablative or reduced-intensity conditioning regimens was used either as consolidation therapy in first remission or in relapsed/refractory patients. The assignment to allo-HSCT vs. consolidation chemotherapy was based on the general health condition, donor availability, disease characteristics, and the patients' preference. With regard to European LeukemiaNet (ELN) risk groups, allo-HSCT was generally recommended as consolidation therapy in first CR in ELN intermediate AML patients with a full match HLA-compatible donor and in patients belonging to the ELN adverse risk group. A partial donor mismatch was accepted after individual risk/benefit assessment, particularly in ELN adverse risk patients. Of all patients, 31% (311/1008) did not proceed to allo-HSCT due to the following reasons: death prior to scheduled allo-HSCT in 21.5% (67/311), age ≥70 years paired with signs of impaired general health/ frailty in 29% (90/311), ELN risk favorable in 11% (34/311), no donor available in 5.5.% (17/311), severe infection prior to scheduled allo-HSCT in 3% (9/311), patient's decision in 2% (7/311) and other reasons in 1.5% (5/311). In 26.5% (82/311), the reasons for not proceeding to allo-HSCT were not evident from the patients' medical records.

### 1.3. Salvage chemotherapy

Treatment strategies for patients with early blast persistence are shown in Figure 2. As salvage chemotherapy for relapsed/refractory AML, Fludarabine 25-30 mg/m$^2$ on 5 days + Cytarabine 1-2 g/m$^2$ on 5 days + G-CSF +/- Idarubicin 8-10 mg/m$^2$ or Mitoxantrone 7 mg/m$^2$ on 3 days were applied (IdaFLAG / MitoFLAG / FLAG). Sorafenib (2 x 400mg/d) was applied "off-label" in some patients (n=5) with relapsed FLT3-ITD-mutated AML beyond induction therapy. Furthermore,

Midostaurin, Gilteritinib or Quizartinib were administered in a few relapsed FLT3-mutated AML patients (n=9). Palliative chemotherapy and/or best supportive care was applied in a few refractory cases (n=33) and some patients with relapsed AML (n=107), who were no longer eligible for an intensive regimen after the first line therapy. Palliative chemotherapy consisted of either hypomethylating agents (HMA) such as Azacytidine (75 mg/m$^2$ i. v. or s. c. on 7 days) or Decitabine (20 mg/m$^2$ on 5 days), oral Etoposide or subcutaneous low-dose Cytarabine 2 x 20 mg/d on 10 days (relapsed AML only).

## 2. Bone marrow assessment and response evaluation

### 2.1 Bone marrow assessment

Bone marrow (BM) assessment was performed at baseline, on day 14-21 of the first induction cycle, and prior to the post induction therapy (either prior to consolidation chemotherapy or prior to allo-HSCT). In the non-transplant cohort, the final post-induction remission status was assessed after completion of two cycles of induction chemotherapy. BM assessment was performed by both morphology (cytology and/or histopathology) and multiparametric flow cytometry. Blast clearance was stated in patients with less than 5% blasts in the BM in both morphological and flow cytometric evaluation. In cases with insufficient quality of the bone marrow aspirate, response evaluation relied on histopathology (<5% blasts vs. >5% blasts in the BM). In our cohort, remission evaluation did not routinely contain the measurable residual disease (MRD) status, however, the ELN recommendations for response evaluation did not include MRD until 2017 [1,2].

### 2.2. Response evaluation

According to ELN, CR was defined as complete remission (< 5% blasts) with hematological recovery, CRi was defined as complete remission with incomplete hematological recovery and MLFS was referred to as morphologic leukemia free state. For the analysis, CR, CRi and MLFS were summarized as “combined remission rate (CRR)”. Partial remission (PR) was defined by a

decrease of BM blasts by at least 50% to a blast percentage in the range of 5% to 25%. Primary refractory disease (RD) was defined as a lack of CR/CRi after two courses of intensive induction treatment. Early blast persistence without any response was designated „early resistant AML", since the term „refractory disease" must not be used prior to completion of at least two cycles of intensive chemotherapy according to ELN criteria [1,2]

## SUPPLEMENTARY REFERENCES


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