

# **Evaluation of the impact of remission induction chemotherapy prior to allogeneic stem cell transplantation in relapsed and poor-response patients with AML (ETAL3-ASAP)**

A phase-III study on the comparison of two treatment strategies for patients with high-risk acute myeloid leukemia by the **Study Alliance Leukemia (SAL)**

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# 1 Protocol Synopsis

## 1.1 Synopsis

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<b>TITLE OF STUDY</b>	Evaluation of the impact of remission induction chemotherapy prior to allogeneic stem cell transplantation in relapsed and poor-response patients with AML
<b>SHORT TITLE</b>	ETAL3-ASAP
<b>BACKGROUND</b>	<p>Patients with high-risk acute myeloid leukemia (AML) who relapsed or showed a poor response to induction chemotherapy have a dismal prognosis. For these patients, allogeneic transplantation is the recommended treatment. While allogeneic transplantation may be considered as the ultimate treatment concept, the treatment path to transplantation is not well defined.</p> <p>The traditional approach to pursue a complete remission by means of aggressive reinduction chemotherapy prior to allogeneic transplantation. This approach is associated with potentially life-threatening toxicities and has limited efficacy. As a result, only some patients will reach allogeneic transplantation in complete remission.</p> <p>To reduce the number of patients who die or who are ineligible for transplantation due to the toxicity of aggressive induction</p>

	<p>chemotherapy, other bridging options have been explored. One promising alternative is to abstain from remission induction. Instead, disease control by means of less aggressive chemotherapy or simply monitoring leukemic proliferation can be considered.</p> <p>Based on the existing literature from uncontrolled phase II studies and retrospective analyses these two approaches may be considered to be comparable. Yet, direct comparisons between these two treatment strategies have not been performed. A randomized controlled trial is the only way to identify if there is non-inferiority of the less toxic approach, compared to the standard approach of remission induction by aggressive chemotherapy prior to allogeneic transplantation.</p>
<p><b>OBJECTIVES</b></p>	<p>The objective of this trial is to compare outcome of two treatment strategies for patients with high-risk AML who failed to achieve or maintain a complete remission with standard therapy. Patients will be randomized between two strategies. The standard strategy is aimed at achieving a complete remission by aggressive salvage chemotherapy using high dose cytarabine and mitoxantrone, and is referred to as the Remission Induction Strategy arm or "RIST". The alternative is a less toxic disease-control strategy of disease monitoring and, if necessary, low-dose cytarabine or mitoxantrone referred to as the Disease Control Strategy arm or "DISC" prior to allogeneic transplantation, which should be performed as soon as possible.</p>
<p><b>OUTCOME(S)</b></p>	<p><b>Primary Endpoint</b> is disease-free survival on day 56 after allogeneic stem cell transplantation. This composite endpoint consists of two major components: i) To have received allogeneic HCT within 16 weeks after randomization and; ii) to be free of disease on 56 days after HCT. The endpoint can be assessed for all patients.</p> <p><b>Secondary Endpoints:</b> Overall survival by treatment arm is the most important secondary endpoint. In addition the rate of allogeneic stem cell transplantation, cumulative incidence of</p>

	<p>CR, and leukemia-free survival will be assessed by treatment arm. The treatment effect will be analysed in patients with relapsed and poor response AML. Further endpoints will be evaluated in pre-defined subgroups of patients.</p>
<p><b>INCLUSION AND EXCLUSION CRITERIA</b></p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>- Signed written informed consent.</li> <li>- Male and female patients of 18 to 75 years of age.</li> <li>- Diagnosis of AML according to WHO criteria.</li> <li>- Patient is fit for aggressive induction chemotherapy and transplantation by assessment of an experienced hematologist.</li> <li>- HLA-identical sibling.</li> </ul> <p style="text-align: center;"><b>or</b></p> <p>HLA-compatible (8/8) unrelated donor with completed confirmatory typing.</p> <p style="text-align: center;"><b>or</b></p> <p>One potential HLA-compatible (8/8) donor <i>plus</i> at least two back-up donors, who are at least 9/10 matches with &gt;90% OptiMatch® probability for each of them.</p> <p><b>For the relapse stratum:</b></p> <ul style="list-style-type: none"> <li>- First AML relapse, defined as ≥5% bone marrow blasts and / or extramedullary AML manifestation.</li> </ul> <p><b>For the poor-responders stratum:</b></p> <ul style="list-style-type: none"> <li>- If patient ≤60 years old: High risk AML according to ELN-criteria and ≥5% bone marrow blasts after the first cycle of induction therapy.</li> <li>- If patient &gt;60 years old: Non-favourable risk AML according to ELN-criteria and ≥5% bone marrow blasts after the first cycle of induction therapy.</li> </ul>

**Exclusion criteria:**

- Acute promyelocytic leukemia (APL).
- WBC count of  $\geq 50$  GPT/L at study inclusion.
- For patients in the poor-responder stratum the first cycle of induction therapy must not contain HDAC, defined as cytarabine at single-doses of  $\geq 1\text{g}/\text{m}^2$ .
- Patient has received more than 80% of the tolerable cumulative anthracycline dose (see chapter 7.2. for definitions and worksheet for calculation).
- Severe organ dysfunction, defined as:
  - o Left ventricular ejection fraction  $< 50\%$ .
  - o DLCO  $< 50\%$ , FEV1/VC  $< 70\%$  despite appropriate treatment.
  - o Patients who receive supplementary continuous oxygen.
  - o Serum bilirubin  $> 1.5 \times \text{ULN}$  (if not considered Gilbert-Syndrome), ASAT/ALAT  $> 5 \times \text{ULN}$ .
  - o Estimated GFR  $< 50$  ml/min.
- Treatment with any investigational drug within 10 days before study entry.
- Uncontrolled infection at the time of enrollment.
- History of allogeneic transplantation.
- Manifestation of AML in the central nervous system.
- Pregnant or breast-feeding women.
- Men unable or unwilling to use adequate contraception methods from start of study treatment to minimum of six months after the last dose of chemotherapy.
- Women with childbearing potential except those who fulfill the following criteria: Post-menopausal or post-operative or continuous and correct application of a contraception method with a Pearl Index  $< 1\%$  or sexual abstinence or vasectomy of the sexual partner.

**INTERVENTIONS**

All patients will be randomized 1:1 to either a remission-induction strategy (RIST) or a disease-control strategy (DISC).

→ **Remission Induction Strategy (RIST arm):**

The remission-induction strategy encompasses the administration of aggressive induction chemotherapy (HAM) and remission control after hematopoietic recovery. The induction chemotherapy has to start within 7 days from randomization as indicated in the following table:

For patients ≤ 60y

Days	1	2	3	4	5
<b>Cytarabine i.v.</b> 3 g/m <sup>2</sup> over 3h every 12 hours	X	X	X		
<b>Mitoxantrone i.v.</b> 10 mg/m <sup>2</sup>			X	X	X

For patients >60y

Days	1	2	3	4	5
<b>Cytarabine i.v.</b> 1 g/m <sup>2</sup> over 3h , every 12 hours	X	X	X		
<b>Mitoxantrone i.v.</b> 10 mg/m <sup>2</sup>			X	X	X

Once a complete remission has been confirmed within 42 days after start of induction treatment, or the disease has proven to be refractory to aggressive chemotherapy, the patient should be referred immediately to a transplant center and transplantation should be scheduled.

→ **Disease Control Strategy (DISC arm):**

The DISC arm aims at disease-monitoring and control until

	<p>start of the conditioning regimen prior to transplantation. The aim is not to induce a remission but to prevent complications from AML with the least toxic approach. Disease-monitoring without anti-leukemic therapy ("Watch and wait") is the preferred approach except for those patients with rapidly proliferating AML (see definitions). Transplantation should be scheduled as soon as possible. Pharmacologic options aimed at disease-control in patients with rapidly proliferating AML comprise low-dose AraC (LDAC) or single-dose mitoxantrone. The principal investigator must provide feedback to the study coordinator within three days from randomization about the chosen approach:</p> <p>Option A) Watch &amp; wait</p> <p><b>or</b></p> <p>Option B) LDAC: cytarabine 20 mg/ m<sup>2</sup> s.c. once a day for 10 days</p> <p><b>and / or</b></p> <p>Option C) Mitoxantrone 10 mg/ m<sup>2</sup> i.v. given as single intravenous infusion</p> <p>In the event of prolonged donor search and delayed start of the conditioning regimen, LDAC may be repeated at monthly intervals and mitoxantrone at weekly intervals up to maximum 3 doses. Patients may be switched from one pharmacologic strategy to the other before the start of conditioning.</p> <p>In both study arms, the final remission assessment will be performed up to Day +56 post-transplantation within 24 weeks after randomization.</p>
<p><b>Duration of study and follow-up</b></p>	<p><u>Duration of study per patient:</u> Up to 24 weeks</p> <p><u>Follow-up:</u> from FPLV until 2 years after LPFV</p>
<p><b>STUDY TYPE</b></p>	<p>The proposed trial is an open, randomized, two-arm, multicenter</p>

	<p>phase-III trial, using disease status, age and cytogenetic risk for treatment allocation.</p> <p>Stratification factors for randomization are disease status (relapse versus poor response AML), cytogenetic risk (adverse versus intermediate/good risk) and age (<math>\leq 60</math> years versus <math>&gt; 60</math> years).</p>
<p><b>STATISTICAL ANALYSIS</b></p>	<p>The primary endpoint of disease-free survival on Day 56 after HCT can be observed for all patients due to sufficient follow up. All patients who do not meet the criteria for this composite endpoint will be considered as failures. The endpoint will be interpreted as the success rate. The primary efficacy analysis will be done with the intent-to-treat and the per protocol population.</p> <p>The null hypothesis is <math>H_0: \pi_2 - \pi_1 \leq -0.05</math>, where <math>\pi_2</math> is the success rate in the DISC arm and <math>\pi_1</math> is the success rate in the RIST arm. The non-inferiority margin is 5%. The null hypothesis will be tested by means of the test for non-inferiority of binomial trials described by Farrington and Manning.</p> <p>No interim analyses are projected. A hierarchical test-strategy will be applied. First, non-inferiority of disease-control versus remission-induction will be tested in the Full Analysis Set (FAS). If non-inferiority can be demonstrated in the FAS, non-inferiority will also be tested in the per protocol population at the same significance level.</p> <p>Secondary endpoints will be analysed in the FAS, the per-protocol population and further subgroups of patients. No formal adjustment for the significance level will be performed for analyses of secondary endpoints. The primary efficacy analysis will be supplemented by the multivariate analysis of overall survival in the FAS. For this purpose a Cox regression model will be fitted.</p>
<p><b>SAMPLE SIZE</b></p>	<p>308 patients ( 154 in each arm).</p>
<p><b>TRIAL DURATION</b></p>	<p><u>First patient in:</u> Q1 2015</p> <p><u>Last patient in:</u> Q1 2018</p>

	<p><u>Last patient, last visit:</u> Q3 2018</p> <p><u>End of follow-up:</u> Q1 2020</p> <p><u>Duration of trial including follow-up:</u> 5 years</p>
<b>PARTICIPATING CENTERS</b>	15 centers – accounting for approximately 100 patients per year.