# Zusammenfassung des Abschlussberichtes

A multicenter Phase I/II trial investigating the safety and efficacy (CR rate and OS) of low dose AraC with Clofarabine in patients ≥ 60 years with AML not eligible for conventional Chemotherapy

*(Prospective, open-label, multicenter, phase I/II, dose-response trial)*

Kurztitel: Clofarabine

EudraCT-Nummer: 2009-017347-33

Register-Nummer: DRKS00000580

Datum der Fassung: 2014-01-28
Status der Fassung: Final1.0


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Studienbeginn: 03.03.2011
Studienabbruch (End of recruitment: 24.02.2012
Studienende (Last patient out): 25.10.2013

# Unterschriften

Die unterzeichnenden Autoren stimmen den Inhalten des vorliegenden Abschlussberichtes durch ihre Unterschriften zu. Die hier berichtete klinische Prüfung wurde nach den Grundsätzen der Deklaration von Helsinki, der Guten Klinischen Praxis (GCP) sowie den geltenden Gesetzen durchgeführt.

Sponsor/Bevollmächtigter des Sponsors

Leiter der Klinischen Prüfung/ Hauptprüfer

Biometriker

Ggf. weitere Autoren des Abschlussberichtes

## Inhaltsverzeichnis

## 1 Study Title

A multicenter Phase I/II trial investigating the safety and efficacy (CR rate and OS) of low dose AraC with Clofarabine in patients ≥ 60 years with AML not eligible for conventional Chemotherapy

## 2 Trial Design

Open-label, prospective, multicenter phase I (Dose-response)/II (Safety), study according AMG (German Drug Law).

## 3 Sponsor/Legal Representative of the Sponsor

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## 5 Trial sites incl. Principal Investigator

| Trial Site | Hauptprüfer |
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| Universitätsklinikum der Ernst-Moritz-Arndt-Universität Greifswald<br>Klinik und Poliklinik für Innere Medizin C, Hämatologie und Onkologie - Transplantationszentrum, Sauerbruchstraße, 17475 Greifswald | Prof. Dr. Gottfried Dölken |
| Universitätsklinikum Rostock, Klinik für Innere Medizin III, Hämatologie, Onkologie, Palliativmedizin, Ernst-Heydemann-Str. 6, 18055 Rostock | Prof. Dr. Christian Junghanss |
| Universität Leipzig, Selbstst. Abteilung f. Hämatologie, Internist. Onkologie und Hämostaseologie, Johannisallee 32 A, 04103 Leipzig | Prof. Dr. Dietger Niederwieser |
| Klinikum Chemnitz gGmbH, Klinik für Innere Medizin III, Hämatologie, Onkologie, Stammzelltransplantation, Bürgerstraße 2, 09113 Chemnitz | PD Dr. Mathias Hänel |
| Otto-von-Guericke-Universität, Universitätsklinikum Magdeburg<br>AöR, Zentrum für Innere Medizin, Klinik für Hämatologie/Onkologie, Leipziger Straße 44, 39120 Magdeburg | OA Dr. Thomas Heinicke |
| Universitätsklinikum Halle (Saale), Universität und Poliklinik für Innere Medizin IV, Onkologie, Hämatologie, Hämostaseologie, Ernst-Grube-Straße 40, 06120 Halle/Saale | Dr. Hans-Heinrich Wolf |

## 6 Publication (References)

n.a.

## 7 Dates and Duration

The first patient was included into this clinical trial at 03-Mar-2011, the follow-up of the last patient ended on 25-Oct-2013. That is, the trial lasted about 20 Months.
The trial was planned in two phases: I – Dose escalation and evaluation and II – Safety + tolerability on the final dose level determined during the dose escalation phase.
After 13 patients had been recruited the recruitment was stopped on 24-Feb-2012. That is, the second phase has been not reached ever.

Trial: First Patient in: 2011-03-03
End of Recruitment 2012-02-24
Last Patient last Visit: 2013-10-25

## 8 Objectives

This final report describes the methods of analysis and results of the final analysis of the Clofarabine study. This phase I/II trial was conducted to assess the safety and tolerability of Clofarabine administration in combination with low dose Ara-C for induction and consolidation treatment of elderly AML patients.

### Primary Objectives

Phase I – Dose escalation

To investigate feasibility of induction therapy with low dose Ara-C (20 mg/m$^2$ sc injection d1-d14) and clofarabine at three different dose levels for the first induction cycle (Clofarabine 10, 15 or 20 mg/m$^2$ 1h iv infusion d1-d5).

Phase II – Safety

To assess safety (in terms of AEs/ARs, SAEs/SARs and Adverse Reactions CTC Grade 4 (AR4)) of induction therapy with low dose AraC in combination with Clofarabine (at the dose level resulting from the dose escalation phase of the trial).

### Secondary Objectives

1. To determine the efficacy in terms of
   a. Response after induction therapy [incidence of complete remission (CR), complete remission with incomplete recovery (CRi), partial response (PR), resistant disease (RD), death during induction therapy]
   b. overall survival (OS)
   c. event-free survival (EFS)
   d. relapse-free survival (RFS)

   of low dose AraC in combination with Clofarabine (at the dose level resulting from the dose escalation phase of the trial)
2. To compare CR rates and overall survival with those of patients treated in the curative and palliative arm of the OSHO study for patients > 60 years (OSHO #69).
3. To analyse the subgroup of patients with intermediate and high risk cytogenetics
4. To determine the feasibility of allogeneic hematopoietic cell transplantation after reaching CR at the end of induction therapy.

# 9 Clinical Endpoints

### Primary Endpoints

This trial is designed to assess safety and feasibility (tolerability) of the induction treatment with Clofarabine in combination with low dose AraC. This is reflected by the following safety endpoints:

1. Adverse and serious adverse events during induction therapy
2. Adverse and serious adverse reactions during induction therapy
3. Adverse Reactions CTC grade 4 (AR4), as defined in section 8.1.

### Secondary Endpoints

- Response after induction therapy, assessed at d21 of the last cycle of induction therapy of the patient, with the following response categories:
    1. Complete remission (CR),
    2. Complete remission with incomplete recovery (CRi),
    3. Partial response (PR),
    4. Resistant disease (RD),
    5. Death during induction therapy (for further details see section 8.2).
- Overall survival (OS), defined as time from the date of enrolment to the day of death from any cause.
- Event-free survival (EFS), defined as time from the date of enrolment to the day of induction failure treatment, or relapse after CR or death from any cause. Patients not known to have experienced any of these events will be censored on the day they were last examined.
- Relapse-free survival (RFS), defined as time from the date of achievement of a complete remission to the day of relapse or death from any cause. Patients not known to have experienced any of these events will be censored on the day they were last examined. RFS is defined only for patients achieving CR.
- Allogeneic hematopoietic cell transplantation performed after reaching CR at the end of induction therapy (yes/no).

Overall survival time was calculated as difference from day of registration to the day of death for dead patients and to the day of study end (planned or not) for patients who survived. The least periods count as censored observations.

Overall survival time was the base of event-free survival time. If a patient on day 21 after start of his last induction cycle was assessed as PD (progression of disease) or SD (stable disease) this was counted as “induction failure”. Patients who suffered a haematological relapse after CR were counted as “relapse”.

# 10 Design/Methods

Clofarabine is a prospective, one-arm, unblinded dose-response study (see chapter 15) without randomisation.

The trial starts with a dose escalation phase with regard to the dose of Clofarabine. Three cohorts of 3-6 patients will be included in the dose escalation phase. All further patients will be treated at the dose level resulting from the dose escalation phase. Patient recruitment will continue until a total of 60 patients are included. For further details see section **Fehler! Verweisquelle konnte nicht gefunden werden.**.

A DMC would have assess the safety aspects of the trial after inclusion of 20 patients, and will recommend whether to stop the trial for safety concerns or not. Because of early recruitment stop the DMC had not met.

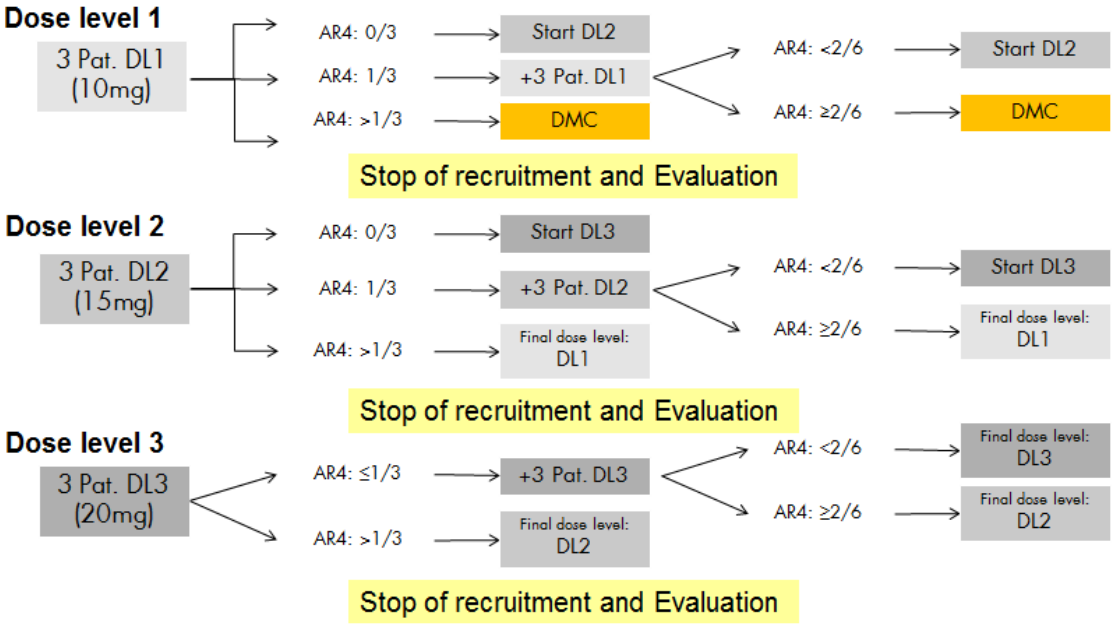



Fig. 10.1: Dose escalation scheme

### Data processing and software

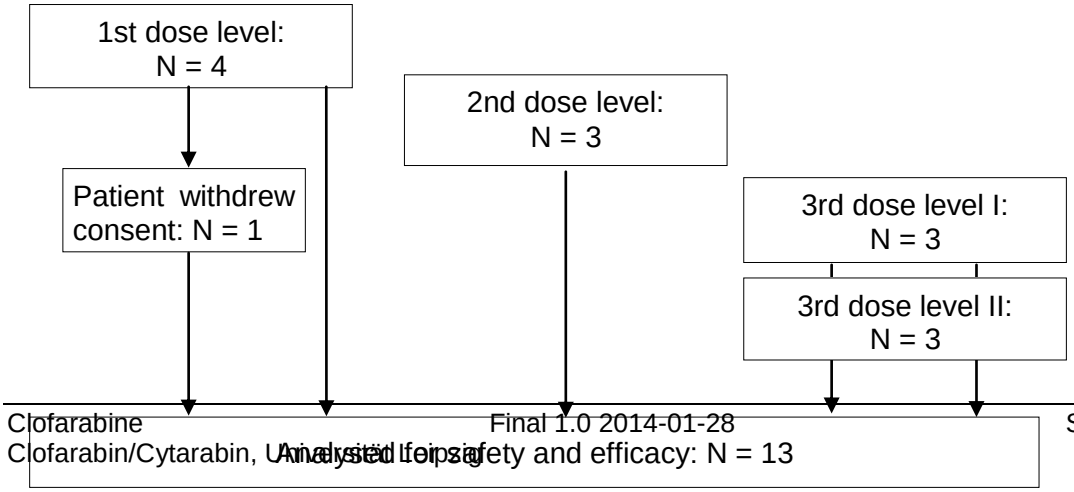
All data were recorded on paper CRFs and later input into an electronical database (eRT). Data quality was saved by double-data entry check and by plausibility checks. Detected inconsistencies were queried and the data were corrected, if necessary.

MedDRA-Coding of concomitant diseases and medications as well as adverse events was performed via the recent English-language MedDRA-Version 16 by October 2013. If suitable, automatic Coding procedures were preferred. A final snapshot of the database was generated as basis for all analyses.

## 11 Number of Patients

Planned: 60, realized: 13
Because the trial was stopped prematurely the ITT analysis population consists only of the recruited13 patients. All patients except the one who withdrew consent belong to the PP set.

### Flow-Diagram



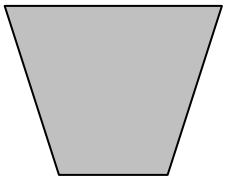
## 12 Inclusion Criteria

1. Diagnosis of AML as defined by WHO
2. Primary or secondary AML
3. Age ≥ 60 years
4. Not eligible for standard/"curative" chemotherapy as described in the schemes
5. Adequate renal and hepatic functions as indicated by ALL of the following laboratory values:

- Serum creatinine ≤ 1.0 mg/dL (≤ 88,4 µmol/l) or if serum creatinine > 1.0 mg/dL (> 88,4 µmol/l), then the estimated glomerular filtration rate (GFR) must be > 60 mL/min/1.73 $m^2$ as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 $m^2$) = 186 x (Serum Creatinine)-1.154 x (age in years)-0.023 x (0.742 if patient is female) x (1.212 if patient is black)
- Serum bilirubin ≤ 1.5 mg/dL (17,1 µmol/l) × upper limit of normal (ULN)
- Aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 2.5 × ULN
- Alkaline phosphatase ≤ 2.5 × ULN

6. Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent.
7. Written informed consent (ICF)

Comorbidity Score; Definition of *"ineligible for curative treatment with standard chemotherapy"*

| Score | Comorbidity groups | Conventional chemotherapy | Intensity of treatment |
|---|---|---|---|
| 0 | low | ***eligible*** |  |
| 1-2 | intermediate | | |
| 3 or more | high | ***not eligible*** | |

| **Comorbidity** | **Definitions** | **HCT-CI weighted scores** |
|---|---|---|
| Arrhythmia | Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias | **1** |
| Cardiac | Coronary artery disease, †congestive heart failure, myocardial infarction, or EF ≤ 50% | **1** |
| Inflammatory bowel disease | Crohn disease or ulcerative colitis | **1** |
| Diabetes | hypoglycaemic but not diet alone | **1** |
| Cerebrovascular disease | Transient ischemic attack or cerebrovascular accident | **1** |
| Psychiatric disturbance | Depression or anxiety requiring psychiatric consult or treatment | **1** |
| Hepatic, mild | Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN | **1** |
| Obesity | Patients with a body mass index > 35 kg/$m^2$ | **1** |
| Infection | Requiring continuation of antimicrobial treatment after day 0 | **1** |
| Rheumatologic | SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica | **2** |
| Peptic ulcer | Requiring treatment | **2** |
| Moderate/severe renal | Serum creatinine > 2 mg/dL ( > 177µmol/l), on dialysis, or prior renal transplantation | **2** |

| Comorbidity | Definitions | HCT-CI weighted scores |
|---|---|---|
| Moderate pulmonary | DLCO and/or $FEV_1$ 66%-80% or dyspnoe on slight activity | **2** |
| Prior solid tumour | Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer | **3** |
| Heart valve disease | Except mitral valve prolapse | **3** |
| Severe pulmonary | DLco and/or $FEV_1 \leq 65\%$ or dyspnoea at rest or requiring oxygen | **3** |
| Moderate/severe hepatic | Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN | **3** |

## 13 Exclusion Criteria

- Diagnosis of AML M3
- Current concomitant chemotherapy, radiation therapy, or immunotherapy with some exceptions (listed in the protocol)
- Use of investigational agents within 30 days or any anticancer therapy within 2 weeks before study entry. The patient must have recovered from all acute toxicities from any previous therapy.
- Have any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver, or other organ system that may place the patient at undue risk to undergo treatment.
- Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
- Hypersensitivity to Clofarabine, AraC or one of their components.
- Pregnant or nursing women.
- Any significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, interfere with consent, study participation, follow up, or interpretation of study results.
- Have had a diagnosis of another malignancy, unless the patient has been disease-free for at least 3 years following the completion of curative intent therapy, with the following exceptions:
- Patients with treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed.
- Patients with organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated or a radical prostatectomy has been performed.
- Psychiatric illness that would prevent granting of informed consent.
- Active viral infection with known human immunodeficiency virus (HIV) or viral hepatitis type B or C.
- Ongoing drug abuse.
- Women with child bearing potency without effective contraception (i. e. implants, injectables, combined oral contraceptives, some IUDs or vasectomised partner) during the conduct of the trial. Patients using hormonal methods of contraception must be informed about possible influences of the study drug on contraception.
- Concomitant participation in other clinical trials: During the verification of the in- and exclusion criteria the trial physician checks, if the patient is participating in any other interventional clinical trials following the AMG at the same time. Should this be the case, the patient will not be included. Simultaneously the patient declares not to take part in any parallel interventional clinical trials following the AMG by signing the informed consent sheet.

# 14 Investigational Medicinal Products incl. Reference Medication

## 14.1 Investigational Medicinal Products

| Generic name | Clofarabine |
|---|---|
| **Brand product** | Evoltra® |
| **Registration** | EU/1/06/334/005 (1 vial) |
| **Manufacturer** | Genzyme Europe B.V.<br>Gooimeer 10<br>1411 DD Naarden<br>Netherlands<br>Tel: +31 (0)35 699 1200<br>Fax: +31 (0)35 699 3214 |
| **Provision of study medication** | Genzyme Europe B.V.<br>Gooimeer 10<br>1411 DD Naarden<br>Netherlands<br>Tel: +31 (0)35 699 1200<br>Fax: +31 (0)35 699 3214 |
| **Pharmaceutical form** | - 20 ml (20 mg Clofarabine) single use vial<br>- clear, transparent solution<br>▪ Additives: - Sodium chloride<br>- Water |
| **Container** | 1 vial in a box |
| **Storage** | Vials must be stored at a temperature under 30˚C, also transient storage at a temperature of 50˚C should be avoided |
| **Stability** | 3 years |
| **Reconstitution/Preparation** | Reconstitution will be performed in the study centres' pharmacy.<br><br>Clofarabine should be filtered through a sterile 0,2 micron syringe filter and then diluted with 0.9% Sodium Chloride Injection. If this is not applicable, Clofarabine should be filtered through a 5 micron syringe filter, then be diluted and should be administered through a 0,22 micron in-line-filter.<br><br>The final volume is at the clinician's discretion depending upon several factors including total clofarabine dose (in mg/m$^2$) and patient age/size, clinical condition and hydration status. The majority of clinical study sites used a final volume of 100-200 ml (0.9 % sodium chloride).<br><br>The dilution should be clear and transparent. Before administration a visual check should ensure that there are no solid particles or discolourings in the dilution. |
| **Stability of dilution** | 3 days at a temperature of 2-8˚C or controlled room temperature/room temperature |
| **Incompatibilities** | To prevent drug incompatibilities, no other medications should be infused concurrently through the same IV lines as clofarabine. Also, no blood products should be administered at the same time as clofarabine |
| **Supplier Lot No. of used Medication** | A453096 |

| Generic name | Cytarabine |
|---|---|
| **Brand product** | Udicil (exemplary) |
| **Manufacturer** | PHARMACIA GmbH<br>ein Unternehmen der PFIZER-Gruppe<br>Pfizerstr. 1<br>76139 Karlsruhe<br>Tel +49-721-61 01-90 00, Fax +49-721-62 03-90 00 |
| **Provision of study medication** | Cytarabine will be provided by each study centre |
| **Pharmaceutical form** | - Dry chemical (lyophilisate)<br>- White, crystalline, odourless<br>- Additives: hydrochloric acid 1,8%; sodium hydrate<br>- Solvent (5 ml): sodium chloride, water for injection |

| | |
|---|---|
| **Container** | Glass container, polyethylene lid |
| **Storage** | Without reservation |
| **Stability** | 5 years |
| **Reconstitution/Preparation** | Dilution with NS 0,9 %, D5W or water for injection |
| **Stability of dilution** | - 0,5 mg/ml: 7 days NS 0,9 %, D5W or water for injection at room temperature<br>- 8-32 mg/ml: 7 days NS 0,9 %, D5W, NS 0,2 % + D5W or water for injection at room temperature<br>- 2 mg/ml: 8 days NS 0,9 % + D5W with 50 mq/ml with KCl at room temperature<br>- 0,2-1,0 mg/ml: 7 days D5W, D5W + NS 0,2 % with 50 mq/l $NaHCO_3$ at room temperature<br>Dilution should be applied within 12 hours for microbiological safety reasons. |
| **Incompatibilities** | In-vitro incompatibility with fluorouracil, gentamicin, penicillin G, oxacillin, Heparin (not with ready for use solution), insulin und methylprednisolone |

### 14.2 Investigational Medicinal Reference Product

n.a.

## 15 Treatment

The trial started with a dose escalation phase with regard to the dose of Clofarabine. Three cohorts of 3-6 patients were included in the dose escalation phase. All further patients were treated at the dose level resulting from the dose escalation phase.

During the dose evaluation phase, the investigational treatment consists of a maximum of four (dose level 1), three (dose level 2) resp. two (dose level 3) induction and a maximum of four consolidation cycles of the combined therapy with Clofarabine and low-dose AraC (refer to figure 10.1).
The dose escalation algorithm is based on the incidence of adverse reactions with CTC Grade 4 during the individually first induction cycle (at least 3 informative patients with respect to AR4 with at minimum survival of 14 days).

Every of at maximum four consolidation cycles consisted of three days of Clofarabine (15 mg/m²) and 7 days of AraC (20 mg/m²) administration (parallel).
AraC will be given in all induction and all consolidation cycles at a dose of 20 mg/$m^2$ per day.

Duration per patient: Every induction cycle comprises 14 days; every consolidation cycle comprises 7 days of treatment. Following cycles started 28-49 days after the preceding cycle.

The treatment plan is described in paragraph 5 of the Trial Protocol. The recruitment of the trial was stopped in phase I (dose escalation on level 3) on 24-Feb-2012.

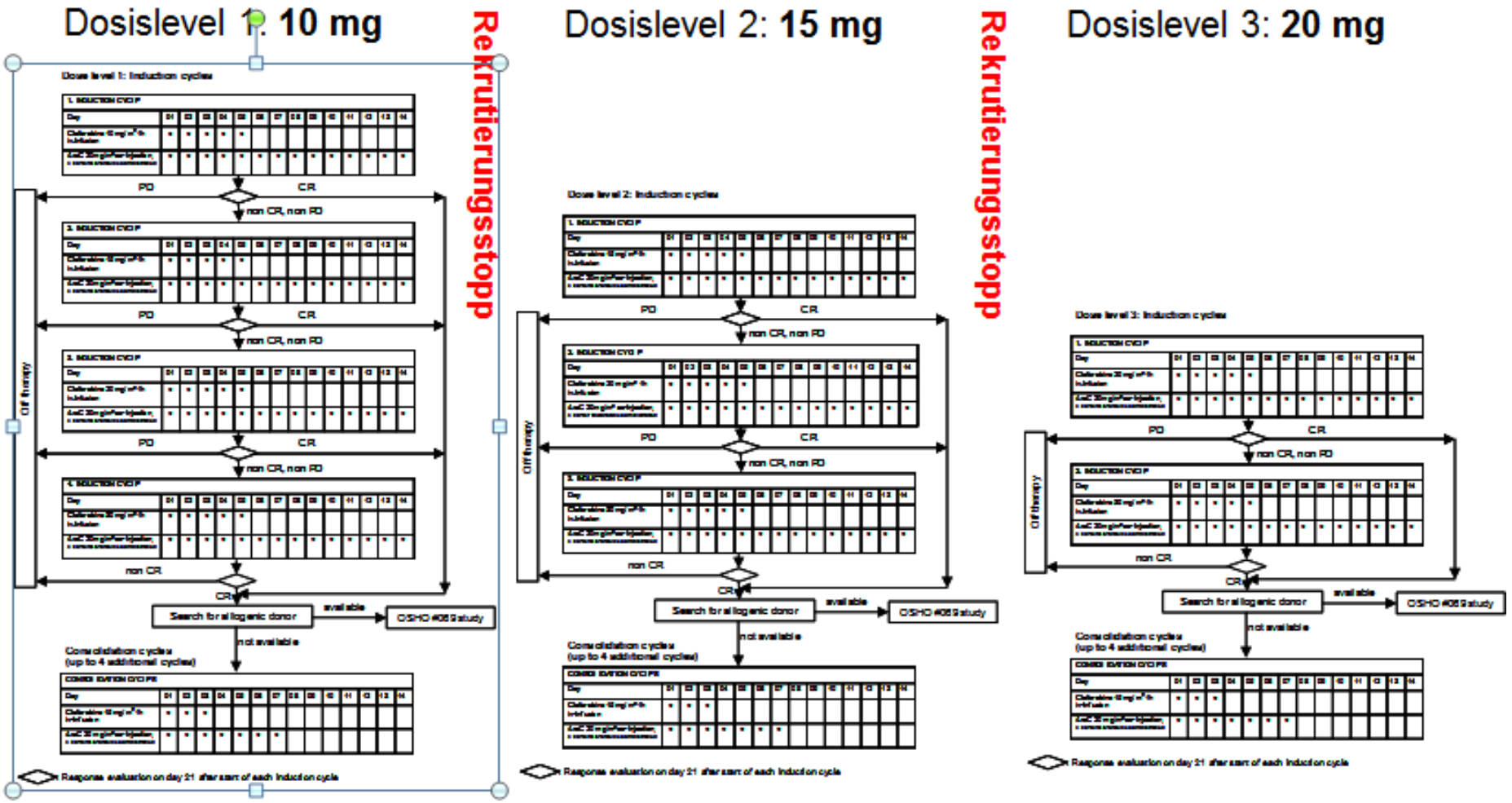
| | **Patients (n)** | |
|---|---|---|
| **Dose level 1** | 4 | At most four induction cycles were planned: five days of Clofarabine and 14 days of AraC (20 mg/m²) administration. Cycle 1 started with a Clofarabine dose of 10 mg/m². 21 days after start of the induction cycle response was evaluated. If CR was achieved donor search for stem cell transplantation started.<br>If CR was not achieved cycle two started after 7 to 28 day with increased dose (15 mg/m²) of Clofarabine and 20 mg/m² AraC. |
| **Dose level 2** | 3 | Maximal three induction cycles of five days Clofarabine and 14 days AraC were planned: The first started with a Clofarabine dose of 15 mg/m², the second of 20 mg/². (A third cycle was not reached.) Ara-C dose was constantly 20 mg/m² per day. Analogous to dose level 1 at most four consolidation cycles were planned. |

| | | |
|---|---|---|
| **Dose level 3** | 6 | Maximal two induction cycles of five days of Clofarabine and 14 days of AraC administration were planned: Induction cycle 1 started with dose 20 mg/m², cycle 2 with dose 30 mg/m². Per day 20 mg/m² Ara-C was applied.<br>Consolidation consisted of maximal four cycles of 3 days of Clofarabine (15 mg/m²) and 7 days of Ara-C (20 mg/m²) administration. |

**Follow-up-Phase**

Planned Follow-ups with intervals to the last administration of study drug:

1. Month 1
2. Month 4
3. Month 7
4. Month 10
5. Month 13


Dosislevel 1: 10 mg
Rekrutierungsstopp
Dosislevel 2: 15 mg
Rekrutierungsstopp
Dosislevel 3: 20 mg
Off therapy
PD
CR
non CR, non PD
non CR
Search for allogenic donor
available
not available
OSHO #088study
Consolidation cycles
(up to 4 additional cycles)
Response evaluation on day 21 after start of each induction cycle

# 16 Statistical Methods/Evaluation process

The study cohort was characterized purely by descriptive statistics, that is, mean ± standard deviation for continuous, number (percent) for categorical variables. Frequencies are estimated inclusive 95% confidence intervals following Wilson (compare Newcomb 1998) and compared by Fisher's exact test.Overall event- and relapse-free survival was analysed and depicted by Kaplan-Meier method. Analogously median survival inclusive 95% confidence interval was calculated.

All analyses were performed by IBM SPSS Statistics, version 20 and the R package {binom}.

According to trial protocol, it was planned to restrict the main analysis to those patients enrolled at the final dose level (see section 11.2 of the trial protocol). A secondary analysis including all patients was to be performed additionally.

Given that only 13 patients were enrolled, all patients will be included, and no analysis restricted to patients on the final dose levels will be performed.

# 17 Results

## 17.1 Analyses of Efficacy

### 17.1.1 Treatment Response

Treatment response by patient and cycle is listed in the table below (17.1).

Tab. 17.1: Therapy and response

| PatID | Induction | | | | | | Consolidation | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st cycle | | 2nd cycle | | 1st cycle | | 2nd cycle | | 3rd cycle | | 4th cycle | |
| | given | response | given | response | given | response | given | response | given | response | given | response |
| 10015 | yes | SD | yes | SD | | | | | | | | |
| 11017 | yes | † | | | | | | | | | | |
| 11020 | yes | PD | $ | | | | | | | | | |
| 11034 | yes | PD | no | | | | | | | | | |
| 10029 | yes | SD | yes | D | | | | | | | | |
| 11048 | yes | PD | | | | | | | | | | |
| 11051 | yes | SD | & | | yes | CR | yes | -- | yes | CRi | yes | CRi |
| 10032 | yes | CRi | ‡ | | | | | | | | | |
| 11065 | yes | SD | ‡ | | | | | | | | | |
| 11079 | yes | CRi | ‡ | | | | | | | | | |
| 11082 | yes | CRi | | | yes | | yes | | yes | | | |
| 11096 | yes | CRi | | | yes | | yes | | yes | # | | |
| 11106 | yes | CRi | | | yes | | yes | | yes | | yes | |

CRi Complete remission with incomplete recovery, SD stable disease, PD progression of disease, D death

† Bone marrow aspiration of patient 11017 failed (punctio sicca). She died two weeks later.
‡ These patients died a few weeks after the 1st induction cycle.
$ Patient 11020 received "Mini MitoFlag due to recidive", died later
# Patient 11096 having 60% blasts after the 1st induction cycle received Daunorubicin and Ara-C (best standard care)
& A second response evaluation on day 30 gave CR and patient 11051 then received consolidation (see 3.3).

Induction response of the 13 patients according to IWG criteria is estimated as:

Table 17.2: Induction response

| Response | N | % [95% CI] |
|---|---|---|
| CR† | 1 /13 | 7.7 [0.4 – 33.3]% |
| CRi | 5 /13 | 38.5 [17.7 – 64.5]% |
| PR | 0 /13 | 0 [0 – 22.8]% |
| SD | 3 /13 | 23.1 [8.2 – 50.3]% |
| PD | 3 /13 | 23.1 [8.2 – 50.3]% |
| Death | 1 /13 | 7.7 [0.4 – 33.3]% |

CI = confidence interval
† Pat. 11051 is counted as CR here (see Tab. 17.1)

Only one CR after induction was observed on dose levels 1 and 2, while 5 of 6 patients treated on dose level 3 had a CRi after induction. These frequencies (1 of 7 vs. 5 of 6) are significantly different (p = 0.029).

### 17.1.2 Overall survival

During the study period 11 of 13 patients died. One patient withdrew his consent, and is censored at time of withdrawal. One patient was still alive. Figure 17.1 shows overall survival.

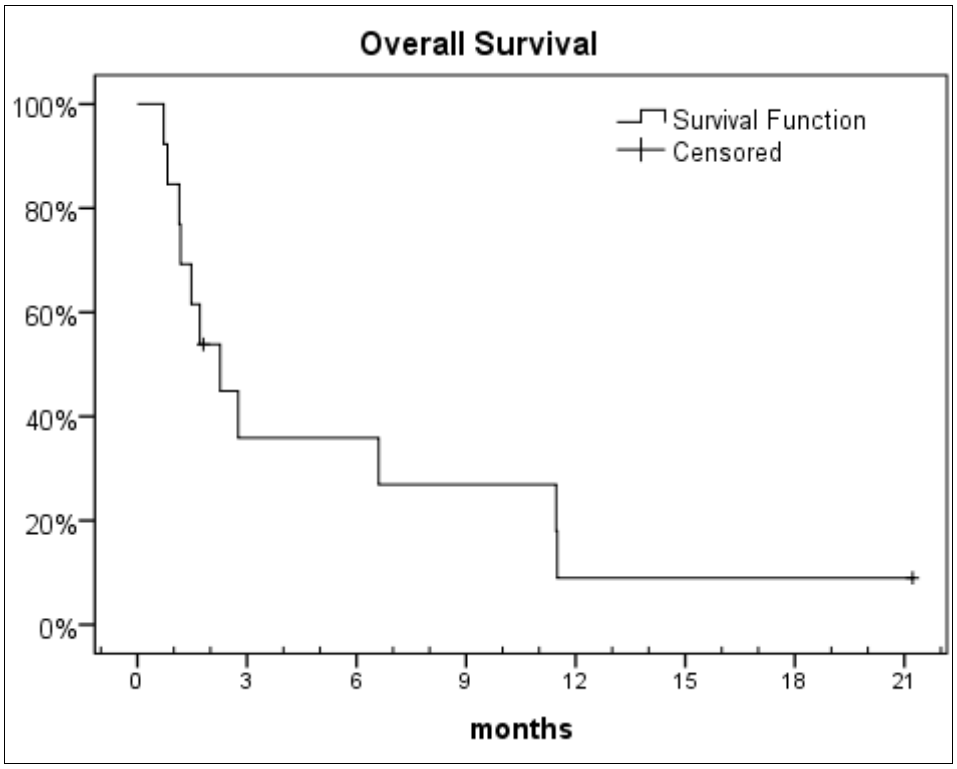



Fig. 17.1: Overall survival

The median survival is 2.27 months (see Table 17.3)

Tab. 17.3: Estimated median overall survival (months)

| Estimate | Std. Error | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 2.27 | 0.67 | 0.96 | 3.58 |

The following Table 17.4 describes causes of death. All deceased patients had either initial disease progression or haematological relapse after CRi. In two cases with haematological relapse, infection resp. urosepsis was considered as main cause of death.

Tab. 17.4: Causes of death

| Cause | Number | Comment |
|---|---|---|
| Progression of disease | 4 | |
| Haematological relapse | 4 | |
| Infection[$] | 4† | |
| Death from other cause | 1‡ | Urosepsis |

†‡ Two patients are counted double. Both had a haematological relapse; one died from an infection, another from urosepsis.

$ Pathogen is not specified.

The median overall survival (in months) by dose level is represented in Tab. 17.5 and depicted by Kaplan Meier curves (Fig. 17.2).

Tab. 17.5: Median overall survival (months) by dose level

| Dose level | Estimate | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 1 | 2.3 | 0.9 | 0.6 | 3.9 |
| 2 | 1.7 | 0.8 | 0.1 | 3.3 |
| 3 | 1.5 | 3.3 | 0.0 | 8.0 |

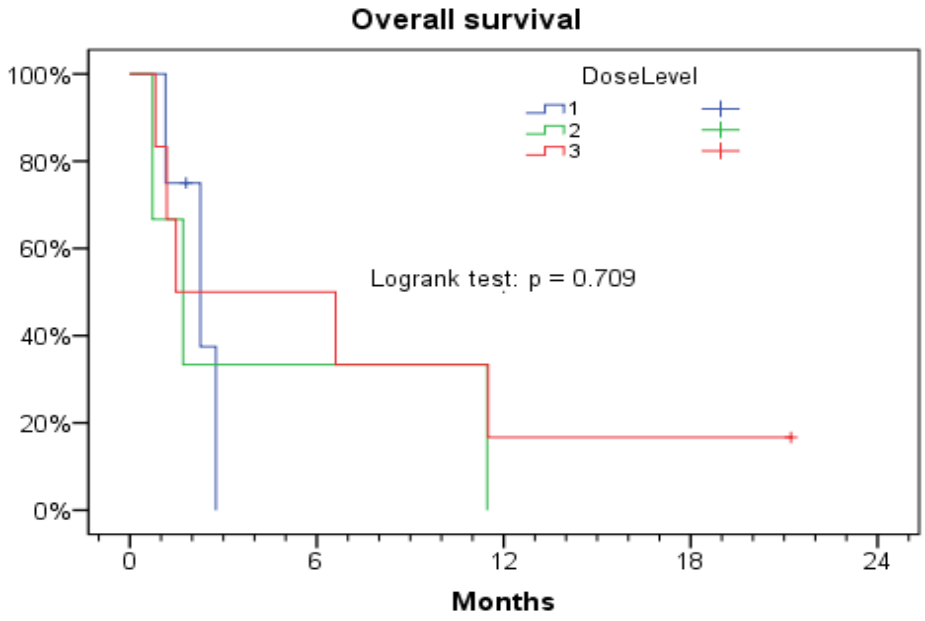



Fig. 17.2: Overall survival by dose level

### 17.1.3 Event-free survival (months)

#### EFS for all 13 patients

All patients suffered an event during the study period. Table 17.6 shows types of event, Figure 17.3 shows the estimated event-free survival curve.

Tab. 17.6: Event-free survival: number of events (first event only)

| Event | Count | % [95% CI] |
|---|---|---|
| Induction failure | 6 | 46.2 [23.2, 70.9]% |
| Relapse | 2 | 15.4 [4.3, 42.2]% |
| Death | 5 | 38.5 [17.7, 64.5]% |
| Total | 13 | |

CI = confidence interval

The median event-free survival is 34 days (refer to Table 17.7).

Tab. 17.7: Estimated median event-free survival (months)

| | | 95% Confidence Interval | |
|---|---|---|---|
| Estimate | Std. Error | Lower Bound | Upper Bound |
| 1.12 | 0.30 | 0.53 | 1.77 |

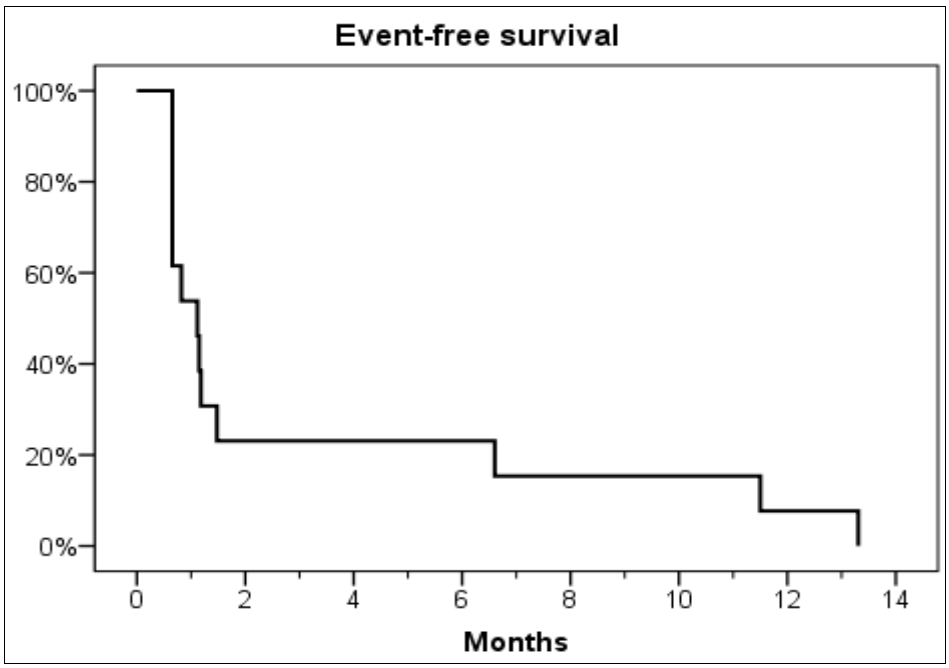



Fig. 17.3: Event-free survival

#### EFS by dose level

Tab. 17.8: Mean EFS by dose level (months)

| Dose Level | Estimate | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 1 | 0.90 | 0.63 | 1.2 |
| 2 | 0.66 | 0.66 | 0.66 |
| 3 | 5.8 | 1.4 | 10.3 |

Please note: Confidence intervals for the median EFS were not available due to the small sample. The estimates for mean are not very reliable for the same reason.

There is a significant (global) difference in EFS between the three dose levels (p = 0.004). If the patients from dose levels 1 and 2 are pooled and compared with dose level 3 this difference remains significant (p = 0.002).

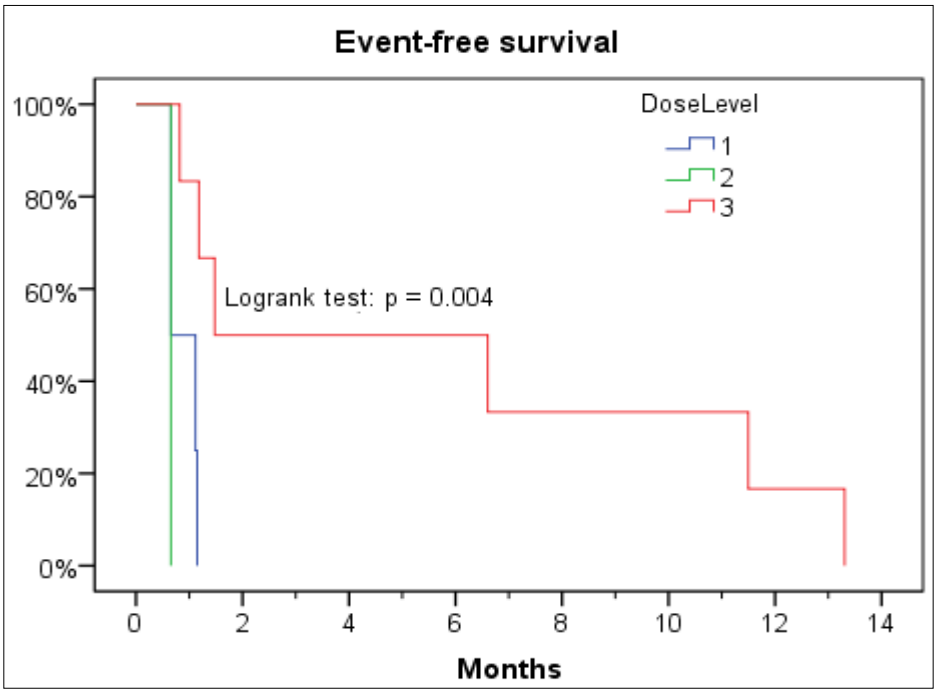



Fig. 17.4: Event-free survival per dose level

### 17.1.4 Relapse-free survival (months)

Only 6 patients achieved CR or CRi. Two of them had a relapse, the other died.

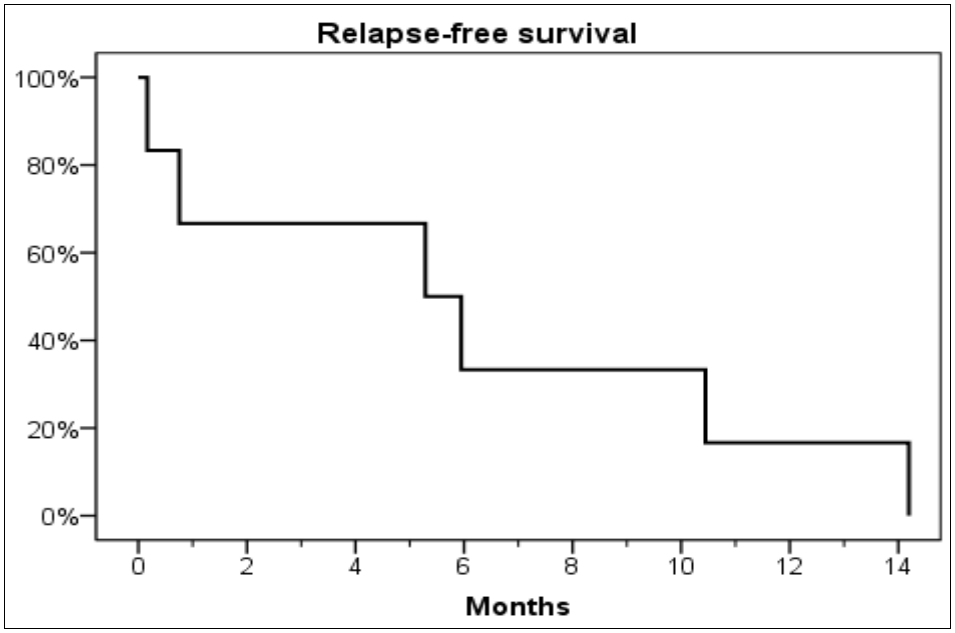



Fig. 17.5: Relapse-free survival

Tab. 17.9 Median relapse-free survival (months)

| | | 95% Confidence Interval | |
|---|---|---|---|
| Estimate | Std. Error | Lower Bound | Upper Bound |
| 5.29 | 3.18 | 0 | 11.5 |

Median relapse-free survival for the 6 patients who had reached CR or CRi is 161 days (compare Tab. 17.9). However, the estimate is not very reliable due to the small number of patients.

## 17.2 Analyses of Safety

This synopsis includes the last obligatory Annual Safety Report.

The main objective of the trial was to assess safety of the combined Clofarabine and Ara-C treatment. We analyse therefore primarily

(1) (Serious) adverse events during induction
(2) (Serious) adverse reactions during induction
(3) Adverse reactions CTC grade 4 during the first 14 days of the first induction cycle

In addition, we describe adverse events and reactions during consolidation therapy.

### 17.2.1 Analysis population

All 13 patients are included into the analysis.

### 17.2.2 Adverse events during induction

The following table 17.10 describe adverse events during induction.
In table 6.1. all adverse events are listed, grouped by induction cycle, dose level and severity (CTC grade 1-2 vs 3-5).
A total of 243 adverse events were reported in 13 patients during the first induction cycle, i.e. on average 18.7 adverse events per patient. From these, 41 adverse events were classified as CTC grade >=3, on average 3.15 adverse events CTC grade >=3 per patient. There is a trend towards a higher number of adverse events CTC grade >=3 with increasing Clofarabine dose: the mean number of events is 2.75 on dose level 1, 3.0 on dose level 2 and 3.15 on dose level 3.

Tab. 17.10: Adverse events during induction cycles

| | | **1st Induction** | | | | | | **2nd Induction** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Dose level** | | | | | | **Dose level** | | | |
| | | **1 N at risk: 4** | | **2 N at risk: 3** | | **3 N at risk: 6** | | **1 N at risk: 1** | | **2 N at risk: 1** | |
| | | **CTC grade** | | **CTC grade** | | **CTC grade** | | **CTC grade** | | **CTC grade** | |
| **System organ class** | **Preferred term** | **1-2** | **3-5** | **1-2** | **3-5** | **1-2** | **3-5** | **1-2** | **3-5** | **1-2** | **3-5** |
| **Cardiac disorders** | Arrhythmia | 2 | 0 | 1 | 1 | 3 | 0 | 0 | 0 | 0 | 0 |
| | **Total†** | **2** | 0 | **1** | **1** | **3** | 0 | | 0 | | 0 |
| **Eye disorders** | Eye haemorrhage | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Eye pain | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | | 0 | | 0 | **2** | 0 | | 0 | | 0 |
| **Gastrointestinal disorders** | Abdominal pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Abdominal pain upper | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | Ascites | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

| System organ class | Preferred term | 1st Induction | | | | | | 2nd Induction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Dose level | | | | | | Dose level | | | |
| | | 1 N at risk: 4 | | 2 N at risk: 3 | | 3 N at risk: 6 | | 1 N at risk: 1 | | 2 N at risk: 1 | |
| | | CTC grade | | CTC grade | | CTC grade | | CTC grade | | CTC grade | |
| | | 1-2 | 3-5 | 1-2 | 3-5 | 1-2 | 3-5 | 1-2 | 3-5 | 1-2 | 3-5 |
| | Diarrhoea | 0 | 0 | 4 | 0 | 3 | 4 | 0 | 0 | 1 | 0 |
| | Intestinal obstruction | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mouth haemorrhage | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Nausea | 3 | 0 | 2 | 0 | 6 | 0 | 0 | 0 | 0 | 0 |
| | Vomiting | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **6** | **0** | **6** | **0** | **15** | **4** | | **0** | **2** | **0** |
| **General disorders and administration site conditions** | Fatigue | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mucosal inflammation | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Oedema peripheral | 0 | 0 | 4 | 0 | 6 | 0 | 0 | 0 | 0 | 0 |
| | Pain | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pyrexia | 2 | 2 | 4 | 0 | 7 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **5** | **3** | **8** | **2** | **14** | **0** | | **0** | | **0** |
| **Immune system disorders** | Hypersensitivity | 1 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **1** | **0** | **2** | **0** | **1** | **0** | | **0** | | **0** |
| **Infections and infestations** | Cystitis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Cystitis escherichia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Enterococcal sepsis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Erysipelas | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Infection | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Lung infection | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Pneumonia | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| | Pneumonia fungal | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| | Sepsis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Soft tissue infection | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Urinary tract infection | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **2** | **4** | **1** | **1** | **6** | **3** | | **1** | | **1** |
| **Injury, poisoning and procedural complications** | Excoriation | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Fall | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **2** | **0** | | **0** | | **0** | | **0** | | **0** |
| **Investigations** | Alanine aminotransferase increased | 0 | 0 | 4 | 0 | 6 | 2 | 0 | 0 | 1 | 0 |
| | Aspartate aminotransferase increased | 2 | 0 | 5 | 0 | 7 | 4 | 0 | 0 | 0 | 1 |
| | Blood alkaline phosphatase increased | 2 | 0 | 2 | 0 | 6 | 0 | 1 | 0 | 1 | 0 |
| | Blood bilirubin increased | 2 | 0 | 3 | 1 | 11 | 0 | 0 | 1 | 1 | 0 |
| | Blood iron | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Weight decreased | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | Weight increased | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **8** | **0** | **15** | **1** | **32** | **6** | **2** | **1** | **3** | **1** |
| **Metabolism and** | Hyperglycaemia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

| System organ class | Preferred term | 1st Induction | | | | | | 2nd Induction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Dose level | | | | | | Dose level | | | |
| | | 1 N at risk: 4 | | 2 N at risk: 3 | | 3 N at risk: 6 | | 1 N at risk: 1 | | 2 N at risk: 1 | |
| | | CTC grade | | CTC grade | | CTC grade | | CTC grade | | CTC grade | |
| | | 1-2 | 3-5 | 1-2 | 3-5 | 1-2 | 3-5 | 1-2 | 3-5 | 1-2 | 3-5 |
| **nutrition disorders** | Hypoproteinaemia | 1 | 0 | 0 | 2 | 9 | 2 | 1 | 0 | 1 | 0 |
| | **Total** | **1** | **0** | **0** | **2** | **9** | **3** | **1** | **0** | **1** | **0** |
| **Musculoskeletal and connective tissue disorders** | Arthralgia | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | Musculoskeletal pain | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pain in extremity | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | | **0** | | **0** | **4** | **0** | | **0** | | **0** |
| **Nervous system disorders** | Altered state of consciousness | 1 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Dizziness | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Headache | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | **Total** | **1** | **1** | **3** | **0** | **2** | **0** | | **0** | **1** | **0** |
| **Psychiatric disorders** | Depression | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | **Total** | | **0** | | **0** | | **0** | **1** | **0** | | **0** |
| **Renal and urinary disorders** | Haematuria | 2 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| | Renal failure | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 1 | 0 |
| | Urethral haemorrhage | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **4** | **0** | **2** | **0** | **7** | **1** | | **0** | **1** | **0** |
| **Respiratory, thoracic and mediastinal disorders** | Cough | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Dyspnoea | 1 | 1 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 1 |
| | Epistaxis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pleural effusion | 0 | 0 | 3 | 0 | 2 | 1 | 0 | 0 | 1 | 0 |
| | **Total** | **2** | **1** | **6** | **2** | **6** | **4** | **0** | **0** | **1** | **1** |
| **Skin and subcutaneous tissue disorders** | Alopecia | 1 | 2 | 1 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| | Blood blister | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Decubitus ulcer | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Dermatitis | 1 | 0 | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| | Intertrigo | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Palmar-plantar erythrodysaesthesia syndrome | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Petechiae | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pruritus | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **2** | **2** | **6** | **0** | **13** | **0** | | **0** | | **0** |
| **Vascular disorders** | Haemorrhage | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Phlebitis | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **1** | **0** | **1** | **0** | | **0** | | **0** | | **0** |
| **TOTAL** | | **37** | **11** | **51** | **9** | **114** | **21** | **4** | **2** | **9** | **3** |

† Totals: Sums = 0 are faded out (white color)

### 17.2.3 Adverse reactions during induction

The following table 17.11. describes adverse reactions during induction, i.e. adverse events deemed to be relate to either Clofarabine or Ara-C or both.

A total of 123 adverse events reported during the first induction cycle were classified as adverse reactions (about 50% of all 243 adverse events). The same percentage holds for the adverse reactions with CTC grade >=3 (20 of 41 Adverse events).

Tab. 17.11 Adverse events during induction related to either Clofarabine or Ara-C or both (=Adverse reactions)

| | | 1st Induction | | | | | | 2nd Induction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Dose level | | | | | | Dose level | | | |
| | | 1 N at risk: 4 | | 2 N at risk: 3 | | 3 N at risk: 6 | | 1 N at risk: 1 | | 2 N at risk: 1 | |
| System organ class | Preferred term | CTC grade | | CTC grade | | CTC grade | | CTC grade | | CTC grade | |
| | | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 | 3-4 |
| **Cardiac disorders** | Arrhythmia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total†** | | 0 | | 0 | **1** | 0 | | 0 | | 0 |
| **Gastrointestinal disorders** | Abdominal pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | Abdominal pain upper | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Diarrhoea | 0 | 0 | 3 | 0 | 1 | 3 | 0 | 0 | 1 | 0 |
| | Nausea | 0 | 0 | 2 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| | Vomiting | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | | 0 | **5** | 0 | **9** | **3** | | 0 | **2** | 0 |
| **General disorders and administration site conditions** | Mucosal inflammation | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Oedema peripheral | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pain | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Pyrexia | 2 | 1 | 1 | 0 | 4 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **4** | **1** | **1** | 0 | **5** | 0 | | 0 | | 0 |
| **Immune system disorders** | Hypersensitivity | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | | 0 | **2** | 0 | | 0 | | 0 | | 0 |
| **Infections and infestations** | Pneumonia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Pneumonia fungal | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| | **Total** | | **1** | | 0 | | **1** | | **1** | | **1** |
| **Investigations** | Alanine aminotransferase increased | 0 | 0 | 3 | 0 | 5 | 2 | 0 | 0 | 1 | 0 |
| | Aspartate aminotransferase increased | 1 | 0 | 4 | 0 | 7 | 4 | 0 | 0 | 0 | 1 |
| | Blood alkaline phosphatase increased | 1 | 0 | 2 | 0 | 6 | 0 | 1 | 0 | 1 | 0 |
| | Blood bilirubin increased | 2 | 0 | 3 | 1 | 9 | 0 | 0 | 1 | 1 | 0 |
| | Weight decreased | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | Weight increased | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **5** | 0 | **13** | **1** | **29** | **6** | **2** | **1** | **3** | **1** |
| **Metabolism and nutrition disorders** | Hypoproteinaemia | 1 | 0 | 0 | 2 | 5 | 0 | 0 | 0 | 1 | 0 |
| | **Total** | **1** | 0 | | **2** | **5** | 0 | | 0 | **1** | 0 |
| **Nervous system disorders** | Altered state of consciousness | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Dizziness | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Headache | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | **Total** | | 0 | | 0 | **2** | 0 | | 0 | **1** | 0 |

| System organ class | Preferred term | 1st Induction Dose level 1 N at risk: 4 CTC grade 1-2 | 1st Induction Dose level 1 N at risk: 4 CTC grade 3-4 | 1st Induction Dose level 2 N at risk: 3 CTC grade 1-2 | 1st Induction Dose level 2 N at risk: 3 CTC grade 3-4 | 1st Induction Dose level 3 N at risk: 6 CTC grade 1-2 | 1st Induction Dose level 3 N at risk: 6 CTC grade 3-4 | 2nd Induction Dose level 1 N at risk: 1 CTC grade 1-2 | 2nd Induction Dose level 1 N at risk: 1 CTC grade 3-4 | 2nd Induction Dose level 2 N at risk: 1 CTC grade 1-2 | 2nd Induction Dose level 2 N at risk: 1 CTC grade 3-4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Psychiatric disorders** | Depression | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | **Total** | | 0 | | 0 | | 0 | **1** | 0 | | 0 |
| **Renal and urinary disorders** | Haematuria | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | Renal failure | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 0 |
| | **Total** | **1** | 0 | **2** | 0 | **4** | 0 | | 0 | **1** | 0 |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnoea | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 |
| | Epistaxis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pleural effusion | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| | **Total** | **1** | 0 | **2** | **1** | **2** | **2** | | 0 | **1** | **1** |
| **Skin and subcutaneous tissue disorders** | Alopecia | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Dermatitis | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | Palmar-plantar erythrodysaesthesia syndrome | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Pruritus | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | | **2** | **5** | 0 | **4** | 0 | | 0 | | 0 |
| **TOTAL** | | **12** | **4** | **30** | **4** | **61** | **12** | **3** | **2** | **9** | **3** |

† Totals: Sums = 0 are faded out (white color)

Most adverse reactions had a possible relationship to both study drugs (Clofarabine and Ara-C). Only a few reactions were classified as related to only one of the drugs:

- Events related to Clofaribine only:
  - Pyrexia grade 4 (one case),
  - Blood alkaline phosphatase increased grade 1 (one case)
- Events related to ARA-C only:
  - Mucosal inflammation grade 2 (one case),
  - Pyrexia grade 1 (one case),
  - Alopecia (two cases).

### 17.2.4 Adverse events during consolidation

Tab. 17.12: Table of adverse events reported at the end of the consolidation cycles

| System organ class | Preferred term | 1st Consolidation N at risk: 4 CTC grade 1-2 Count | 2nd Consolidation N at risk: 4 CTC grade 1-2 Count | 2nd Consolidation N at risk: 4 CTC grade 3-4 Count | 3rd Consolidation N at risk: 4 CTC grade 1-2 Count | 3rd Consolidation N at risk: 4 CTC grade 3-4 Count | 4th Consolidation N at risk: 2 CTC grade 1-2 Count |
|---|---|---|---|---|---|---|---|
| **Cardiac disorders** | Arrhythmia | 0 | 0 | 0 | 1 | 0 | 0 |
| | Cardiac failure | 0 | 0 | 0 | 1 | 0 | 0 |
| | **Total†** | | | 0 | **2** | 0 | |
| **Eye disorders** | Eye haemorrhage | 0 | 1 | 0 | 0 | 0 | 0 |
| | **Total** | | **1** | 0 | | 0 | |
| **Gastrointestinal** | Abdominal pain upper | 0 | 1 | 0 | 0 | 0 | 0 |

| System organ class | Preferred term | 1st Consolidation N at risk: 4 | 2nd Consolidation N at risk: 4 | | 3rd Consolidation N at risk: 4 | | 4th Consolidation N at risk: 2 |
|---|---|---|---|---|---|---|---|
| | | CTC grade | CTC grade | | CTC grade | | CTC grade |
| | | 1-2 | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 |
| | | Count | Count | Count | Count | Count | Count |
| **disorders** | Diarrhoea | 1 | 0 | 0 | 2 | 0 | 1 |
| | Haemorrhoids | 0 | 0 | 0 | 0 | 0 | 1 |
| | Intestinal obstruction | 1 | 0 | 0 | 1 | 0 | 1 |
| | Nausea | 1 | 3 | 0 | 3 | 0 | 2 |
| | Proctalgia | 0 | 0 | 0 | 0 | 0 | 1 |
| | Vomiting | 1 | 1 | 0 | 1 | 0 | 1 |
| | **Total** | **4** | **5** | 0 | **7** | 0 | **7** |
| **General disorders and administration site conditions** | Oedema peripheral | 1 | 1 | 0 | 1 | 0 | 0 |
| | Pain | 0 | 0 | 0 | 1 | 0 | 0 |
| | Pyrexia | 2 | 3 | 0 | 1 | 0 | 1 |
| | **Total** | **3** | **4** | 0 | **3** | 0 | **1** |
| **Immune system disorders** | Hypersensitivity | 0 | 0 | 0 | 0 | 0 | 1 |
| | **Total** | | | 0 | | 0 | **1** |
| **Infections and infestations** | Clostridial infection | 1 | 0 | 0 | 0 | 0 | 0 |
| | Cystitis escherichia | 1 | 0 | 0 | 0 | 0 | 0 |
| | Escherichia infection | 0 | 1 | 0 | 0 | 0 | 0 |
| | Oral herpes | 0 | 1 | 0 | 0 | 0 | 0 |
| | Urinary tract infection | 1 | 2 | 0 | 2 | 0 | 1 |
| | **Total** | **3** | **4** | 0 | **2** | 0 | **1** |
| **Investigations** | Alanine aminotransferase increased | 3 | 3 | 0 | 1 | 0 | 1 |
| | Aspartate aminotransferase increased | 3 | 3 | 0 | 3 | 0 | 2 |
| | Blood alkaline phosphatase increased | 2 | 2 | 0 | 1 | 0 | 1 |
| | Blood bilirubin increased | 2 | 2 | 0 | 3 | 0 | 1 |
| | **Total** | **10** | **10** | 0 | **8** | 0 | **5** |
| **Metabolism and nutrition disorders** | Hypoproteinaemia | 1 | 1 | 1 | 1 | 1 | 1 |
| | **Total** | **1** | **1** | **1** | **1** | **1** | **1** |
| **Musculoskeletal and connective tissue disorders** | Osteoarthritis | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **1** | | 0 | | 0 | |
| **Nervous system disorders** | Dizziness | 1 | 2 | 0 | 1 | 0 | 0 |
| | Tremor | 1 | 0 | 0 | 0 | 0 | 0 |
| | **Total** | **2** | **2** | 0 | **1** | 0 | |
| **Psychiatric disorders** | Depressed mood | 0 | 0 | 1 | 0 | 0 | 0 |
| | **Total** | | | **1** | | 0 | |
| **Skin and subcutaneous tissue disorders** | Alopecia | 3 | 3 | 0 | 3 | 0 | 2 |
| | Pruritus | 0 | 0 | 0 | 0 | 0 | 1 |
| | Stasis dermatitis | 0 | 0 | 0 | 1 | 0 | 0 |
| | **Total** | **3** | **3** | 0 | **4** | 0 | **3** |

| | | 1st Consolidation N at risk: 4 | 2nd Consolidation N at risk: 4 | | 3rd Consolidation N at risk: 4 | | 4th Consolidation N at risk: 2 |
|---|---|---|---|---|---|---|---|
| | | CTC grade | CTC grade | | CTC grade | | CTC grade |
| | | 1-2 | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 |
| System organ class | Preferred term | Count | Count | Count | Count | Count | Count |
| **Vascular disorders** | Phlebitis | 0 | 1 | 0 | 1 | 0 | 0 |
| | **Total** | | **1** | **0** | **1** | **0** | |
| **TOTAL** | | **27** | **31** | **2** | **29** | **1** | **19** |

† Totals: Sums = 0 are faded out (white color)

### 17.2.5 Serious Adverse Events

Tab. 17.13: List of Serious Adverse Events (SAEs)

| Pat.-ID | Dose Level | Start SAE | Cycle | Days‡ | Death | Life - threatening | Hospitali-sation | Prefer Term | Outcome | Severity | Relation to | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Clofarabine | Ara-C |
| 10029 | 2 | 21-Jun-11 | Ind 1 | 18 | Yes | | | Pneumonia | Fatal | 4 | No | No |
| 10032 | 3 | 01-Oct-11 | Ind 1 | 16 | Yes | | Yes | Disorientation | Fatal | 4 | Poss | Poss |
| 10032 | 3 | | | | | | | Respiratory failure | Fatal | 4 | Poss | Poss |
| 10032 | 3 | | | | | | | Sepsis | Fatal | 4 | Poss | Poss |
| 10032 | 3 | | | | | | | Nephropathy toxic | Fatal | 2 | Poss | Poss |
| 11017 | 1 | 04-Apr-11 | Ind 1 | 32 | | Yes | | Cardiovascular insufficiency | | 3 | No | No |
| 11017 | 1 | | | | | Yes | | Pyrexia | | 3 | No | No |
| 11017 | 1 | | | | | Yes | | Klebsiella sepsis | | 4 | No | No |
| 11048 | 2 | 11-Jul-11 | Ind 1 | 18 | Yes | | | Metabolic acidosis | Fatal | 5 | No | No |
| 11065 | 3 | 23-Sep-11 | Ind 1 | 2 | | | Yes | Lymph node abscess | Recovered | 3 | Poss | Poss |
| 11079 | 3 | 05-Dec-11 | Ind 1 | 17 | Yes | | | Enterococcal sepsis | Fatal | 5 | No | No |
| 11079 | 3 | | | | Yes | | | Pneumonia fungal | Fatal | 5 | No | No |
| 11096 | 3 | 28-Feb-12 | Ind 1 | 43 | | | Yes | Enteritis | Recovered | 3 | No | No |
| 11096 | 3 | | | | | | Yes | General physical health deterioration | Recovered | 3 | No | No |
| 11082 | 3 | 10-May-12 | Cons 2 | 38† | | | Yes | Cardiac failure | Recovered | 3 | No | No |
| 11082 | 3 | | | | | | Yes | Oedema peripheral | Recovered | 3 | No | No |

Abbreviations: Y = Yes, Poss = Possible, Ind = Induction, Cons = Consolidation, Severity 3 = Severe, 4 = Life-threatening, 5 = Death related to SAE
‡ Days after the start of the cycle

**Please note:** The last SAE was no included in the ASR 2012 because it was first reported later.

### 17.2.6 Causes of death/End of Study

The following Table 17.14 describes causes of death. All deceased patients had either initial disease progression or haematological relapse after CRi. In two cases with haematological relapse, infection resp. urosepsis was considered as main cause of death.

Tab. 17.14: Overview over study termination

| | Number | Comment |
|---|---|---|
| Progression of disease | 4 | |
| Haematological relapse | 4 | |
| Infection $ | 4† | |
| Death from other cause | 1‡ | Urosepsis |
| Planned end of study | 1 | |
| Withdrawal of consent | 1 | |

†‡ Two patients are counted double. Both had a haematological relapse; one died from an infection, another from urosepsis.

$ Pathogen is not specified.

## 18 Discussion and Conclusions

Clearly, AML is a very severe disease and the study population included in the Clofarabine study has per se a dismal prognosis.

However, the hope that elderly AML patients could benefit from induction and consolidation chemotherapy with Clofarabine and low-dose Ara-C could not be confirmed with this small cohort. After one year only one patient is alive; and this patient experienced a haematological relapse in month 14.

The induction response rate was 46.2 [23.2, 70.9]% and was thus lower than anticipated and reported in the literature (Burnett et al. 2006 a, b; see Trial Protocol 1.4.3). However, only 6 patients were treated on the highest dose level. Response rate and event-free survival are significantly higher for patients on dose level 3 as compared to dose level1 and 2. This difference does not transfer into improved overall survival, but this might be due to the small sample size. Therefore, it might be argued that the Clofarabine doses used in dose level 1 and 2 were too low to induce treatment response.

Unfortunately, enrolment was terminated prematurely, and the small sample size does not allow for more reliable estimates.

No patient achieved CR after induction therapy, therefore no patient could be considered for allogeneic cell transplantation. The observed CRis were of short duration; with a median overall survival of 2.27 months.

Concerning safety, most observed toxicities were only mild to moderate. Severe toxicity classified CTC grade 4 or higher was the exception. However, all patients experienced mild to moderate acute toxicities during treatment.

Given the unsatisfactory prognosis, even moderate toxicities may be considered unnecessarily burden for some for these patients.

## Limitations and generalizability

The validity of this study is very limited due to the small sample and its bicenctric setting.

## Evidence in the context of other studies

This study was designed to evaluate safety of Clofarabine and low-dose Ara-C for induction and consolidation treatment of older AML patients.

When compared with historical data, no relevant survival benefit is detectable with Clofarabine and low-dose Ara-C (see Figs. 18.1, 18.2).

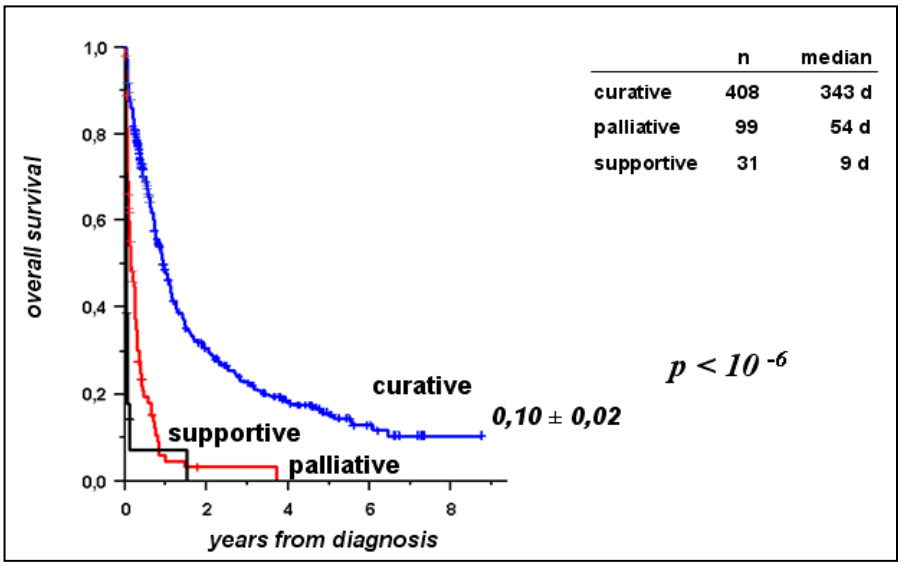



Fig. 18.1: Overall survival elderly patients treated between 1998 and 2004 in the OSHO#038 and #045 studies (Protocol, Fig. 3, p. 15)

Recruitment of the trial was considerably slower than planned. The coordinating investigator decided on 2012-02-24 on behalf of the study sponsor University Leipzig to stop the trial. The reason for this premature study termination was safety concerns raised by the manufacturer of the study drug, Genzyme Europe B.V., related to early toxicity in another trial performed in Spain.

**Justification for early termination of the trial**

Genzyme´s decision to withdraw its support is based on safety data of another study in Spain, demonstrating increased early mortality in this trial compared with published early mortality data in other investigator-sponsored and Genzyme-sponsored trials of this drug combination.

**Consequences of early termination** for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product.

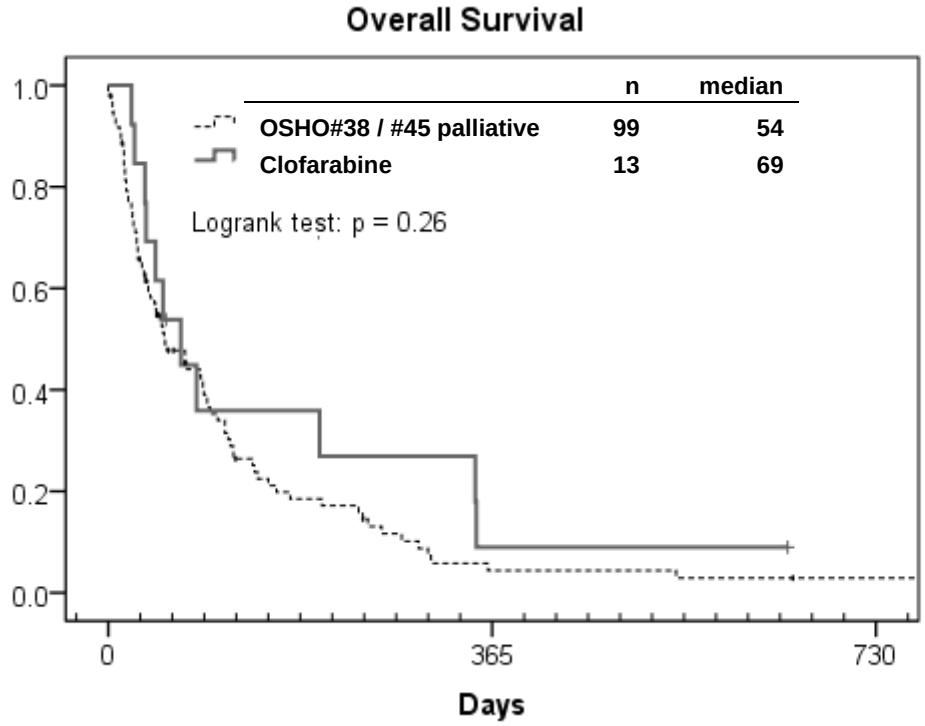



Fig. 18.2: Overall survival in the Clofarabine study compared to overall survival of the OSHO #038 and #045 trials (palliative treatment intention)

The Clofarabine study (OSHO #78) was terminated prematurely by Sanofi at the end of the dose escalation phase. That is, only 13 patients had been included yet. This gives rarely new evidence concerning risk benefit assessment. The observed results can be considered as single case studies. Toxicity of Clofarabine and AraC within the two weeks of induction cycles was not extreme: Fever in one patient was the only case of CTC grade 4 or more. But 8 of 13 patients died later from day 20 until 69 in the first or second induction cycle, respectively. Deaths from relapse/persisting AML as well from infection are typical for this disease. One patient withdrew in the 2$^{nd}$ induction cycle.

# 19 Appendix

## References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2. Newcombe RG (1998): Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine 17: 857-872
3. Burnett A, Baccarani M, Johnson P, et al. Effectiveness of clofarabine in elderly AML patients with adverse cytogenetics unfit for intensive chemotherapy. Blood 2006;108(11 part 1):562a. Abstract 1985.
4. Burnett A, Baccarani M, Johnson P, et al. Effectiveness of clofarabine in elderly AML patients with adverse cytogenetics unfit for intensive chemotherapy. Poster# 1985 presented at American Society of Hematology, Orlando, FL, 09-12 December 2006.


## Abbreviations and Definitions

| | |
|---|---|
| AC | Ara-C |
| AE | Adverse event |
| AR | Adverse reaction |
| AML | Acute myeloid leukemia |
| AR4 | Adverse reactions CTC of grade 4 or 5 |
| AraC | cytarabine or cytosine arabinoside |
| BMI | Body mass index |
| BSA | Body surface area |
| CI | Confidence interval |
| CL | Clofarabine |
| Cons | Consolidation |
| CR | Complete remission |
| CRi | Complete remission with incomplete recovery |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | Event-free survival |
| eRN | eResearch Network™ |
| FU | Follow-up |
| HR | Hematological relapse |
| ICF | Informed consent form |
| Ind | Induction |
| ITT | Intention to treat |
| IWG | International Working Group |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| NA | Not available |
| OS | Overall survival |
| OSHO | Ostdeutsche Studiengruppe Hämatologie und Onkologie e.V. |
| PatID | Patient ID |
| PD | Progression of disease |
| PR | Partial response |
| RFS | Relapse-free survival |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SD | Stable Disease |
| SOC | System Organ Class |
| SPSS | Statistical Package of the Social Sciences |
| SQL | Structured Query Language (Sprache für Datenbankabfragen) |
| StdDev | Standard deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| WHO | World Health Organization |