Evaluation of Efficacy and Toxicity of Intensified Consolidation Therapy in AML Patients ≥60 Years

Name of tested drugs:
Daunorubicin, Etoposide, ARA-C, Mitoxantrone, Fludarabine, Pegfilgrastim

Indication studied:
Evaluation of the efficacy and toxicity of intensified consolidation chemotherapy in patients with AML aged ≥60 years

Open single arm phase IV study evaluating the efficacy and toxicity of intensified consolidation chemotherapy in patients with AML aged ≥60 years

Sponsor:
Medical University of Vienna

Study Number: AKH-AML-0108; EudraCT Number: 2007-005806-29

Phase IV study

Study initiation date (first patient enrolled): 17.07.2008
Date of early study termination: 21.01.2015

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Date of the report: 18.12.2015

1. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Medical University of Vienna</td><td rowspan="3">Individual Study Table
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Volume:
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<tr><td>Name of Finished Product:</td></tr>
<tr><td>Name of Active Ingredient:</td></tr>
<tr><td colspan="3">Title of Study: Evaluation of Efficacy and Toxicity of Intensified Consolidation Therapy in AML Patients ≥60 Years</td></tr>
<tr><td colspan="3">Investigators: Wolfgang R. Sperr, Peter Valent, Ulrich Jaeger, Paul Knoebl, Christian Sillaber, Maria-Theresa Krauth, Alexander Hauswirth, Hermine Agis, Michael Kundi, Michael Girschikofsky, Dieter Lutz, Otto Krieger, Ansgar Weltermann, Sigrid Machherndl-Spandl, Klaus Geissler, Thamer Sliwa, Peter Großschmidt, Rainer Pöhnl, Heinz Kienzer, Veronika Buxhofer Ausch, Karin Strecker</td></tr>
<tr><td colspan="3">Study centre(s): Medical University of Vienna, Department of Internal Medicine I
Medical University of Vienna, Institute of Environmental Health
Hospital of the Elisabethinen Linz, 1st Medical Department
Krankenhaus Hietzing, 5th Medical Department
Kaiser-Franz-Josef-Spital, 3rd Medical Department
Donauspital, 2nd Medical Department</td></tr>
<tr><td colspan="3">Publication (reference)</td></tr>
<tr><td colspan="2">Studied period (years): 2008 - 2012</td><td>Phase of development: IV</td></tr>
<tr><td colspan="3">Objectives: Evaluation of the efficacy and toxicity of intensified consolidation chemotherapy in patients with AML aged ≥60 years</td></tr>
<tr><td colspan="3">Methodology: Open single arm trial</td></tr>
<tr><td colspan="3">Number of patients (planned and analysed): planned n= 100, analysed n= 64</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion: AML, age ≥ 60 years, eligible for intensive chemotherapy</td></tr>
<tr><td colspan="3">Test product, dose and mode of administration, batch number (not applicable):
Daunorubicin, Etoposide, ARA-C, Mitoxantrone, Fludarabine, Pegfilgrastim
Induction 1 = DAV 3+5+7: Daunorubicin, 45 mg/m² iv (over 15 min) day 1-3; ARA-C, 2 x 100 mg/m² iv (over 15 min) day 1-7; Etoposide, 100 mg/m² iv (over 1h) day 1-5; Pegfilgrastim 6 mg sc on day 8 at the decision of the Principal Investigator
Induction 2 = MIDAC-light: ARA-C, 2 x 1000 mg/m² iv (over 3h) day 1, 3, 5; Mitoxantrone, 12 mg/m² iv (over 30min) day 3, 5; Pegfilgrastim 6 mg sc on day 6 or Filgrastim starting on day 6 at the decision of the Principal Investigator
Induction 3 = FLAG: Fludarabine, 30 mg/m² iv (over 30min) day 1-5; ARA-C, 2000 mg/m² iv (over</td></tr>
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4h) day 1-5; Pegfilgrastim 6 mg sc on day 6 or Filgrastim starting on day 6 at the decision of the Principal Investigator

Consolidation 1 = FLAG: Fludarabine, 30 mg/m² iv (over 30min) day 1-5; ARA-C, 2000 mg/m² iv (over 4h) day 1-5; Pegfilgrastim 6 mg sc on day 6

Consolidation 2 & 4 = IDAC-P: ARA-C, 2 x 1000 mg/m2 iv (over 3h) day 1, 3, 5; Pegfilgrastim 6 mg sc on day 6

Consolidation 3 = IDAC: ARA-C, 2 x 1000 mg/m2 iv (over 3h) day 1, 3, 5

Duration of treatment: was scheduled for 6 months

Reference therapy, dose and mode of administration, batch number: single arm study, thus no reference therapy

Criteria for evaluation:

Efficacy:

- The number of chemotherapy-cycles patients received (including patients fraction having received all cycles of consolidation chemotherapy) and the drop out rate
- Proportion of subjects in CR after induction therapy
- Probability of survival, continuous complete remission and disease free survival

Safety:

- Adverse event profile (coded according current version of Medical Dictionary for Regulatory Activities (MedDRA))
- Quality of life (ECOG, Charlson Score)

Statistical methods:

Because of the early termination, we only used descriptive statistical methods to describe the results of this trial. To characterize the proportion of subgroups these are given in percent and absolute numbers if appropriate. Continuous variables are described as median, minimum/maximum in the text. In the figures the median, interquartile range and range (minimum/maximum) are provided. The probability of survival was calculated according to the method of Kaplan and Meier. No statistical testing for significance was applied.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Because of the early termination, not all planned endpoints – especially secondary - can be adressed and statistical analysis had to be restricted to descriptive statistical methods. Sixty-four patients with acute myeloid leukemia (AML) were included in the trial. Following induction therapy 43 patients (64.1%) achieved a complete remission (CR), 4 (6.2%) died (ED) and 19 (19.7%) had no CR (NR). Of the NR-patients, 7 were withdrawn after the 1st and 3 after the 2nd induction cycle. Eight had

persistent AML despite 3 cycles of induction therapy. Thirty-nine of the 43 CR patients proceeded to consolidation therapy, 4 were withdrawn because of early relapse, spontaneous internal bleeding, aggravation of dementia, or a severe protocol violation. All 4 planned consolidations cycles could be administered in 23/39 patients (59.0%); 5/39 (12.8%) received 3 cycles, 3/39 (7.7%) 2 cycles, and 8/39 (20.5%) 1 cycle of consolidation therapy. Relapse (n=8; 20.5%) was the major cause of withdrawal, followed by persistent cytopenias (n=4; 10.2%), severe infection during a prior treatment cycle (n=2; 5.1%), and hematopoietic stem cell transplantation (n=1). Four patients died in the consolidation phase, 2 died related and 2 died unrelated to therapy. The median duration of neutropenia (<0.5G/L; WBC<1G/L) was 9 days (range: 4-28 days) in the 1st (FLAG), 7 days (range: 3-14 days) in the 2nd (IDAC-peg), 12 days (range: 3-21 days) in the 3rd (IDAC), and 7.5 days (range: 5-19 days) in the 4th consolidation (IDAC-peg). Neutropenic fever (>38°C) occurred in 56.2% of the consolidation cycles (cycle 1, 48.7%; cycle 2, 58.1%; cycle 3, 60.7%; cycle 4, 60.9%). Patients were hospitalized for a median of 23 days per cycle of consolidation therapy (cycle 1, 23 days; cycle 2, 21 days; cycle 3, 28 days; cycle 4, 22 days). The median overall survival was 1.1 years, the probability to be alive after 5 years 32%. There were differences in the outcome between patients aged <75 years and ≥75 years (median survival: 1.5 versus 0.5 years, respectively). Patients with monosomal karyotype (Mkpos) had the worst outcome (median survival: Mkpos, 0.6 years; non-monosomoal or normal karyotype 1.5 or 2.1 years, respectively). The survival of patients with mutated NPM1 was favorable compared to those with wild type NPM1 (median survival 1.3 versus 0.7 years). Similar results were obtained for continuous complete remission and disease free survival. To analyse the efficacy of G-CSF, the duration of neutropenia and hospitalization was compared between consolidation cycles with IDAC where G-CSF was given routinely on day 6 (i.e. cycle 2 and 4) and the 3rd consolidation with IDAC, were G-CSF was only given based on ASCO. The duration of neutropenia differed markedly between the cycles with G-CSF, cycle 2 and cycle 4 (7 days, range 4-28 days; 7.5 days, range 5-19 days, respectively) and cycle 3 (11.5 days; range: 3-14 days). Similarly, the duration of hospitalization differed substantially (consolidation 2, 20 days, range: 13-42 days; consolidation 4, 22 days, range: 9-40 days versus consolidation 3, 29 days, range: 7-41 days).

SAFETY RESULTS:

During the trial, we recorded a total number of 1229 adverse events, 3442 reports of abnormal values in the laboratory chemistry, and 5018 abnormal values in the peripheral blood counts. Since AML is characterized by an abnormal peripheral blood count and AML specific chemotherapy always results in a pancytopenia - requiring support with red cell and platelet concentrates in most cases - the number of abnormal values in the peripheral blood counts was to be expected. The same holds true for elevation in CRP above the upper level of normal in 2720/3442 reports. Analysing the toxicity of the treatment, laboratory parameters

indicating liver function (transaminases, alkaline phosphatase) and kidney function (creatinine, BUN) were of particular interest. A total number of 1832 slight elevations of liver and/or kidney parameters classified as i.e. grade I toxicity were observed in 55 patients. Grade II liver and/or kidney toxicity was found in 24 patients. There were 9 patients who had grade III toxicity and 3 with grade IV toxicity. With regard to the AEs, the evolution of SAEs and significant AEs was of interest. Overall, 38 patients had 52 SAEs. Of these SAEs, 15 were fatal and two deaths during consolidation were assumed to be related to treatment. 37 were SAEs other than death and occurred in 23 patients. The most frequent SAEs according to the MedDRA system organ class were infections and infestations (n=17). Moreover, 49 significant adverse events that occurred in 22 patients were not considered as SAEs. The most frequent significant AEs according to the MedDRA system organ class there were blood and lymphatic system disorders (n=1) as well as infections and infestations (n=8) and gastrointestinal disorders (n=7).

CONCLUSION:

Together, our data show that intensified consolidation chemotherapy can be administered in AML patients aged ≥60 years. The majority of patients received all planned 4 consolidation cycles, although toxicity was observed. Bad predictive factors for survival and CCR were age ≥ 75 years, monosomal karyotype and NPMwt. Finally, the administration of Pegfilgrastim in consolidation therapy shortened not only the duration of neutropenia but also the duration of hospitalization during consolidation therapy in AML patients.

Date of the report: 18.12.2015

2. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse evnet
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ARA-C	Cytarabin
BNP	brain natriuretic peptide
bm	Bone marrow
CBC	Complete blood count
Chemotherapy course	A Chemotherapy course starts at the first day of administration of chemotherapy and ends after complete recovery of the peripheral blood counts, the day before the first chemotherapy for the next course or the subject leaves (or is withdrawn from) the study, whichever comes first.
Consolidation 1 chemotherapy	FLAG Fludarabine, 30 mg/m² iv day 1-5 (5 doses) ARA-C, 2000 mg/m² iv day 1-5 (5 doses) Pegfilgrastim 6 mg at day 6
Consolidation 2, Consolidation 3, and Consolidation 4 chemotherapy	IDAC ARA-C, 2 x 1000 mg/m^2 iv day 1, 3, 5 (6 doses)
CCR	Continuous complete remission
CR	Complete remission
CTM	Clinical Trial Mamagement GmbH
DAV	Induction chemotherapy with daunorubicin, etoposid, ARA-C
DFS	Disease free survival
ED	Early death
End of course	The end of Induction 1 to 3 and consolidation 1 to 4 is the day of complete recovery of the peripheral blood counts, the day before the first chemotherapy for the next course or the day the subject leaves (or is withdrawn from) the study, whichever comes first.
End of study	The last day of study related observations
G-CSF	Granulocyte colony stimulating factor
HSCT	Hematopoietic stem cell transplantation
IDAC	Intermittent intermediate dose ARA-C ARA-C, 2 x 1000 mg/m2 day 1, 3, 5
Induction 1 chemotherapy	DAV 3+5+7 Daunorubicin, 45 mg/m² iv day 1-3 (3 doses) ARA-C, 2 x 100 mg/m² iv day 1-7 (14 doses) Etoposide, 100 mg/m² iv day 1-7 (5 doses) Peg-Filgrastim 6 mg sc on day 8 at decision of the Principal Investigator
Induction 2 chemotherapy	MIDAC-light ARA-C, 2 x 1000 mg/m² iv day 1, 3, 5 (6 doses) Mitoxantrone, 12 mg/m² iv day 3, 5 (2 doses) Peg-Filgrastim 6 mg sc on day 6 or Filgrastim starting on day 6 at decision of the Principal Investigator
Induction 3 chemotherapy	FLAG Fludarabine, 30 mg/m² iv day 1-5 (5 doses) ARA-C, 2000 mg/m² iv day 1-5 (5 doses)

	Peg-Filgrastim 6 mg sc on day 6 or Filgrastim starting on day 6 at decision of the Principal Investigator
Infectious complication	A microbial infection identified by pathogen, and/or clinically, and/or radiographically identified features
Febrile neutropenia	Temperature ≥ 38°C, and ANC < 0.5 G/L
MedDRA	Medical Dictionary for Regulatory Activities
Neutrophil recovery	Absolute neutrophil count (ANC) ≥ 1.0 G/L for three days or ANC ≥ 10.0 G/L
NR	No remission
SAE	Sever adverse event
Screening phase	Period of time between first study inclusion assessment and study day 1
Severe neutropenia	ANC < 0.5 G/L or WBC < 1G/L (if ANC is not available)
Study day 1	Study day 1 is defined as the first day of chemotherapy administration in induction 1 chemotherapy
SUSAR	serious related and unexpected adverse event

4. ETHICS

4.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

We confirmed that the study was submitted to the Independent Ethics Committee (=IEC) of the Medical University of Vienna, the IEC of the City of Vienna and the IEC of the Hospital of the Elisabethinen Linz. There protocol was reviewed and approved by the IECs. Moreover, all amendments were reviewed and approved by the IECs.

4.2 ETHICAL CONDUCT OF THE STUDY

We confirm that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

4.3 PATIENT INFORMATION AND CONSENT

After the establishment of the diagnosis, all patients with AML were informed about the nature and status of their disease, and about therapeutic options. Patients aged 60 or more years were screened for the study. All patients fulfilling the study inclusion criteria were informed about the possibility to participate in the trial. Before a subject's participation in the trial, the investigators were responsible for obtaining the written informed consent from each subject or a legally acceptable representative has explained the aims, methods, anticipated benefits and potential hazards of the study. Only after adequate information and after written informed consent the protocol specific procedures that were not routine clinical practice and that require specifically investigations to qualify for this study were performed. Routine clinical practice performed in all AML patients that did or did not contribute in the study included vital signs, height, weight, echocardiography, AML diagnostic bone marrow, clinical chemistry and CBC from a local laboratory/hospital.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study was as follows. Sponsor of the Study was the Medical University of Vienna. The principal investigator and coordinating investigator was Wolfgang R. Sperr. There was a central monitoring. This was carried out by Clinical Trial Management GmbH (CTM). CTM in collaboration with the Medical University of Vienna

also did the administration. Michael Kundi, from the Medical University of Vienna (Institute of Environmental Health) did the statistical work.

Contributing centers were the Medical University of Vienna (Department of Internal Medicine I, Institute of Environmental Health), the Hospital of the Elisabethinen Linz (1st Medical Department), Krankenhaus Hietzing (5th Medical Department), Kaiser-Franz-Josef-Spital (3rd Medical Department), Donauspital Vienna (2nd Medical Department).

6. INTRODUCTION

Acute myeloid leukemia (AML) is a life-threatening hematopoietic neoplasm characterized by uncontrolled proliferation and accumulation of myeloid blast cells without significant maturation [1,2]. The prognosis and clinical picture in AML vary depending on the genes that underwent deregulation, cell type involved, and the specific biological properties of the clone [1-7]. In distinct variants of AML, cytogenetic features are indicative of a favorable prognosis [8-11]. If treated appropriately the rate of cure in these patients is relatively high [5-11]. In other patients, the outcome is poor or unpredictable.

The incidence of AML increases with age. In fact, more than 50% of all AML patients are over 60 years at diagnosis [1,2,13-14]. Whereas for younger patients treatment strategies are well established, the treatment of AML in the elderly deserves special consideration [14-21]. Thus, in a considerable number of patients, the poor performance status or/and co-morbidity may prohibit intensive myelosuppressive therapy [18-23].

For induction treatment, most chemotherapy regimens employed in elderly AML patients have been the same (some of them in dose-reduced form) as applied in younger adults [1,13,14,24-28]. However, the outcome in the elderly is poor compared to younger patients. This appears to be due to a relatively high rate of treatment-related deaths as well as to poor prognostic features in these patients [1,13,14,24-28]. Nevertheless, long-term survival in elderly AML patients receiving remission induction polychemotherapy is superior compared to those who are considered for palliative treatment with hydroxyurea or low dose ARA-C [1,13,14,24-28].

It is generally appreciated that intensive post remission therapy with repetitive cycles of chemotherapy is important to maintain remission in patients with AML [29-32]. In younger patients, intensive consolidation treatment (high dose chemotherapy or allogeneic stem cell transplantation) is the established approach [33-34]. Beyond the age of 60 years, however, no

generally accepted treatment strategy has become available so far. In most series, consolidation treatment consisted of 1 to 2 cycles of chemotherapy employing the same agents that were used for induction treatment [13,25-28]. The overall survival at 5 years that was achieved using such regimens amounted to approximately 10% [13,25-28]. Thus, only a small group of elderly patients with AML are cured using these regimens. In this regard, it is tempting to speculate, that one reason for the unfavourable survival in elderly AML patients is, that a relatively low dose of chemotherapy is given in consolidation chemotherapy in these patients. In a more recent study, intermediate doses of ARA-C (500 mg twice daily on days 1-3) together with mitoxantrone were applied to elderly AML patients for post remission treatment with slightly superior effects on leukemia-free and overall survival but also with an increase in toxicity [32]. In 1994, the CALGB study group introduced the high dose intermittent ARA-C regimen (HiDAC; 2 x 3 g/m^2 on days 1, 3, and 5) as effective consolidation for patients with *de novo* AML [34]. In the vast majority of patients aged <60, this regimen was well tolerated [34,35]. However, in a significant number of elderly patients (≥60 years), severe neurotoxicity occurred [34]. Therefore, the administration of HiDAC was recommended only for patients under 60 years. In previous publications, we were able to demonstrate that repetitive intermittent intermediate dose ARA-C is an effective, well-tolerated consolidation treatment in patients aged ≥60 [14]. In this analysis on post-remission therapy, we administered 4 cycles of intermediate dose ARA-C (1000 mg/m^2, days 1,3,5) in a consecutive group of elderly patients (aged ≥60) presenting with de novo AML. 53% of these patients received all 4 cycles, 19% received 3 cycles, 15% 2 cycles, and 12% received only one cycle. Overall, the treatment was well tolerated without signs of severe neurotoxicity. The median number of days with severe neutropenia (ANC<500/µL or WBC < 1G/L if ANC is not available) were 9 (range: 1-17). Neutropenic fever (>38°C) occurred in 49% of all patients during the first cycle, in 60% during the second cycle, in 44% during the third cycle, and in 72% during the fourth consolidation cycle. Of all patients, only one died during consolidation (cardiac failure), but none died from hematologic toxicity. The median overall survival, disease-free survival (DFS), and continuous complete remission (CCR) were 11.1 months, 15.5 months, and 17.9 months, respectively. The DFS and CCR at 3 years were 28% and 32%, respectively [14].

As described above, the non-hematologic toxicity in this group of elderly AML patients was low. There were no cases of severe neurotoxicity, major nephrotoxicity, or severe hepatotoxicity, and no patient had to be withdrawn from the treatment due to treatment related non-hematologic toxicity. Thus, the reduction of ARA-C from $3g/m^2$ to $1g/m^2$ seems to

results in a marked reduction of the non-hematologic toxicity. However, in 55.2% of the patients neutropenic fever occurred, and in 41.4% of all consolidation cycles, G-CSF was administered as primary or secondary use (primary use of G-CSF: prophylactic administration in case of a known history of severe infection during one of the preceding cycles of chemotherapy; secondary use: because of a severe infection during prolonged neutropenia). No patient died during post remission treatment from severe infection. However, severe infections were the primary cause to withhold further chemotherapy in our patients. Thus, neutropenic fever and/or infections were major problems during consolidation therapy.

Intensive polychemotherapy is required for the eradication of neoplastic cells in AML, but usually also induces severe myelosuppression, resulting in pancytopenia, including severe neutropenia [14,34,35]. In this regard, it is noteworthy that neutropenic fever occurred in about 50% of the consolidation cycles analysed in our patients in a previous study with severe infections being the primary cause to withhold further chemotherapy [14,34]. Thus, neutropenic fever and/or infections are major problems during the consolidation therapy with intermediate dose ARA-C.

The hematopoietic growth factor G-CSF is a major regulator of neutrophil development and function. G-CSF is known to stimulate early granulopoiesis in vitro and has potential to reduce the duration of chemotherapy-induced neutropenia and to prevent associated complications [37,38]. It has been demonstrated, that the use of G-CSF (filgrastim) is save and not affecting the CR-rate or the duration of CR in patients with AML [50-66]. Various studies have demonstrated, that the time to neutrophil recovery is significantly shorter in AML-patients receiving G-CSF compared to the controls, resulting in a shorter duration of hospitalization, less intravenous antibiotics and/or antifungal treatment (14,34). Pegfilgrastim (the protein filgrastim to which a 20 kilodalton poly[ethylen] glycol [PEG] molecule is bound) has been shown to be equally effective in stimulating granulopoiesis compared to filgrastim [39,67]. In contrast to filgrastim, pegfilgrastim has to be administered only once per chemotherapy cycle since neutrophils are the exclusive site of pegfilgrastim clearance. However, so far it has not been evaluated, whether the administration of pegfilgrastim would shorten the duration of hospitalisation during consolidation treatment in larger studies. To address this point, a small pilot case series has recently been conducted and the respective outcome presented (40). In this series, the median duration of aplasia in patients receiving IDAC followed by the administration of pegfilgrastim was 6 days (n=3), and in patients receiving HiDAC followed by pegfilgrastim, aplasia was 9 days (40). In the so far published

AML-cohort that received IDAC or HiDAC without primary support by G-CSF, the duration of aplasia was 9 days and 12 days, respectively (14,36).

7. STUDY OBJECTIVES

Primary objective:

- Tolerability (number of cycles of consolidation therapy; toxicity) of intensified consolidation therapy in elderly AML patients
- The number of consolidation cycles and the adverse event profile was recorded in these patients.

Secondary objectives:

- The rate of complete remission (CR) following induction chemotherapy
- Relapse rate after intensified chemotherapy
- Overall survival, continuous complete remission and disease free survival
- Quality of life (ECOG, Charlson Score)
- Evaluation of prognostic factors like age, karyotype, leukocyte count, histologic (CD34 positive cells, micro vessel density, fibrosis) and biochemical markers (like tryptase).
- Percent patients with ANC ≥500/μL or WBC ≥1000/μL on day 10
- Incidence and duration of febrile neutropenia (days per cycle with ANC <500 cells/μL or WBC ≥1000/μL and temperature ≥38°C)
- Days in hospital
- Efficacy and pharmacokinetics of pegfilgrastim in consolidation therapy

8. INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

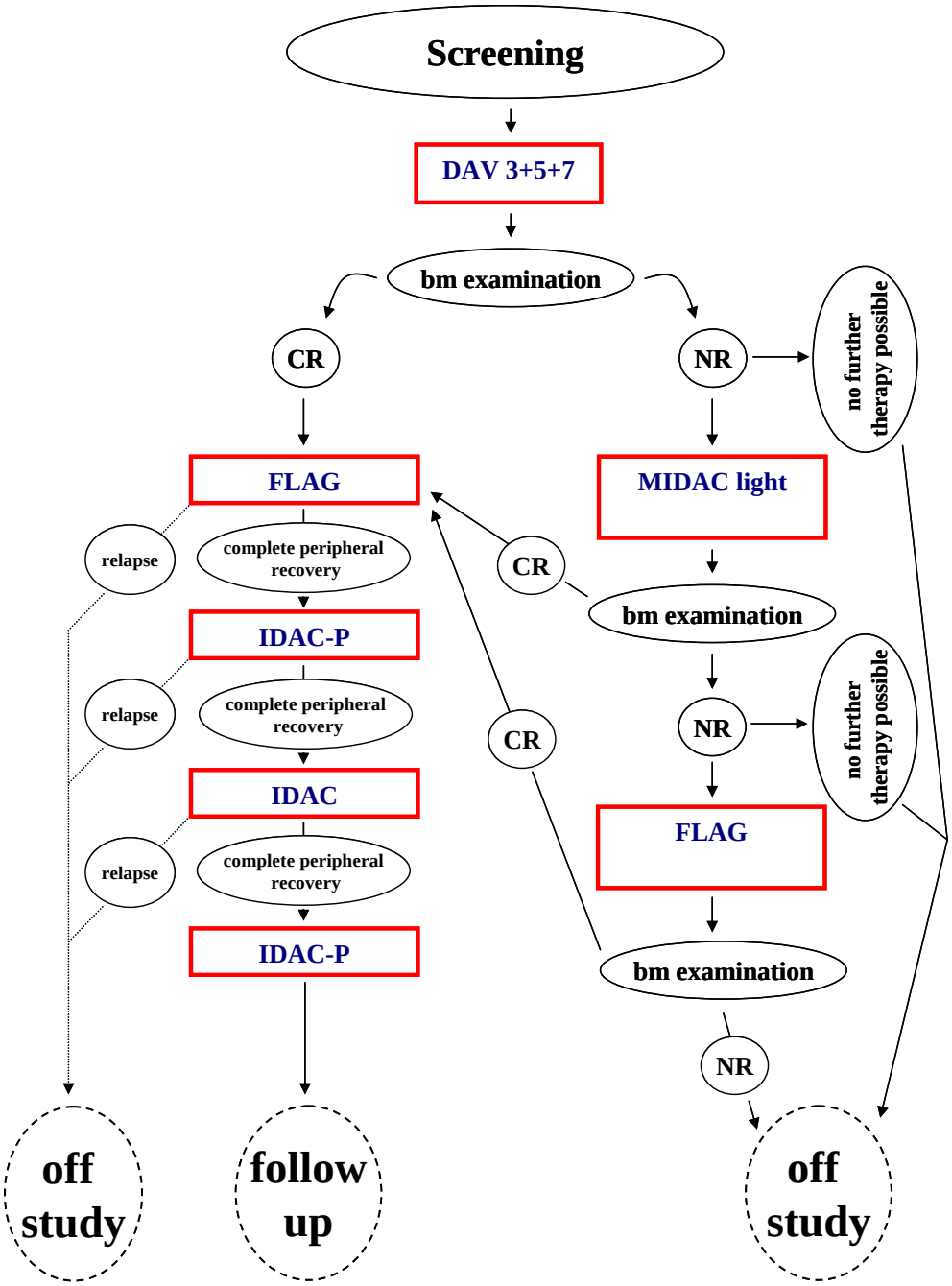
This is a multi-center, single arm phase IV study trial. The primary objective was to analyse the tolerability (number of cycles of consolidation therapy; toxicity) of intensified consolidation therapy in elderly AML patients. For this purpose, only patients with AML aged ≥ 60 years were included. To avoid heterogeneity in the study population caused by differences in the induction treatment (i.e. variation in the dosage of chemotherapy, type of chemotherapy used) the induction therapy was administered following a standardized protocol.

In the 1st induction DAV i.e. daunorubicin (45 mg/m² iv, over 15 min, day 1-3), ARA-C (2 x 100 mg/m² iv, over 15 min, day 1-7), and etoposide (100 mg/m² iv, over 1h, day 1-5) was given. Subjects not in remission (>5% myeloblasts in bone marrow smears, presence of Auer-rods) after the 1st induction were planned to receive a 2nd induction cycle. Patients in whom no further therapy could be administered were withdrawn from the study and end of treatment and follow-up evaluations were performed. All patients in CR (complete remission is defined by complete recovery of the peripheral blood counts, <5% myeloblasts in bone marrow, and no Auer-rods present in bone marrow smears) will receive intensive consolidation therapy.

The 2nd induction with MiDAC light, administered in case of blast cell persistence after the 1st induction contained ARA-C (2 x 1000 mg/m² iv, over 3h, day 1, 3, 5), mitoxantrone (12 mg/m² iv, over 30min, day 3, 5). Subjects not in remission after the 2nd induction were planned to receive a 3rd induction cycle. Patients in whom no further therapy was possible were withdrawn from the study and end of treatment and follow-up evaluations were performed. All patients in CR were planned to receive up to 4 cycles of intensive consolidation therapy.

The 3rd induction with FLAG, administered in case of blast cell persistence after the 2nd induction consisted of fludarabine (30 mg/m² iv, over 30min, day 1-5) and ARA-C (2000 mg/m² iv, over 4h, day 1-5). All subjects not in remission after the 3rd induction or in CR but unfit for further chemotherapy were withdrawn from the study and end of treatment and follow-up evaluations were performed. All other patients that achieved a CR were planned to receive up to 4 cycles of intensive consolidation therapy. During induction therapy all patients were scheduled to receive G-CSF (prefilgrastim or filgrastim) from the first day after the end of chemotherapy until recovery of granulocytes.

Figure 1



Flow chart of the treatment plan
bm, bone marrow; CR, complete remission; DAV, daunorubicin (45 mg/m² iv, over 15 [min], day 1-3), ARA-C (2 x 100 mg/m² iv, over 15 [min], day 1-7), and etoposide (100 mg/m² iv, over 1[h], day 1-5); FLAG, fludarabine (30 mg/m² iv, over 30min, day 1-5) and ARA-C (2000 mg/m² iv, over 4h, day 1-5), Pegfilgrastim 6 mg sc on day 6 or Filgrastim starting on day 6; IDAC, ARA-C, 2 x 1000 mg/m2 iv (over 3h) day 1, 3, 5; IDAC-P, ARA-C, 2 x 1000 mg/m2 iv (over 3h) day 1, 3, 5, Pegfilgrastim on day 6; MIDAC-light, ARA-C, 2 x 1000 mg/m² iv (over 3h) day 1, 3, 5; Mitoxantrone, 12 mg/m² iv (over 30min) day 3, 5, Pegfilgrastim 6 mg sc on day 6 or Filgrastim starting on day 6; NR, no remission

In the 1st consolidation, the FLAG regimen was administered (see above). In the 2nd, 3rd, and 4th consolidation intermediate dose ARA-C (2 x 1000 mg/m² iv, over 3h, day 1, 3, 5) was applied. Subjects who had a relapse after a consolidation cycle and patients in whom no further therapy could be administered were withdrawn from the study, and end of treatment and follow-up evaluations were performed. All other patients have received the next consolidation cycle (up to cycle 4) after complete recovery of peripheral blood counts.

Pegfilgrastim 6 mg sc was administered routinely on day 6 of consolidation in cycles 1, 2, and 4. In Consolidation 3 G-CSF was not automatically given. However, in this cycle G-CSF was administered in patients with prolonged aplasia or severe infections during a previous cycle (i.e. secondary administration of G-CSF in case of severe infections allowed according ASCO guidelines) [41]. The number of cycles of consolidation therapy administered in each patients, the profile of adverse events profile and in case of a withdrawal of a patient from further therapy the cause of withdrawal were recorded. An overview on the treatment protocol is provided in figure 1.

8.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The primary purpose of this study was the evaluation of the efficacy and toxicity of intensified consolidation chemotherapy in patients with AML aged ≥60 years. To analyse the tolerability of such an intensive consolidation protocol, the number of consolidation cycles administered in each patient was evaluated. Moreover, we recorded the adverse event profile. To address the second point, the efficacy the outcome and the survival of the patients were of interest. In this regard, a long-term observation of our cohort of elderly patients (aged ≥ 60 years) with AML was of particular importance. Thus, the trial was planned as a single arm phase IV study and no control cohort was chosen. With this design, also a number of secondary endpoints like the rate of complete remission (CR) following induction chemotherapy, relapse rate after intensified chemotherapy, overall survival, continuous complete remission and disease free survival, prognostic factors for survival could be addressed. To analyse the efficacy pegfilgrastim in consolidation therapy pegfilgrastim was administered routinely on day 6 of consolidation 2 and 4 (employing IDAC) whereas in consolidation 3 (employing IDAC) no primary administration of pegfilgrastim was given. With this approach, a comparison of the duration of aplasia between consolidation 2, 3, and 4 could provide evidence for the efficacy of pegfilgrastim applied during consolidation therapy.

8.3 SELECTION OF STUDY POPULATION

After the establishment of the diagnosis, all patients with AML were informed about the nature and status of their disease, and about therapeutic options. Patients aged 60 or more years were screened for the study.

8.3.1 Inclusion Criteria

The aim of the introduction of our inclusion criteria was to provide a population suitable for our treatment plan. First of all the diagnosis of AML has to be proven and the patients' age. Moreover, the general shape of the patient must have allowed intensive chemotherapy and the patients had to give their written informed consent.

- Confirmed de novo AML (≥ 20 % myeloblasts in the bone marrow) as evidenced by the absence of any other antecedent hematologic disease of > 8 months duration, prior chemotherapy, prior radiation therapy, or a previous myelodysplastic syndrome for at least 8 months.
- Patients must have a morphologically confirmed diagnosis of AML with FAB classification other than M3 or WHO classification other than APL t(15;17), based on bone marrow aspiration and biopsy.
- Patients must have reached their 60^{th} birthday.
- ECOG performance status of 0, 1 or 2.
- Life expectancy >3 months
- Adequate organ function to receive intensive chemotherapy
- Written informed consent.

8.3.2 Exclusion Criteria

To provide detailed criteria why a patients was unfit for intensive chemotherapy due to the presence of pre- or co-existing disorders unrelated to the AML (co-morbidities) the set of exclusion criteria was prepared. This set is also defined as particular disease related criteria e.g. presence of APL that would have been indicative for other types of chemotherapy.

- Patients with APL

- Subjects with blast transformation of chronic myeloid leukemia or leukemia developing from myeloproliferative diseases.
- Leukemia following a documented myelodysplastic syndrome known for more than 8 months.
- Patients with a concurrent malignancy, except stage 1 cervical intraepithelial carcinoma and basal cell carcinoma.
- Previous treatment with chemotherapy or radiation.
- Patients must not have received systemic chemotherapy or more than one dose of intrathecal chemotherapy for acute leukemia. Administration of hydroxyurea or etoposid to control high blast cell counts prior to induction-chemotherapy is permitted.
- Patients with known hypersensitivity to Escherichia coli derived products
- Patients receiving antibody based or cell based immunotherapies
- Patients who have known HIV-infection.
- Impaired hepatic or renal function i.e.: ALT and/or AST > 2.5 x ULN; bilirubin > 2 x ULN; Serum creatinine > 2 x ULN (after adequate hydration) (unless these are most likely caused by AML organ infiltration)
- Severe cardiac disease: Patients must not have a severely reduced left ventricular function (shortening fraction >20% as assessed by 2-D ECHO within 42 days prior initiation of induction therapy), unstable cardiac arrhythmias or unstable angina.
- Severe obstructive or restrictive pulmonary disease.
    - Psychiatric, addictive, or any disorder, which compromises ability to give truly informed consent for the participant in this study.
    - Concerns for subject's compliance with the protocol procedures.

8.3.3 Removal of Patients from Therapy or Assessment

All patients had the right to withdraw their consent to participate in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. In case of such a withdrawal the consent to participate the patients was withdrawn from the study.

During the induction phase, all subjects who were not in remission (>5% myeloblasts in bone marrow smears, presence of Auer-rods) after a cycle of induction therapy and in whom no further therapy could be administered were withdrawn from the study. Moreover, all subjects were withdrawn from the study who were not in remission after the 3rd induction or were in

CR but unfit for further chemotherapy. Patients in CR and being in the consolidation phase (4 planned cycles) were withdrawn from the study when they had a relapse after a consolidation cycle or when no further therapy could be administered.

The investigator also had the right to withdraw a subject from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, stem cell transplantation or other reasons.

8.4 TREATMENTS

8.4.1 Treatments Administered

All patients received one course of standard induction chemotherapy consisting of daunorubicin, etoposide and ARA-C (DAV 3+5+7) followed by the administration of pegfilgrastim, i.e.

Induction 1 (DAV 3+5+7)

- Daunorubicin, 45 mg/m² iv (over 15 min) days 1-3 (3 doses)
- ARA-C, 2 x 100 mg/m² iv (over 15 min) days 1-7 (14 doses)
- Etoposide, 100 mg/m² iv (over 1h) days 1-5 (5 doses)
- Pegfilgrastim 6 mg sc on day 8 or Filgrastim at the decision of the Principal Investigator) starting on day 8 until neutophil recovery

In case of a very high WBC or bilirubin (because of infiltration by leukemic blasts), the administration of DAV 3+5+7 could be modified as follows: ARA-C days 1-7, etoposid days 3-7 and daunorubicine days 5-7. AML diagnostic bone marrows, including cellularity assessment and percentage myeloblasts were taken at neutrophil recovery (ANC $\geq$ 1.0 G/L).

In case of blast cell persistence after the 1st induction a 2nd induction cycle consisting of ARA-C and Mitoxantrone (MiDAC light) followed by the administration of G-CSF (at the decision of the Principal Investigator) was given, i.e.

Induction 2 (MIDAC-light)

- ARA-C, 2 x 1000 mg/m² iv (over 3h) days 1, 3, 5 (6 doses)
- Mitoxantrone, 12 mg/m² iv (over 30min) days 3, 5 (2 doses)
- Pegfilgrastim 6 mg sc on day 6 or Filgrastim (at the decision of the Principal Investigator) starting on day 6 until neutophil recovery

In patients not in CR after the 2nd induction, a 3rd induction cycle, FLAG, consisting of Fludarabine and ARA-C followed by G-CSF (at the decision of the Principal Investigator) was administered, i.e.

Induction 3 (FLAG)

- Fludarabine, 30 mg/m² iv (over 30min) days 1-5 (5 doses)
- ARA-C, 2000 mg/m² iv (over 4h) days 1-5 (5 doses)
- Pegfilgrastim 6 mg sc on day 6 or filgrastim (at the decision of the Principal Investigator) starting on day 6 until neutophil recovery

All patients in CR after induction therapy were planned to receive 4 cycles of intensive consolidation therapy. In case of a high-risk profile, the patient could be withdrawn from the study and proceed to allogeneic or autologous stem cell transplantation according to the decision of the local investigator. Subjects not in remission after the induction phase were withdrawn from the study. Consolidation chemotherapy was not given before ANC was ≥ 1.0 G/L and platelets count ≥ was 100 G/L, but as soon as possible after peripheral trilineage recovery. The 1st consolidation consisted of FLAG, i.e.

Consolidation 1 (FLAG)

- Fludarabine, 30 mg/m² iv (over 30min) days 1-5 (5 doses)
- ARA-C, 2000 mg/m² iv (over 4h) days 1-5 (5 doses)
- Pegfilgrastim 6 mg on day 6

As soon as possible after peripheral trilineage recovery (ANC ≥ 1.0 G/L; ≥ 100 G/L), the 2nd consolidation was given with IDAC-P, i.e.:

Consolidation 2 (IDAC-P)

- ARA-C, 2 x 1000 mg/m^2 iv (over 3h) day 1, 3, 5 (6 doses)
- Pegfilgrastim 6 mg sc on day 6

As soon as possible after peripheral trilineage recovery the 3rd consolidation was given. To be able to analyse the efficacy Pegfilgrastim in consolidation therapy Pegfilgrastim was not administered routinely during this cycle of IDAC, i.e.:

Consolidation 3 (IDAC)

- ARA-C, 2 x 1000 mg/m^2 iv (over 3h) day 1, 3, 5 (6 doses)

However, in this cycle G-CSF only was administered in patients with prolonged aplasia or severe infections during a previous cycle (i.e. secondary administration of G-CSF in case of severe infections allowed according ASCO guidelines [41]). After peripheral trilineage recovery, the 4th consolidation was given employing IDAC-P, i.e.:

Consolidation 4 (IDAC)

- ARA-C, 2 x 1000 mg/m^2 iv (over 3^h) day 1, 3, 5 (6 doses)
- Pegfilgrastim 6 mg sc on day 6

8.4.2 Identity of Investigational Product(s)

All cytostatic drugs were obtained from suppliers approved by the pharmacy of the investigational center. These drugs were formulated, packaged, labelled, and stored according to local manufacturer, supplier and institutional procedures. Responsibility for obtaining supplies of these drugs has rested with the local investigators. Investigators referred to the relevant package inserts for further information on chemotherapy dosage, administration, adverse reactions and contraindications.

8.4.3 Method of Assigning Patients to Treatment Groups

Since this was a single arm trial, there was no assignment of patients to particular treatment groups

8.4.4 Selection of Doses in the Study

As we used routinely applied chemotherapy schemes, the doses or dose ranges used in the study were chosen on the basis of prior publication employing these drugs in the therapy of AML.

8.4.5 Selection and Timing of Dose for each Patient

As we used routinely applied chemotherapy schemes, the timing of dose in each chemotherapy cycle in the study were chosen on the basis of prior publication employing these drugs in the therapy of AML.

In case of blast cell persistence during the induction phase the next cycle of induction chemotherapy was initiated. In all patients assigned to intensive consolidation therapy the chemotherapy was not given before ANC were ≥ 1.0 G/L and platelet count ≥ was 100 G/L, but as soon as possible after peripheral trilineage recovery.

8.4.6 Blinding

We report on an open single arm phase IV trial. Thus, there was no blinding.

8.4.7 Prior and Concomitant Therapy

Patients were not allowed to have received systemic chemotherapy or more than one dose of intrathecal chemotherapy for acute leukemia. Only the administration of hydroxyurea or etoposid to control high blast cell counts prior to induction-chemotherapy was permitted.

Throughout the study, the investigators could prescribe any concomitant medications or treatments necessary to provide adequate supportive care except:

- Any investigational agents
- Any other hematopoietic growth factors (apart from G-CSF)
- Radiotherapy
- WBC-transfusions
- Other cytoreductive agents

All prescription of concomitant antibiotics as well as all medications given in case of an adverse event (AE) (names, generic names, indication, quantity administered, routes, and dates of administration) was recorded in the CRFs. Any other concomitant medications or treatments necessary to provide adequate supportive care could be given without recording in CRFs.

8.4.8 Treatment Compliance

To administer induction and consolidation therapy in AML patients have to be hospitalized. Therefore, all medication given was documented in the clinical charts of the patients. By this, we could ensure and document the treatment compliance.

8.5 EFFICACY AND SAFETY VARIABLES

8.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Each study site was responsible for analysing the bone marrow, the blood for clinical chemistry and CBC with differential counts. In table 1 the physical examination laboratory assessments necessary in the screening phase as well as during the therapy are described.

Table 1

Physical examination	Clinical chemistry	Complete blood count	Other labs
Head, throat, neck Cardiovascular Pulmonary Abdomen Breast/Chest Musculoskeletal Skin Lymph nodes Neurological	Sodium Potassium Chloride Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN Creatinine Uric acid Total bilirubin Alkaline phosphatase LDH AST (SGOT) ALT (SGPT)	Red blood cell count Hemoglobin Hematocrit Reticulocytes Platelets White blood cell count Differential • Bands/Stabs • Eosinophils • Lymphocytes • Monocytes • Myeloblasts • Promyelocytes • Myelocytes • Metamyelocytes	Bone marrow assessment BNP Tryptase Flow cytometry

Prior to the initiation of chemotherapy, the following assessment had to be completed within 14 days, i.e.:

- AML-diagnostic bone marrow including cellularity assessment, percentage of myeloblasts in smears, FAB type, WHO type, cytogenetics, PCR tests for CBFβ/MYH11, AML/ETO, PML/RARα, and BCR/ABL. Immunphenotyping was performed according to institutional guidelines and should include progenitor subsets if possible.
- Echocardiography within the last six months
- Medical history, physical examination including weight and height, ECG, vital signs, ECOG performance status
- A complete blood count including WBC with differential count, platelet count, RBC, hemoglobin, and hematocrit.
- Serum sample for clinical chemistry panel will be taken within the last 14 day
- BNP [=brain natriuretic peptide] (if the test is available).

Prior to each induction chemotherapy the subject's height and weight used to calculate body surface area and chemotherapy drug dosages had to be taken. There had to be also a physical examination including weight, ECG, vital signs, ECOG performance status. During each induction therapy, starting at the day before the start of chemotherapy administration until neutrophil recovery (ANC>1000) the following tests and/or data collection had to be performed, i.e.:

- A complete blood count including WBC with differential count, platelet count, RBC, hemoglobin and hematocrit had to be taken daily
- Serum sample for clinical chemistry panel were taken at least twice a week (unless otherwise needed).
- Daily temperature logs were maintained.

An AML-diagnostic bone marrow including cellularity assessment, percentage of myeloblasts, FAB type, WHO type (cytogenetics, molecular biology, phenotyping if appropriate) was mandatory after each induction chemotherapy at recovery of the peripheral blood counts or day 40 whichever is earlier.

Prior to each cycle of consolidation therapy a physical examination including weight, ECG, vital signs, and an ECOG performance status had to be done. In case of the presence of a specific breakpoint-associated fusion gene like CBFβ/MYH11 or AML1/ETO regular bone marrow aspiration for the monitoring of the disease by RT-PCR was done prior to each consolidation therapy. The following tests and/or data collection had to be performed during consolidation chemotherapy.

- A complete blood count including WBC with differential count, platelet count, RBC, hemoglobin and hematocrit has to be taken the day before the start of chemotherapy administration, on day 3 and 6 as well as daily from day 10 of chemotherapy until neutrophil recovery (ANC >1000).
- Serum sample for clinical chemistry panel were taken at least the day before the start of chemotherapy administration and during consolidation twice a week (unless otherwise needed).
- Daily temperature logs were maintained.

All efficacy and safety variables were checked by the local study site (principal investigator or subinvestigators). Each study site was responsible for rating the recorded results and for

rating the severity and likelihood of drug causation of adverse events. The severity of toxicities was on a scale with appropriate clinical definitions: mild (=1), moderate (=2), severe (=3), life threatening (=4), fatal (=5) (Table 2, 3). The relationship of an adverse event to the clinical procedure was assessed with yes, possible, or no. An adverse event was defined as any new, undesirable medical event or change (worsening) of preexisting condition, which occurs during treatment, whether or not considered to be procedure/therapy-related. Elective hospitalizations for pre-planned treatment (e.g. elective cosmetic procedures, or treatment of AML) were not judged as serious adverse events.

Table 2

Grading scales

	SCALE	Clinical definitions
1	MILD	Aware of signs or symptoms, but easily tolerated
2	MODERATE	Discomfort enough to cause interference with usual activity
3	SEVERE	Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING	Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event; it does not refer to an event with hypothetically might have caused death if it were more severe
5	Fatal	

A serious adverse event (SAE) was defined as a significant hazard or side effect, regardless of the investigator's opinion on the relationship to investigational procedure. SAEs include, but were not limited to any event that (at any time of the investigational procedure) was:

- fatal
- life threatening (places the subject at immediate risk of death)
- lead to a persistent or significant disability/incapacity
- lead to hospitalization except:
    - Planned as per protocol medical/surgical procedure
    - Routine health assessment requiring admission for baseline/trending of health status documentation (e.g. routine colonoscopy)

Table 3a

Grading scale of toxicity provided for this study

TOXICITY	GRADE				
	0	1	2	3	4
HAEMATOLOGICAL (Key: WNL = within normal limits, N=upper limit of normal range					
White Blood Count	≥4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	<1.0
Haemoglobin	WNL	75.0 - WNL	50.0 74.9	25.0 - 49.9	< 25.0
Granulocyte/Bands	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Lymphocytes	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Haemorrhage (Clinical)	None	Mild, no transfusion: petechiae	Gross, 1-2 units transfusion per episode	Gross, 3 -4 units transfusion per episode	Massive < 4 units per episode
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≥ 0.24 x N
Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	< 2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	< 3.00 x N
Infection	None	Mild	Moderate	Severe	Life threatening
Gastrointestinal					
Nausea	None	1 able to eat, reduced but reasonable intake	Intake significantly decreased but still can eat	No significant intake	…
Vomiting	None	1 episode in 24 hours	2 - 5 episodes in 24 hours	6 - 10 episodes in 24 hours	> 10 episodes in 24 hours, or requiring parenteral support
Diarrhoea	None	Increase of 2 - 3 stools/day over pre-Rx	Increase of 4 - 6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7 - 9 stools/day, or incontinence or severe cramping	Increase of ≥ stools/day or grossly bloody diarrhoea, or need for parenteral support.
Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, oedema, or ulcers, but can eat	Painful erythema, oedema, or ulcers and cannot eat	Requires parenteral or enteral support.
LIVER (Key: WNL = within normal limits, N = upper limit of normal range					
Bilirubin	WNL	…	< 1.5 X N	1.5 - 3.0 x N	> 3.0 x N
Transaminase (SGOT, SGPT)	WNL	≥ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Alk Phos or 5'Nucleotidase	WNL	≥ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
Clinical	No change from baseline	…	…	Precoma	Hepatic coma
RENAL (Key: WNL = within normal limits, N=upper limit of normal range)					
Creatine	WNL	< 1.5 - 2.0 N	1.5 - 3.0 N	3.1 - 6.0 x N	>6.0 x N
BUN	≤ 1.25 x N	1.26-2.5 x N	1.6-5 x N	5.1-10 x N	>10 x N
Proteinurea	No change	1 + or < 0.3 g% or <3g/l	2-3+ or 0.3 - 1.0g% or 3 - 10 g/l	4 + or > 1.0 g% or >10 g/l	Nephrotic syndrome
Haematuria	Neg	Micro only	Gross, no clots	Gross + clots	Requires transfusion
Metabolic (Key: WNL = within normal limits, N=upper limit of normal range)					
Hyperglycaemia (mmol/l	< 6.5	6.5 - 8.9	9.0 - 13.9	14.0 - 27.8	>27.8 or ketoacidosis
Hypoglycaemia (mmol/l)	> 3.5	3.1 - 3.5	2.2 - 3.0	1.7 - 2.1	> 1.7
Amylase	WNL	<1.5 x N	1.5 - 2.0 x N	> 2.1 - 5.0 x N	> 3.38
Hypercalaemia (mmol/l)	< 2.70	2.70 - 2.89	1.90 - 3.14	3.15 - 3.38	< 3.00 x N
Hypocalaemia (mmol/l)	> 2.10	2.10 - 1.95	1.94 - 1.75	1.74 - 1.51	≤ 1.50
Hypomagnesemia (mmol/l)	> 0.70	0.70 - 0.58	0.57 - 0.43	0.42 - 0.26	≤ 0.25

Table 3b

Grading scale of toxicity provided for this study

TOXICITY	**GRADE**				
	0	1	2	3	4
NEUROTOXICITY					
Consciouness	Alert	transient lethargy	Somnolence <50% of waking hours	Somnolence ≥50% of waking hours	coma
Peripheral	Non	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or marked motor loss	paralysis
CARDIAC					
Dyshythmias	None	Asymptomatic, transient requiring no therapy	Recurrent or persistent, no therapy required	Requires treatment	Requires monitoring: or ventricular tachycardia or fibrillation
Function	None	Asymptomatic decline of resting ejection fraction by less than 20% of baseline value	Asymptomatic decline of resting ejection fraction by more than 20% of baseline value	Mild CHF responsive to therapy	Severe or refractory CHF
Ischaemia	None	Non -specific T-wave flattening	Asymptomatic ST and T-wave changes suggesting ischaemia	Angina without evidence for infarction	Acute infarction
Pericardial	None	Asymptomatic effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion: drainage required	Tamponade: drainage urgently required
Hypertension	None or no change	Asymptomatic transient increase > 20 mm Hg (Dia) or to > 150/100 if BP previously nl. No treatment required	Recurrent or persistent increase > 20 mm Hg (dia) or to > 150/100 if BP previously nl. No treatment required	Requires therapy	Hypertensive crisis
Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalisation	Requires therapy and hospitalisation: resolves within 48 hrs of stopping the agent	Requires therapay and hospitalisation for > 48 hrs after stopping the agent
OTHER					
Alopecia	No loss	minimal loss	Moderate, patchy alopecia	Complete alopecia but reversible	nonreversible alopecia
Pulmonary	None or no change	Asymptomatic, with abnormality in PFT's	Dyspnoea on significant exertion	Dyspnoea at normal level of activity	Dyspnoea at rest
Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalised symptomatic macular, papular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
Hand-Foot syndrome	No symptoms	Mild paraesthesias +/or numbness of fingers +/or toes	Moderate paraesthesias +/or numbness with or without local dermatitis	Painful swelling of distal phalanges with or without local dermatitis	Not applicable
Allergy	None	Transient rash or drug fever < 38°c (100.4°F)	Urticaria, drug fever ≥ 38°c (100.4°F), mild bronchospasm	Serum sickness or bronchospasm: requires parenteral medication	Anaphylaxis
Fever in absence of infection	None	37.1 - 38.0°C (98.7 - 100.4°F)	38.1 - 40 .0°C (100.5 - 104.0°F)	> 40.0°C (104.0°F) for less than 24 hours	> 40.0°C (104.0°F) for ≥ 24 hrs, or fever with hypotension

Table 3c

Grading scale of toxicity provided for this study

TOXICITY	**GRADE**				
	0	1	2	3	4
OTHER					
Fatigue	No change in Performance score (ECOG) *and* not PS4	Performance score (ECOG) decrease in 1 level, but not to PS 4	Performance score (ECOG) decrease in 2 levels, but not to PS 4	Performance score (ECOG) decrease in 3 levels, but not to PS 4	Performance score (ECOG) decrease to PS 4
Chills	None	Chilly sensation, no rigors	mild rigors, no medication required	Severe rigors, requires medication	Not applicable
Myalgias	None	Mild muscular aching: no medication required	Moderate aching requiring medication: no associated enzyme (CPK) elevation	Severe muscular aching requiring medication: associated enzyme (CPK) elevation	Not applicable
Weight gain/loss	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	> 20.0%	…

- Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into the study; appropriate documentation required)
- Admission encountered for other life circumstances that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, family circumstances, administrative)

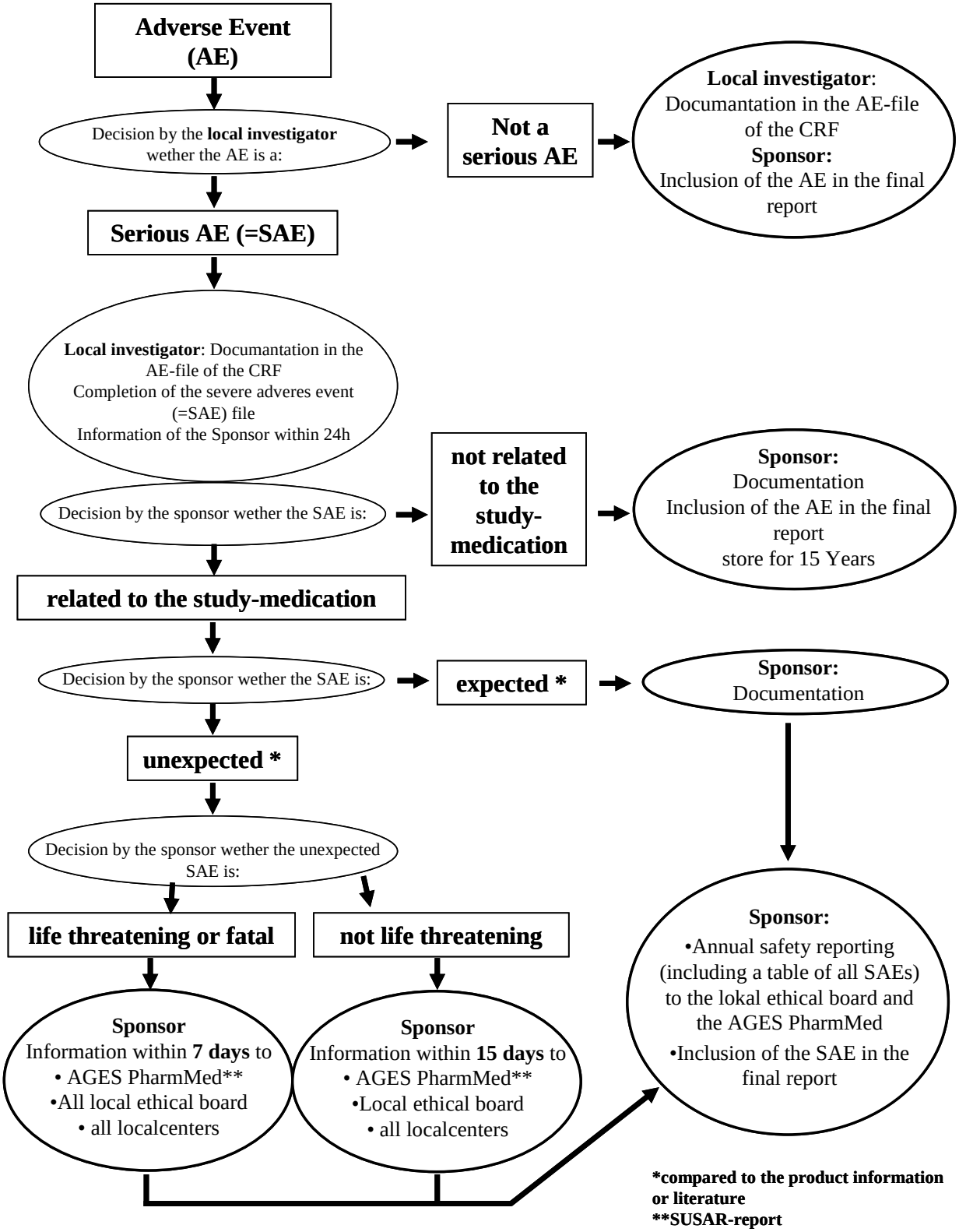
The sponsor was responsible to inform the ethics committee, the regulatory authorities and the concerned investigators about all serious related and unexpected adverse events (SUSARS). Medically significant adverse events were followed until resolved or considered stable or until patient´s death.

All deaths occurring during this study, including deaths within 30 days after the last administration of chemotherapy and deaths up to the last formal induction bone marrow puncture (1, 2 or 3) had to be reported to the sponsor. It was up to the investigator's clinical judgement, to decide whether an adverse event is of sufficient severity to require the subject's removal from the study. A scheme depicting the recording and reporting of AEs is provided in Figure 2.

8.5.2 Appropriateness of Measurements

All efficacy or safety assessments performed in the trial were standard (i.e., widely used and generally recognised as reliable, accurate and relevant).

Figure 2


Adverse Event (AE)
Decision by the local investigator wether the AE is a:
Not a serious AE
Local investigator: Documantation in the AE-file of the CRF
Sponsor: Inclusion of the AE in the final report
Serious AE (=SAE)
Local investigator: Documantation in the AE-file of the CRF
Completion of the severe adveres event (=SAE) file
Information of the Sponsor within 24h
Decision by the sponsor wether the SAE is:
not related to the study-medication
Sponsor: Documentation
Inclusion of the AE in the final report
store for 15 Years
related to the study-medication
Decision by the sponsor wether the SAE is:
expected *
Sponsor: Documentation
unexpected *
Decision by the sponsor wether the unexpected SAE is:
life threatening or fatal
not life threatening
Sponsor
Information within 7 days to
• AGES PharmMed**
•All local ethical board
• all localcenters
Sponsor
Information within 15 days to
• AGES PharmMed**
•Local ethical board
• all localcenters
Sponsor:
•Annual safety reporting (including a table of all SAEs) to the lokal ethical board and the AGES PharmMed
•Inclusion of the SAE in the final report
*compared to the product information or literature
**SUSAR-report

8.5.3 Primary Efficacy Variable(s)

The primary objective of this study was to analyse, whether intensified consolidation chemotherapy can be administered in AML patients aged ≥60 years. The number of consolidation cycles administered in each patient was one of the efficacy variables. In addition the adverse event profile was recorded throughout the study.

8.5.4 Drug Concentration Measurements

Serum sample were taken at diagnosis as well as at the time of bm-puncture for remission evaluation. These samples were stored at -20°C or below at the study site and shipped to the study center (Dept. of Int. Med.I, Div. of Hematology and Hemostaseology, Medical University of Vienna) at least once a year.

In a subgroup of patients the serum levels of G-CSF were analysed in the füllow up around day 10, 15, 20 and 25 after the administration of G-CSF. The serum samples were stored at the local study site at -20°C or below and analyzed at the end of the study. After all samples had been collected they were sent to an external laboratory (i.e. CellTrend GmbH/Zentrum für molekulare Onkologie GmbH; Im Biotechnologiepark, TGZ II; D-14943 Luckenwalde), where G-CSF levels were determined using commercially available ELISA (R&D Systems Minneapolis, MN). As standard curve, a specific Pegfilgrastim standard was used.

8.6 DATA QUALITY ASSURANCE

To assure and control the quality of documentation regular monitoring was implemented. An external company, i.e. CTM (Clinical Trials Management GmbH, Kärntner Ring 6/6, 1010 Vienna, Austria) did the monitoring.

Each site was responsible for analysing of routine clinical laboratory parameters including bone marrow, blood for clinical chemistry and CBC with differential counts and no assurance and quality control systems were implemented to assure the quality of the data. The serum levels of Pegfilgrastim were analysed centrally in an external laboratory.

8.7 STATISTICALMETHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

8.7.1 Statistical and Analytical Plans

In the protocol a statistical plan was established before the statistical analysis was-performed. Missing data were not planned to be displaced. No interim analyses were planned. The aim of the statistical analysis of this study was to provide data on the average number of cycles and the number of patients who received all cycles of consolidation chemotherapy. In addition, the study has examine the dropout rate, the incidence and duration of febrile neutropenia (ANC <500 cells/µL or WBC < 1G/L if ANC is not available, temperature >38°C) as well as the adverse event profile. The approach to the statistical analysis of these data was planned to be descriptive and explorative in nature. Categorical endpoints were summarized by the number and percentage of subjects in each category. Continuous endpoints were given by median, lower and upper quartiles, minimum and maximum.

The comparison between cycle 2, 3 and 4 with regard to the duration of ANC <500 cells/µL or WBC < 1G/L (if ANC is not available) and duration of hospitalisation was planned to be done using the Wilcoxon test.

8.7.2 Determination of Sample Size

Approximately 100 patients receiving at least 1 cycle of consolidation therapy were planned. Determination of sample size was based on the width of the confidence interval for adverse events of medium to high frequency (10-30%) and the potential to detect a difference in the tolerated number of cycles compared to historical controls. In order to limit the width of the 95% confidence interval to +/-10% and to have an 80% chance to detect a difference of average cycle number of one third of a standard deviation at the 5% significance level, approximately 100 patients were needed to be included. The study analysis was descriptive and explorative in nature.

8.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Three changes had to be done in the study protocol. Firstly, in December 2009 changes were necessary to adapt the protocol to NCI-CTC, add MedDRA to the end-points, harmonize the protocol and correct typos. Secondly, the study protocol was amended in July 2014. In these amendments, we did three modifications of the trial protocol.

1. The criteria for evaluating a neutropenia were changed. In the initial protocol duration of neutropenia was defined as the number of days with ANC <500 cells/µL. After the amendment it was possible to take the days with WBC < 1000 cells/µL to calculate if no

ANC-values were available. This became necessary since regular ANC counts were not available for every day during aplasia.

2. The case report form (CRF) pages containing adverse event reporting by investigator, e.g. start date, stop date, frequency, severity, study relation and action taken for this event were allowed to serve as the source data.

3. The period of follow up was modified. Initially, source data related to the follow up and follow up events had to be documented in each center and collected and analysed centrally (after recalling from centers) after 1, 3, and 5 years. After the amendment, source data related to the follow up and follow up events had to be documented in each center and to be collected and analysed centrally (after recalling from centers) after 1, 3, and 5 years or until 15. Sep. 2014, whatever comes first. This had to be modified because of the slow recruitment and the increasing risk of an early termination of the trial.

Thirdly, the study had to be closed early prior to the recruitment of all planned patients. Overall, the recruitment was much slower than expected. One explanation is that a lower number of centers were contributed to the trial in the first years, since two of five planned centers were not able to participate. The recruitment period of the centers included thereafter, was shorter and thus the number of included patients smaller. Due to the long duration of the trial, patients suitable for this study were included in competing trials. Therefore, the study was closed on January 21st, 2015 after an entire recruitment period of 7 years.

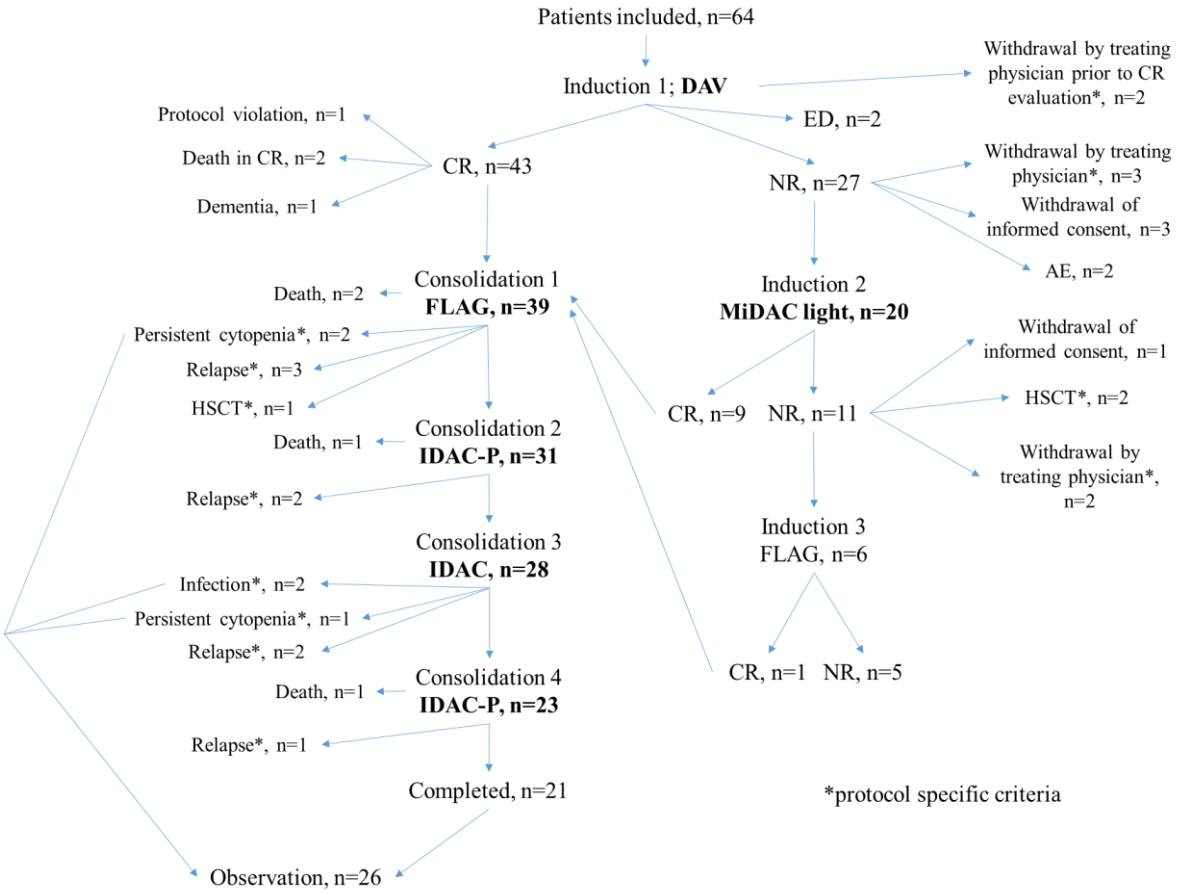
All changes were made by the principal investigators and subinvestigators at the medical University of Vienna in accordance with the principal investigators of the local sites. There are a number of possible implications for the interpretation of the study because of these changes. Primarily because of the early termination not all planned endpoints – especially secondary - can be answered. Moreover, the statistical power of the results is markedly reduced. In case of no significant results, it cannot be excluded that these data would have become significant in case the total number of planned patients would have been included. On the other hand, borderline significant results are more questionable.

9. STUDY PATIENTS

9.1 DISPOSITION OF PATIENTS

Over all 64 patients were included in the study. Following the 1st induction chemotherapy 33 entered a CR. Of these 2 patients died in CR, 1 patient was excluded because of a severe protocol violation and 1 had to be excluded due to worsening of a dementia. Two patients

Figure 3



Flow chart of patient disposition

CR, complete remission; DAV, daunorubicin (45 mg/m² iv, day 1-3), ARA-C (2 x 100 mg/m² iv, day 1-7), and etoposide (100 mg/m² iv, day 1-5); ED, early death; FLAG, fludarabine (30 mg/m² iv, day 1-5) and ARA-C (2000 mg/m² iv, day 1-5), pegfilgrastim 6 mg sc on day 6 or filgrastim starting on day 6 at the decision of the Principal Investigator; HSCT, hematopoietic stem cell transplantation; IDAC, ARA-C, 2 x 1000 mg/m2 iv day 1, 3, 5; IDAC-P, ARA-C, 2 x 1000 mg/m2 iv day 1, 3, 5, pegfilgrastim on day 6; MIDAC-light, ARA-C, 2 x 1000 mg/m² iv day 1, 3, 5; mitoxantrone, 12 mg/m² iv day 3, 5, pegfilgrastim 6 mg sc on day 6 or filgrastim starting on day 6 at the decision of the Principal Investigator; NR, no remission

died during induction and 2 were withdrawn from the study during induction therapy by the treating physician. From the 27 NR patients 20 received a second induction, 3 were withdrawn by their treating physician, 3 have withdrawn their informed consent, and 2 were excluded due to adverse events. Induction 2 resulted in 9 CR and 11 NR. All CR received further consolidation therapy. Two NR patients were withdrawn by the treating physician, 2 patients underwent "rescue" hematopoietic stem cell transplantation (HSCT), and 1 patient had withdrawn the informed consent. The other 6 NR patients underwent a 3rd induction. One of them achieved a CR and received further consolidation therapy, the other (n=5) had a blast cell persistence. Following the induction-phase, 39 patients were in CR and eligible for consolidation therapy. Two patients died during the 1st consolidation, 1 from infection and 1 due to diarrhoea (suspected GI tract infection). Following the 1st consolidation 3 patients relapsed and 1 patient underwent HSCT. In 2 patients no further therapy was feasible because of persistent cytopenia. The 2nd consolidation was administered in 31 patients. One patient died during consolidation because of CNS bleeding and 2 patients relapsed following the 2nd consolidation. In 28 patients the 3rd consolidation was given. Two patients relapsed after this therapy and 3 were excluded from further chemotherapy because of severe infections during the 3rd consolidation (n=2) or persistent cytopenia (n=1). Of the 23 patients, eligible for the 4th consolidation 1 patient died and 1 had a relapse after chemotherapy. A flow chart of the disposition of patients is provided in figure 3.

9.2 PROTOCOL DEVIATIONS

Two patients had not met all study inclusion or exclusion criteria. One had an elevation of liver enzymes slightly more than twice the upper limit of normal. Since this was judged as being associated with disease, the patient was kept in the study. The second patient had a diagnosed prostatic carcinoma. However, no cytostatic therapy was given prior to the diagnosis of AML or was necessary during therapy. Therefore, this patient continued on trial. During the trial a severe violation of the chemotherapy protocol occurred in one patient. In this patient, a second cycle of induction chemotherapy was administered instead of a first cycle of consolidation therapy. Thus, this patient was excluded from further analysis. The most frequent protocol deviations occurred with the administration of G-CSF. Table 1 shows the overall deviations and individual deviation occurring per consolidation cycle in detail. The most frequently observed violation was the administration of filgrastim instead of pegfilgrastim (n=11) during the consolidation cycles. This was followed by the delayed

administration of pegfilgrastim (n=8), the outline administration of G-CSF in 3rd consolidation therapy, the delayed administration of filgrastim instead of pegfilgrastim (n=3), the administration of pegfilgrastim too early and the additional administration of G-CSF despite pegfilgrastim administerd on day 6. Table 5 shows the detailed listing of deviations that have occurred, broken down by center.

Table 4

Deviations in the administration of G-CSF

	Cons. 1	Cons. 2	Cons. 3	Cons. 4	All cons.
Delayed administration of pegfilgrastim	4	2	0	2	8
Filgrastim instead of pegfilgrastim	8	2	0	1	11
Administration of pegfilgrastim too early	1	0	0	0	1
Routine administration of G-CSF in 3rd Cons	0	0	3	0	3
Filgrastim instead of pegfilgrastim and delayed	0	0	0	3	3
Additional G-CSF despite pegfilgrastim on day 6	0	0	0	1	1
All	13	4	3	7	27

Cons, consolidation therapy; G-CSF, granulocyte colony stimulating factor

Table 5

List of protocol deviations in each center

	AKH WIEN	ELI LINZ	KFJ	SMZ OST	HIETZING
Delayed administration of pegfilgrastim	7	1	0	0	0
Filgrastim instead of Pegfilgrastim	2	9	0	0	0
Pegfilgrastim too early	0	0	0	1	0
Routine administration of G-CSF in 3rd consolidation	1	1	1	0	0
Filgrastim delayed	2	0	0	1	0
Additional G-CSF despite Pegfilgrastim on day 6	1	0	0	0	0
deviation of inclusion criteria	0	2	0	0	0
Deviation of chemotherapy	0	0	1	0	0

10. EFFICACY EVALUATION

10.1 DATA SETS ANALYSED

In the evaluation of the trial, three reporting groups were used, the overall group, the induction 1-3 group and the consolidation 1-4 group.

The overall group comprises all participants that had received at least one dose of induction 1 therapy. In this group, the rate of complete remission following induction chemotherapy was analyzed. Moreover, survival analysis was done based on the date of the overall group i.e. the calculation of overall survival, continuous complete remission and disease-free survival. Using the survival data, prognostic factors including age, karyotype, and molecular markers (fusion proteins, mutations like KIT, NPM, FLT3) were analysed. Finally, the comparison of quality of life (ECOG, Charlson Score) recorded prior to the 1st induction, prior to the 2nd consolidation and at the end of treatment examination was done in this cohort.

The induction 1-3 group consists of all participants that received at least one dose of induction 1 therapy like the overall group. However, in this group only (adverse) events occurring during the induction phase, i.e.1st, 2nd, and 3rd induction were analysed.

All participants that had received at least one dose of consolidation therapy were grouped in the consolidation 1-4 cohort. This group was used to evaluate the primary objective of the study, i.e. to analyse the tolerability of intensive consolidation chemotherapy in elderly patients. The numbers of consolidation chemotherapy-cycles given in each patient, the dropout rate, but also the adverse event profile found in this group were examined. Additionally questions in these patients were the efficacy and pharmacokinetic of G-CSF treatment in the consolidation group. The percentage of patients with ANC≥500/µL or WBC ≥1000 cell/µL on day 10, the incidence and duration of febrile neutropenia (=days per cycle with ANC <500 cells/µL or WBC <1000 cell/µL and temperature ≥38°C) were recorded. Moreover, a comparison between the 2nd consolidation cycle (with routine administration of G-CSF on day 6), 3rd consolidation (cycle without the routine administration of G-CSF), and 4th consolidation cycle (again with the routine administration of G-CSF on day 6) with regard to the duration of ANC <500 cells/µL (WBC <1000 cell/µL) and duration of hospitalisation was done.

10.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Overall, 64 Caucasian patients were analysed. The median age was 69.9 years ranging from 60.1 years to 85.2 years. 17 patients were aged ≤ 65 years, 46 aged 65-84 years and 1 patient aged ≥85 years. There were 25 females and 39 males. The first patient was included in the trial on 17. July 2008, the last in 19.November 2012. The observation period lasted until 15. Sep. 2014. The Charlson Comorbidity Score was evaluated in all 64 patients. Of our patients 48 (75.0%) had no comorbidities, 10 (15.6%) had one comorbidity, 4 (6.37%) had two comorbidities, 1 (1.6%) had three, and 1 (1.6%) five. With regard to particular comorbidities there were 8 cases with diabetes (2 with end organ failure), 4 with chronic pulmonary disease, 3 with myocardial infarction, peripheral vascular disease, or cerebrovascular disease each, and 1 with congestive heart failure, connective tissue disease, ulcer disease, renal disease (moderate or severe) or metastatic solid malignancy (i.e. metastatic prostatic carcinoma without treatment) each. Peripheral blood counts, proBNP, CRP, liver and kidney parameters are shown in table 6 and 7.

Table 6

Peripheral blood counts at diagnosis

	Leukocytes (G/L)	Hemoglobine (g/dL)	Platelets (G/L)
Median	6.95	9.4	72
Minimum	0.7	7.8	12
Maximum	146.2	14.5	304
Number of missing data	5	5	5

Table 7

Laboratory chemistry at diagnosis

	proBNP	BUN	Crea	ALP	LDH	AST	ALT	CRP
Median	303.9	18.15	1.04	70	308	25	24	1.49
Minimum	33.7	8	0.68	33	139	13	7	0.09
Maximum	2720	43.4	2.47	176	2413	221	128	24.9
Number of missing data	11	12	12	11	12	9	10	8

proBNP, brain natriuretic peptide; BUN, blood urea nitrogen; Crea, creatinine; ALP, alkaline phosphatase; LDH, lactate dehydrogenase, AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein

The major inclusion criterion was the presence of an AML except acute promyelocytic leukemia (= AML M3). All patients were classified according the FAB and WHO 2008 criteria. Detailed results are depicted in Table 8. With regard to the karyotype, HOVON criteria as well as modified SWOG criteria were applied [51,52]. In 52 patients, cytogenetic analysis was available. According HOVON the distribution of patients was as follows: 1 patient (1.9%) with core binding factor leukemia, 25 patients (48.1%) with normal karyotype, 11 patients (21.2%) with non-monosomal karyotype, and 15 patients (28.8%) with monosomal karyotype. Following modified SWOG criteria, 1 patient (1.9%) had a favorable karyotype, 41 patients (78.8%) had an intermediate karyotype, and 10 patients (19.2%) had an unfavorable karyotype. Results of molecular markers, including FLT3 ITD, NPM1, and KIT mutation (D816V) as well or from a multiplex PCR including AML/ETO, CBFa/MYH11, and MLL1-AF10 were available in 50, 39, 27 and 53 cases respectively. FLT3 ITD was found in 8 cases, NPM1 mutations in 11, KIT D816V and in 3 AML/ETO and MLL1-AF10 in 1 patient each. Demographic and baseline characteristics were collected in the overall group and the induction 1-3 group.

Table 8

Classification of leukemia according to FAB and WHO 2008 in all patients

FAB	n	%	WHO 2008	n	%
AML M0	8	7.8	AML with 11q23 abnormalities	1	1.6
AML M1	19	29.7	AML with t(8;21)	1	1.6
AML M2	11	17.2	AML with inv(16); t(16/16)	1	1.6
AML M4	11	17.2	AML without maturation	15	23.4
AML M4eo	1	1.6	AML minimally differentiated	9	14.1
AML M5	7	10.9	AML with maturation	10	15.6
AML M6	2	3.1	Acute myelomonocytic leukemia	10	15.6
AML M7	3	4.7	Acute monocytic leukemia	7	10.9
AML unc	2	3.1	Acute erythroid leukemia	2	3.1
			Acute megakaryocytic leukemia	3	4.7
			AML with dysplasia; without prior MDS	4	6.3
			NOT DETERMINABLE	1	1.6
	64	100		64	100.0

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; unc, unclassified

The consolidation 1-4 group consisted of 39 patients that had achieved a CR following the induction therapy and had received at least the 1st cycle of consolidation therapy. The median age was 69.9 years, ranging from 60.1 to 78.8 years. Nine patients were aged ≤ 65 years, 30 aged 65-84 years, No patient was aged ≥85 years. There were 15 females and 24 males. The duration of the study and observation period were identical to the overall group.

The Charlson Comorbidity Score was evaluated prior to the 1st induction in all 39 patients; 31 (79.5%) had no comorbidities, 6 (15.4%) had one comorbidity, 1 (2.6%) had two comorbidities, and 1 (2.6%) had five comorbidities. With regard to particular comorbidities, there were 4 cases with diabetes mellitus (2 with end organ failure), 3 with peripheral vascular occlusive disease, 2 with chronic pulmonary disease, and 1 with myocardial infarction, connective tissue disease or metastatic solid malignancy (i.e. metastatic prostatic carcinoma without treatment) each. The distribution of the patients among the different FAB and WHO 2008 subgroups is depicted in Table 9.

Table 9

Classification of leukemia according FAB and WHO 2008 in all patients eligible for intensive consolidation therapy

FAB	n	%	WHO 2008	n	%
AML M0	4	2.6	AML with 11q23 abnormalities	0	0.0
AML M1	12	30.8	AML with t(8;21)	1	2.6
AML M2	7	17.9	AML with inv(16); t(16/16)	1	2.6
AML M4	5	12.8	AML without maturation	10	25.6
AML M4eo	1	2.6	AML minimally differentiated	4	10.3
AML M5	5	12.8	AML with maturation	7	17.9
AML M6	2	5.1	Acute myelomonocytic leukemia	5	12.8
AML M7	2	5.1	Acute monocytic leukemia	5	12.8
AML unc	1	2.6	Acute erythroid leukemia	2	5.1
			Acute megakaryocytic leukemia	2	5.1
			AML with dysplasia; without prior MDS	2	5.1
			AML unc	0	0.0
	39	100		39	100.0

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; unc, unclassified = not determinable

Cytogenetic analysis at diagnosis was available in 30 patients. According to the HOVON criteria, the distribution of patients was as follows: 1 patient (3.3%) with core binding factor leukemia, 16 patients (53.3%) with normal karyotype, 5 patients (16.7%) with non monosomal karyotype, and 8 patients (26.7%) with monosomal karyotype. Following modified SWOG criteria, 1 patient (3.3%) had a favorable karyotype, 20 patients (66.7%) had an intermediate karyotype, and 9 patients (30.0%) had an unfavorable karyotype. Molecular analyses for FLT3 ITD, NPM1, KIT D816V and multiplex PCR (including AML/ETO, CBFa/MYH11, and MLL1-AF10) were available in 29, 26, 19 and 34 patients, respectively. FLT3 ITD was found in 4 cases, NPM1 in 9, kit in 2, AML/ETO and MLL1-AF10 in 1 patient each.

The overall reporting group consisted of all patients recruited in the study and of all data collected during the entire observation period. Induction reporting group 1-3 consisted of all patients recruited in the study as well. However, only data until the end of induction therapy (CR or End of study) were recorded in this group. The consolidation reporting group 1-4 included all patients that had achieved a CR and had received at least the 1st cycle of consolidation therapy. Both, induction reporting group 1-3 and the consolidation reporting group 1-4 were used to better describe and evaluate the adverse events observed in this study. Moreover, both were subgroups of the overall reporting group. A diagram showing the relationship between the entire sample and the two analysis groups is provided in figure 4.

10.3 MEASUREMENTS OF TREATMENT COMPLIANCE

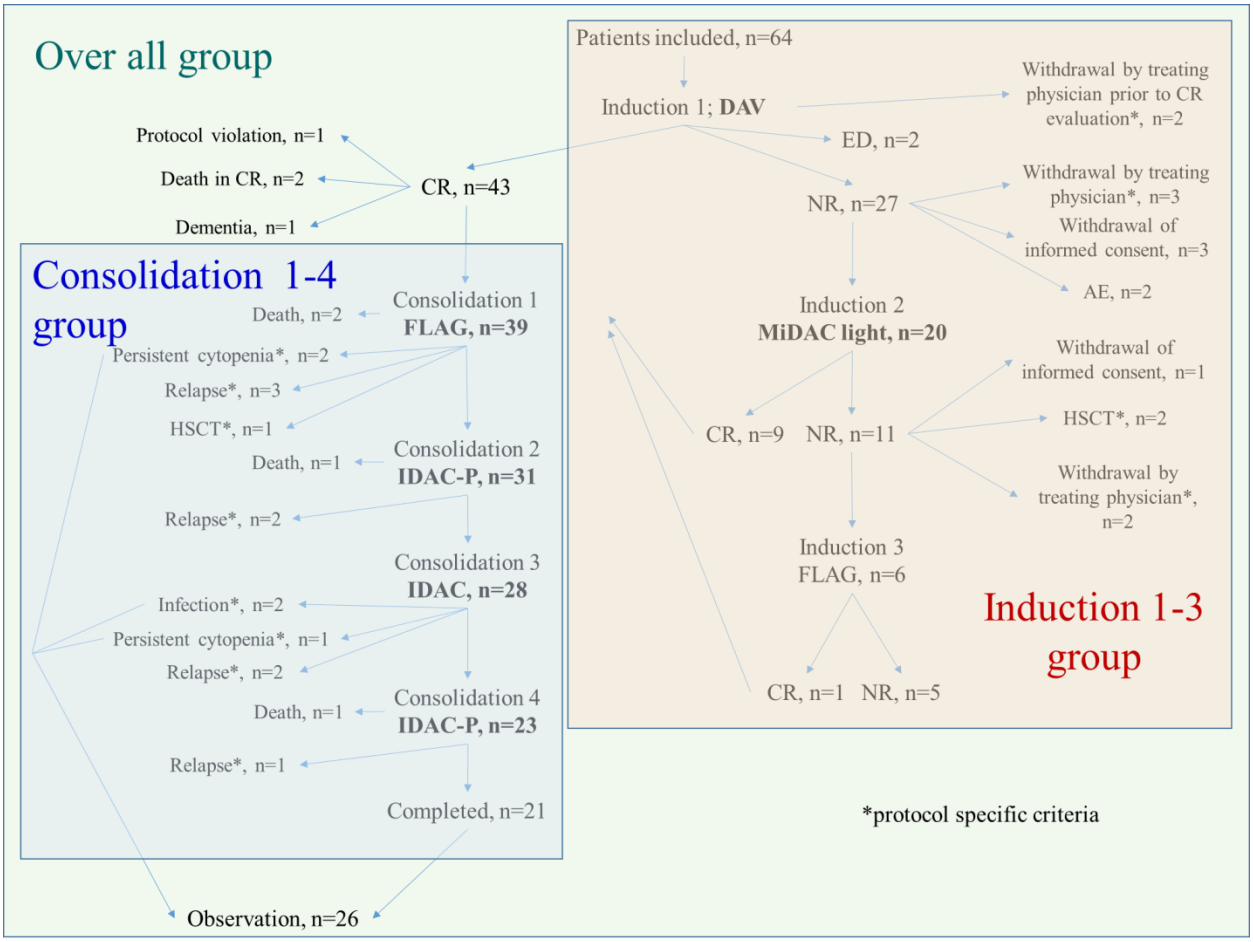
All patients had to be hospitalized for the administration of the induction and consolidation therapy. Therefore, all medication including the chemotherapy and G-CSF given, was documented daily in the clinical charts of the patients. Since the therapy was administered by clinical staff we could ensure and document the treatment compliance.

10.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

10.4.1 Analysis of Efficacy

Over all 64 patients were included in the trial and have received the first cycle of induction therapy. Two patients were withdrawn from the study because of adverse events during the

Figure 4



Flow chart of the relationship between the entire sample and the analysis groups
CR, complete remission; DAV, daunorubicin (45 mg/m² iv, day 1-3), ARA-C (2 x 100 mg/m² iv, day 1-7), and etoposide (100 mg/m² iv, day 1-5); ED, early death; FLAG, fludarabine (30 mg/m² iv, day 1-5) and ARA-C (2000 mg/m² iv, day 1-5), pegfilgrastim 6 mg sc on day 6 or Filgrastim starting on day 6 at the decision of the Principal Investigator ; HSCT, hematopoietic stem cell transplantation; IDAC, ARA-C, 2 x 1000 mg/m2 iv day 1, 3, 5; IDAC-P, ARA-C, 2 x 1000 mg/m2 iv day 1, 3, 5, pegfilgrastim on day 6; MIDAC-light, ARA-C, 2 x 1000 mg/m² iv day 1, 3, 5; mitoxantrone, 12 mg/m² iv day 3, 5, pegfilgrastim 6 mg sc on day 6 or filgrastim starting on day 6 at the decision of the Principal Investigator; NR, no remission

first induction therapy. One patient had a severe infection during prolonged aplasia (>40 days) and the other a refractory thrombopenia resulting in a subdural hematoma. In 33 patients (51.6%) the first induction resulted in a CR. 4 patients (6.1%) died during the induction therapy and 27 (42.2%) did not achieve a CR. 7 patients with blast cell persistence were removed from the trial. 3 had withdrawn their consent, in 2 additional patients therapy was withhold due to adverse events and in 2 others because of investigators decision. In 20

patients with persistence leukemia, a 2nd cycle of induction therapy was given; 9 of these patients (45%) achieved a complete remission, 11 (55%) had resistant disease. Of these, 1 has withdrawn his consent, 2 were removed from the trial based on investigators decision and 2 received rescue HSCT. Thus, 6 patients received a 3rd induction. Only 1 of them achieved a CR, the other patients had to be removed from the study based on the protocol due to persistent disease. Together, following the induction phase, 43 patients (64.1%) achieved a CR, 4 (6.2%) died during the induction therapy and in 19 (19.7%) no CR could be achieved.

Of the 43 CR patients, 4 did not receive consolidation therapy. One patient had recurrence of disease prior to the 1st consolidation, another died because of a spontaneous internal bleeding. Two patients had to be removed, because of a severe protocol violation (wrong protocol in consolidation 1) in one, due to aggravation of dementia in another. In 39 patients (60.9%) consolidation therapy could be initiated.

All 4 planned courses of consolidation treatment could be administered in 23/39 patients (59.0%). 5 patients (12.8%) received three, and 3 patients (7.7%) two cycles of IDAC with or without G-CSF support. In 8 patients (20.5%), the treatment had to be discontinued after the 1st cycle of consolidation therapy with FLAG. Relapse was the major cause (n=8; 20.5%) to discontinue consolidation treatment. 4 patients (10.2%) were withdrawn because of persistent cytopenias. In 2 patients (5.1%) no 4th consolidation cycle was given because of severe infection during a prior treatment cycle and 4 (10.2%) died in the consolidation phase. 2 died from treatment related complications on day 33 and 10 after 1st and 4th consolidation, respectively. The other 2 died after complete recovery. These death were not related to prior treatment on day 38 (diffuse alveolar damage) and on day 26 (CNS bleeding despite normal platelets and coagulation) of 1st and 2nd consolidation respectively. One patient underwent HSCT due to high-risk disease after the first consolidation. Table 10 shows the causes to withdraw patients from further consolidation treatment in more detail.

Treatment-associated hematologic toxicity and the duration of hospitalization are shown in Table 11. The median duration of neutropenia was 8 days (range: 9-28 days), 9 days (range: 4-28 days) in consolidation 1 (FLAG), 7 days (range: 3-14 days) in consolidation 2 (IDAC-peg), 12 days (range: 3-21 days) in consolidation 3 (IDAC), and 7.5 days (range: 5-19 days) in consolidation 4 (IDAC-peg).

Neutropenic fever (>38°C) occurred in 68/121 consolidation cycles (56.2%), in 19/39 patients (48.7%) during the 1st, 18/31 patients (58.1%) during the 2nd, 17/28 patients (60.7%) during the 3rd, and 14/23 patients (60.9%) during 4th course of consolidation treatment. The median

Table 10

Causes of withdrawal from further consolidation cycles

	Death related to therapy	Death unrelated to therapy	Relapse	HSCT	Infection in a prior cycle	persisting cytopenia	All withdrawals per cycle
1st consolidation	1	1	3	1	0	2	8
2nd consolidation	0	1	2	0	0	0	3
3rd consolidation	0	0	2	0	2	1	5
4th consolidation	1	0	1	0	0	1	3
All consolidations	2	2	8	1	2	4	19

HSCT, hematopoietic stem cell transplantation

Table 11

Hematologic toxicity of the therapy

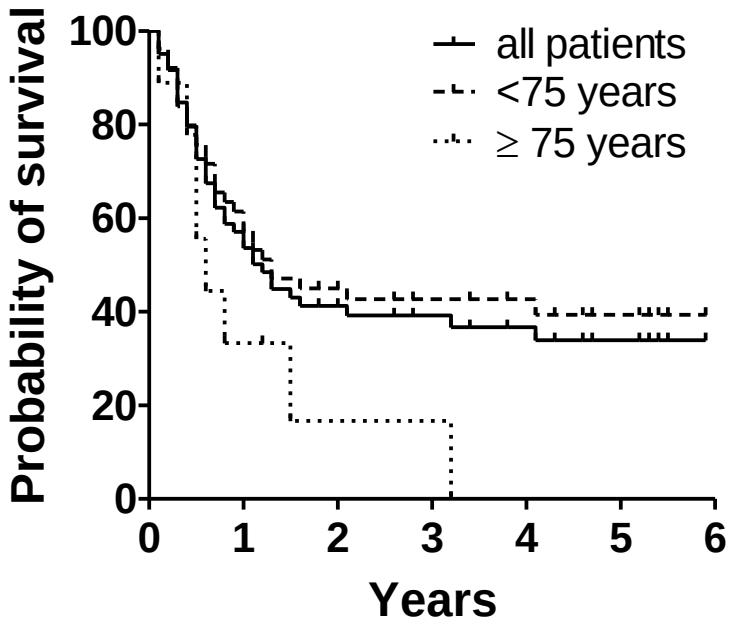
Consolidation scheme	1st cons. FLAG	2nd cons. IDAC-peg	3rd cons. IDAC	4th cons. IDAC-peg	All cons. -
Duration of neutropenia, median days (range)	9 (4-28)	7 (3-14)	12 (3-21)	7.5 (5-19)	8 (3-28)
Duration of hospitalization, median days (range)	23 (6-42)	21 (10-36)	28 (7-41)	22 (7-40)	23 (6-42)
Days with fever >38°C, median days (range)	0 (0-5)	1 (0-8)	1 (0-7)	1 0-6)	1 (0-8)
Percentage of cycle with fever >38°C	48.7	58.1	60.7	60.9	56.2
Number of packed red cell concentrates, median (range)	6 (2-15)	4 (0-8)	4 (0-6)	4 (0-6)	4 (2-15)
Number of platelet concentrates, median (range)	3 (0-13)	3 (1-8)	2 (1-7)	3 (1-10)	3 (0-13)

Cons, consolidation therapy; IDAC-peg, IDAC with the routine administration of Pegfilgrastim

duration of fever was 1 day (range: 0-27 days). Overall, 4 patient died; 2 related to the therapy and 2 unrelated to therapy (see above). The median number of packed red cell and platelets concentrates were given per consolidation cycle were 4 (range: 0-15) and 3 (range 0-13), respectively. Table 11 provides a detailed list of concentrates applied in the 1st, 2nd, 3rd and 4th cycle of consolidation. Overall, the patients were hospitalized for a median of 23 days per cycle of consolidation therapy, ranging between 6 and 42 days. In the 1st cycle of

consolidation (FLAG), median time of hospitalization was 23 days (range 6-42 days). In consolidation 2 (IDAC-peg) the median duration was 21 days (range 10-36 days), in consolidation 3 (IDAC) 28 days (range 7-41 days), and in consolidation 4 (IDAC-peg) the median duration was 22 days (range 7-40 days). Together, the longest duration of hospitalization and neutropenia was found in the 3rd consolidation cycle (without routine administration of G-CSF), followed by the 1st consolidation (FLAG, being the most intensive consolidation), the 4th and 2nd consolidation (both with IDAC-peg). We did not record any severe i.e. grade III or IV nephrotoxicity. There was one case with grade III and one case with grade IV liver toxicity observed during the 1st and 2nd consolidation respectively. The profile of adverse events is shown below (section 11.3).

Figure 5



Survival of all patients
The survival is shown by the solid line. The dashed line represents the survival of patients aged <75 years, the dotted line the survival of patients aged ≥ 75 years with a median survival of 1.5 years and 0.5 years, respectively.

The median overall survival was 1.1 years, the 75% survival was 0.5 years and the 25% survival was not reached so far (Figure 5). The probability to be alive 5 years after the start of therapy is 32%. There were major differences in the overall survival of patients aged <75 years and ≥ 75. In particular, while the probability of survival after 5 years was 39% in the

group aged <75 years, no patient was alive after 5 years in the group ≥ 75 years (Figure 5). Cytogenetic analysis was available in 52 patients. Patients with monosomal karyotype had the poorest outcome compared to the other groups. No difference could be observed among patients with normal and non-monosomal karyotype (Table 12). Analysis for FLT3 ITD and NPM1 were done in 50 and 40 patients respectively. No differences were seen between patients with FLT3 ITD (n=8) and patients without FLT3 ITD (n=42; Table 12). The survival of the 12 patients with mutated NPM1 was favorable compared to the survival to the 28 patients with wild type NPM1. Women (n=25) had a slightly favorable survival compared to men (n=39; Table 12).

Table 12

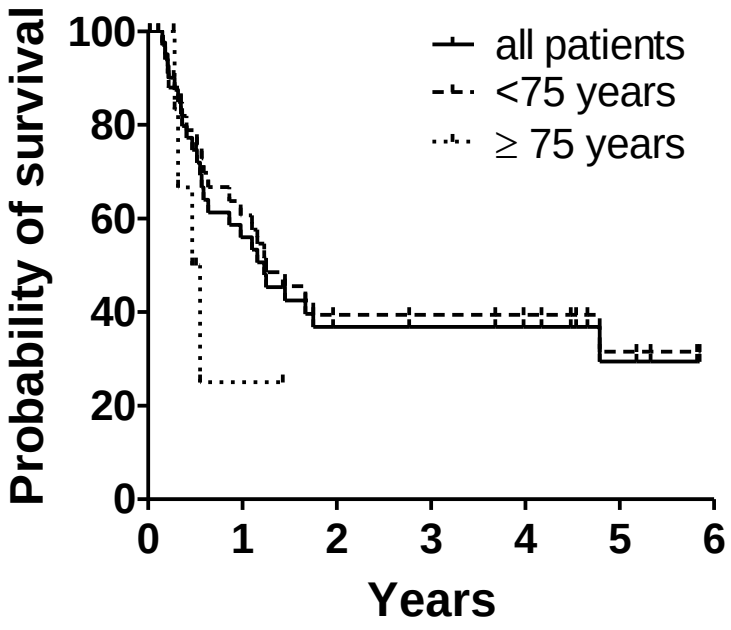
Comparison of the median survival, the 75% and 25% survival among the different groups according karyotype (HOVON criteria), FLT3 ITD and NPM1

		Survival (years)		
		75%	50%	25%
Karyotype	CBF (n=1)	nr	Nr	nr
	CN (n=25)	0.7	1.5	nr
	Mkneg (n=11)	0.5	2.1	nr
	Mkpos (n=15)	0.3	0.6	0.8
FLT3 ITD	neg (n=42)	0.6	1.3	nr
	pos (n=8)	0.5	0.7	nr
NPM1	wt (n=28)	0.5	1.3	nr
	mut (n=12)	0.7	Nr	nr
Gender	female	0.5	1.2	nr
	male	0.4	1.1	nr

CBF, core binding factor leukemia; CN, normal karyotype; Mkneg, non monosomal karyotype; Mkpos; monosomal karyotype; neg, negative; nr, not reached; pos, positive

The CCR could be calculated in the patients that had received at least 1 cycle of consolidation chemotherapy. The median CCR was 1.25 years, the 75% CCR was 0.47 years and the 25% CCR was not reached so far (Figure 6). The probability to be alive and in CCR 5 years after the start of therapy is 29%. Only a few patients aged ≥ 75 years (n=6) were included in the analysis. Their median CCR of 0.47 years was clearly inferior compared to the CCR of the patients aged <75 years with a median CCR of 1.25 years (Figure 6). Karyotyping was available in 30/39 patients. Patients with monosomal karyotype had the worst outcome. None

Figure 6



CCR of the patients
The CCR is shown by the solid line. The dashed line represents the CCR of patients aged <75 years, the dotted line the CCR of patients aged ≥ 75 years.

Table 12

Comparison of the median CCR the 75% and 25% survival among the different groups according karyotype (HOVON criteria), FLT3 ITD and NPM1

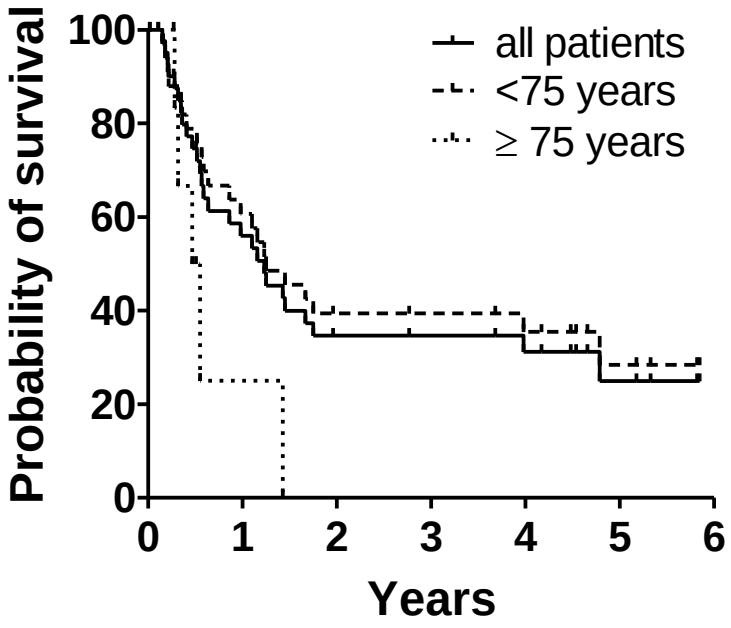
		CCR		
		75%	50%	25%
Karyotype	CBF (n=1)	nr	nr	nr
	CN (n=25)	0.6	1.2	4.8
	Mkneg (n=11)	1.6	nr	nr
	Mkpos (n=15)	0.2	0.4	0.5
FLT3 ITD	neg (n=42)	0.4	1.2	nr
	pos (n=8)	0.5	0.6	nr
NPM1	wt (n=28)	0.6	1.3	nr
	mut (n=12)	0.6	4.8	nr
Gender	female	0.5	1.2	nr
	male	0.4	1.1	nr

CBF, core binding factor leukemia; CN, normal karyotype; Mkneg, non monosomal karyotype; Mkpos; monosomal karyotype; neg, negative; nr, not reached; pos, positive

of these patients had achieved a long lasting CR. Only slight differences were observed among patients with normal and non monosomal karyotype (Table 12). Analysis for FLT3 ITD and NPM1 were done in 29 and 26 patients respectively. Again, no differences were observed among cases with FLT3 ITD (n=4) and cases without FLT3 ITD (n=25; Table 12). The survival of the 11 patients with mutated NPM1 was favorable compared to the survival to the 17 patients with wild type NPM1. However, the survival analyses for karyotyping and molecular markers have to be interpreted with caution due to the low number of patients included. The survival of women (n=25) was slightly better compared to men (n=24; Table 12).

Like the CCR, the DFS was calculated in the patients that had received at least 1 cycle of consolidation chemotherapy with a median of 1.23 years (75% survival 0.38 years, 25% survival not reached; Figure 7). Again the few patients aged ≥ 75 years (n=6) included in the analysis had a clearly inferior DFS (median: 0.47 years) compared to the DFS of the patients aged <75 years with a median of 1.25 years (Figure 7). In only a limited number of patients the karyotype or results from for molecular studies were available. Again, patients with

Figure 7



DFS of the patients

The DFS is shown by the solid line. The dashed line represents the DFS of patients aged <75 years, the dotted line the DFS of patients aged ≥ 75 years.

monosomal karyotype had the poorest outcome. None of these patients had a DFS over one year contrasting patients with normal karyotype or non-monosomal karyotype (Table 13). Again, no differences was observed among cases with FLT3 ITD (n=4) and cases without FLT3 ITD (n=25; Table 13). The survival of the 11 patients with mutated NPM1 was favorable compared to the survival to the 17 patients with wild type NPM1. The survival of women (n=25) was slightly better compared to men (n=24; Table 13).

Table 13
Comparison of the median DFS the 75% and 25% survival among the different groups according karyotype (HOVON criteria), FLT3 ITD and NPM1

		CCR		
		75%	50%	25%
Karyotype	CBF (n=1)	nr	nr	nr
	CN (n=25)	0.6	1.2	4.8
	Mkneg (n=11)	1.7	nr	nr
	Mkpos (n=15)	0.2	0.4	0.5
FLT3 ITD	neg (n=42)	0.4	1.2	4.8
	pos (n=8)	0.5	0.6	0.6
NPM1	wt (n=28)	0.6	1.2	1.8
	mut (n=12)	0.6	4.8	4.8
Gender	female	0.5	1.2	nr
	male	0.4	1.1	nr

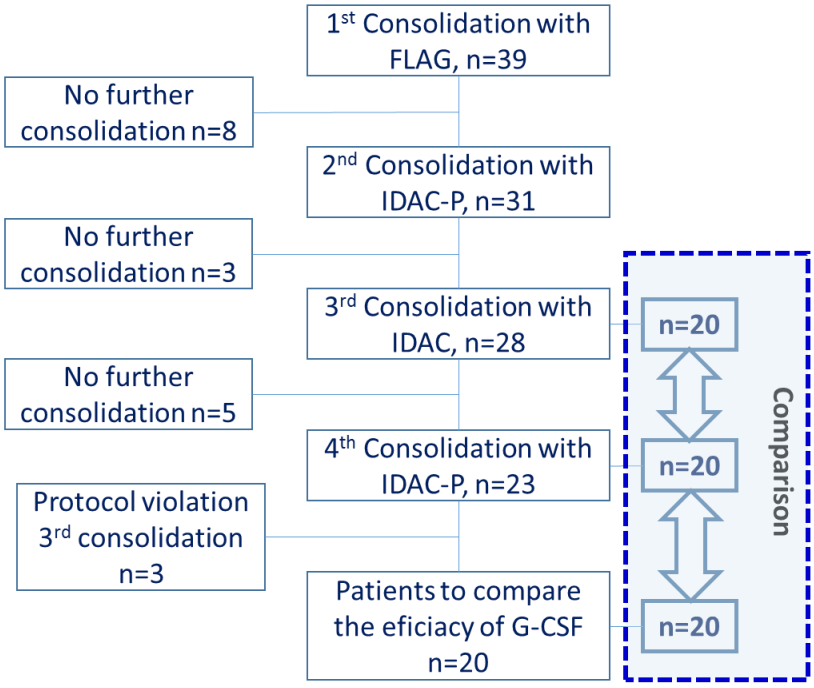
CBF, core binding factor leukemia; CN, normal karyotype; Mkneg, non monosomal karyotype; Mkpos; monosomal karyotype; neg, negative; nr, not reached; pos, positive

Serial analysis of the CCI (prior to induction therapy, prior to the 3rd consolidation and/or at the end of study visit) was performed to analyse the changes in the profile of comorbidities during the antileukemic therapy. In 6 patients a worsening of comorbid conditions was seen comparing to the CCI between the first analysis and the time after the 2nd consolidation. Two patients acquired two additional comorbidities i.e. myocardial infarction and diabetes in one and cerebrovascular disease and diabetes in the other. In the remaining 4 patients' congestive heart failure, a cerebrovascular disease and diabetes were found. Comparing the CCI between the analysis prior to the 3rd consolidation and the end of study visit in two patients an additional comorbidity was observed, i.e. a congestive heart failure and a cerebrovascular disease.

The induction reporting group was used to selectively describe the adverse events occurring during the induction phase of the antileukemic therapy. This is shown in section 11.3. Other results that could be assessed in this group including CR-rate, number of induction cycles were already evaluated in the overall reporting groups.

The consolidation 1-4 group was used to selectively evaluate the adverse events occurring during the induction phase as shown in section 11.3. Moreover, in this group the effect of the routine administration of G-CSF was analysed with regard to the duration of hospitalization, neutropenia and days with fever> 38°C. The data on all patients in the consolidation phase is shown in Table 11. However, to analyse the effect of G-CSF in more detail, only patients that have received all four planned cycles of chemotherapy per protocol were evaluated (Figure 8).

Figure 8

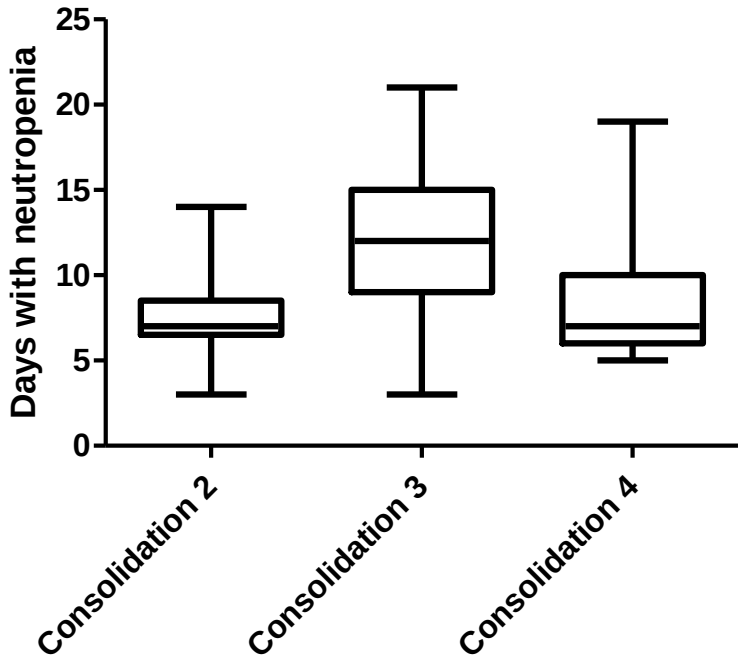


Selection of the patients eligible for the comparison of the effect of G-CSF from the consolidation 1-4 reporting group

In these 20 patients the duration of neutropenia was 7 days (range 4-28 days) in consolidation 2, 11.5 days (range: 3-14 days) in consolidation 3, and 7.5 days (range: 5-19 days) in consolidation 4. Thus, there was a markedly difference seen in the duration of neutropenia among the 2nd and 3rd consolidation as well as among the 3rd and 4th consolidation cycle

(Figure 9). This occurred, although 6/20 patients (30%) had received G-CSF during the 3rd consolidation according to the ASCO criteria as allowed by the study protocol.

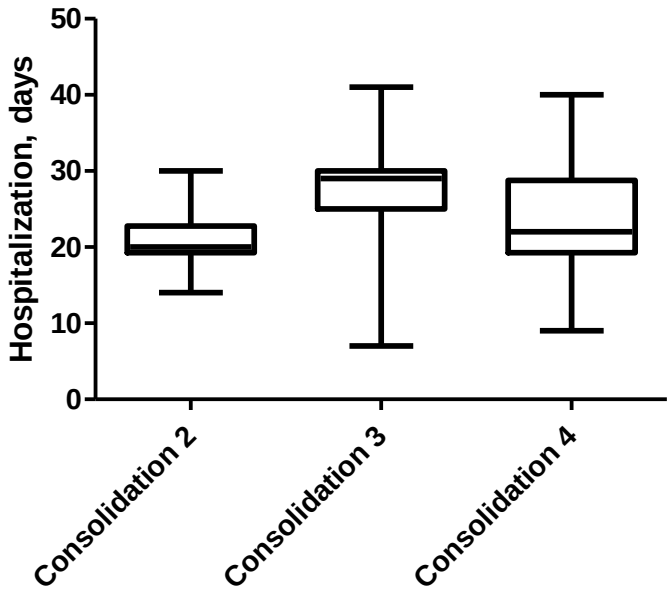
Figure 9



Comparison of the duration of neutropenia between the 2nd, 3rd, and 4th consolidation cycle The box represents the 25-75% percentile of days with neutropenia in each group, the horizontal line within boxes defines the median, and the whiskers represent the range.

These differences in neutropenia also resulted in a markedly difference in the duration of hospitalization between these consolidation cycles. The 20 patients treated per protocol were hospitalized for 20 days (range 13-42 days) in consolidation 2, 29 days (range 7-41 days) in consolidation 3, and 22 days (range: 9-40 days) in consolidation 4 (Figure 10). In contrast to the duration of neutropenia and hospitalization, no difference was found in the incidence of fever >38°C among the 2nd, 3rd, and 4th consolidation therapy. Fever occurred in 15/20 cycles (75%) in consolidation 2, 11/20 cycles (55%) in consolidation 3, and 13/20 cycles (65%) in consolidation 4. The duration of fever was short in the majority of cycles in consolidation 2, 3, and 4, with 1.5 days (range: 0-5 days), 1 day (range: 0-5 days), and 1.5 days (range: 0-6 days), respectively.

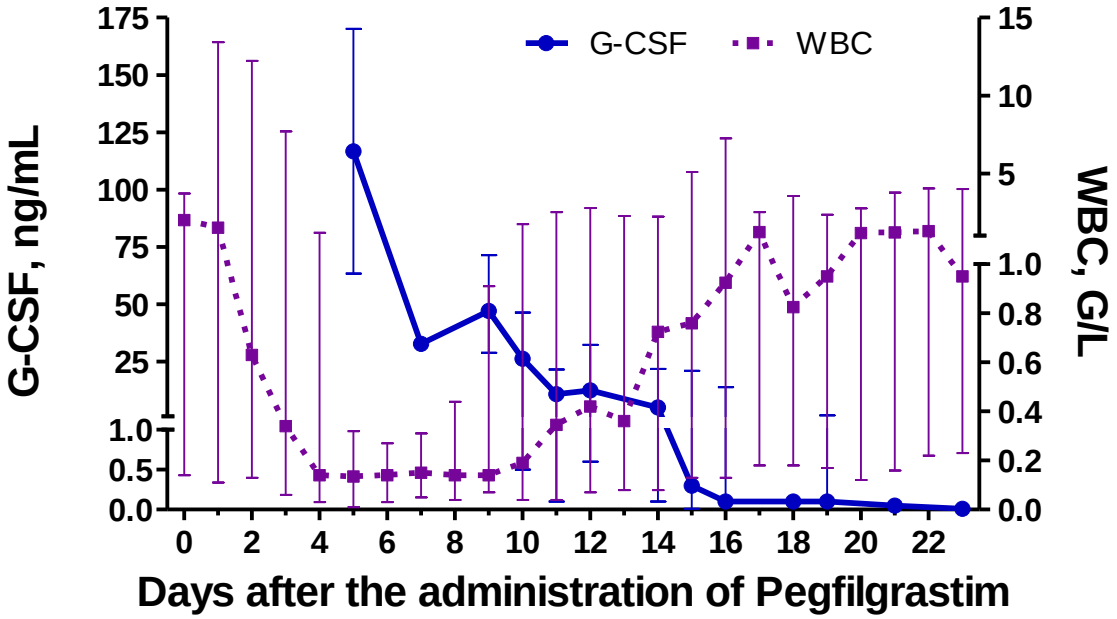
Figure 10



Comparison of the duration of hospitalization between the 2nd, 3rd, and 4th consolidation cycle The box represents the 25-75% percentile in each group, the horizontal line within boxes defines the median, and the whiskers represent the range.

Another question was how long plasma levels of pegfilgrastim were detectable. For this purpose the concentration of G-CSF in the patients´ plasma was measured serially in 18 consolidation cycles (FLAG, n=16; IDAC, n=2). These measurements were done after the administration of pegfilgrastim i.e. between days 11 and 35 after start of chemotherapy. G-CSF was detectable in all serum samples taken before day 21 of chemotherapy i.e. day 16 after the administration of pegfilgrastim. Thereafter, the number of samples with detectable cytokine levels decreased. The last serum samples with detectable cytokine level was taken on day 27 of chemotherapy i.e. day 22 after pegfilgrastim administration. There was a clear association between G-CSF levels and the peripheral WBC. In patients with an early increase of WBC and granulocyte counts, there was an early decrease of G-CSF and vice versa. The time course of cytokine levels and WBC counts is depicted in figure 11.

Figure 11



G-CSF levels and WBC counts

G-CSF levels (solid line) and WBC (dashed line) are presented as median and range in 18 consolidation cycles (FLAG, n=16; IDAC, n=2). Each point represents the median of the measurements available for this time point. Day 1 is the first day of pegfilgrastim administration.

10.4.2 Statistical/Analytical Issues

Because of the early termination, not all planned endpoints – especially secondary - could be adressed and due to the low number of cases, the statistical power of the results would be rather low. Thus, we used descriptive statistical methods to describe the results of this trial. To characterize the proportion of subgroups these are given in percent and absolute numbers if appropriate. Continuous variables are described as median, minimum and maximum in the text. In figures the median, interquartile range, minimum and maximum are provided. The probability of survival was calculated according to the method of Kaplan and Meier. No statistical testing for significance was applied. No adjustments were made for demographic or baseline measurements or concomitant therapy. Drop-outs and missing data were not replaced. There were no adjustments for multiple comparisons necessary. In this trial, no interim analysis was planned in the initial protocol and no analysis of the data set collected was performed throughout the recruitment period. Since this was an open trial there was no blind-breaking.

10.4.2.1 Multicenter Studies

The base line data are shown for each center in the section 13.1 demographic data, for comparison among the centers. Half of the patients i.e. 32 were recruited in a single center, followed by the next center with 15 patients. In the three remaining centers 7 and twice 5 patients were included in the trial. In general, the data are matching. Only in case of multiple subgroups there are extremes and spikes because of the low number of cases.

10.4.2.2 Multiple Comparison/Multiplicity

There was no multiple testing, as this point is not applicable.

10.4.2.3 Use of an "Efficacy Subset" of Patients

All data were analysed in the overall reporting group and are shown in this report. An "efficacy subset" was only used to analyse the efficiacy of G-CSF during consolidation therapy. For this purpose only patients receiving the same chemotherapy scheme i.e. IDAC were eligible. Moreover, as stated in the protocol of the trial, consolidation 2 applying IDAC and routinely G-CSG on day 6, consolidation 3 with IDAC (G-CSF allowed only according to ASCO criteria) and consolidation 4 again applying IDAC and routinely G-CSF on day 6 were compared. The duration of neutropenia, hospitalization, and fever as well as the incidence of fever were compared between the 2^{nd} and 3^{rd} cycle as well as between the 3^{rd} and 4^{th} cycle. To avoid a bias (i.e. exclusion of patients with complications, different number of patients in the 2^{nd}, 3^{rd} and 4^{th} consolidation cycle), only patients that had received the 4^{th} consolidation course were included in this analysis. Finally, 3 patients had to be excluded because they had received routinely G-CSF during consolidation 3. However, the data and results observed in the "efficacy subset" were in line with those of the overall reporting group.

10.4.3 Tabulation of Individual Response Data

In the tabulation of individual data shown in section 15.2.6 the identification numbers are given per patient, the center the patient was treated, sex, age, FAB and WHO subtype of the leukemia, subgroup according the karyotype. FLT3 ITD status, NPM1 status, number of induction cycles given, outcome of the induction phase and the last chemo administered (induction 1, 2, or 3; consolidation 1, 2, 3, or 4).

10.4.4 Drug Dose, Drug Concentration, and Relationships to Response

The dose of chemotherapy could vary in each patient according the body surface. Detailed information on the chemotherapies and doses of cytostatic drugs in mg/m² applied in this trial are provided in section 8.4.1 (treatments administered). Pegfilgrastim was administered in a dose of 6 mg (s.c.) regardless the body surface area, age, sex, or weight of the patient.

10.4.5 Drug-Drug and Drug-Disease Interactions

This point is not applicable. There was no apparent relationship between response and any concomitant therapy and between response and any past and/or concurrent illness.

10.4.6 By-Patient Displays

Not applicable

10.4.7 Efficacy Conclusions

Primarily because of early termination, not all planned endpoints – especially secondary - can be answered and statistical analyses have been restricted to descriptive statistical methods. The primary question was whether intensified consolidation chemotherapy can be administered in AML patients aged ≥ 60 years. This question can be answered with yes, based on the data available in this report. The majority of patients tolerated the intensive therapy and 3 cycles could be applied in 71.8% of the patients. The major cause to withdraw a patient was relapse (n=8), despite intensive treatment. However, 2 patients died during consolidation, and 2 died between 2 cycles of consolidation. Moreover, 4 patients were removed due to persistent cytopenia. Thus, the selection of patients according to karyotype and molecular markers may be of particular importance. However, since the patients' number was too small for statistically relevant subgroup analysis this has to be answered in forthcoming trials. The adverse event profile is shown in section 11.3 and will be discussed in section 12.

The rate of CR following induction chemotherapy was 64.1%, which is in line with our own previous results applying the same induction strategy [14]. As already mentioned, the relapse rate has been improved but remains still high, despite intensive therapy. Thus, maintenance strategies or intensive therapy with HSCT are of importance. The overall survival, continuous complete remission and disease-free survival is favourable compared to previous data. A number of patients survived the first 5 years after initiation of chemotherapy. Thus, these data prove that at least a subgroup of elderly patient benefits from intensive therapy and can

achieve a long-term survival. The evaluation of prognostic factors including age, karyotype, and molecular markers was problematic due to the low number of patients. Age was an important predictive factor, since there was a clear difference between the survival of patients aged <75 and ≥ 75 years as shown in the section 10.4.1 "analysis of efficacy" (Figures 6-8). Also, the karyotype was of importance and the different groups showed marked differences in their survival. With regard to the molecular markers, there was a difference between patients with NPM1wt and NPM1mut in the survival, whereas the curves of the different groups according to FLT3 IDTD were superposed. The routine administration of pegfilgrastim on day 6 of consolidation therapy (the first day after chemotherapy) resulted in a clear shortening of neutropenia and a reduction of the time of hospitalisation. The treatment was save and thus can be recommended an consolidation therapy in elderly AML patients.

11. SAFETY EVALUATION

To evaluate the extent of exposure (dose, duration, number of patients) the number of consolidation cycles applicable per patients were recorded to determine the degree to which safety can be assessed from the study. All adverse events were recorded, including the serious adverse events, the significant AEs and their duration.

11.1 EXTENT OF EXPOSURE

Overall, 4 cycles of consolidation therapy were planned for patients achieving a CR. From 39 patients that had received the 1st consolidation cycle with FLAG, 3 could not continue further treatment due to treatment related toxicity (i.e. persistent cytopenias, n=2; treatment related death, n=1). HSCT because of high risk disease (n=1), death unrelated to therapy (n=1) and recurrence of AML (n=3) was the cause of withdrawal in another 5 patients. No patients discontinued consolidation therapy because of treatment related toxicity after the 2nd consolidation cycle (but 2 patients had a relapse) but 1 patient died after recovery of the peripheral blood from a cerebral bleeding. In 3 patients treatment related toxicity resulted in an early termination of consolidation therapy after cycle 3, two relapsed. During the 4th consolidation a total number of 2 events of treatment related toxicity were observed, i.e. 1 case of therapy related death and 1 case with persistent cytopenia.

11.2 ADVERSE EVENTS (AEs)

To better correlate the adverse events and severe adverse events with the status of disease, the numbers, duration, and severity of AEs were recorded in 3 reporting groups, i.e. the overall reporting group (including the AEs seen during the screening phase, induction phase, consolidation phase, follow up phase and at end of treatment), induction 1-3 reporting group (focusing on events occurring during the 1st, 2nd, and 3rd induction), and consolidation 1-4 reporting group (covering the 4 consolidation cycles and the time between these cycles).

11.2.1 Brief Summary of Adverse Events

In the entire study, 1229 adverse events occurred and are listed in the overall reporting group. In the induction 1-3 reporting group 669 AEs were recorded, and in the consolidation 1-4 reporting group 506 AEs occured. The majority of AEs, i.e. 1095 was not related to the study medication, a possible relationship was claimed in 28 events and 104 events were considered to have a definitive relationship to the treatment in the overall reporting group. In 2 events no information of the relationship could be provided. In the induction 1-3 reporting group a relation between AE and treatment was reported in 59 events, in 20 adverse events a relation was assumed to be possible, and 589 events were not related to the treatment. In the consolidation 1-4 reporting group, 42 events were related to the therapy, 8 had a possible relationship and 456 were not related. There were 52 SAE and 1177 non serious AEs.

11.2.2 Display of Adverse Events

Classified according MedDRA system organ class code, there were 152 blood and lymphatic system disorders, 11 cardiac disorders, 1 congenital, familial and genetic disorders, 39 ear and labyrinth disorders, 1 endocrine disorder, 11 eye disorders, 135 gastrointestinal disorders, 107 general disorders and administration site conditions, 7 hepatobiliary disorders, 4 immune-system disorders, 223 infections and infestations, 26 injury, poisoning and procedural complications, 15 investigations, 37 metabolism and nutrition disorders, 60 musculoskeletal and connective tissue disorders, 1 neoplasms benign, malignant and unspecified (including cysts and polyps), 52 nervous system disorders, 29 psychiatric disorders, 11 renal and urinary disorders, 1 reproductive system and breast disorder, 68 respiratory, thoracic and mediastinal disorders, 49 skin and subcutaneous tissue disorders, 2 surgical and medical procedures, and 39 vascular disorders. With regard to severity there were 52 SAEs and 1177 non severe AEs

as stated above. Using 5 groups to define the severity/intensity, there were 750 mild, 392 moderate, 53 severe, 14 life threatening and 15 fatal events reported. Five events were not specified. Concerning the stage of therapy, 33 AEs occurred during the screening phase (reported in the overall reporting group only), 669 in the induction 1-3 reporting group, 506 in the consolidation 1-4 reporting group, 7 during the follow up and 14 AEs were reported at the end of treatment (reported in the overall reporting group only). The median number of AEs per reporting group was 4 (range: 0-21) in the overall reporting group, 7 (range 0-21) in the induction 1-3 reporting group, and 3 (range 0-18) in the consolidation reporting group. The median number of AEs per particular chemotherapy cycle was 7.5 (range: 1-21) in induction 1, 6 (range: 0-19) in induction 2, 3.5 (range: 1-8) in induction 3, 3 (range: 0-18) in consolidation 1, 3 (range: 0-11) in consolidation 2, 4 (range: 0-13) in consolidation 3, and 4 (range: 0-11) in consolidation 4. A detailed description of the relationship between MedDRA system organ class code, severity, stage of therapy, relation of AE to therapy, and patients ID is provided in the summary table of AEs classified according MedDRA system organ class code part 1-9 in the section 13.3.1.

The median duration of the AEs was 4 days in the overall reporting group and induction 1-3 reporting group, and 3 days in the consolidation 1-4 reporting group. When correlating the duration with the severity the median duration of mild AEs was 2 days, 6 days for moderate AEs, 3 days for severe AEs, 21 for life threatening AEs, and 1 in case of a fatal AE in the overall reporting group. In the 5 AEs not specified in the overall reporting group the median duration was 1 day. In the induction 1-3 reporting group the median duration of mild AEs was 2 days, 7 days in moderate AEs, 4 days in severe AEs, 4 in life threatening and AEs, 3.5 in fatal AE. In the consolidation 1-4 reporting group the median duration of mild AEs was 2 days, 5 days in moderate AEs, 2.5 days in severe AEs, 13.5 in life threatening AEs, and 2 in fatal AE. A detailed listing of the number of AEs per chemotherapy cycle in the entire group and broken down by center as well as the median number of AEs per chemotherapy cycle in the entire group and broken down by center can be found in section 13.3.1.

11.2.3 Analysis of Adverse Events

In the entire study, 1229 adverse events were captured in the overall reporting group. Of these 33 AEs occurred during the screening phase, 669 in the induction 1-3 reporting group, 506 in the consolidation 1-4 reporting group, 7 during the follow up and 14 were reported at the end of treatment visit. Thus even prior to the administration of the therapy, AEs were seen. In this regard, it has to be considered, that in patients with AML a high proportion of

AEs (often life threatening) are caused by the leukemia, including infections, bleedings, or hyperleukocytosis. This point is supported by the fact, that only 104 AEs i.e. 8.5% of all AEs were related, and 28 AEs i.e. 2.3% of all AEs were possibly related to the treatment. Thus, in 10.8% of the AEs a relation to the AML treatment was suspected whereas the vast majority was disease related. In line with this observation, there was a difference in the prevalence of AEs between the induction 1-3 reporting group and the consolidation 1-4 reporting group. In the induction 1-3 reporting group 90 cycles of chemotherapy were administerd and 669 AEs were recorded resulting in a median number of AEs of 7 per cycle of chemotherapy. In the consolidation 1-4 reporting group 506 AEs occurred during 121 cycles of chemotherapy with median number of 3 AEs per cycle.

Another major problem of AML therapy is the neutropenia leading to systemic infections or inflammation in various organ systems. This is also reflected by the prevalence of AEs. Infections and infestations had a high prevalence in our patients with a total number of 223 events. Cytopenia itself was also a frequent AE resulting in 152 events reported as blood and lymphatic system events. Other frequently observed events were gastrointestinal disorders n=135), general disorders and administration site conditions (n=107), respiratory, thoracic and mediastinal disorders (n=68) and musculoskeletal and connective tissue disorders (n=60). While gastrointestinal disorders and general disorders and administration site conditions can be interpreted as side effects associated with chemotherapy, respiratory, thoracic and mediastinal disorders or musculoskeletal and connective tissue disorders are more likely to be a result from infections.

The fact that some AEs were reported at the end of treatment visit can be explained by the fact that a number of patients had persistent disease or had to been withdrawn from further therapy during the induction phase (n=25) and that relapsing leukemia is one of the major problems in the treatment of AML. In this trial, 8 patients of the consolidation 1-4 reporting group (20.5%) had recurrence of disease despite ongoing treatment.

11.2.4 Listing of Adverse Events by Patient

A detailed list on all adverse events for each patient, including the same event on several occasions is listed in appendix 15.2.7, giving both preferred term and the original term used by the investigator. The rows: “test drug/investigational product dose described per in absolute amount, mg/kg or mg/m² at time of event” and “the duration of test drug/investigational product treatment” were omitted. The reason was that the therapy (drugs and doses) for each treatment period/phase of the study (that is given in the row: “Study

treatment at time of event or most recent study treatment taken") is defined in the protocol and can be found in the section 8.4.1 i.e. "Treatments administered" in this report (see above). The drug concentration in the serum at an event was not known.

11.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

11.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

A detailed list of all severe adverse events for each patient, including the same event on several occasions is listed in appendix 15.2.7 i.e. "SAEs occurring during this trial". The rows: "test drug/investigational product dose described per in absolute amount, mg/kg or mg/m² at time of event", "the duration of test drug/investigational product treatment", and "drug concentration in the serum at an event" were not included in the table (for explanation see above).

11.3.1.1 Deaths

Overall, 15 patients died during the study procedures or during the follow up (i.e. after 5 years or until 15. Sep. 2014, whatever came first). All deaths during the study, including the post treatment follow-up period, are listed in section 13.3.2 i.e."SAEs resulting in death during the study. Three deaths were assumed to be related to treatment procedures (in consolidation 1, consolidation 4, and induction 1), all others were not related to therapy.

Most patients died during or after the induction therapy; 3 of them died prior to the evaluation of CR on day 11 (2 patients) and day 16 of induction. In a patient that died on day 57 of induction 1 the last bone marrow examination drawn on day 31 had been "empty" and the patient had been withdrawn from the study based on this bone marrow examination. In all other patients that died during or following the induction phase blast cell persistence was observed.

Of the patients that died during the consolidation phase one died following a relapse (58 days after the initiation of the last consolidation). Two deaths were related to treatment procedures, i.e. severe infection on day 19 and cardiac arrest on day 31 of the last consolidation cycle. Two others were not related to therapy, i.e. CNS bleeding on day 26 (after complete recovery of the peripheral blood including the platelet count) and diffuse alveolar damage (after complete recovery of the peripheral blood) on day 36 of the prior consolidation cycle.

11.3.1.2 Other Serious Adverse Events

Overall, there were 37 serious adverse events other than death that occurred in 23 patients (median number: 1; range 1-3). The most frequent SAEs according to the MedDRA system organ class were infections and infestations (n=17). Other SAEs were gastrointestinal disorders (n=7), renal and urinary disorders (n=4), nervous system disorders (n=3), general disorders and administration site conditions (n=2), injury, poisoning and procedural complications (n=2), blood and lymphatic system disorders (n=1), and cardiac disorders (n=1). A detailed overview of all AEs according to MedDRA lowest level term is shown in the table in section 14.3.2 i.e. "SAEs other than death". Of all SAEs, 33 were considered not related to therapy, in 1 a possibly relation was suspected and 3 were related to the treatment. With regard to severity/intensity 10 events were assessed life threatening, 4 mild, 15 moderate, and 8 severe. The events occurred during induction 1 (n=13), induction 2 (n=5), consolidation 1 (n=9), consolidation 2 (n=2), consolidation 3 (n=1), consolidation 4 (n=3), and after the end of treatment (n=4). They resulted in hospitalization of 17 patients and prolonged hospitalization of 10 patients. Concomitant therapy was administered in 29 patients and in 1 patient "other" actions were taken.

11.3.1.3 Other Significant Adverse Events

Overall, there were 49 significant adverse events not considered as SAEs. They occurred in 22 patients (median number: 2; range 1-7). The most frequent AEs according to the MedDRA system organ class were blood and lymphatic system disorders (n=19) as well as infections and infestations (n=8) and gastrointestinal disorders (n=7). Other AEs described were respiratory, thoracic and mediastinal disorders (n=4), general disorders and administration site conditions (n=3), musculoskeletal and connective tissue disorders (n=3), cardiac disorders (n=1), hepatobiliary disorders (n=1), metabolism and nutrition disorders (n=1), renal and urinary disorders (n=1), and vascular disorders (n=1). A detailed listing according MedDRA lowest level term can be found in the table in section 14.3.2 i.e. "Significant adverse events". Of all AEs, 44 were considered not related to therapy and 5 were considered to be related to the treatment. With regard to severity/intensity 4 events were assessed to be life threatening and 45 severe. The events occurred during induction 1 (n=26), induction 2 (n=9), consolidation 1 (n=3), consolidation 2 (n=5), consolidation 3 (n=2), and consolidation 4 (n=1). In 39 patients concomitant therapy was administered in 10 patients, no actions were taken.

11.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

9 patients died during the induction phase of the antileukemic therapy. 3 died prior to the evaluation of CR. All 3 died do to a severe infection in neutropenia on day 11 (patient 029, pneumonia; patient 033, sepsis) or day 16 (patient 023, severe infection) of the 1st induction therapy. In two patients the neutropenia was supposed to be leukemia associated and thus not related to therapy (patients 023 and 033). In one patient, the leucopenia was related to induction therapy (patient 029). Patient 058 died on day 57 of the 1st induction therapy from septic multi-organ failure (still in cytopenia). A bone marrow examination drawn on day 31 had shown an "empty" marrow. Thus, the patient was withdrawn from the study. Another bone marrow examination on day 43 of induction therapy revealed a similar result. The other patients had a blast cell persistence following the induction phase. Patients 010 and 047 had received the 1st cycle of induction therapy. They had a blast cell persistence, were unfit for further induction therapy and died on day 50 (patient 010) and on day 44 (patient 047) of the 1st induction cycle. Patient 005 and 024 had received the 2nd induction and had a persistence of leukemia. In the follow up phase patient 005 refused further cytostatic therapy, patient 010 had a severe infection. They died on day 65 and on day 50 of the 2nd induction cycle, respectively. Patient 057 had a persistence of leukemia despite 3 cycles of induction chemotherapy. Thus, the patient had to be withdrawn from the trial according to the protocol (died on day 30 of the 3rd induction).

6 patients died after having achieved a CR. Patient 030 had an gatrointestinal bleeding resulting in death on day 35 of the first induction. Patient 013 showed a relapse diagnosed on day 41 of the 2nd consolidation therapy and died from leukemia on day 58. Patients 017 and 061 died on day 31 respectively on day 36 of the 1st consolidation therapy. In patient 017 a severe prolonged infection resulted in a general weakness and neurological deterioration. The patient died from cardiac arrest. This SAE was stated to be related to therapy. Patient 061 had recovered from therapy but had to be readmitted to the hospital due to pulmonary problems and died due to diffuse alveolar damage (not related to therapy) on day 36 of the prior consolidation cycle. A similar case was patient 012. He was discharged following peripheral recovery from the 2nd consolidation but was readmitted because of CNS bleeding on day 26 and died on the same day (after complete recovery of the peripheral blood). There were no hints of a relation to therapy. Patient 034 died on day 19 of the 4th cycle of consolidation therapy because of septicemia related to therapy.

11.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

When analysing AEs in AML it has to be considered that leukemia is a life-threatening disease associated with high mortality rates. A substantial number of patients requires intensive care during induction or consolidation therapy. Likewise, it has been shown, that 15% of patients receiving intensive induction therapy required admission to an intensive care unit [69]. Risk factors in these patients were disease and patients related i.e. were low fibrinogen, presence of an infection, and the presence of comorbidities. Thus, the occurrence of AEs in this trial was not unexpected. The median number of events per patient was 18, ranging from 3 to 52 events. In 21 patients the occurrence of an AE resulted in the withdrawal of the patient from the trial (i.e. patients 006, 010, 012, 015, 017, 019, 021, 022, 023, 025, 029, 030, 033, 034, 050, 053, 056, 058, 060, 061, 064). The other patients were withdrawn because of blast cell persistence despite induction therapy (n=5), refusal of the patients to continue treatment and/or observation (n=5), HSCT due to high risk profile (n=3), relapse of leukemia (n=9), or severe protocol violation (n=1). Of the 15 patients that had a fatal SAE in 10 (66.7%) the SAEs were responsible for the withdrawal of the patient form further therapy, in 5 (33.3%) the SAE occurred after the withdrawal of the patient from the study. Of the 23 patients with SAEs other than death, the AE resulted in 4 (17.4%) patients in a withdrawal of the patient form further therapy. It is note worthy that in 8 of the 23 patients (34.8%) with a SAE other than death, a fatal SAE occurred in the follow up phase. In 7 patients (30.4%) the SAE occurred after the withdrawal of the patient from the trial and in 4 patients (17.4%) the trial was completed despite the SAE. Overall, there were 22 patients with significant adverse events not considered as SAEs. In 1 of them (4.5%) the event caused the withdrawal of the patient from further therapy. In 9 patients (40.9%) a SAE resulted in withdrawal from the study and in 12 patients (54.5%) the event occurred after the withdrawal. In 5 patients AEs were considered neither severe nor significant but were the reason to stop further chemotherapy. An overview of the number of AEs in each patient, presence or absence of SAEs and significant AEs, as well as their relation to the completion of the trial and causes of withdrawal is shown in a separate Table in section 13.3.3 i.e. “Number of AEs per patient, SAEs, significant AEs and their correlation with study completion (part 1)” and “Number of AEs per patient, SAEs, significant AEs and their correlation with study completion (part 2)”.

All events like fatal SAEs, SAEs other than death, significant AEs and non serious, not significant AEs were in the scope of AEs known to occurr in patient treated for AML with

intensive or dose reduced chemotherapy. Thus, none of the SAEs reported during the study period had to be considered as SUSAR.

11.4 CLINICAL LABORATORY EVALUATION.

11.4.1 Listing of Individual Laboratory Measurements by Patient (15.2.8) and Each Abnormal Laboratory Value (13.3.4)

The results of all safety-related laboratory tests are available in tabular listings in the appendix (section 15.2.8; "Peripheral blood counts" and "Laboratory chemistry"). Abnormal values of the peripheral blood count were seen in all patients due to the natural course of AML and all 5018 peripheral blood counts are depicted in the table peripheral blood counts in the section appendix (15.2.8) Thus no separate table with abnormal peripheral blood counts were prepared for section 13.3.4. Elevation of the CRP above the upper level of normal was observed in 2720/3442 reports of the laboratory chemistry (79%) and elevated LDH levels were seen in 570/3442 reports. Abnormal laboratory values i.e. grade II, grade III (italic), and grade IV (italic & bold) for BUN, creatinine, transaminases, and alkaline phosphatase are shown in section 13.3.4. i.e. Abnormal laboratory values: grade II; grade III (italic); grade IV (italic & bold) for BUN, creatinine, transaminases, and alkaline phosphatase part 1-3). The normal range is shown in section 13.2.4 as well (Upper level of normal).

11.4.2 Evaluation of Each Laboratory Parameter

The duration of aplasia was compared between consolidation cycles 2 and 3 as well as between consolidation cycles 3 and 4. For this purpose the period of ANC < 0.5 G/L (or WBC < 1 G/L) was determined. Detailed results are shown in section 10.4.1 (Analysis of Efficacy). To monitor the toxicity of chemotherapy, regular analysis of the laboratory chemistry were done. In this regard, the kidney function (BUN, creatinine) and the liver values (transaminases and alkaline phosphatase were of particular importance. Overall, there were 3 episodes of grade IV liver toxicity in 3 patients (033, 034, 061) seen during the consolidation 1, consolidation 4 and the end of treatment. No grade IV kidney toxicity was observed. Eight events with grade III liver toxicity were reported in 8 patients (010, 011, 026, 034, 042, 044, 058, and 060) during induction 1 (n=6), consolidation 2 (n=1) and the end of treatment visit (n=1). One patient (057) developed elevated creatinine (up to 4.63 mg/dL) resembling a kidney toxicity grade III. A grade II liver toxicity was found in 23 patient (002, consolidation 4; 004, end of treatment; 007, induction 1; 011, consolidation 1; 012, consolidation 2; 015, screening; 017, consolidation 1; 018, consolidation 2; 020, consolidation 2; 020, consolidation 4; 021, consolidation 3; 025,

induction 2; 026, consolidation 4; 027, induction 2; 038, induction 1; 041, induction 1; 043, consolidation 1; 044, screening; 050, induction 1; 053, induction 1; 056, consolidation 1; 059, induction 1; 059, consolidation 1) and a grade II kidney toxicity occurred in 7 patients (006; induction 1; 011, consolidation 1; 017, consolidation 1; 22, induction 1; 042, induction 1; 050, screening; 061, consolidation 1). Finally 1832 laboratory reports with slightly elevation of liver and/or kidney laboratory parameters (grade I toxicity) were observed in 55 patients. The normal laboratory ranges are shown in a table in section 13.2.4.

11.4.2.1 Laboratory Values Over Time

During the therapy there was a decrease in the number of patients from cycle to cycle (see 9.1 DISPOSITION OF PATIENTS; Figure 3). Moreover, during each chemotherapy visit the lab results differed from day to day in each single patient. Thus, a general comparison of normal and abnormal laboratory values at each visit did not make sense. However, we analysed grade II, III, and IV toxicities with regard to liver and kidney function. The highest frequency of grade II, III, and IV toxicities was seen during the induction phase. During the 1st induction phase toxicities grade II or higher occurred in 18/64 cycles (28.1%). The number of AEs was markedly lower during cycle 2 and 3 (see figure 12). However, the number of patients was also much lower in the 2nd and 3rd induction and a selection bias (only patients considered fit received further induction cycles) has to be considered. Moreover, these cycles were only administered in patients with blast cell persistence. During consolidation therapy the percentage of chemotherapy cycle with the occurrence of toxicities grade II, II, or IV ranged between 3.6% and 13.0%. Figure 12 provides the date of all liver and kidney toxicities that were recorded during the consolidation phase and the end of treatment visit. Again, the problem of a direct comparison is the different number of patients. Another problem that makes general comparisons difficult is the low number of patients and events.

11.4.2.2 Individual Patient Changes

Overall, toxicities grade II, II, and IV were recorded in 31 patients. In the majority (n=21) of them such a toxicity was only seen in 1 cycle. In 15 patients (002, 007, 010, 012, 017, 020, 025, 026, 034, 041, 042, 050, 058, 060, and 061) no further chemotherapy was administered.

Figure 12

Patients' identifier	Number of inducting cycles administered	Screening	Induction 1	Induction 2	Induction 3	Consolidation 1	Consolidation 2	Consolidation 3	Consolidation 4	End of treatment visit	Last chemotherapy
002	1			-	-				**L2**		Consolidation 4
004	1			-	-					**L2**	Consolidation 4
006	3		**K2**								Induction 3
007	1		**L2**								Induction 1
010	1		**L3**								Induction 1
011	1			-	-	**L2/K2**	**L3**				Consolidation 3
012	1			-	-		**L2**				Consolidation 2
015	1	**L2**		-	-						Consolidation 3
017	1			-	-	**L2/K2**					Consolidation 1
018	1			-	-		**L2**				Consolidation 4
020	1			-	-		**L2**		**L2**		Consolidation 4
021	2				-			**L2**			Consolidation 4
022	1		**K2**	-	-						Consolidation 3
025	2			**L2**							Induction 2
026	1		**L3**	-	-				**L2**		Consolidation 4
027	3		**L2**								Induction 3
033	1									**L4**	Induction 1
034	2		**L3**		-				**L4**		Consolidation 4
038	2		**L2**								Induction 2
041	1		**L2**								Induction 1
042	1		**L3**								Induction 1
043	1		**K2**	-	-	**L3**					Consolidation 4
044	1	**L2**	**L3**	-	-						Consolidation 4
050	1	**K2**	**L2**								Induction 1
053	2		**L2**		-						Consolidation 1
056	1			-	-	**L2**					Consolidation 3
057	3		**K2**								Induction 3
058	1		**K3**							**L3**	Induction 1
059	1		**L2**	-	-	**L2**					Consolidation 4
060	1		**L2**								Induction 1
061	2				-	**L4/K2**					Consolidation 1
Number of grade 2-4 toxicities per treatment phase		3	18	1		6	4	1	3	3	
Number of patients per treatment phase		64	64	20	6	39	31	28	23	64	
Percentage of grade 2-4 toxicities per treatment phase		4.7	28.1	5.0	0.0	15.4	12.9	3.6	13.0	4.7	

Grade II, III, and IV liver and kidney toxicity observed during the therapy per patient. The horizontal open bars represent the course of therapy per patient until the last chemotherapy administered (grey indicates that the patient was withdrawn). The hyphen (-) indicated that this induction cycle was not necessary in this patient. L2, L3, L4 stands for liver toxicity grade II, III, IV, respectively. K2, K3 stands for kidney toxicity grade II, III, respectively.

In 8 patients blast cell persistence occurred during the induction phase (1st induction, n=6; 2nd induction, n=1) and was causative for the withdrawal (007, 010, 025, 041, 042, 050, 058, 060). Two patients had serious adverse events resulting in a withdrawal after consolidation 2 (017, 061). In 4 patients (002, 021, 026, 034) the events occurred during the last consolidation cycle and no further therapy was planned. In the 3 patients (004, 020, 038) the toxicities were recorded at the end of treatment visit. In 3 patients liver and kidney toxicities were found in the same cycle (011, 017, 061) and 8 patients developed toxicities ≥ grade II in two treatment cycles. For more details, see figure 12.

11.4.2.3 Individual Clinically Significant Abnormalities

No grade IV kidney toxicities were recorded during this trial, but there were 3 cases of grade IV liver toxicities (033, 034, 061). All liver and kidney toxicities occured during episodes of severe infections that are also reported as SAEs. In this regard, it has to be considered, that the patients received broad antimicrobial therapy at this time. Thus, the severe infection together with the co-medication can explain the toxicities recorded.

11.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs (i.e. blood pressure, pulse) and physical findings (i.e. weight, height) were captured at screening, induction therapy 1, 2 and 3, consolidation 1, 2, 3, and 4 as well as at the end of treatment visit. The median systolic blood pressure was 130 mm/Hg (range: 80-175 mm/Hg) there were no major differences between the difference phases of therapy as shown in table 15. The median heart rate overall was 75/min (range (50-125/min), again without major differences between the difference phases of therapy the pulse was recorded. With regard to weight there was a markedly lower median weight of 66.7kg at the end of therapy (range: 55-118kg) compared to the screening visit with 75kg (range: 50-125 kg). Therefore, we analysed the weight in the follow up in each patient. The weight remained stable (i.e. +/- 2kg) in 17 patients in the follow up. Seven patients showed an increase in their weight > 2kg with 4 patients with mild weight gain (>2-5kg) and 3 patients with a moderate weight gain (>5 -10kg). Vice versa 30 patients had a decrease in their weight >2kg. 10 had a mild weight loss of >2-5kg, 11 a moderate i.e. >5-10kg and in 9 patients a weight loss of <10kg was observed.

Table 15

Vital signs and physical findings during the different visits

	all			Screening			Induction 2		Induction 1	
	Weight	Height	Pulse	Weight	Height	Pulse	Weight	Pulse	Weight	Pulse
median	**75**	**170,5**	**78**	**80**	**170,5**	**80**	**77,15**	**82,5**	**85,8**	**81**
min	50	153	53	53	153	53	50,5	78	70	68
max	125	195	128	122	195	105	125	100	106	94
	SysBP	DiaBP		SysBP	DiaBP		SysBP	DiaBP	SysBP	DiaBP
median	**130**	**80**		**132,5**	**79,5**		**120**	**80**	**139,5**	**84**
min	80	50		100	50		98	60	110	70
max	176	110		170	95		160	108	140	91

	Consolidation 1		Consolidation 2		Consolidation 3		Consolidation 4		End of treatment	
	Weight	v	Weight	Pulse	Weight	Pulse	Weight	Pulse	Weight	Pulse
median	**74**	**80**	**75**	**76**	**75**	**79,5**	**77,3**	**74**	**66,7**	**75**
min	50	61	50	60	51	60	53	57	55	60
max	115	109	115	93	112	96	117,3	92	118	128
	SysBP	DiaBP	SysBP	DiaBP	SysBP	DiaBP	SysBP	DiaBP	SysBP	DiaBP
median	**130**	**80**	**130**	**79**	**130**	**80**	**136**	**80**	**120**	**70**
min	80	50	107	50	100	60	90	60	85	60
max	170	105	163	95	170	90	160	96	176	110

DiaBP, diastolic blood pressure; max, maximum; min, minimum; SysBP, systolic blood pressure

11.6 SAFETY CONCLUSIONS

During the trial, we recorded a total number of 1229 adverse events, 3442 reports of abnormal values in the laboratory chemistry, and 5018 abnormal values in the peripheral blood counts. With regard to the abnormal laboratory results, a number of facts have to be considered. As already stated, AML is characterized by abnormal peripheral blood counts. The majority of patients present severe thrombopenia and anemia. Moreover, AML specific chemotherapy always results in a pancytopenia requiring support with red cell and platelet concentrates in most cases. To define the hematologic toxicity in these patients, the duration of absolute neutropenia, the number of red cell and platelet concentrates needed during the therapy is more appropriate. These data are provided in the section 10.4.1 (Analysis of Efficacy) of this report. Looking at the laboratory chemistry there is an elevation in CRP above the upper level of normal in 2720/3442 reports. Again, AML related factors but also the known side effects of standard chemotherapy against leukemia are responsible. Analysing the toxicity of the

treatment laboratory parameters indicating the liver (transaminases, alkaline phosphatase) and kidney function (creatinine, BUN) were recorded. A total number of 1832 slight elevation of liver and/or kidney laboratory parameters i.e. grade I toxicity were observed in 55 patients. Grade II liver and/or kidney toxicity was found in 24 patients. There were 9 patients that had grad III toxicities and 3 with grade IV.

With regard to the AEs, the evolution of SAEs and significant AEs is of interest. Overall, 38 patients had 52 SAEs. Of these SAEs, 15 were fatal. Three deaths were assumed to be related to treatment procedures, all others were not related to therapy. 37 were SAEs other than death and occurred in 23 patients. The most frequent SAEs according to the MedDRA system organ class were infections and infestations (n=17). Moreover, 49 significant adverse events that occurred in 22 patients were not considered as SAEs. The most frequent AEs according to the MedDRA system organ class there were blood and lymphatic system disorders (n=19) as well as infections and infestations (n=8) and gastrointestinal disorders (n=7).

12. DISCUSSION AND OVERALL CONCLUSIONS

The incidence of acute myeloid leukemia (AML) increases with age. More than 50% of all AML patients are diagnosed at an age of 60 years or beyond [13-21,42]. In contrast to younger patients, where treatment strategies are well established, the treatment of AML in the elderly deserves special considerations [13-21,43]. There is always the question whether the patient will benefit from intensive chemotherapy especially in patients aged >70 years [49]. To analyse the feasibility and effects of intensive induction and consolidation therapy in patients aged ≥ 60 years was the aim of this study. Because of the early termination of our trial, not all planned endpoints – especially secondary - can be answered in detail and statistical analysis was restricted to descriptive statistical methods.

As stated in the section efficacy analysis a total number of 64 patients were included in the trial. Following up to 3 induction cycles 43 patients (64.1%) achieved a CR. These data are in line with those already published by us and other groups [13, 43-47]. With regard to the feasibility is of interest that 6 patients were withdrawn during or after induction 1 because they were considered unfit for further therapy and 4 died during induction 1. Moreover, 3 have withdrawn their consent. During the 2nd and 3rd cycle of induction no patient died, but 3 were withdrawn after induction 2 because they were considered unfit for further therapy and 1

has withdrawn his consent. Another 3 patients had to be withdrawn after achieving a CR because of early relapse, a spontaneous gastrointestinal bleeding, or aggravation of dementia. Thus, although the majority of patients aged ≥ 60 years achieved a CR, there are patients not eligible for further therapy because of resistant leukemia or general deterioration. Therefore, the analysis of risk factors and prognostic factors is of particular importance. However, due to the low number of patients in our trial, no analysis of such predictive factors was possible. To summarize the experience of intensive induction therapy seen in this trial it can be stated that this treatment is feasible in patients aged ≥ 60 years. With regard to the NR patients, it is noteworthy, that waiting for a short time-period before initiation of induction chemotherapy did not affect the overall prognosis in patients with AML, as reported in an Frensh study [48]. Whether such a strategy will avoid treatment in patients without prospects to achieve a CR of long-term survival has to be evaluated in forthcoming studies.

Of the 64 patients, 43 achieved a CR and 39 patients (60.9% of the 64 patients) were eligible for consolidation therapy. As already stated, 3 did not receive consolidation therapy because of relapse, unrelated death, or being unfit. Another patient was withdrawn because of a severe protocol violation. In the group of 39 patients the primary objectives of this study, i.e. “can intensified consolidation chemotherapy be administered in AML patients aged ≥ 60 years” and “the number of consolidation cycles and the adverse event profile” was analysed. All four planned courses of consolidation treatment could be administered in 23/39 patients, 5/39 received three, 3/39 two and 8/39 one consolidation cycle. These results are similar to our previous published data [14]. However, in contrast to these data, in the present trial FLAG was used as consolidation 1 instead of IDAC. This represents an intensification of consolidation chemotherapy. Therefore, these data are the first to prove, that an intensified consolidation can savely be administered in patients aged ≥ 60 years. Moreover, the majority i.e. 59% of the patients tolerated all cycles. However, despite this intensive consolidation, relapse was the major cause (n=8) to discontinue consolidation treatment. Although the intensity of the therapy was not enough to avoid reoccurrence of leukemia in all patients, a number of adverse events as reported in section 13.3.2 occurred. Two died from treatment related complications, 2 after recovery of the peripheral blood from reason unrelated to therapy and on patient after a relapse. Moreover, there were 15 not fatal SAEs and 11 significant AEs as shown in tables “SAEs other than death” and “Significant Adverse Events” in section 13.3.2. However, only a minor proportion of SAEs or significant AEs resulted in the withdrawal from further therapy. The causes of withdrawal are shown in table 10 of section 10.4.1 (Analysis of Efficacy). Apart of death and relapse, persistent cytopenias and

severe infections during a prior treatment cycle were responsible for toxicities and were responsible to withhold further chemotherapy. In this regard also grade III (n=6) and IV (n=3) liver and kidney toxicities have to be mentioned. They were recorded during the consolidation phase (see figure 12 in the section 11.4.2.2 Individual Patient Changes). Overall, there were substantial side effects observed during the intensive consolidation therapy. However, we also found that the majority of these AEs and toxicities were manageable and consolidation therapy could be continued in most of the patients. Nevertheless, it is of importance to be aware of such problems. First of all the patients have to be informed appropriately on the risks and benefits of this kind of therapy. Secondly, the monitoring of the patients has to consider these particular problems to detect AEs early. When evaluating the tolerability of a treatment scheme apart from AEs and acute toxicities the follow up of comorbidities presented at diagnosis are of interest. Likewise, there are the questions whether comorbidities evolve during the therapy, or whether the general shape deteriorates with time under therapy. For this purpose we have serially analysed the CCI (screening, after the 2nd consolidation and/or at the end of study visit). There was a moderate increase in comorbid conditions in our patients, i.e. 6 increases from the screening phase to the evaluation after the 2nd consolidation, and another 2 increases after the 3rd consolidation. Cardiovascular disorder and diabetes were the most frequent disorders. In this regard, it has to be discussed that these comorbidities most probably did not develop during the consolidation phase but became evident. Likewise, the monitoring of the laboratory chemistry facilitated the detection of an overt diabetes. On the other hand, a cardiovascular disorder can become symptomatic because of infections or episodes of anemia during AML treatment. To the best of our knowledge, these are the first data describing the serial analysis of the CCI prior, during and after intensive chemotherapy for AML. To analyse changes in the general shape of the patients the weight was evaluated prior, during and at the end of therapy. Interestingly, there was a markedly lower median weight at the end of therapy compared to the screening phase (see section 11.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY). Looking at the follow up in each patient markedly differences were found. The weight remained stable in 17 patients and showed an increase 7 patient. The largest group i.e. 30 patients had a loss of weight. Ten showed a mild weight loss (>2-5kg), 11 a moderate (>5-10kg) and 9 a weight loss of <10kg. These results show that the repetitive cycles of chemotherapy result in a decrease of general shape.

As shown in the section 10.4.1 (Analysis of Efficacy; figure 5) the median overall survival was 1.1 years and the probability to be alive 5 years after the start of therapy is 32%. These

results are better compared to previous published data [14,49,50] and show, that a group of patients aged ≥ 60 years can achieve long-term survival if treated appropriately. Considering the side effects of the treatment, it is of particular importance to search for predictive factors indicating that patients will benefit from such an intensive treatment and in which patients other treatment strategies would be more appropriate. In this regard, established predictive variable like age, karyotype and molecular markers (FLT3 and NPM1) were analysed. As visible in figure 5 (section 10.4.1) there were marked differences in the outcome of patients aged <75 years and ≥ 75 years with a median survival of 1.5 years and 0.5 years, respectively. The probability of survival after 5 years was 39% in the group aged <75 years, whereas no patient was alive after 5 years in the group ≥ 75 years. Although slightly different, these results are in line with previously published data [14,49]. (Figure 5). The prognostic importance of karyotyping has been demonstrated in various papers [51-53]. In our study cohort patients with monosomal karyotype had the poorest outcome compared (Table 12, section 10.4.1). These data are in line with the paper of Breems et al. [51]. In the analysis of molecular markers i.e. FLT3 ITD and NPM1 no differences were seen between patients with or without FLT3, whereas the survival of patients with mutated NPM1 was favorable compared to those with wild type NPM1. It is well known that NPM1 and FLT3-ITD are the most important predictive markers in patients with AML [54-57]. These markers are of particular importance in patients with CN leukemia [54-57]. In patients aged ≥ 60 years included in Cancer and Leukemia Group B frontline trials the predictive value of FLT3-ITD was seen in patients aged 60-69, in the groups aged >70 years it was less pronounced [56,57]. In addition, NPM1mut was of favorable prognostic impact in older patients with CN-AML, especially those ≥ 70 years [56,57]. In line with these results, NPM1 was a favorable molecular marker in our cohort. Interestingly, FLT3 had no discriminative potential in our group of patients. This influence of age or differences in the FLT3-ITD/FLT3-wt ration could be an explanation for this lack of discriminative potential in our cohort [57,58]. Moreover, the low number of individuals per analysis has to be considered and limits the strength of our conclusions. To summarize the search for potential predictive factors, it can be stated that in our cohort age ≥ 75 years, monosomal karyotype and NPMwt seem to be unfavorable predictive factors for survival.

The relapse free survival is also shown in the section 10.4.1 (Analysis of Efficacy; figure 6) with a median CCR of 1.25 years and the probability of 29% to be alive in 5 years. Again, this is in line with our own previous results. Howerver, in contrast to other papers we clearly could demonstrate that long-term relapse free survival can be achieved even in a population

aged ≥60 years [14,49,50]. In the few patients aged ≥ 75 years the median CCR was 0.47 years and thus is clearly inferior compared to the cohort aged <75 years (median CCR of 1.25 years; Figure 6; section 10.4.1). Like for survival, karyotype and the molecular marker NPM1 are of prognostic importance.

Another secondary objective of our trial was to evaluate the efficacy and pharmacokinetics of pegfilgrastim in consolidation therapy. To analyse the efficiacy of the routine administration of G-CSF the consolidation 1-4 group comprised of 39 patients was used. To analyse the effect of G-CSF in detail, only patients that have received the last 3 cycles of consolidation per protocol (i.e. 2nd and 4th consolidation with IDAC and routine administration of G-SCF, 3rd consolidation with IDAC and no routine G-CSF but G-CSF according to ASCO criteria allowed) were eligible. In these 20 patients the duration of hospitalization and absolute neutropenia (ANC <500 cell/µL or WBC <1000 cell/µL) were compared between the 2nd, 3rd, and 4th consolidation (Figure 9 & 10, section 10.4.1). The duration of neutropenia was 7 days in consolidation 2, 11.5 days in consolidation 3, and 7.5 days in consolidation 4. Thus, there was a markedly difference in the duration of neutropenia among the 2nd and 3rd consolidation as well as among the 3rd and 4th consolidation cycle (Figure 9, section 10.4.1). This occurred although 30% of the patients had received G-CSF during the 3rd consolidation according ASCO criteria. These differences in neutropenia resulted in an also marked difference in the duration of hospitalization between these consolidation cycles (2nd consolidation, 20 days; 3rd consolidation, 29 days; 4th consolidation, 22 days; figure 10, section 10.4.1). It is generally accepted that the time of neutropenia can be shortened by application of G-CSF [59-67]. However, wether G-CSF therapy also results in a shorter time of hospitalization is discussed controversially [60,61,65,67] and with regard to the application in consolidation therapy only limited data are available [60]. In our trial we were able to show that the administration of G-CSF shortens not only the duration of neutropenia but also the duration of hospitalization in consolidation therapy of AML.

Another question was how long plasma levels of pegfilgrastim were detectable. For this purpose, the concentration of G-CSF in the patient's plasma was measured in 18 consolidation cycles. G-CSF was detectable in all serum samples taken before day 21 of chemotherapy or day 16 after the administration of pegfilgrastim. Thereafter, the number of samples with detectable cytokine levels decreased. As published, with the re-increase of WBC and granulocyte counts, there was a decrease of G-CSF (figure 11) [68]. This was of interest since the clearance of pegylated filgrastim is dependent on the presence of granulocytes. In consolidation almost normal granulocyte counts were detectable up to day 10 or 11 of

chemotherapy. Thus up to 5-6 days after the administration of pegfilgrastim on day 6 granulocyte could have reduced G-CSF. However, our analysis clearly showed that measurable G-CSF levels are detectable in the patients until recovery of the WBC and ANC. These are the first data to demonstrate the long-term effect of Pegfilgrastim in consolidation therapy of AML.

Together, our data show, that intensified consolidation chemotherapy can be administered in AML patients aged ≥ 60 years and results in an improved survival. The majority of patients received all planned 4 consolidation cycles, although a substantial toxicity was observed. Unfavourable factors for survival and CCR were age ≥ 75 years, monosomal karyotype and NPMwt Finally, the administration of Pegfilgrastim in consolidation therapy shortened not only the duration of neutropenia but also the duration of hospitalization during the consolidation therapy of AML.

13. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

13.1 DEMOGRAPHIC DATA – COMPARISSION AMONG CENTERS

Comparison of the median age between the entire group and the different participating centers

	Age		
	Median	Minimum	Maximum
All patients	69.9	60.1	85.2
AKH WIEN	69.7	60.1	78.8
HIETZING	73.0	68.3	77.5
ELI LINZ	72.1	62.2	85.2
KFJ	63.5	61.0	63.5
SMZ OST	69.7	66.8	77.6

Comparison of the FAB-subgroups between the entire group and the different participating centers

	All patients		AKH WIEN		HIETZING		ELI LINZ		KFJ		SMZ OST	
	n	%	n	%	n	%	n	%	n	%	n	%
AML M0	8	7.8	5	15.6	1	14.3	0	0.0	0	0.0	2	40.0
AML M1	19	29.7	8	25.0	1	14.3	6	40.0	3	60.0	1	20.0
AML M2	11	17.2	7	21.9	2	28.6	2	13.3	0	0.0	0	0.0
AML M4	11	17.2	5	15.6	2	28.6	3	20.0	1	20.0	0	0.0
AML M4 EO	1	1.6	0	0.0	0	0.0	0	0.0	1	20.0	0	0.0
AML M5	7	10.9	3	9.4	0	0.0	2	13.3	0	0.0	2	40.0
AML M6	2	3.1	2	6.3	0	0.0	0	0.0	0	0.0	0	0.0
AML M7	3	4.7	1	3.1	0	0.0	2	13.3	0	0.0	0	0.0
AML un-classifiable	2	3.1	1	3.1	1	14.3	0	0.0	0	0.0	0	0.0
n	64		32		7		15		5		5	

Comparison of the WHO-subgroups between the entire group and the different participating centers

	All patients		AKH WIEN		HIETZING		ELI LINZ		KFJ		SMZ OST	
	n	%	N	%	n	%	n	%	n	%	n	%
AML with 11q23 abnormalities	1	1.6	1	3.1	0	0.0	0	0.0	0	0.0	0	0.0
AML with t(8;21)	1	1.6	1	3.1	0	0.0	0	0.0	0	0.0	0	0.0
AML with inv(16); t(16/16)	1	1.6	0	0.0	0	0.0	0	0.0	1	20.0	0	0.0
AML without maturation	15	23.4	6	18.8	2	28.6	4	26.7	3	60.0	0	0.0
AML minimally differentiated	9	14.1	6	18.8	0	0.0	0	0.0	0	0.0	3	60.0
AML with maturation	10	15.6	5	15.6	1	14.3	4	26.7	0	0.0	0	0.0
Acute myelomonocytic leukemia	10	15.6	4	12.5	2	28.6	3	20.0	1	20.0	0	0.0
Acute monocytic leukemia	7	10.9	3	9.4	0	0.0	2	13.3	0	0.0	2	40.0
Acute erythroid leukemia	2	3.1	2	6.3	0	0.0	0	0.0	0	0.0	0	0.0
Acute megakaryocytic leukemia	3	4.7	1	3.1	0	0.0	2	13.3	0	0.0	0	0.0
AML with dysplasia; without prior MDS	4	6.3	2	6.3	2	28.6	0	0.0	0	0.0	0	0.0
Unclassifiable	1	1.6	1	3.1	0	0.0	0	0.0	0	0.0	0	0.0
n	64		32		7		15		5		5	

Comparison of the laboratory chemistry between the entire group and the different participating centers

Center		BUN	CREAT	ALP	LDH	AST	ALT	CRP
All patients	median	18.15	1.04	70	308	25	24	1.49
	min	8	0.68	33	139	13	7	0.09
	max	43.4	2.47	176	2413	221	128	24.9
	Missing data	12	12	11	12	9	10	8
AKH WIEN	median	64	3.895	231.9	16.95	1.035	70	320
	min	12	0.72	33.7	8	0.68	33	150
	max	222	125.26	2720	43.4	1.43	153	2413
	Missing data	3	0	0	1	1	1	1
HIETZING	median	125.5	19	1.11	56	358	30.5	23
	min	40	10	0.78	43	139	13	7
	max	387	30	2.47	101	960	56	57
	Missing data	1	0	0	0	1	1	0
ELI LINZ	median	228	18.8	1.12	77	283	26.5	24.5
	min	47	11.3	0.85	54	158	16	12
	max	2220	31.6	1.51	176	670	150	56
	Missing data	2	4	4	3	4	1	3
KFJ	median	642	-	-	-	-	-	-
	min	339	-	-	-	-	-	-
	max	1534	-	-	-	-	-	-
	Missing data	0	5	5	5	5	5	5
SMZ OST	median	-	18.5	1.1	61	261.5	25.5	17
	min	-	18	1	48	218	15	0
	max	-	19	1.2	165	364	58	99
	Missing data	5	3	3	2	1	1	1

Comparison peripheral blood between the entire group and the different participating centers

Center		Hemoglobine, g/dL	Platelets, G/L	Leukocytes, G/L
All patients	median	9.4	72	6.95
	min	7.8	12	0.7
	max	14.5	304	146.2
	Missing data	5	5	5
AKH WIEN	median	9.65	64	3.895
	min	7.8	12	0.72
	max	14.5	222	125.26
	Missing data	0	0	0
HIETZING	median	9.2	92	17.6
	min	7.8	46	2.74
	max	10.7	304	91.2
	Missing data	0	0	0
ELI LINZ	median	9.4	56	8.8
	min	8.1	15	0.7
	max	11.2	137	146.2
	Missing data	-	-	-
KFJ	median	-	-	-
	min	-	-	-
	max	-	-	-
	Missing data	5	5	5
SMZ OST	median	10.3	94	9.6
	min	9.3	33	3.3
	max	12.6	149	21.36
	Missing data	0	0	0

Comparison of the subgroups of karyotyping according HOVON criteria between the entire group and the different participating centers

	Number				Percent			
	CBF	CN	Mkneg	Mkpos	CBF	CN	Mkneg	Mkpos
AKH WIEN	1	12	5	10	3.3	43.3	17.8	43.5
HIETZING	0	3	2	1	0.0	50.0	33.3	16.7
ELI LINZ	0	5	3	4	0.0	41.7	25.0	33.3
KFJ	-	-	-	-	-	-	-	-
SMZ OST	0	4	0	0	0.0	100.0	0.0	0.0
All patients	1	25	11	15	1.9	48.1	21.2	28.8

Comparison of the subgroups of karyotyping according modified SWOG criteria between the entire group and the different participating centers

	Number			Percent		
	favorable	intermediate	unfavorable	favorable	intermediate	unfavorable
AKH WIEN	1	18	11	3.3	60.0	36.7
HIETZING	0	5	1	0.0	83.3	16.7
ELI LINZ	0	7	5	0.0	58.3	41.7
KFJ	0	0	0	0.0	0.0	0.0
SMZ OST	0	4	0	0.0	100.0	0.0
All patients	1	34	17	1.9	65.4	32.7

Comparison of molecular markers between the entire group and the different participating centers

	FLT3 ITD		AML/ETO		CBFa/MYH11		MLL1-AF10		NPM1		Kit	
Number	pos	neg	pos	neg	pos	neg	pos	neg	mut	wt	mut	wt
AKH WIEN	3	22	1	28	0	28	1	26	5	12	0	17
HIETZING	3	4	0	7	0	7	0	7	1	4	1	3
ELI LINZ	2	12	0	13	0	13	0	13	4	9	2	2
KFJ	0	0	0	0	0	0	0	0	0	0	0	0
SMZ OST	0	4	0	4	0	4	0	4	1	3	0	2
All patients	8	42	1	52	0	52	1	50	11	28	3	24

Comparison of molecular markers between the entire group and the different participating centers

	FLT3 ITD		AML/ETO		CBFa/MYH11		MLL1-AF10		NPM1		Kit	
Number	pos	neg	pos	neg	pos	neg	pos	neg	mut	wt	mut	wt
AKH WIEN	12.0	88.0	3.4	96.6	0.0	100.0	3.7	96.3	29.4	70.6	0.0	100.0
HIETZING	42.9	57.1	0.0	100.0	0.0	100.0	0.0	100.0	20.0	80.0	25.0	75.0
ELI LINZ	14.3	85.7	0.0	100.0	0.0	100.0	0.0	100.0	30.8	69.2	50.0	50.0
KFJ	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SMZ OST	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	25.0	75.0	0.0	100.0
All patients	16.0	84.0	1.9	98.1	0.0	100.0	2.0	98.0	28.2	71.8	11.1	88.9

Comparison of the number of comorbidities recorded by using the CCI between the entire group and the different participating centers

	Number of patients					
Number of comorbidities	All	AKH WIEN	HIETZING	ELI LINZ	KFJ	SMZ OST
0	48	22	7	11	3	5
1	10	6	0	3	1	0
2	4	3	0	0	1	0
3	1	0	0	1	0	0
4	0	0	0	0	0	0
5	1	1	0	0	0	0
6	0	0	0	0	0	0
7	0	0	0	0	0	0

Comparison of the number of comorbidities recorded by using the CCI between the entire group and the different participating centers

	Percentage					
Number of comorbidities	All	AKH WIEN	HIETZING	ELI LINZ	KFJ	SMZ OST
0	75.0	68.8	100.0	73.3	60.0	100.0
1	15.6	18.8	0.0	20.0	20.0	0.0
2	6.3	9.4	0.0	0.0	20.0	0.0
3	1.6	0.0	0.0	6.7	0.0	0.0
4	0.0	0.0	0.0	0.0	0.0	0.0
5	1.6	3.1	0.0	0.0	0.0	0.0
6	0.0	0.0	0.0	0.0	0.0	0.0
7	0.0	0.0	0.0	0.0	0.0	0.0

13.2 EFFICACY DATA

Classification of leukemia according FAB in all patients and broken down by center

	All patients		AKH WIEN		HIETZING		ELI LINZ		KFJ		SMZ OST	
	n	%	n	%	n	%	n	%	n	%	n	%
AML M0	8	7,8	5	15,6	1	14,3	0	0,0	0	0,0	2	40,0
AML M1	19	29,7	8	25,0	1	14,3	6	40,0	3	60,0	1	20,0
AML M2	11	17,2	7	21,9	2	28,6	2	13,3	0	0,0	0	0,0
AML M4	11	17,2	5	15,6	2	28,6	3	20,0	1	20,0	0	0,0
AML M4 EO	1	1,6	0	0,0	0	0,0	0	0,0	1	20,0	0	0,0
AML M5	7	10,9	3	9,4	0	0,0	2	13,3	0	0,0	2	40,0
AML M6	2	3,1	2	6,3	0	0,0	0	0,0	0	0,0	0	0,0
AML M7	3	4,7	1	3,1	0	0,0	2	13,3	0	0,0	0	0,0
AML unc	2	3,1	1	3,1	1	14,3	0	0,0	0	0,0	0	0,0
	64	100	32	100	7	100	15	100	5	100	5	100

Classification of leukemia according WHO 2008 in all patients and broken down by center

	All patients		AKH WIEN		HIETZING		ELI LINZ		KFJ		SMZ OST	
	n	%	n	%	n	%	n	%	n	%	n	%
AML with 11q23 abnormalities	1	1,6	1	3,1	0	0,0	0	0,0	0	0,0	0	0,0
AML with t(8;21)	1	1,6	1	3,1	0	0,0	0	0,0	0	0,0	0	0,0
AML with inv(16); t(16/16)	1	1,6	0	0,0	0	0,0	0	0,0	1	20,0	0	0,0
AML without maturation	15	23,4	6	18,8	2	28,6	4	26,7	3	60,0	0	0,0
AML minimally differentiated	9	14,1	6	18,8	0	0,0	0	0,0	0	0,0	3	60,0
AML with maturation	10	15,6	5	15,6	1	14,3	4	26,7	0	0,0	0	0,0
Acute myelomonocytic leukemia	10	15,6	4	12,5	2	28,6	3	20,0	1	20,0	0	0,0
Acute monocytic leukemia	7	10,9	3	9,4	0	0,0	2	13,3	0	0,0	2	40,0
Acute erythroid leukemia	2	3,1	2	6,3	0	0,0	0	0,0	0	0,0	0	0,0
Acute megakaryocytic leukemia	3	4,7	1	3,1	0	0,0	2	13,3	0	0,0	0	0,0
AML with dysplasia; without prior MDS	4	6,3	2	6,3	2	28,6	0	0,0	0	0,0	0	0,0
NOT DETERMINABLE	1	1,6	1	3,1	0	0,0	0	0,0	0	0,0	0	0,0
	64	100	32	100	7	100	15	100	5	100	5	100

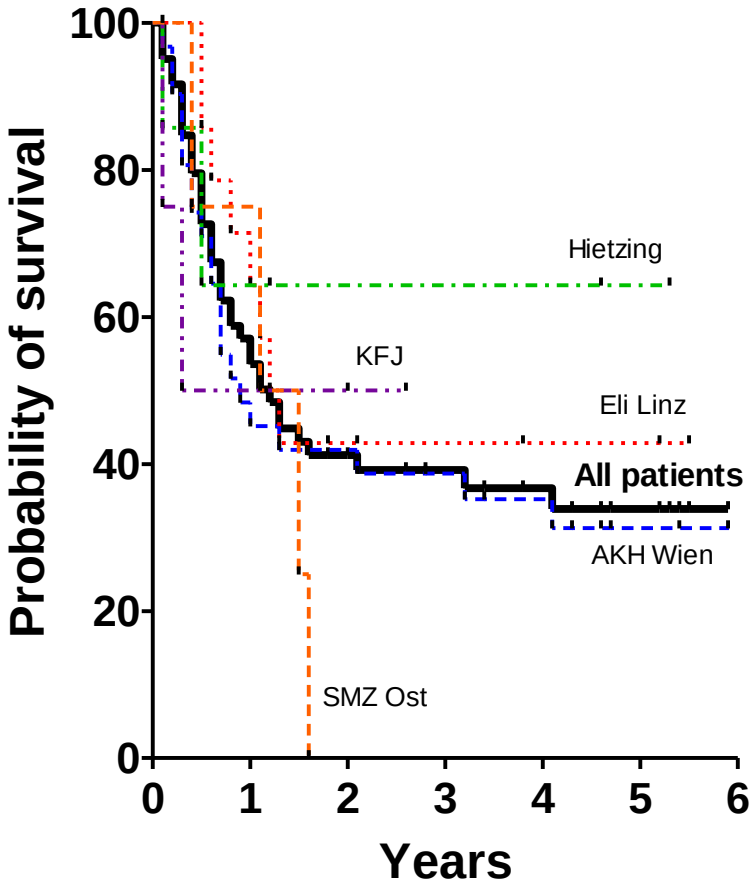
CR, number of patients and rate in all patients and patients broken down by center

	n	CR n	CR-rate %
All patients	64	43	69,4
AKH WIEN	32,0	20	62,5
HIETZING	7,0	4,0	57,1
ELI LINZ	15,0	11,0	73,3
KFJ	5,0	4,0	80,0
SMZ OST	5,0	4	80

Number of patients receiving consolidation 1 to 4 broken down by center

	Consolidation 1	Consolidation 2	Consolidation 3	Consolidation 4
All patients	39	31	28	23
AKH WIEN	19	17	15	11
HIETZING	3	2	2	2
ELI LINZ	11	8	7	6
KFJ	3	2	2	2
SMZ OST	3	2	2	2

Survival of all patients and the patients broken down by center



13.3 SAFETY DATA

13.3.1 Displays of Adverse Events

Summary table of AEs classified according MedDRA system organ class code (Part 1)

		Mild			Moderate			Sever			life threatening			fatal			not defined			
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	all
Blood and lymphatic system disorders		**27**		**27**	**21**	**3**	**55**	**3**		**13**			**4**				**1**			**154**
	screening						3 024* 035* 061*							1 010*							4
	induction 1	10 008* 011* 013* 018* 021* 026* 055* 055* 056* 059*		11 003* 006* 006* 016* 020* 038* 045* 057* 061* 062* 064*	7 002* 004* 006* 014* 024* 033* 045*	2 030* 046*	33 001* 003* 005* 007* 015* 021* 022* 031* 032* 034* 037* 039* 040* 041* 042* 042* 042* 043* 044* 048* 048* 049* 050* 050* 050* 050* 052* 052* 052* 060* 061* 063*	1 003*		6 015* 035* 036* 037* 038* 058*			4 035* 035* 037* 038*							74
	induction 2	3 001* 021* 024*		4 006* 021* 057* 061*	1 009*		4 032* 034* 039* 053*	1 025*		1 038*							1 005*			15
	induction 2	2 001* 057*						1 001*												3
	consolidation 1	3 003* 014* 055*		7 015* 018* 020* 044* 046* 046* 064*	3 011* 012* 017*		6 032* 040* 043* 048* 048* 049*														19
	consolidation 2	4 002* 004* 011* 055*		3 018* 028* 035*	2 008* 014*		3 049* 049* 063*			2 034* 062*											14
	consolidation 3	5 002* 004* 011* 014* 056*		1 032*	4 015* 018* 021* 022*	1 015*	3 044 049 063			1 048*											15
	consolidation 4			1 059**	4 004* 008* 014* 055*		8 031* 044* 049* 049* 062* 063* 024* 035*			1 034*				010*							14
Cardiac disorders				**6**			**3**			**1**			**1**	**1**						**12**
	induction 1			5 003* 018* 022* 047* 061*			1 010*			1 058*										7
	induction 2						1 054*													1
	consolidation 2			1 021*			1 063*													2
	end of treatment												1 058*	1 017*						1
Congenital, familial and genetic disorders							**1**													**1**
	screening						1 044*													1
Ear and labyrinth disorders				**38**		**1**	**1**													**40**
	screening			1 044*																1
	induction 1			13 006* 011* 015* 016* 017* 017* 024* 038* 039* 051* 055* 061* 063*		1 022*	1 035*													15

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 2)

		Mild			Moderate			Sever			life threatening			fatal			not defined			
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	all
Ear and labyrinth disorders	induction 2			3 006* 057*																3
	induction 3			2 006* 057*																2
	consolidation 1			5 018* 022* 037* 039* 053*																5
	consolidation 2			4 018* 018* 021* 063*																4
	consolidation 3			5 048* 056* 056* 062* 063*																5
	consolidation 4			4 020* 021* 035* 063*																4
	end of treatment			1 060*																1
Endocrine disorders				**1**																**1**
	induction 1			1 048*																0
Eye disorders				**6**			**5**													**11**
	induction 1			1 024*			3 023* 024* 044*													4
	induction 2			1 024*																1
	consolidation 1			3 008* 014* 017*			2 062*													5
	consolidation 2			1 008*																1
Gastrointestinal disorders		**10**	**5**	**67**	**4**	**1**	**38**			**10**										**135**
	screening						1 057*													1
	induction 1	8 004* 005* 005* 025* 051* 056* 059* 060*	007* 051*		1 045*		14 006* 006* 009* 012* 023* 037* 042* 042* 057* 057* 057* 062* 062*			4 010* 010* 010* 010*											27
	induction 2	1 005*	2 021** 021	13 001* 005* 005* 005* 006* 009* 009* 009* 025* 025* 032* 036* 057*	1 024*		4 061* 061* 061* 061*			1 061*											22
	induction 3			3 006* 009* 057*	1 009*		3 009* 057* 057*														7
	consolidation 1			20 011* 011* 012* 012* 012* 014* 016* 016* 016* 017* 017* 018* 020* 021* 035* 044* 049* 053* 056*	1 056*	1 018*	8 011* 012* 012* 012* 012* 012* 034* 056*			2 012* 061*											32

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 3)

		Mild			Moderate			Sever			life threatening			fatal			not defined			
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	all
Gastrointestinal disorders	consolidation 2		2 011* 056*	9 004* 011* 011* 014* 018* 021* 021* 056* 063*			4 008* 012* 056* 062*			3 002* 002* 012*											18
	consolidation 3	1 004*		16 004* 008* 011* 016* 018* 018* 034* 034* 044* 049* 056* 056* 062* 062* 062* 062*			2 015* 056*														19
	consolidation 4		1 016*	6 004* 004* 004* 014* 035* 062*			2 034* 034*														9
		2	**1**	**52**	**1**		**43**			**3**						**4**			**1**	**107**
General disorders and administration site conditions	screening						1 040														1
	induction 1	1 001*	1 060*				20 007* 009* 010* 013* 022* 023* 024* 024* 024* 031* 035* 036* 042* 042* 044* 059* 059* 062* 062* 063*			3 010* 037* 053*											25
	induction 2	1 024*		10 001* 001* 006* 009* 009* 024* 032* 034* 036* 053*			7 006* 021* 024* 024* 038* 038* 040*														18
	induction 3				1 027*																1
	consolidation 1			12 004* 008* 011* 014* 018* 018* 032* 037* 037* 039* 039* 055*			4 014* 031* 032* 045*												1 014*		17
	consolidation 2			10 011* 011* 015* 022* 022* 026* 028* 034* 044* 063*			2 021* 037*														12
	consolidation 3			13 004* 008* 016* 018* 020* 020* 034* 035* 044* 048* 062* 063* 063*			4 043* 044* 044* 062*														17
	consolidation 4			7 004* 004* 020* 034* 035* 048* 063*			5 004* 008* 031* 034* 062*														12

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 4)

		Mild			Moderate			Sever			life threatening			fatal			not defined			
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	all
	follow up															4 005* 047* 057* 058*				4
Hepatobiliary disorders		**1**		**2**		**2**	**1**			**1**										**7**
	induction 1						1 007*													1
	induction 2					2 024* 024*														2
	consolidation 1			1 018*						1 012*										2
Immune system disorders		**1**		**2**			**1**													**4**
	induction 1	1 001*		1 026*																2
	induction 2						1 021*													1
	consolidation 3			1 018*																1
Infections and infestations		**1**	**2**	**99**	**2**	**2**	**98**			**11**	**1**		**2**	**1**		**3**			**1**	**223**
	screening			3 013* 017* 038*			10 001* 007* 007* 015* 024* 037* 049* 054* 057* 059*			1 010*										14
	induction 1		**1** 003*	**3** 063* 063* 064*	**2** 029* 029*	**2** 003* 030*	**32*** 003* 005* 007* 007* 007* 008* 011* 022* 022* 024* 024* 025* 031* 036* 036* 038* 039* 040* 041* 041* 043* 044* 046* 047* 050* 051* 053* 054* 061* 061* 062* 063*			**4** 010* 023* 038* 058*									**1** 003*	**45**
	induction 2			15 001* 005* 006* 006* 009* 021* 024* 024* 025* 053* 057* 057* 061* 063* 063*			10 005* 021* 024* 025* 038* 053* 054* 054* 054* 057*			5 025* 025* 039* 057* 061*											30
	induction 3		1 001*	3 001* 006* 057*			1 027*													5
	consolidation 1		1 003*	26 011* 011* 012* 012* 013* 014* 014* 015* 016* 018* 020* 020* 022* 028* 037* 037* 039* 039* 049* 049* 053* 055* 056* 062* 062* 063*			12 011* 012* 035* 036* 037* 040* 040* 043* 043* 045* 053* 063*			1 017*			1 017*					41

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 5)

		Mild			Moderate			Sever			life threatening			fatal			not defined			
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	all
Infections and infestations	consolidation 2	1 002*		19 004* 008* 008* 011* 012* 014* 014* 014* 014* 016* 018* 018* 021* 021* 021* 026* 032* 062* 063*			11 008* 012* 035* 037* 037* 055* 062* 063* 063* 063* 063*														31
	consolidation 3			16 002* 004* 008* 014* 014* 016* 018* 022* 032* 055* 056* 062* 062* 062* 062* 063*			13 011* 015* 021* 022* 032* 032* 032* 040* 040* 043* 056* 062* 062*														29
	consolidation 4			14 002* 002* 004* 004* 014* 018* 018* 020* 020* 021* 044* 044* 055* 059*			8 008* 008* 031* 031* 043* 043* 062* 063*				1 034*										23
	follow up						1 008*									1 024*				2
	end of treatment												1 058*	1 034*		2 010* 023*				4
Injury, poisoning and procedural complications				**14**	**1**		**11**													**26**
	screening						1 024													1
	induction 1			6 003* 007* 014* 017* 023* 044*	1 060*		4 016* 017* 025* 058*													11
	induction 2			2 006* 039*			2 006* 024*													4
	induction 3			1 001*																1
	consolidation 2			2 014* 021*			1 031*													3
	consolidation 3			1 048*			2 018* 034*													3
	consolidation 4			2 034* 062*			1 034*													3
	consolidation 3			16 002* 004* 008*			13 011* 015* 021*													29
Investigations				**9**			**6**													**15**
	screening			1 032*																1
	induction 1			2 003* 013*			4 027* 031* 032* 053*													6
	induction 2			2 036* 061*			1 027*													3
	consolidation 1			2 011* 064*			1 034*													3
	consolidation 2			1 044*																1
	consolidation 3			1 048*																1

NR, not related; PR, possibly related; R, related

Summary table of AEs classified according MedDRA system organ class code (Part 6)

		Mild			Moderate			Sever			life threatening			fatal			not defined			all
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	
Metabolism and nutrition disorders				**22**		**1**	**12**			**2**										**37**
	screening			1 001*																1
	induction 1			13 001* 004* 008* 009* 010* 024* 033* 038* 044* 053* 053* 054* 055*		1 057*	10 006* 007* 007* 010* 010* 024* 024* 055* 062* 062*													24
	induction 2			2 001* 025*			1 025*			1 061*										4
	induction 3									1 009*										1
	consolidation 1			3 012* 018* 062*			1 048*													4
	consolidation 2			1 002*																1
	consolidation 4			2 002* 004*																2
Investigations				**9**			**6**													**15**
	screening			1 032																1
	induction 1			2 003* 013*			4 027* 031* 032* 053*													6
	induction 2			2 036* 061*			1 027*													3
	consolidation 1			2 011* 064*			1 034*													3
	consolidation 2			1 044*																1
	consolidation 3			1 048*																1
Metabolism and nutrition disorders				**22**		**1**	**12**			**2**										**37**
	screening			1 001*																1
	induction 1			13 001* 004* 008*		1 057*	10 006* 007* 007*													24
Musculoskeletal and connective tissue disorders		**13**		**30**	**4**		**10**	**1**		**2**										**60**
	screening			1 060*																1
	induction 1	2 011*		14 003* 006* 011* 021* 021* 022* 024* 024* 025* 039* 044* 051* 054* 061*	2 023* 050*		2 060* 060*			1 058*										21
	induction 2	2 024* 025*		2 021* 024*	1 024*		1 006*			1 009*										7
	consolidation 1	1 048*		3 014* 017* 020*			1 017*													5
	consolidation 2	5 014* 020* 022* 048* 049*		3 014* 014* 031*			3 008* 034* 062*													11
	consolidation 3	2 022* 059*		6 011* 018* 021* 021* 035* 056*				1 048*												9
	consolidation 4	1 055*		1 018*	1 048*		3 008* 021* 021*													6
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**consolidation 1**						**1** 1 032*													**1** 1

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 7)

		Mild			Moderate			Sever			life threatening			fatal			not defined			all
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	
Nervous system disorders				**40**			**10**			**1**						**1**				**52**
	induction 1			12 001* 007* 007* 012* 014* 018* 018* 018* 024* 042* 056* 062*			3 017* 023* 060*													15
	induction 2			2 036* 054*			1 024*													3
	induction 3			1 001*																1
	consolidation 1			8 011* 014* 017* 018* 018* 049* 053* 059*			6 017* 031* 039* 053* 056* 017*			1 017*											15
	consolidation 2			4 011* 028* 048* 056*												1 012*				5
	consolidation 3			7 016* 018* 021* 048* 056* 056* 056*																7
	consolidation 4			6 016* 020* 034* 034* 048* 055*																6
Psychiatric disorders				**25**			**4**													**29**
	screening			3 060* 060* 042*																3
	induction 1			12 007* 013* 018* 023* 023* 023* 026* 026* 035* 056* 056* 062*			3 006* 007* 035*													15
	induction 2			2 009* 054*																2
	consolidation 1			4 012* 012* 014* 056*			1 013*													5
	consolidation 2			4 008* 056* 056* 056*																4
Renal and urinary disorders				**5**			**2**	**1**		**2**			**1**							**11**
	induction 1			2 003* 029*			1 057*			1 058*			1 029*							5
	consolidation 1			2 017* 046*			1 012*													3
	consolidation 2			1 008*																1
	end of treatment							1 057*		1 058*										2
Reproductive system and breast disorders				**1**																**1**
	induction 1			1 007*																1
				43			**19**			**5**						**1**				**68**
	screening			1 039*																1
Respiratory, thoracic and mediastinal disorders	induction 1			24 011* 011* 012* 013* 015* 016* 017* 020*			11* 001* 003* 003* 010* 013* 013* 053* 057*			2 061 062										37

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 8)

		Mild			Moderate			Sever			life threatening			fatal			not defined			all
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	
Respiratory, thoracic and mediastinal disorders				024* 024* 032* 035* 037* 039* 039* 042* 048* 049* 054* 060* 061* 061* 062* 062*			057* 057* 061*													
	induction 2			4 001* 005* 036* 053*			5 024* 025* 025* 025* 032*			3 057* 057*										12
	consolidation 1			2 014* 049*																2
	consolidation 2			3 011* 055* 063*																3
	consolidation 3			6 020* 035* 056* 062* 062* 063*			1 044*													7
	consolidation 4			3 014* 020* 062*																3
	end of treatment						2 023* 057*									1 061*				3
Skin and subcutaneous tissue disorders		**2**	**5**	**24**	**12**		**2**	**4**												**49**
	induction 1	3 005* 008* 008*	2 018* 051*	12 007* 010* 020* 036* 037* 038* 038* 039* 053* 054* 060* 061*			4 005* 005* 012* 055*													21
	induction 2			2 034* 053*			1 025*													3
	induction 3			1 036*																1
	consolidation 1	1 059*		10 004* 004* 013* 014* 018* 022* 026* 036* 048* 053*																11
	consolidation 2	1 018*		3 011* 018* 048*																4
	consolidation 3		1 018*	3 048* 048* 063*																4
	consolidation 4		1 018*	3 004* 035* 048*			1 062*													5
Surgical and medical procedures				**1**			**1**											**2**		**4**
	induction 1			1 061*			1 041*													2
	consolidation 1																	2 031* 055*		2

NR, not related; PR, possibly related; R, related; *Patient identification number

Summary table of AEs classified according MedDRA system organ class code (Part 9)

		Mild			Moderate			Sever			life threatening			fatal			not defined			
		R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	R	PR	NR	all
Vascular disorders				**24**			**13**			**1**						**1**				**39**
	screening			3 044* 058* 059*																3
	induction 1			4 020* 021* 044* 060*			6 001* 006* 008* 016* 053* 058*													10
	induction 2			4 005* 024* 036* 039*			1 021*													5
	consolidation 1			6 011* 011* 022* 039* 046* 063*			5 017* 017* 017* 022* 049*			1 017*										12
	consolidation 2			3 004* 014* 062*			1 037*													4
	consolidation 3			3 004* 018* 035*																3
	consolidation 4			1 062*																1
	end of treatment															1 030*				1

NR, not related; PR, possibly related; R, related; *Patient identification number

Number of AEs per chemotherapy cycle in the entire group and broken down by center

	INDUCTION			CONSOLIDATION				All cycles
	1	2	3	1	2	3	4	
All patients	509	135	25	181	118	120	87	1175
AKH WIEN	322	88	22	111	78	64	46	731
HIETZING	28			14	6	11	6	65
ELI LINZ	110	36	3	42	31	41	33	296
KFJ	15			7	3	0	0	25
SMZ OST	34	11		7	0	4	2	58

Median number of AEs per cycle in the entire group and broken down by center

	INDUCTION			CONSOLIDATION			
	Median number/cycle (range)			Median number/cycle (range)			
	1	2	3	1	2	3	4
All patients	7.5 (1-21)	6 (0-19)	3.5 (1-8)	3 (0-18)	3 (0-11)	4 (0-18)	4 (0-11)
AKH WIEN	9 (3-21)	9 (0-19)	5.5 (3-8)	4 (0-18)	4 (0-11)	4 (0-13)	4 (0-11)
HIETZING	3 (2-7)	-	-	5 (2-7)	3 (3-3)	5.5 (2-9)	3 (2-4)
ELI LINZ	7 (1-19)	4 (1-6)	1.5 (1-2)	3 (2-7)	2.5 (1-11)	5 (0-15)	4 (3-10)
KFJ	2 (2-6)	-	-	2 (1-4)	1.5 (0-3)	0 (0)	0 (0)
SMZ OST	4 (2-15)	5.5 (1-10)	-	3 (1-3)	0 (0)	2 (2-2)	1 (0-2)

Number of SAEs per chemotherapy cycle in the entire group and broken down by center

	INDUCTION			CONSOLIDATION				All cycles
	1	2	3	1	2	3	4	
All patients	15	5	0	9	3	1	3	36
AKH WIEN	11	4	0	6	2	0	1	24
HIETZING	0	-	-	0	0	0	0	0
ELI LINZ	1	0	0	0	1	1	2	5
KFJ	3	-	-	2	0	0	0	5
SMZ OST	0	1	-	1	0	0	0	2

13.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

SAEs resulting in death during the study

Patients identifier	Rem	Last chemotherapy administered	Type of last visit	death date day of last chemotherapy	Relation to therapy	Report of last visit	Reported Term for the Disposition Event
005	NR*	Induction 2	Follow up	65	NR	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS	Death
010	NR*	Induction 1	End of treatment	50	NR	DEATH	Infection
012	CR	Consolidation 2	Consolidation 2	26	NR	DEATH	CNS bleeding
013	CR	Consolidation 2	Follow up	58	NR	RELAPSE OF DISEASE DURING CONSOLIDATION THERAPY ACCORDING BONE MARROW EXAM.	Intracerebral bleeding
017	CR	Consolidation 1	End of treatment	31	R	DEATH	Death (cardiac arrhythmia suspected)
023	ED	Induction 1	End of treatment	16	NR	DEATH	Infection
024	NR*	Induction 2	Follow up	150	NR	OTHER. PERSISTENT DISEASE	Infection
029		Induction 1	Induction 1	11	R	PAT DIED IN PNEUMONIA WHILE ZYTOPENIA DURING INDUCTION 1	Pneumonia
030	CR	Induction 1	End of treatment	35	NR	PATIENT DIED BECAUSE OF AN ACUTE BLEEDING INTERNAL	Internal bleeding
033	ED	Induction 1	Induction 1	11	NR	DEATH DUE TO SEPSIS	Sepsis gram neg.
034	CR	Consolidation 4	End of treatment	19	R	DEATH. MULTIPLE ORGAN FAILURE.	Sepsis
047	NR*	Induction 1	Follow up	44	NR	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS	Multi-organ failure
057	NR*	Induction 3	Follow up	30	NR	FAILURE TO ACHIEVE COMPLETE REMISSION FOLLOWING 3 COURSES OF INDUCTION THERAPY	Disease progression
058	ED	Induction 1	Follow up	57	NR	PATIENT WITHDRAWN ON INVESTIGATOR DECISION	Multi-organ failure
061	CR	Consolidation 1	End of treatment	36	NR	DEATH	Diffuse alveolar damage

CR, complete remission; ED, death prior to CR evaluation; NR*, no remission; NR, not related; R, related Rem, remission state after induction

SAEs other than death

MedDRA System Organ Class	Number	MedDRA Lowest Level Term	Patients identifier	Visit	Action taken	Severity/ Intensity	Relation to therapy
Blood and lymphatic system disorders	1	Neutropenia	015	INDUCTION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	MODERATE	NR
Cardiac disorders	1	Atrial fibrillation	058	END OF TREATMENT	CONCOMITANT THERAPY - OTHER	LIFE THREATENING	NR
Gastrointestinal disorders	7	Diarrhea recurrent	061	CONSOLIDATION 1	CONCOMITANT THERAPY - HOSPITALIZATION	SEVERE	NR
		Diarrhea	061	INDUCTION 2	HOSPITALIZATION	SEVERE	NR
		Gastro intestinal bleeding	010	INDUCTION 1	CONCOMITANT THERAPY	LIFE THREATENING	NR
		Gastro intestinal bleeding	012	CONSOLIDATION 1	CONCOMITANT THERAPY - HOSPITALIZATION	MODERATE	NR
		Ileus	012	CONSOLIDATION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	SEVERE	NR
		Nausea	057	INDUCTION 1	CONCOMITANT THERAPY - HOSPITALIZATION	MODERATE	NR
		Obstipation	035	CONSOLIDATION 4	CONCOMITANT THERAPY - HOSPITALIZATION	MILD	NR
General disorders and administration site conditions	2	Fever	037	CONSOLIDATION 2	HOSPITALIZATION	MODERATE	NR
		Thoracic pain	014	CONSOLIDATION 1	HOSPITALIZATION - OTHER	MODERATE	NR
Infections and infestations	17	Abscess leg	008	CONSOLIDATION 4	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION - OTHER	MODERATE	NR
		Aspergilloma	003	INDUCTION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION - OTHER	MODERATE	NR
		Clostridium colitis	005	INDUCTION 2	CONCOMITANT THERAPY - HOSPITALIZATION	MODERATE	NR
		Erysipelas	057	INDUCTION 2	CONCOMITANT THERAPY - HOSPITALIZATION	SEVERE	NR
		Febrile infection	007	INDUCTION 1	CONCOMITANT THERAPY - HOSPITALIZATION	MODERATE	NR
		Febrile infection	045	CONSOLIDATION 1	HOSPITALIZATION	MODERATE	NR
		Gastroenteritis	014	CONSOLIDATION 2	HOSPITALIZATION	MILD	NR
		Gastrointestinal infection	012	CONSOLIDATION 1	CONCOMITANT THERAPY - HOSPITALIZATION	MILD	NR
		Infection	010	INDUCTION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	SEVERE	NR
		Infection	010	INDUCTION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	LIFE THREATENING	NR
		Infection	023	INDUCTION 1	CONCOMITANT THERAPY	LIFE THREATENING	NR
		Infection	024	INDUCTION 2	CONCOMITANT THERAPY - HOSPITALIZATION	MODERATE	NR
		Pneumonia	025	INDUCTION 2	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	SEVERE	NR
		Pneumonia	034	CONSOLIDATION 4	CONCOMITANT THERAPY	LIFE THREATENING	R
		Pneumonia	058	END OF TREATMENT	CONCOMITANT THERAPY - OTHER	LIFE THREATENING	NR
		Sepsis	029	INDUCTION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	LIFE THREATENING	R
		Septic shock	017	CONSOLIDATION 1	CONCOMITANT THERAPY	LIFE THREATENING	NR
Injury, poisoning and procedural complications	2	Subdural hematoma	060	INDUCTION 1	CONCOMITANT THERAPY	MODERATE	R
		Vertebral fracture	034	CONSOLIDATION 3	HOSPITALIZATION	MODERATE	NR
Nervous system disorders	3	Dementia	050	END OF TREATMENT	PROLONGATION OF HOSPITALIZATION - OTHER	MODERATE	NR
		Neurological status deterioration	017	CONSOLIDATION 1	OTHER	SEVERE	NR
		Paresthesia	017	INDUCTION 1	CONCOMITANT THERAPY - HOSPITALIZATION	MODERATE	NR
Renal and urinary disorders	4	Acute renal failure	057	INDUCTION 1	CONCOMITANT THERAPY - OTHER	SEVERE	PR
		Acute renal failure	058	END OF TREATMENT	CONCOMITANT THERAPY - OTHER	LIFE THREATENING	NR
		Hematuria	046	CONSOLIDATION 1	CONCOMITANT THERAPY - HOSPITALIZATION	MILD	NR
		Renal insufficiency	029	INDUCTION 1	CONCOMITANT THERAPY - PROLONGATION OF HOSPITALIZATION	LIFE THREATENING	NR

NR, not related; PR, possibly related; R, related

Significant Adverse Events (Part 1)

MedDRA System Organ Class	Number	MedDRA Lowest Level Term	Patients identifier	Visit	Action taken	Severity/ Intensity	Relation to therapy
Blood and lymphatic system disorders	19	Anemia	035	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Febrile neutropenia	001	INDUCTION 3	CONCOMITANT THERAPY	SEVERE	R
		Febrile neutropenia	010	SCREENING	CONCOMITANT THERAPY	SEVERE	R
		Febrile neutropenia	015	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Febrile neutropenia	025	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	R
		Febrile neutropenia	036	INDUCTION 1	NO ACTION TAKEN	SEVERE	NR
		Febrile neutropenia	058	INDUCTION 1	NO ACTION TAKEN	SEVERE	NR
		Leucopenia	035	INDUCTION 1	CONCOMITANT THERAPY	LIFE THREATENING	NR
		Leucopenia	037	INDUCTION 1	NO ACTION TAKEN	LIFE THREATENING	NR
		Neutropenia	003	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	R
		Neutropenic fever	034	CONSOLIDATION 2	CONCOMITANT THERAPY	SEVERE	NR
		Neutropenic fever	034	CONSOLIDATION 4	NO ACTION TAKEN	SEVERE	NR
		Neutropenic fever	037	INDUCTION 1	NO ACTION TAKEN	SEVERE	NR
		Neutropenic fever	038	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Neutropenic fever	038	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
		Neutropenic fever	048	CONSOLIDATION 3	CONCOMITANT THERAPY	SEVERE	NR
		Neutropenic fever	062	CONSOLIDATION 2	CONCOMITANT THERAPY	SEVERE	NR
		Thrombopenia	035	INDUCTION 1	CONCOMITANT THERAPY	LIFE THREATENING	NR
		Thrombopenia	038	INDUCTION 1	NO ACTION TAKEN	LIFE THREATENING	NR
Cardiac disorders	1	Atrial fibrillation	058	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
Gastrointestinal disorders	7	Emesis	012	CONSOLIDATION 2	CONCOMITANT THERAPY	SEVERE	NR
		Nausea	002	CONSOLIDATION 2	CONCOMITANT THERAPY	SEVERE	NR
		Nausea	010	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Nausea	010	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Vomiting	002	CONSOLIDATION 2	CONCOMITANT THERAPY	SEVERE	NR
		Vomiting	010	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Vomiting	010	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
General disorders and administration site conditions	3	Mucositis	037	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Mucositis	053	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Reduced general condition	010	INDUCTION 1	NO ACTION TAKEN	SEVERE	NR
Hepatobiliary disorders	1	Cholecystolithiasis	012	CONSOLIDATION 1	NO ACTION TAKEN	SEVERE	NR
Infections and infestations	8	Infection	010	SCREENING	CONCOMITANT THERAPY	SEVERE	NR
		Infection	017	CONSOLIDATION 1	CONCOMITANT THERAPY	SEVERE	NR
		Infection	023	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Infection	038	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Infection	061	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
		Pneumonia	025	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
		Pneumonia	058	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Tonsillitis	039	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
Metabolism and nutrition disorders	1	Hypokalemia	061	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
Musculoskeletal and connective tissue disorders	3	Cytarabine syndrome	048	CONSOLIDATION 3	CONCOMITANT THERAPY	SEVERE	R
		Rhabdomyolysis	058	INDUCTION 1	NO ACTION TAKEN	SEVERE	NR
		Shoulder pain	009	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
Renal and urinary disorders	1	Acute renal failure	058	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR

NR, not related; PRR, related

Significant Adverse Events (Part 2)

MedDRA System Organ Class	Number	MedDRA Lowest Level Term	Patients identifier	Visit	Action taken	Severity/ Intensity	Relation to therapy
Respiratory, thoracic and mediastinal disorders	4	Dyspnea	057	INDUCTION 2	CONCOMITANT THERAPY	SEVERE	NR
		Pleural effusion	057	INDUCTION 2	CONCOMITANT THERAPY - OTHER	SEVERE	NR
		Pneumothorax	062	INDUCTION 1	CONCOMITANT THERAPY	SEVERE	NR
		Pulmonary vascular disorder	061	INDUCTION 1	NO ACTION TAKEN	SEVERE	NR
Vascular disorders	1	Hypotension	017	CONSOLIDATION 1	CONCOMITANT THERAPY	SEVERE	NR

NR, not related; PRR, related

13.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Number of AEs per patient, SAEs, significant AEs and their correlation with study completion (part 1)

Patients identifier	AE, n	Fatal SAE	Not fatal SAE	significant AEs	Last chemotherapy	End of Study	Cause of withdrawal
001	25	no	no	yes	INDUCTION 3	WITHDRAWN	PERSISTENT DISEASE
002	15	no	no	yes	CONSOLIDATION 4	COMPLETED	
003	17	no	yes	yes	CONSOLIDATION 1	WITHDRAWN	RELAPSE
004	32	no	no	no	CONSOLIDATION 4	COMPLETED	
005	20	yes	yes	no	INDUCTION 2	WITHDRAWN	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS
006	28	no	no	no	INDUCTION 3	WITHDRAWN	ADVERSE EVENT
007	23	no	yes	no	INDUCTION 1	WITHDRAWN	RELAPSE
008	29	no	yes	no	CONSOLIDATION 4	COMPLETED	
009	18	no	no	yes	INDUCTION 3	WITHDRAWN	PERSISTENT DISEASE
010	20	yes	yes	yes	INDUCTION 1	WITHDRAWN	DEATH
011	37	no	no	no	CONSOLIDATION 3	WITHDRAWN	RELAPSE
012	30	yes	yes	yes	CONSOLIDATION 2	WITHDRAWN	DEATH
013	15	yes	no	no	CONSOLIDATION 2	WITHDRAWN	RELAPSE
014	35	no	yes	no	CONSOLIDATION 4	COMPLETED	
015	16	no	yes	yes	CONSOLIDATION 3	WITHDRAWN	ADVERSE EVENT
016	18	no	no	no	CONSOLIDATION 4	COMPLETED	
017	25	yes	yes	yes	CONSOLIDATION 1	WITHDRAWN	DEATH
018	46	no	no	no	CONSOLIDATION 4	COMPLETED	
019	3	no	no	no	INDUCTION 1	WITHDRAWN	ADVERSE EVENT
020	26	no	no	no	CONSOLIDATION 4	COMPLETED	
021	41	no	no	no	CONSOLIDATION 4	WITHDRAWN	ADVERSE EVENT
022	20	no	no	no	CONSOLIDATION 3	WITHDRAWN	ADVERSE EVENT
023	17	yes	yes	yes	INDUCTION 1	WITHDRAWN	DEATH
024	42	yes	yes	no	INDUCTION 2	WITHDRAWN	PERSISTENT DISEASE
025	22	no	yes	yes	INDUCTION 2	WITHDRAWN	ADVERSE EVENT
026	10	no	no	no	CONSOLIDATION 4	COMPLETED	
027	4	no	no	no	INDUCTION 3	WITHDRAWN	PERSISTENT DISEASE
028	6	no	no	no	CONSOLIDATION 4	COMPLETED	

AE, adverse event; n, number; SAE, severe adverse event

Number of AEs per patient, SAEs, significant AEs and their correlation with study completion (part 2)

Patients identifier	AE, n	Fatal SAE	Not fatal SAE	significant AEs	Last chemotherapy	End of Study	Cause of withdrawal
029	6	yes	yes	no	INDUCTION 1	WITHDRAWN	DEATH
030	3	yes	no	no	INDUCTION 1	WITHDRAWN	DEATH
031	13	no	no	no	CONSOLIDATION 4	COMPLETED	
032	18	no	no	no	CONSOLIDATION 3	WITHDRAWN	RELAPSE
033	3	yes	no	no	INDUCTION 1	WITHDRAWN	DEATH
034	24	yes	yes	yes	CONSOLIDATION 4	WITHDRAWN	DEATH
035	25	no	yes	yes	CONSOLIDATION 4	COMPLETED	
036	14	no	no	yes	CONSOLIDATION 1	WITHDRAWN	RELAPSE
037	20	no	yes	yes	CONSOLIDATION 2	WITHDRAWN	RELAPSE
038	16	no	no	yes	INDUCTION 2	WITHDRAWN	HSCT
039	20	no	no	yes	CONSOLIDATION 1	WITHDRAWN	HSCT
040	9	no	no	no	CONSOLIDATION 4	COMPLETED	
041	4	no	no	no	INDUCTION 1	WITHDRAWN	SIGNIFICANT PROTOCOL DEVIATION
042	12	no	no	no	INDUCTION 1	WITHDRAWN	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS
043	10	no	no	no	CONSOLIDATION 4	WITHDRAWN	RELAPSE
044	26	no	no	no	CONSOLIDATION 4	COMPLETED	
045	5	no	yes	no	CONSOLIDATION 1	WITHDRAWN	RELAPSE
046	6	no	yes	no	CONSOLIDATION 4	COMPLETED	
047	3	yes	no	no	INDUCTION 1	WITHDRAWN	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS
048	27	no	no	yes	CONSOLIDATION 4	COMPLETED	
049	17	no	no	no	CONSOLIDATION 4	COMPLETED	
050	7	no	yes	no	INDUCTION 1	WITHDRAWN	ADVERSE EVENT
051	7	no	no	no	INDUCTION 1	WITHDRAWN	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS
052	3	no	no	no	INDUCTION 1	WITHDRAWN	REFUSAL OF PATIENT TO CONTINUE TREATMENT AND/OR OBSERVATIONS
053	24	no	no	yes	CONSOLIDATION 1	WITHDRAWN	ADVERSE EVENT
054	13	no	no	no	INDUCTION 2	WITHDRAWN	HSCT
055	19	no	no	no	CONSOLIDATION 4	COMPLETED	
056	39	no	no	no	CONSOLIDATION 3	WITHDRAWN	ADVERSE EVENT
057	33	yes	yes	yes	INDUCTION 3	WITHDRAWN	PERSISTENT DISEASE
058	14	yes	yes	yes	INDUCTION 1	WITHDRAWN	ADVERSE EVENT
059	15	no	no	no	CONSOLIDATION 4	COMPLETED	
060	16	no	yes	yes	INDUCTION 1	WITHDRAWN	ADVERSE EVENT
061	28	yes	yes	no	CONSOLIDATION 1	WITHDRAWN	DEATH
062	52	no	no	yes	CONSOLIDATION 4	COMPLETED	
063	34	no	no	no	CONSOLIDATION 4	COMPLETED	
064	4	no	no	no	CONSOLIDATION 1	WITHDRAWN	ADVERSE EVENT

AE, adverse event; n, number; SAE, severe adverse event

13.3.4 Abnormal Laboratory Value Listing (Each Patient)

Abnormal laboratory values: grade II; grade III (italic); grade IV (italic & bold) for BUN, creatinine, transaminases, and alkaline phosphatase (part 1)

SUBJID	Age	Race	Sex	Weight	Height	Visit	Day of treatment cycle	Day since 1st sample	BUN mg/dL	Creat mg/dL	ALP U/L	AST U/L	ALT U/L
002	66,6	caucasian	M	176	90	CONSOLIDATION 4	-2	163	14,8	0,96	78	65	137
002	66,6	caucasian	M	176	90	CONSOLIDATION 4	1	165	12,3	1,01	81	73	169
002	66,6	caucasian	M	176	90	CONSOLIDATION 4	4	168	15	1,03	76	63	137
002	66,6	caucasian	M	176	90	FOLLOW UP	119	343	16,4	1,15	69	63	138
002	66,6	caucasian	M	176	90	FOLLOW UP	172	396	22,5	1,18	64	103	214
004	69,4	caucasian	F	162	66	END OF TREATMENT	1	224	6,1	0,77	113	23	113
006	64,1	caucasian	M	173	121	INDUCTION 1	23	23	34,6	2,61	40	10	11
007	70,1	caucasian	M	172	78	INDUCTION 1	3	3	13,3	0,91	75	182	16
007	70,1	caucasian	M	172	78	INDUCTION 1	4	4	13,9	0,87	75	163	15
010	69,5	caucasian	M	178	80	INDUCTION 1	37	37	17,4	1,01	326	141	66
010	69,5	caucasian	M	178	80	INDUCTION 1	38	38	21,6	1	421	145	66
010	69,5	caucasian	M	178	80	INDUCTION 1	40	40	27,3	0,97	407	95	53
010	69,5	caucasian	M	178	80	INDUCTION 1	42	42	32	1	374	95	47
010	69,5	caucasian	M	178	80	INDUCTION 1	46	46	58,4	1,15	258	206	84
010	69,5	caucasian	M	178	80	INDUCTION 1	47	47	72,4	1,4	224	*329*	135
010	69,5	caucasian	M	178	80	INDUCTION 1	49	49	91,8	1,52	182	144	137
011	75,0	caucasian	F	163	75	CONSOLIDATION 1	20	63	20,4	2,57	71	30	15
011	75,0	caucasian	F	163	75	CONSOLIDATION 2	14	98	11,1	0,73	191	159	*263*
011	75,0	caucasian	F	163	75	CONSOLIDATION 2	16	100	12,9	0,71	144	51	130
012	75,9	caucasian	M	174	103	CONSOLIDATION 2	22	126	12,7	0,8	406	77	84
015	61,5	caucasian	M	195	98	SCREENING	-2	-2	17,8	1,16	97	221	128
017	72,7	caucasian	M	168	81	CONSOLIDATION 1	17	62	76,8	1,54	189	39	23
017	72,7	caucasian	M	168	81	CONSOLIDATION 1	19	64	81,5	1,38	210	55	44
017	72,7	caucasian	M	168	81	CONSOLIDATION 1	23	68	64,2	1,08	363	54	39
018	70,0	caucasian	F	172	71	CONSOLIDATION 2	11	116	22	0,83	196	70	88
018	70,0	caucasian	F	172	71	CONSOLIDATION 3	-3	178	19,7	0,76	153	66	93
018	70,0	caucasian	F	172	71	CONSOLIDATION 4	-1	235	17,4	0,72	149	69	97
018	70,0	caucasian	F	172	71	CONSOLIDATION 4	24	259	18,6	0,77	187	75	111
018	70,0	caucasian	F	172	71	CONSOLIDATION 4	28	263	15,7	0,76	160	88	150
018	70,0	caucasian	F	172	71	CONSOLIDATION 4	34	269	20,3	0,78	163	86	144
018	70,0	caucasian	F	172	71	END OF TREATMENT	1	278	14	0,76	155	91	145
020	69,9	caucasian	M	163	78	CONSOLIDATION 2	-1	92	15,8	0,91	78	64	147
020	69,9	caucasian	M	163	78	CONSOLIDATION 2	4	96	26,1	1,12	71	65	130
020	69,9	caucasian	M	163	78	CONSOLIDATION 2	42	134	14,2	0,97	94	71	169
020	69,9	caucasian	M	163	78	CONSOLIDATION 3	-1	139	17	0,9	91	67	161
020	69,9	caucasian	M	163	78	CONSOLIDATION 3	35	174	16,8	1,06	105	73	161
020	69,9	caucasian	M	163	78	CONSOLIDATION 3	49	188	16,5	0,86	115	60	154
020	69,9	caucasian	M	163	78	CONSOLIDATION 4	-1	195	16,2	0,88	101	71	171
021	71,3	caucasian	M	172	77,7	CONSOLIDATION 3	55	265	17,9	0,9	64	84	188
022	70,6	caucasian	M	178	116	INDUCTION 1	11	11	41,5	2,6	62	22	25
025	62,9	caucasian	F	166	70	INDUCTION 2	41	82	19	0,91	143	109	96

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Creat, creatinine; F, female; M, male

Abnormal laboratory values: grade II; grade III (italic); grade IV (italic & bold) for BUN, creatinine, transaminases, and alkaline phosphatase (part 2)

SUBJID	Age	Race	Sex	Weight	Height	Visit	Day of treatment cycle	Day since 1st sample	BUN	BUN mg/dL	Creat mg/dL	ALP U/L	AST U/L
026	64,6	caucasian	F	165	53	INDUCTION 1	8	8	10,9	0,74	66	67	89
026	64,6	caucasian	F	165	53	INDUCTION 1	9	9	13,3	0,7	104	*223*	*210*
026	64,6	caucasian	F	165	53	INDUCTION 1	10	10	8,9	0,68	121	110	*184*
026	64,6	caucasian	F	165	53	INDUCTION 1	12	12	8,8	0,64	133	30	113
026	64,6	caucasian	F	165	53	CONSOLIDATION 4	17	170	13,7	0,67	94	67	90
027	61,0	caucasian	M	179	82,5	INDUCTION 2	6	55	20,5	0,75			134
033	85,2	caucasian	M	172	86,6	END OF TREATMENT	1	12	55,3	3,27	66	***1709***	***1267***
034	75,9	caucasian	F	154	56,5	INDUCTION 1	4	4	38,1	0,98	80	146	139
034	75,9	caucasian	F	154	56,5	INDUCTION 1	5	5	51,7	1,16	71	*205*	164
034	75,9	caucasian	F	154	56,5	INDUCTION 1	6	6	33,9	0,85	93	*226*	*232*
034	75,9	caucasian	F	154	56,5	INDUCTION 1	7	7	28,6	0,66	93	135	*204*
034	75,9	caucasian	F	154	56,5	INDUCTION 1	8	8	29,2	0,65	86	75	162
034	75,9	caucasian	F	154	56,5	INDUCTION 1	9	9	29,9	0,57	87	46	122
034	75,9	caucasian	F	154	56,5	INDUCTION 1	10	10	25,9	0,7	87	37	94
034	75,9	caucasian	F	154	56,5	INDUCTION 2	-3	16	7,6	0,55	305	93	147
034	75,9	caucasian	F	154	56,5	INDUCTION 2	1	19	10,2	0,45	310	34	89
034	75,9	caucasian	F	154	56,5	INDUCTION 2	2	20	16,9	0,46	272	20	66
034	75,9	caucasian	F	154	56,5	CONSOLIDATION 4	19	228	30,2	1,48	166	***2490***	***1450***
034	75,9	caucasian	F	154	56,5	END OF TREATMENT	1	229	68,3	*3,17*	274	***7351***	***2753***
038	67,4	caucasian	F	169	70	INDUCTION 1	5	5	15,5	0,7	84	76	106
038	67,4	caucasian	F	169	70	INDUCTION 1	6	6	15	0,65	79	50	93
041	75,6	caucasian	M	167	83	INDUCTION 1	20	20	14	1,3	55		187
041	75,6	caucasian	M	167	83	INDUCTION 1	20	20	14	1,3	55		190
041	75,6	caucasian	M	167	83	INDUCTION 1	23	23	12	1,2	59	71	185
041	75,6	caucasian	M	167	83	INDUCTION 1	27	27	14	1	99	59	140
042	72,1	caucasian	F	163	68,8	INDUCTION 1	21	21	34	1,9			
042	72,1	caucasian	F	163	68,8	INDUCTION 1	23	23	21	1,1	265		18
042	72,1	caucasian	F	163	68,8	INDUCTION 1	25	25	14	0,8	*547*	74	22
042	72,1	caucasian	F	163	68,8	INDUCTION 1	29	29	34	1,1	344	12	6
043	63,5	caucasian	F	158	56	CONSOLIDATION 1	5	41	9	0,8	65	60	103
044	67,2	caucasian	M	172	85	SCREENING	-2	-2			147	150	
044	67,2	caucasian	M	172	85	INDUCTION 1	1	1	17,9	1,4			*280*
044	67,2	caucasian	M	172	85	INDUCTION 1	3	3	47	1,27			165
050	75,4	caucasian	F	172	80	SCREENING	-3	-3	27	2,47	50	37	12
050	75,4	caucasian	F	172	80	SCREENING	-2	-2	25	1,92			
050	75,4	caucasian	F	172	80	INDUCTION 1	28	28	13	0,71	94	173	40
050	75,4	caucasian	F	172	80	INDUCTION 1	31	31	13	0,63	135	124	33
050	75,4	caucasian	F	172	80	INDUCTION 1	35	35	18	0,65	149	121	29
050	75,4	caucasian	F	172	80	INDUCTION 1	36	36	17	0,63	160	121	33
050	75,4	caucasian	F	172	80	INDUCTION 1	37	37	17	0,61	163	138	40
050	75,4	caucasian	F	172	80	INDUCTION 1	38	38	18	0,63	162	116	38
050	75,4	caucasian	F	172	80	INDUCTION 1	39	39	18	0,65	157	97	37
053	74,1	caucasian	F	168	69	INDUCTION 1	8	8	35,1	0,8	76	106	99
053	74,1	caucasian	F	168	69	INDUCTION 1	9	9	32,2	0,81	107	144	156

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Creat, creatinine; F, female; M, male

Abnormal laboratory values: grade II; grade III (italic); grade IV (italic & bold) for BUN, creatinine, transaminases, and alkaline phosphatase (part 3)

SUBJID	Age	Race	Sex	Weight	Height	Visit	Day of treatment cycle	Day since 1st sample	BUN mg/dL	Creat mg/dL	ALP U/L	AST U/L	ALT U/L
053	74,1	caucasian	F	168	69	INDUCTION 1	10	10	26,6	0,8	96	102	152
053	74,1	caucasian	F	168	69	INDUCTION 1	11	11	22	0,76	100	53	112
056	61,9	caucasian	F	170	70	CONSOLIDATION 1	4	36	10,5	0,79	70	91	147
056	61,9	caucasian	F	170	70	CONSOLIDATION 1	5	37	10,5	0,75	62	80	130
056	61,9	caucasian	F	170	70	CONSOLIDATION 1	7	39	13	0,77	82	77	147
056	61,9	caucasian	F	170	70	CONSOLIDATION 1	10	42	18,6	0,8	77	59	148
056	61,9	caucasian	F	170	70	CONSOLIDATION 1	14	46	14,8	0,8	68	34	105
056	61,9	caucasian	F	170	70	CONSOLIDATION 3	23	169	9,8	0,78	77	30	89
057	72,8	caucasian	M	168	70	INDUCTION 1	2	2	56,8	3,4			
057	72,8	caucasian	M	168	70	INDUCTION 1	3	3	87,3	*4,63*	65	81	60
057	72,8	caucasian	M	168	70	INDUCTION 1	4	4	60,4	3,6	59	45	45
057	72,8	caucasian	M	168	70	INDUCTION 1	5	5	45,4	3,2	58	32	38
057	72,8	caucasian	M	168	70	INDUCTION 1	6	6	51,3	*3,66*	60	26	32
057	72,8	caucasian	M	168	70	INDUCTION 1	7	7	49,9	3,18			
057	72,8	caucasian	M	168	70	INDUCTION 1	8	8	61,6	3,45	68	32	32
057	72,8	caucasian	M	168	70	INDUCTION 1	9	9	64,8	3,14	62	33	32
057	72,8	caucasian	M	168	70	INDUCTION 1	10	10	61,5	2,73			
058	70,5	caucasian	M	174	83	END OF TREATMENT	1	29	60,8	2,92	35	*594*	246
059	68,2	caucasian	F	160	60	INDUCTION 1	18	18	5,2	0,57	276	12	11
059	68,2	caucasian	F	160	60	INDUCTION 1	19	19	4,2	0,59	309	14	12
059	68,2	caucasian	F	160	60	INDUCTION 1	22	22	4,9	0,54	420	16	18
059	68,2	caucasian	F	160	60	INDUCTION 1	26	26	13,8	0,68	488	23	30
059	68,2	caucasian	F	160	60	CONSOLIDATION 1	-2	33	14,2	0,6	285	25	26
060	62,2	caucasian	F	160	68	INDUCTION 1	5	5	17,5	0,88	246	62	132
060	62,2	caucasian	F	160	68	INDUCTION 1	8	8	21,8	0,92	271	51	104
060	62,2	caucasian	F	160	68	INDUCTION 1	12	12	19,9	0,88	322	57	148
060	62,2	caucasian	F	160	68	INDUCTION 1	14	14	18,7	0,89	344	49	*183*
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	14	106	28	1	81	***5571***	***3231***
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	15	107		1	86	***2373***	***2820***
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	16	108	29	0,7	94	*954*	***2039***
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	17	109	29	0,7	90	*531*	***1554***
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	18	110	24	0,7	78	180	*933*
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	19	111	21	0,6	73	88	*597*
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	20	112	20	0,7	77	60	*426*
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	22	114	38	0,9	72	37	*253*
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	23	115	31	0,7	67	30	150
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	35	127	59	1	60		25
061	67,8	caucasian	M	170	86,3	CONSOLIDATION 1	36	128	60	1,1	87		36
061	67,8	caucasian	M	170	86,3	END OF TREATMENT	1	129	82	1,5	150		57

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Creat, creatinine; F, female; M, male

Normal Ranges of

	BUN mg/dL	Creat mg/dL	ALP U/L	AST U/L	ALT U/L
Male	8 - 23,1	0,7 - 1,2	40 - 130	< 50	< 50
Female	8 - 23,1	0,5 - 0,9	35 - 105	< 35	< 35

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