Clinical Study Synopsis (EudraCT Number 2008-004583-40)

Name of Sponsor:	Universitätsklinikum Münster Albert-Schweitzer-Campus 1 48149 Münster	
Name of Finished Product:	Vidaza®	
Name of Active Ingredient:	5-Azacytidine	
Title of Study:	A randomized, multi-center phase II trial to assess the efficacy of 5-azacytidine added to standard primary therapy in elderly patients with newly diagnosed AML	
Study centres and corresponding investigators:	Universitätsklinikum Münster	Prof. Dr. med. C. Müller-Tidow

Publication (reference):	Krug U, Koschmieder A, Schwammbach D, Gerss J, Tidow N, et al. (2012) Feasibility of Azacitidine Added to Standard Chemotherapy in Older Patients with Acute Myeloid Leukemia — A Randomised SAL Pilot Study. PLoS ONE 7(12): e52695. doi:10.1371/journal.pone.0052695	
Study initiation date (first patient enrolled): Run-in part: Controlled part: Premature stop of randomization and stop of therapy with 5-Azacytidine: Study completion date:	 08 SEPT 2009 29 APR 2010 09 DEC 2011 08 DEC 2012	
Phase of development:	Phase II	
Objectives:	<u>Run-in dose-finding part:</u> The primary endpoint was safety and toxicity of both dose levels. <u>Controlled part:</u> <u>Primary</u> • to compare the median Event Free Survival (EFS) of all AML patients between the 5-azacytidine and the control group <u>Secondary</u> • to compare the median Event Free Survival (EFS) of AML patients with different cytogenetic and molecular risk groups • to compare the median Overall Survival (OS) of all AML patients between the 5-azacytidine and the control group • to compare the median Overall Survival (OS) of AML patients with different cytogenetic and molecular risk groups • to compare Relapse Free Survival (RFS) of AML patients between the 5-azacytidine and the control group • to compare the rate of early response after the first induction cycle between	

	the 5-azacytidine and the control group • to compare the Complete Remission (CR) rate of the 5-azacytidine and the control group • to compare the CR rate of AML patients with different cytogenetic and molecular risk groups • to compare the rate of molecular remissions of the 5-azacytidine and the control group • to compare the toxicity of the 5-azacytidine and the control treatment • to compare the evidence of minimal residual disease of all AML patients between the 5-azacytidine and the control group after induction therapy and in the course of the first remission • to compare the development of biomarkers indicating the course of disease, including genetic, epigenetic, transcriptional and protein markers as well as indicators of neo-angiogenesis in leukemic blasts, bone marrow, peripheral blood cells, serum and plasma • to compare the global methylation pattern and the methylation of selected gene promoters in the bone marrow and peripheral blood cells between the 5-azacytidine and the control group at different time points • to evaluate the predictive value of changes of the methylation pattern for response in the 5-azacytidine group
Methodology:	The present clinical trial is a prospective, controlled, randomized, open, multi-center phase II study with parallel group design and fixed sample size and with a preceding dose-finding run-in period. Patients older than 60 years with newly diagnosed AML (except APL) were included. <u>Run-in dose-finding part:</u> As a safety step for the combination therapy of 5-azacytidine and standard induction resp. consolidation therapy, the trial was preceded by a run-in part. Patients in this part of the study were randomized 1:1 between dose level 1 (37.5 mg/m2/day 5-azacytidine, n=6) and dose level 2 (75 mg/m2/day 5-azacytidine, n=6). Patients received one or two induction therapy cycles with cytarabine (100 mg/m²/d 24 h i.v., days 1 to 7) and daunorubicin (45 mg/m² 2 h i.v., days 3 to 5) preceded by 5-azacytidine 37.5 or 75 mg/m2/day i.v. on days (-5) to (-1) before start of each induction therapy. All patients who achieved a complete remission after one or two cycles of induction therapy received 2 cycles of consolidation therapy with cytarabine (1000 mg/m² i.v. twice daily, days 1, 3, 5) preceded by 5-azacytidine 37.5 or 75 mg/m2/day s.c. on days (-5) to (-1) before start of each consolidation therapy. Dose limiting toxicity (DLT) was defined here as prolonged pancytopenia ≥ 42 days from start of last cytotoxic therapy. A patient was evaluable if either 1. at least one therapy cycle with 5-azacitidine plus induction therapy was completed or 2. patient received at least one day of therapy and a DLT occurred. <u>Controlled phase:</u> In the controlled phase of the trial patients were randomized 1:1 between Arm A (chemotherapy preceded by 5-azacytidine + maintenance therapy with 5-azacytidine) and Arm B (chemotherapy without preceding 5-azacytidine and without maintenance therapy). Chemotherapy was the same as in the run-in dose-finding part except of the dose of daunorubicin which was increased from 45 mg/m² to 60 mg/m² (Amendment Protocol Version 4.1 (11.01.2010)). Patients in CR or in incomplete CR after induction therapy received consolidation therapy. The dose of 5-azacytidine in Arm A was 75 mg/m2/day on days (-5) to (-1) before start of each chemotherapeutic cycle. In Arm A patients in CR or incomplete CR with platelets > 70,000/µl and neutrophils > 1,000/µl after consolidation therapy received maintenance therapy with 5-azacytidine 75 mg/m2/day s.c. days 1-5 on a 28-day cycle. Maintenance therapy was administered until one year after start of induction therapy.

	Patients in Arm B did not receive maintenance therapy but were followed up until one year after start of induction therapy.
Number of patients:	Run-in dose-finding part: planned: 12 (+6) patients included: 12 patients randomized: 12 patients Controlled phase: planned: 216 patients included: 215 patients randomized: 214 patients
Diagnosis and main criteria for inclusion:	<u>Inclusion criteria:</u> • Patients with newly diagnosed AML (except APL) according to the FAB or WHO classification, including AML evolving from MDS or other hematological diseases and AML after previous cytotoxic therapy or radiation (secondary AML). • Bone marrow aspirate or biopsy must contain ≥ 20% blasts of all nucleated cells or differential blood count must contain ≥ 20% blasts. In AML FAB M6 ≥ 30% of non-erythroid cells in the bone marrow must be leukemic blasts. In AML defined by cytogenetic aberrations the proportion of blasts may be < 20%. • Age ≥ 61 years • Informed consent, personally signed and dated to participate in the study • Male patients enrolled in this trial must use adequate barrier birth control measures during the course of the 5-azacytidine treatment and for at least 3 months after the last administration of 5-azacytidine. <u>Exclusion criteria (among others):</u> • Patients who are not eligible for standard chemotherapy • Hyperleukocytosis (leukocytes > 20,000/µl) at study entry. These patients should be treated with hydroxyurea or receive leukocytapheresis treatment (if leukocytes > 100,000/µl) according to routine practice and entered into the study when leukocyte counts of 20,000/µl or below are reached. This applies only for the controlled part of the study. • Known central nervous system manifestation of AML • Cardiac Disease: Heart failure NYHA class 3 or 4; unstable coronary artery disease (Myocardial infarction more than 6 months prior to study entry is permitted); serious cardiac ventricular arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted) • Chronically impaired renal function (creatinin clearance < 30 ml/min) • Inadequate liver function (ALT and AST ≥ 2.5 x ULN) if not caused by leukemic infiltration • Total bilirubin ≥ 1.5 x ULN if not caused by leukemic infiltration • Known HIV and/or hepatitis C infection • Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy • Evidence or recent history of CNS disease, including primary or metastatic brain tumors, seizure disorders • Uncontrolled active infection • Concurrent malignancies other than AML with an estimated life expectancy of less than two years • History of organ allograft • Previous treatment of AML except hydroxyurea and up to 2 days of ≤100 mg/m2/d cytarabine • Previous therapy with 5-azacytidine (i.e. for an antecedent myelodysplastic syndrome)
Test product, dose and mode of administration, batch number:	<u>5-Azacytidine (Vidaza®)</u> <u>Run-in dose-finding part:</u> 37.5 or 75 mg/m2/day as an intravenous infusion over 15 - 30 minutes once daily on days (-5) to (-1) before start of each induction therapy and 37.5 or 75 mg/m2/day as a subcutaneous injection on days (-5) to (-1) before start of each consolidation therapy

	Controlled part: 75 mg/m2/day as an intravenous infusion over 15 - 30 minutes once daily on days (-5) to (-1) before start of each induction therapy, 75 mg/m2/day as a subcutaneous injection on days (-5) to (-1) before start of each consolidation therapy and subsequently maintenance therapy with 75 mg/m2/day s.c. days 1-5 on a 28-day cycle until one year after start of induction therapy. Batch numbers: 09F0278, 10F0196, 11F0063, OE149AA, 1J447A, 1L467A, O6309AA, OC128AA, OD137AA, 9J101AA
Duration of treatment:	Until maximal 1 year after start of induction therapy
Reference therapy, dose and mode of administration, batch number:	Not applicable
Criteria for evaluation: Efficacy:	The primary efficacy variable was median Event Free Survival (EFS). EFS was defined as time interval from day 1 of study treatment until treatment failure, relapse from CR, relapse from morphologic leukemia-free state, or death from any cause, whichever occurred first. The time point at which the patient was resistant to therapy or survived induction without a CR or morphologic leukemia free state was noted. For a patient with none of these events before the end of study follow-up, observation of EFS was censored at the date of his or her last follow-up examination. Secondary efficacy variables included median Overall Survival (OS), Relapse Free Survival (RFS), rate of early response after the first induction cycle, Complete Remission (CR) rate, rate of molecular remissions, evidence of minimal residual disease, development of biomarkers and methylation pattern. Response criteria are defined according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Cheson BD, et al. J Clin Oncol 2003; 21(24):4642-9)
Safety:	AEs and SAEs were recorded up to and 42 days after the last protocol treatment including standard chemotherapy. AEs and SAEs for patients in Arm B were recorded up to one year after start of induction therapy or until end of trial participation, whichever happened earlier, but at least 42 days after last protocol treatment (equal period as those for patients in Arm A receiving maintenance therapy). Severity was assessed according to CTCAE 3.0. Safety assessments included performance status, physical examination, vital signs, body weight, differential blood count, chemistry including liver function, creatinine and coagulation, and if required urinalysis, ECG, echocardiography / MUGA scan and ultrasound of the abdomen.
Statistical methods:	The statistical analysis was performed according to the intention to treat principle (ITT analysis). The primary endpoint (median EFS) was compared between both treatment arms using a two-sided Logrank test. This part of the analysis was considered as confirmatory. Patients undergoing bone marrow transplantation were censored for EFS, OS and RFS at the time of bone marrow transplantation. For safety analysis, patients were analysed according to the received study treatment (as treated analysis).
SUMMARY – CONCLUSIONS	**Run-in dose-finding part:** 6 patients were treated with dose level 1 (37.5 mg/m2/day 5-azacytidine) and

SUMMARY – CONCLUSIONS	6 patients were treated with dose level 2 (75 mg/m2/day 5-azacytidine). No dose limiting toxicity occurred in either dose level. Nine severe adverse events occurred in five patients, two in the 75 mg/m2 dose level (two patients) and seven in the 37.5 mg/m2 dose level (three patients). In two patients, the SAEs had a fatal outcome. 19 AE's in ten patients were grade 3 or higher, seven in the 75 mg/m2 dose level and twelve of them in the 37.5 mg/m2 dose level. With the exception of 5 AE´s, all other SAEs and AEs grade 3 or 4 occurred during induction therapy. 162 AE's of all grades occurred, among them 102 in the 75 mg/m2 dose level and 62 in the 37.5 mg/m2 dose level. The most frequently occurring AE's were: fever (11), peripheral edemas (8), diarrhea (8), nausea (8), vomiting (8), and exanthema (6). Infections (20 versus 7), AE's of the cardiovascular (19 versus 7), musculoskeletal (5 versus 0) and gastrointestinal system (27 versus 22) were more frequent in the 75 mg/m2 compared to the 37.5 mg/m2 dose level. With the exception of one cardiac failure grade 4 in the 37.5 mg/m2 arm, all AE's of the cardiovascular system were grade ≤ 2. Median time to regeneration after induction therapy for patients in 37.5 mg/m2 and the 75 mg/m2 dose level was 23 and 25 days to a leukocyte count of > 1,000/µl, 29 and 28 days to a neutrophil count > 500/µl and 22 and 30 days to a transfusion-independent platelet count > 20,000/µl, respectively (all comparisons not significant). In nine consolidation courses applied to five patients in CR, median time to regeneration was 22 days for leukocytes, 27 days for neutrophils and 22 days for platelets. Both dose levels could be safely administered prior to standard cytotoxic induction and consolidation therapy. Therefore, the independent Data Monitoring Committee (DMC) suggested 75 mg/m2 for 5 days as the recommended dose for the controlled part of the trial. **<u>Controlled part:</u>** 105 patients were randomized in Arm A and 109 patients in Arm B. Median age was 70 years in both arms. In Arm A 61 patients were male and 44 were female. In Arm B 62 patients were male and 47 were female. In Arm A 70 patients had a de novo AML and 31 patients had a secondary AML (4 patients n.k.), in Arm B 77 patients had a de novo AML and 32 had a secondary AML. Median proportion of blasts in bone marrow was 63% (mean 60 ± 24%) in Arm A and 55% (mean 58 ± 24%) in Arm B (p = 0.5755). Median leucocyte count was 5.17 GPt/l (mean 11.03 ± 19.83 GPt/l) in Arm A and 5.00 GPt/l (mean 7.21 ± 8.98 GPt/l) in Arm B (p = 0.1538). Median LDH was 340 U/l (mean 573 ± 930 U/l) in Arm A and 307 U/l (mean 401 ± 281 U/l) in Arm B (p = 0.0928). Distribution of ECOG performance status (p = 0.1077):

	Missing	ECOG 0	ECOG 1	ECOG 2	ECOG 3
Arm A (N = 105)	4	23	65	13	.
Arm B (N = 109)	5	36	54	12	2

FAB-classification:

FAB	Arm A	Arm B
ns	3	2
M0	4	8
M0/M2	1	.
M1	19	14
M1/M2	1	1
M2	26	22
M4	17	20
M4/M5	.	2
M4eo	2	3
M5	13	16
M6	5	4
M7	3	4
not known	11	13
total	105	109

Distribution of cytogenetic risk groups (p = 0.0571):

	n.k.	Good	Intermediate	High
Arm A (N = 105)	3 (2.9%)	4 (3.8%)	59 (56.2%)	39 (37.1%)
Arm B (N = 109)	3 (2.8%)	4 (3.7%)	77 (70.6%)	25 (22.9%)

Distribution of molecular risk groups (within the cytogenetic intermediate group with normal karyotype) (p = 1.000):

	.	n.k.	Good	Intermediate
Arm A (N = 105)	60 (57.1%)	3 (2.9%)	9 (8.6%)	33 (31.4%)
Arm B (N = 109)	50 (45.9%)	7 (6.4%)	11 (10.1%)	41 (37.6%)

Premature study termination:
91 of 105 patients in Arm A and 87 of 109 patients in Arm B had a premature study termination. The most frequent reasons for withdrawal were refractory disease after induction therapy (Arm A: 29 patients, Arm B: 31 patients), relapse (Arm A: 15 patients, Arm B: 17 patients), AE´s (Arm A: 9 patients, Arm B: 7 patients) and death (Arm A: 15 patients, Arm B: 12 patients).

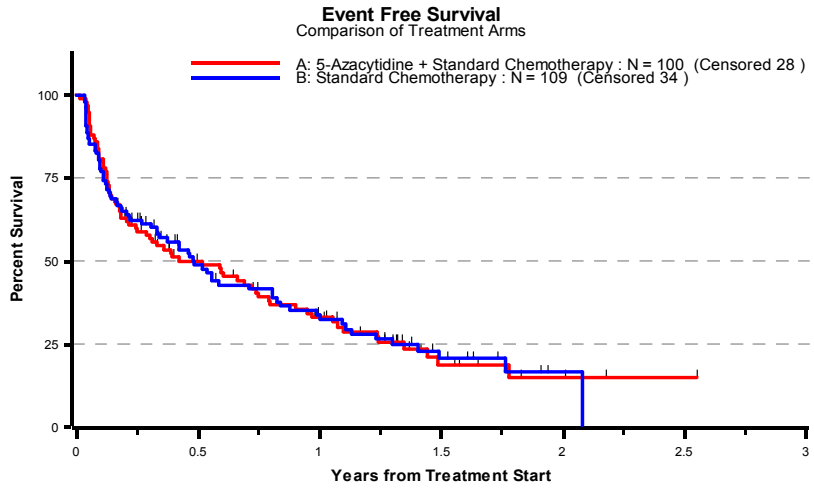
EFFICACY RESULTS:

Primary:

- Median Event Free Survival (EFS) – Comparison of Treatment Arms:

The primary endpoint (median EFS) was compared between both treatment arms using a two-sided Logrank test.

No significant difference in Event Free Survival between the treatment arms could be detected (p = 0.96304). Median EFS was 6 months in both treatment arms.



(A: 5-Azacytidine + Standard Chemotherapy : 6 Mon., B: Standard Chemotherapy : 6 Mon., p = 0.96304)

Secondary:

- Median Event Free Survival – Comparison of patients with different cytogenetic and molecular risk groups:

Median EFS in patients with cytogenetic good risk:
Arm A (N = 4, censored 4): n.a.
Arm B (N = 4, censored 2): 5 months
(two-sided Logrank test: p = 0.15730)

Median EFS in patients with cytogenetic intermediate risk:
Arm A (N = 57, censored 16): 9 months
Arm B (N = 77, censored 25): 9 months

(two-sided Logrank test: p = 0.93943)

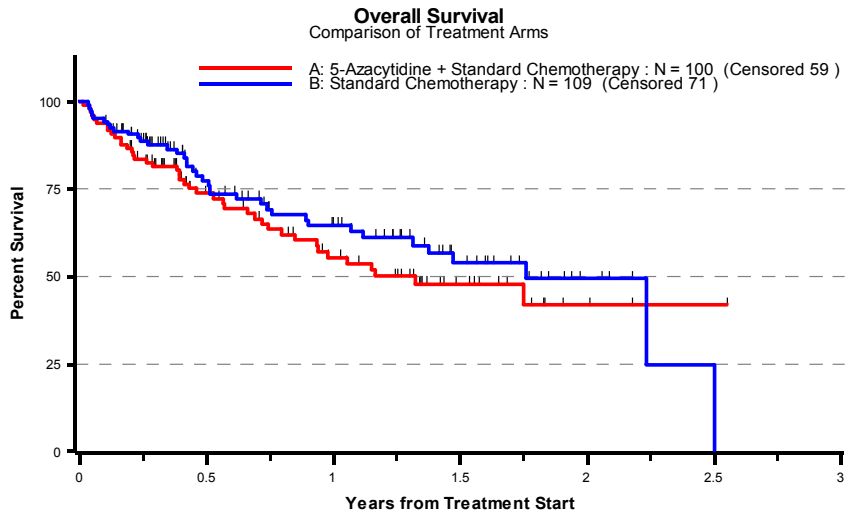
Median EFS in patients with cytogenetic high risk:
Arm A (N = 37, censored 7): 2 months
Arm B (N = 25, censored 7): 2 months
(two-sided Logrank test: p = 0.67742)

Median EFS in patients with molecular good risk:
Arm A (N = 8, censored 4): 22 months
Arm B (N = 11, censored 6): 12 months
(two-sided Logrank test: p = 0.76271)

Median EFS in patients with molecular intermediate risk:
Arm A (N = 32, censored 7): 9 months
Arm B (N = 41, censored 12): 7 months
(two-sided Logrank test: p = 0.74144)

- Median Overall Survival (OS) – Comparison of Treatment Arms:

A noticeable difference in OS between the treatment arms could not be detected (p = 0.35007). Median OS was 16 months in Arm A and 21 months in Arm B.



(A: 5-Azacytidine + Standard Chemotherapy : 16 Mon., B: Standard Chemotherapy : 21 Mon., p = 0.35007)

- Median Overall Survival – Comparison of patients with different cytogenetic and molecular risk groups:

Median OS in patients with cytogenetic good risk:
Arm A (N = 4, censored 4): n.a.
Arm B (N = 4, censored 2): 5 months
(two-sided Logrank test: p = 0.15730)

Median OS in patients with cytogenetic intermediate risk:
Arm A (N = 57, censored 34): 21 months
Arm B (N = 77, censored 52): 27 months
(two-sided Logrank test: p = 0.30866)

Median OS in patients with cytogenetic high risk:
Arm A (N = 37, censored 20): 11 months
Arm B (N = 25, censored 16): 13 months
(two-sided Logrank test: p = 0.59298)

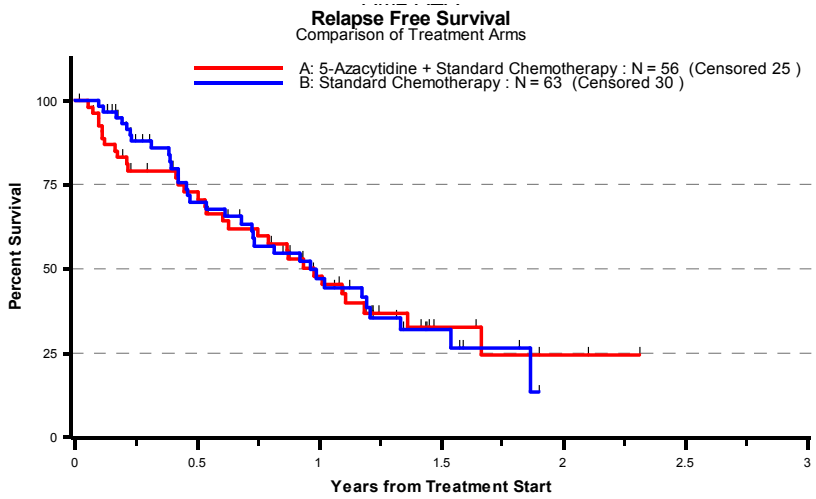
Median OS in patients with molecular good risk:

Arm A (N = 8, censored 7): n.a.
Arm B (N = 11, censored 9): 21 months
(two-sided Logrank test: p = 0.59838)

Median OS in patients with molecular intermediate risk:
Arm A (N = 32, censored 19): n.a.
Arm B (N = 41, censored 23): 18 months
(two-sided Logrank test: p = 0.94386)

- Relapse Free Survival (RFS) – Comparison of Treatment Arms:

A noticeable difference in RFS between the treatment arms could not be detected (p = 0.94657). RFS was 12 months in both treatment arms.



(A: 5-Azacytidine + Standard Chemotherapy : 12 Mon., B: Standard Chemotherapy : 12 Mon., p = 0.94657)

- Early response rate after the first induction cycle – Comparison of Treatment Arms:

In Arm A 37 of 100 patients (37%) had a proportion of < 5% blasts in bone marrow (BM) after the first induction cycle vs. 43 of 109 patients (39.45%) in Arm B.
43 patients (43%) in Arm A vs. 44 patients (40.37%) in Arm B had a proportion of ≥ 5% blasts in BM.
Among the other patients bone marrow was not assessable or bone marrow examination was not recorded resp. not done.
(p = 0.7763)

- Complete Remission (CR) rate – Comparison of Treatment Arms:

48 of 100 patients (48%) in Arm A had a complete remission (CR, CRc, CRm) after induction therapy vs. 57 of 109 patients (52.29%) in Arm B (p = 0.5807).

Results of Induction Therapy	Arm A	Arm B
n. k. / not applicable	3 (3%)	.
Morphologic Leukemia-free State (MLF)	10 (10%)	11 (10.09%)
Morphologic Complete Remission (CR)	44 (44%)	54 (49.54%)
Cytogenetic Complete Remission (CRc)	1 (1%)	2 (1.83%)
Molecular Complete Remission (CRm)	3 (3%)	1 (0.92%)
Partial Remission (PR)	1 (1%)	1 (0.92%)
Resistant disease	23 (23%)	27 (24.77%)
Death in Aplasia	.	1 (0.92%)
Indeterminate Cause	15 (15%)	12 (11.01%)

Total	100 (100%)	109 (100%)

- Complete Remission (CR) rate – Comparison of patients with different cytogenetic and molecular risk groups:

Complete Remission (CR, CRc, CRm) rate in patients with cytogenetic good risk:
Arm A: 3 of 4 patients (75.00%)
Arm B: 4 of 4 Patients (100.00%)
(p = 1.0000)

Complete Remission (CR, CRc, CRm) rate in patients with cytogenetic intermediate risk:
Arm A: 32 of 57 patients (56.14%)
Arm B: 43 of 77 patients (55.84%)
(p = 1.0000)

Complete Remission (CR, CRc, CRm) rate in patients with cytogenetic high risk:
Arm A: 12 of 37 patients (32.43%)
Arm B: 10 of 25 patients (40.00%)
(p = 0.5954)

Complete Remission (CR, CRc, CRm) rate in patients with molecular good risk:
Arm A: 7 of 8 patients (87.50%)
Arm B: 8 of 11 patients (72.73%)
(p = 0.6027)

Complete Remission (CR, CRc, CRm) rate in patients with molecular intermediate risk:
Arm A: 16 of 32 patients (50.00%)
Arm B: 19 of 41 patients (46.34%)
(p = 0.8159)

SAFETY RESULTS:

Number of administered chemotherapy cycles:

	Induction therapy			**Consolidation therapy**		
	No	1. Cycle	2. Cycle	No	1. Cycle	2. Cycle
Arm A N = 105	9	96 (95*)	35 (32*)	62	43 (36*)	29 (21*)
Arm B N = 109	0	109	30	50	59	44

* Number of patients with chemotherapy + preceding 5-azacytidine

Number of administered maintenance therapy cycles (months) in Arm A:

19 of 105 patients in Arm A received at least one cycle (month) of maintenance therapy with 5-azacytidine. Only 1 patient received 10 cycles (months) of maintenance therapy.

Maintenance therapy with 5-azacytidine									
1. Month	2. Month	3. Month	4. Month	5. Month	6. Month	7. Month	8. Month	9. Month	10. Month

19 (1*)	15 (1*)	12 (4*)	8 (4*)	7 (4*)	6 (2*)	6 (1*)	6 (2*)	3 (0*)	1 (0*)

* Patients with reduced dose

Number of AE´s (AT – as treated: at least one dose Azacytidine or Chemotherapy):

1529 AE´s occurred in 99 patients treated with at least one dose of 5-azacytidine (Arm AT-A) vs. 1487 AE´s in 110 patients treated with chemotherapy only (Arm AT-B). Mean number of AE's was 15.44 ± 12.95 in Arm AT-A vs. 13.52 ± 11.72 in Arm AT-B. Median number of AE's was 12.00 in Arm AT-A vs. 10.00 in Arm AT-B.

In Arm AT-A 216 AEs were CTCAE grade 3, 72 grade 4 and 26 grade 5. In Arm AT-B 183 AE´s were grade 3, 43 grade 4 and 22 grade 5.

Most of the AE´s occurred within 60 days after start of treatment (mean number of AE's: 11.32 ± 8.97 in Arm AT-A vs. 9.55 ± 6.82 in Arm AT-B, median 9.00 vs. 8.00).

51% of the patients in Arm AT-A had at least one SAE after start of treatment vs. 31% in Arm AT-B (p = 0.0047). This difference between the treatment arms is noticeable.

Number of deaths:

	Arm A (N = 100)	**Arm B (N = 109)**	**p-value**
Number of deaths within 30 days after start of treatment	6	5	0.7607
Number of deaths within 60 days after start of treatment	12	9	0.4905
Number of deaths within 90 days after start of treatment	16	12	0.3154

Number of MedDRA-Codes with CTCAE grade 3-5 within the primary System Organ Classes (SOC):

Primary SOC	**CTCAE Grade**	**Arm A**	**Arm B**
General Disorders and administration site conditions	3	29	24
	4	6	4
	5	2	4
	total	37	32
Surgical and medical procedures	3	1	1
	4	.	.
	5	.	.
	total	1	1
Endocrine disorders	3	.	1
	4	.	.
	5	.	.
	total	.	1
Respiratory, thoracic and mediastinal disorders	3	14	15
	4	5	2
	5	1	1
	total	20	18
Reproductive system and breast disorders	3	1	.
	4	.	.
	5	.	.
	total	1	.
Skin and subcutaneous tissue disorders	3	7	3
	4	.	.
	5	.	.
	total	7	3
Renal and urinary disorders	3	1	3
	4	2	1
	5	1	1
	total	4	5

Blood and lymphatic system disorders	3	61	51
	4	39	19
	5	.	.
	total	100	70
Gastrointestinal disorders	3	14	14
	4	5	3
	5	3	1
	total	22	18
Immune system disorders	3	.	1
	4	.	2
	5	.	1
	total	.	4
Nervous system disorders	3	4	2
	4	1	.
	5	1	2
	total	6	4
Vascular disorders	3	9	4
	4	1	.
	5	1	.
	total	11	4
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3	1	.
	4	1	.
	5	1	1
	total	3	1
Cardiac disorders	3	4	4
	4	6	1
	5	5	1
	total	15	6
Infections and infestations	3	58	52
	4	7	9
	5	13	11
	total	78	72
Hepato-biliary disorders	3	2	.
	4	.	.
	5	.	.
	total	2	.
Psychiatric disorders	3	2	.
	4	.	.
	5	.	.
	total	2	.
Musculoskeletal and connective tissue disorders	3	3	8
	4	.	.
	5	.	.
	total	3	8
Metabolism and nutrition disorders	3	7	4
	4	1	1
	5	.	.
	total	8	5
Investigations	3	8	9
	4	4	2
	5	.	.
	total	12	11
Injury, poisoning and procedural complications	3	5	.
	4	.	.
	5	1	.
	total	6	.
Total	3	231	196
	4	78	44
	5	29	23
	total	338	263

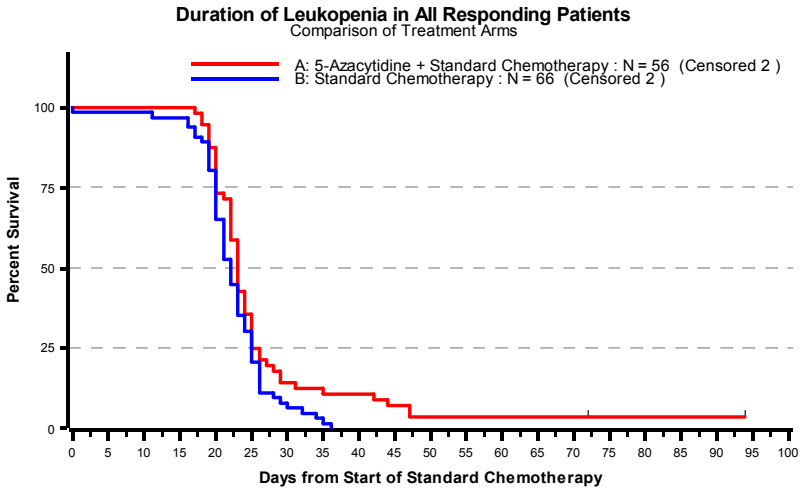
Number of MedDRA-Codes (CTCAE grade 3-5) with primary or secondary SOC “Cardiac Disorders” or Preferred Term (PT) “Akute respiratorische Insuffizienz”, “Atemnot” or “Elektrokardiogramm QT verlängert”:

CTCAE Grade	Arm A	Arm B
3	11	11
4	8	2
5	5	2
Total	24	15

Number of MedDRA-Codes (CTCAE grade 3-5) with primary or secondary SOC “Infections and Infestations” or Preferred Term (PT) “Fieber” or “Lungeninfiltration” or ”Febrile Neutropenie” or “Körpertemperatur erhöht”:

CTCAE Grade	Arm A	Arm B
3	108	107
4	15	12
5	13	11
Total	136	130

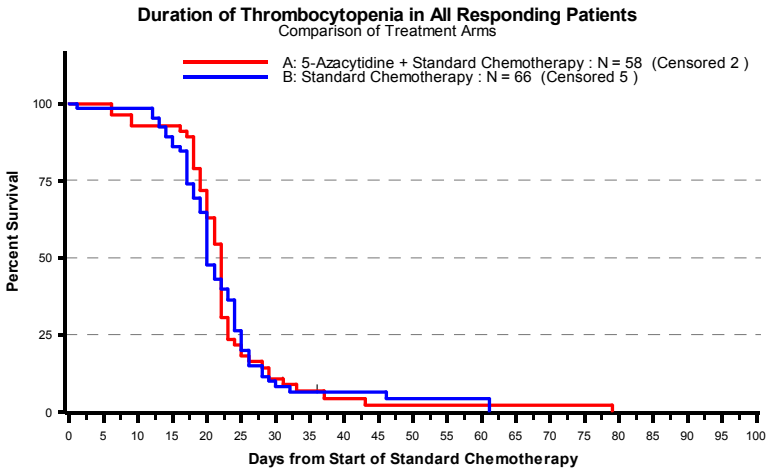
Duration of leukopenia (leucocytes < 1 GPt/l) after the last induction chemotherapy cycle in responding patients (MLF, CR, CRc, CRm):



(A: 5-Azacytidine + Standard Chemotherapy : 23 Days, B: Standard Chemotherapy : 22 Days, p = 0.04262)

There is a noticeable difference in duration of leukopenia between the treatment arms (p = 0.04262).

Duration of thrombocytopenia (thrombocytes < 25 GPt/l) after the last induction chemotherapy cycle in responding patients (MLF, CR, CRc, CRm):



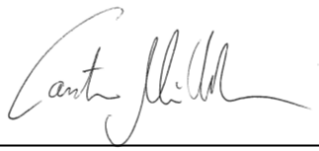
(A: 5-Azacytidine + Standard Chemotherapy : 22 Days, B: Standard Chemotherapy : 20 Days, p = 0.78014)

CONCLUSIONS:

No significant difference in the primary endpoint Event Free Survival was detected between the treatment arms. Median EFS was 6 months in both arms which is considerably longer than initially expected (3 months vs. 4.5

	months). Noticeable differences between the treatment arms in EFS within different cytogenetic and molecular risk groups, in OS, RFS and complete remission rate of all patients and within different cytogenetic and molecular risk groups and in the early response rate could not be detected. Distribution of baseline characteristics was overall balanced between the treatment arms. In Arm A, 37.1% of the patients were in the cytogenetic high risk group vs. 22.9% in Arm B (p = 0.0571).This difference might have contributed to the slight trend for longer overall survival in Arm B. The number of patients with cytogenetically good risk (or favorable mutation profile (NPM-mutant, FKT3-wildytpe)) was too small to evaluate the observed trends to longer EFS and OS in Arm A. More patients in Arm AT-A (51%) than in Arm AT-B (31%) had at least one SAE after start of treatment (p = 0.0047). This difference is statistically noticeable and points towards increased toxicity with the addition of Azacytidine to intensive chemotherapy in older patients with AML. There were more cardiac disorders and vascular disorders grade 3-5 in Arm AT-A than in Arm AT-B (MedDRA-Codes with primary SOC "Cardiac Disorders" 15 vs. 6, MedDRA-Codes with primary SOC "Vascular Disorders" 11 vs. 4). Musculoskeletal and connective tissue disorders grade 3-5 were more frequently in Arm AT-B than in Arm AT-A (8 vs. 3). Statistically, these differences were not noticeable. It is nonetheless possible that the addition of 5-azacytidine to standard chemotherapy might increase cardiac toxicity. Duration of leukopenia (leucocytes < 1 GPt/l) after the last induction chemotherapy cycle in responding patients (MLF, CR, CRc, CRm) was longer in Arm A than in Arm B (p = 0.04262). This difference depended on a few patients that experienced a significant delay. The median duration of leukopenia differed by one day. Given that infection problems were not noticeably increased in Arm A it is unlikely that increased hematopoietic toxicity was clinically significant. No difference in efficacy between the treatment arms could be detected but there is an indication of higher toxicity in Arm A.

I have read this report and confirm that to the best of my knowledge it accurately describes the results of the study.

Date ___Dec 4th , 2013____ Signature 

Prof. Dr. med. Carsten Müller-Tidow (CI)