Summary of the Trial Report
[Synopsis according to ICH E3]

Response-Adapted Sequential Azacitidine And Chemotherapy in Patients > 60 Years Old With Newly Diagnosed AML Eligible for Chemotherapy and allogeneic hematopoietic cell transplantation: A Multicentre Phase I/II study of the East German Hematology and Oncology Study Group (OSHO)

RAS-AZIC (OSHO #083)

Name of Finished Product/Name of Active Substance:
Vidaza®/Azacitidine
ARA-cell®/Cytarabine
Mitoxantron HEXAL®/Mitoxantrone

Indication/Diagnosis:
Acute myeloid leukemia (AML)

Phase of Development:
I/II

EudraCT-Number:
2010-023584-17

Registration-Number:
DRKS00004519

Date of report: 2019-05-08
Version: final 1.0

Trial start: 2012-12-13
End of Trial: 2018-05-25

Coordinating investigator
PD Dr. med. Haifa Kathrin Al-Ali, Leipzig
Medical consultant
Universität Leipzig, Medizinische Fakultät
Department für Innere Medizin
Selbstständige Abteilung für Hämatologie und Internistische Onkologie
Johannisallee 32A
04103 Leipzig

Prof. Dr. med. Dr. h.c. D. Niederwieser
Universitätsklinikum AöR
Department für Innere Medizin
Selbstständige Abteilung für Hämatologie und Internistische Onkologie
Johannisallee 32A
04103 Leipzig

Sponsor
University of Leipzig
Ritterstr. 26
04109 Leipzig

Legal representative of the sponsor:
PD Dr. med. Haifa Kathrin Al-Ali

Author of the report
PD Dr. med. Haifa Kathrin Al-Ali
Phone: +49 (0) 345 557 4909
Fax: +49 (0) 345 557 2224
E-mail: haifa.al-ali@uk-halle.de
Department für Innere Medizin
Selbstständige Abteilung für Hämatologie und Internistische Onkologie
Johannisallee 32A, 04103 Leipzig

Signatures

The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

Legal representative of the sponsor and coordinating investigator	PD Dr. med. Haifa Kathrin Al-Ali	08.05.2019 Date
Biometry	Dr. rer. nat. Oana Brosteanu	13.05.2019 Date
Further authors	Nicole Köppe-Bauernfeind, MSc	13.05.2019 Date

Table of content

1 Name of the Sponsor/Company

University of Leipzig
Ritterstr. 26
D-04109 Leipzig

Representative of the Sponsor

Name:	PD Dr. med. Haifa Kathrin Al-Ali
Institution:	Universität Leipzig, Medizinische Fakultät, Department für Innere Medizin, Selbstständige Abteilung für Hämatologie und Internistische Onkologie
Address:	Johannisallee 32A, 04103 Leipzig
Phone:	+49 (0) 345 557 4909
Fax:	+49 (0) 345 557 2224
Email:	haifa.al-ali@uk-halle.de

2 Name of Finished Product	3 Name of active Ingredient
Vidaza	Azacitidine
various (only defined by active substance) e.g. ARA-cell®	Cytarabine
various (only defined by active substance) e.g. Mitoxantron HEXAL®	Mitoxantrone

4 Individual study table

Not applicable

5 Title of Study

Response-Adapted Sequential Azacitidine And Chemotherapy in Patients > 60 Years Old With Newly Diagnosed AML Eligible for Chemotherapy and allogeneic hematopoietic cell transplantation: A Multicentre Phase I/II study of the East German Hematology and Oncology Study Group (OSHO).

6 Investigator	7 Study Centres
PD Dr. Haifa Katrin Al-Ali	Universitätsklinikum Leipzig Selbstst. Abteilung f. Hämatologie, Internist. Onkologie und Hämostaseologie Johannisallee 32 A 04103 Leipzig
Prof. Dr. Georg Maschmeyer	Ernst von Bergmann Klinikum Potsdam Zentrum für Hämatologie, Onkologie und Strahlenheilkunde, Klinik für Hämatologie und Onkologie Charlottenstraße 72 14467 Potsdam
PD Dr. Mathias Hänel	Klinikum Chemnitz gGmbH Klinik für Innere Medizin III, Hämatologie, Onkologie, Stammzelltransplantation Bürgerstraße 2 09113 Chemnitz
PD Dr. Christoph Kahl	Klinikum Magdeburg gGmbH Klinik für Hämatologie und Onkologie Birkenallee 34 39130 Magdeburg

Dr. Maxi Wass	Universitätsklinik Halle Abt. für Hämatologie und Onkologie Ernst-Grube-Str. 40 06120 Halle
PD Dr. Herbert Sayer	Helios-Klinikum Erfurt 4. Medizinische Klinik, Hämatologie und internistische Onkologie, Hämostaseologie Nordhäuser Straße 74, 99089 Erfurt

8 Publications

Congress abstracts:

1. Blood 2017 130:1334 (ASH 2017)
2. Blood 2018 132:83 (ASH 2018)

9 Studied period (in years)

First patient in: 13.12.2012

Last patient out: 25.05.2018

10 Phase of Development

Phase I/II. All Investigational Medicinal Products were authorized.

11 Objectives

Objectives of Phase I – Dose evaluation

- To investigate feasibility of azacitidine administered 75mg/m^2/day subcutaneously for 5 or 7 days followed by conventional AML induction chemotherapy in terms of dose limiting toxicity (DLT)
- To define the azacitidine total dose (5 or 7 days) per cycle to be administered in the phase II part of the trial

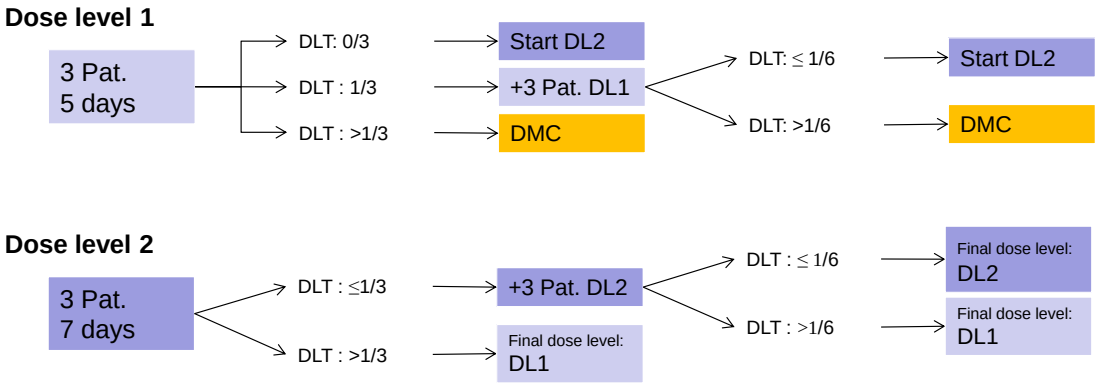
Objectives of Phase II – Efficacy and Safety

To assess efficacy and safety of induction therapy with response-adapted sequential azacitidine and conventional AML induction chemotherapy in patients > 60 years with newly diagnosed AML (at the dose level resulting from the dose evaluation phase of the trial)

12 Methodology

This study was a prospective, single-arm, open-label phase I/II multicentre trial with a monocentric dose evaluation phase (phase I) followed by a multicentric evaluation of a sequential therapy schedule (phase II).

In phase I patients received best supportive care combined with azacitidine followed by the standard conventional AML induction chemotherapy. Azacitidine was administered 75 mg/m2/day sub-cutaneously for 5 or 7 days to evaluate the dose limiting toxicity (DLT) and to define the azacitidine total dose (5 or 7 days) for phase II.



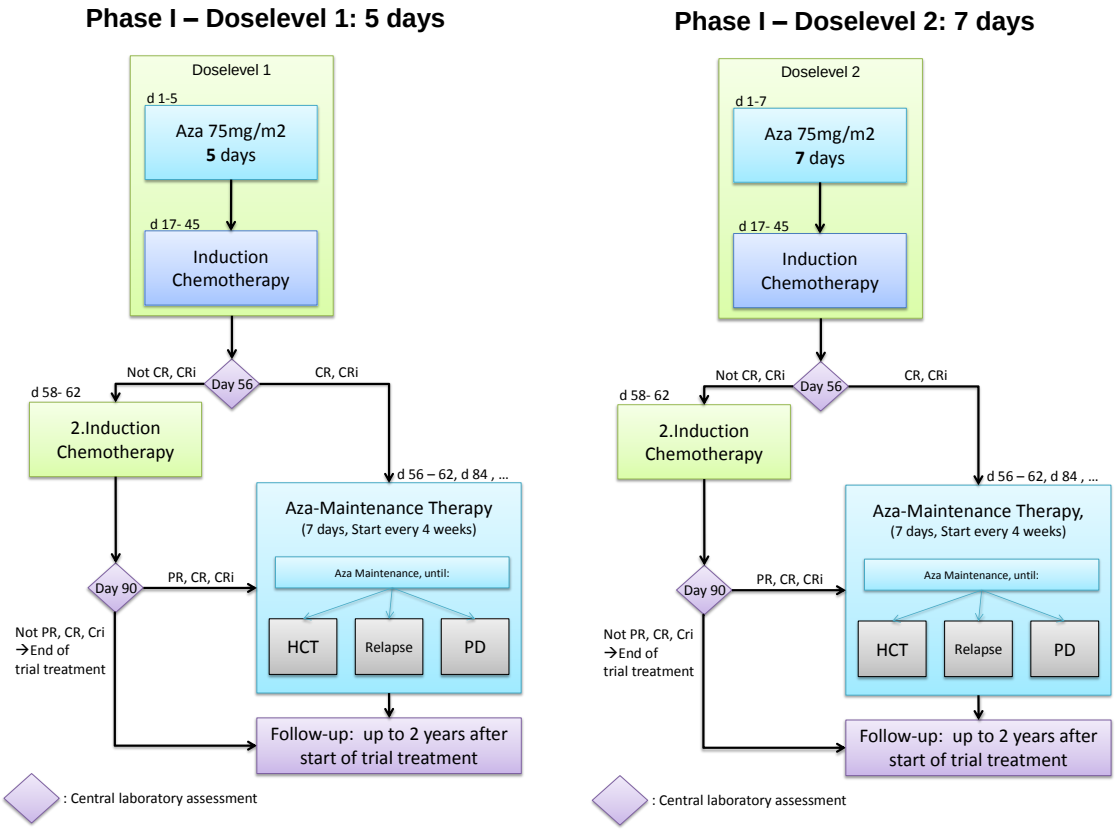


Figure 1: Phase I - Dose levels 1 and 2

In phase II patients received best supportive care combined with the prior determined dose of azacitidine for 7 days alone or followed by up to two cycles of chemotherapy according to a sequential therapy schedule.

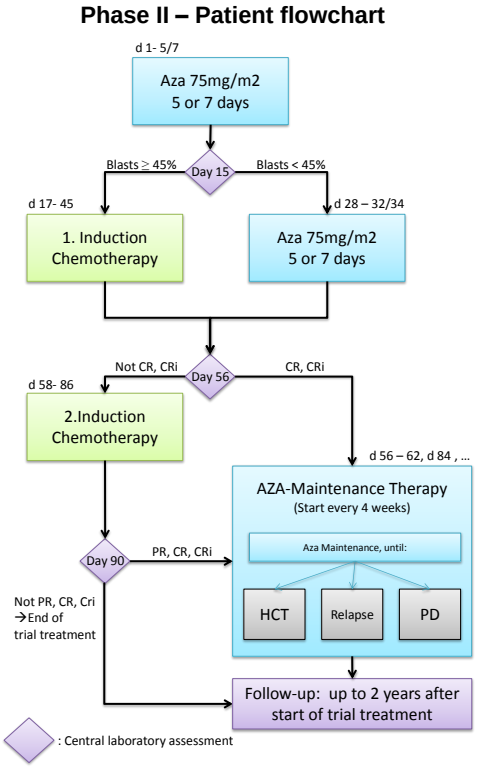


Figure 2: Phase II

The individual sequential therapy schedule depended on the response to the respective prior therapy cycle and followed by azacitidine maintenance therapy for patients achieving CR, CRi or PR.

13 Number of patients (planned and analysed)

Planned number:	110 – 113 patients (6-12 patients were planned to participate in phase I)
Registered/screened subjects:	114
Recruited subjects	113
Analyzed patients:	112 for safety, 109 enrolled on maximum tolerated dose for efficacy
Drop-outs:	29

For details see the CONSORT Flow Diagramm in the appendix 21.1.

14 Diagnosis and main criteria for inclusion

All patients had to meet all of the following **inclusion criteria**:

1. Newly diagnosed (within the last 28 days) and untreated AML (> 20% blasts in the bone marrow based on the WHO classification) including:
   - de novo AML
   - AML secondary to prior myelodysplastic disease
   - AML secondary to exposure to potentially leukemogenic therapies or agents (eg, radiation therapy, alkylating agents, topoisomerase II inhibitors) with the primary malignancy in remission for at least 2 years
2. Age > 60years
3. Eligible for intensive chemotherapy and allogeneic hematopoietic cell transplantation
4. Serum bilirubin levels ≤ 1.5 x the upper limit of normal (ULN). Higher levels are acceptable if these can be attributed to
5. active hemolysis (as indicated by positive direct Coombs' testing, decreased haptoglobin level, elevated indirect bilirubin and/or lactate dehydrogenase [LDH]),
6. or ineffective erythropoiesis (as indicated by bone marrow findings)
7. Serum glutamic-oxaloacetic transaminase (SGOT) (aspartate aminotransferase [AST]) level ≤ 2 x ULN
8. Serum glutamic-pyruvic transaminase (SGPT) (alanine aminotransferase [ALT]) level ≤ 2 x ULN
9. serum creatinine levels ≤ 1.5 x ULN
10. Left ventricular ejection fraction by echocardiography > 50%
11. Women of childbearing potential may participate, providing they meet the following conditions:
    - must agree to use effective contraceptive methods throughout the study and for 6months following the date of the last dose of study medication
    - must have a negative serum pregnancy test obtained within 72 hours prior to day 1.
12. Males with female partner of childbearing potential must agree to use effective contraceptive methods throughout the study and should avoid fathering a child for 6 months following the date of the last dose of study medication.
13. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Appendix A)
14. Capable of giving informed consent
15. Written informed consent

Patients were excluded for ANY of the following **exclusion criteria**:

1. **Acute promyelocytic leukaemia (AML M3)**
2. Previous cytotoxic or any other hypomethylating or biological treatment for AML, exception: hydroxyurea
3. Any diagnosis of malignant disease within the previous 12 months (excluding basal cell carcinoma with no complications)
4. Hepatic tumors in the medical history

5. Known or suspected hypersensitivity to azacitidine (incl. additives), Mitoxantrone (incl. additives), Ara-C (incl. additives)
6. Patients with serious concomitant medical illness:
   - severe congestive heart failure [grade ≥ 3 according to CTCAE] or
   - clinically unstable ischemia or
   - acute myocardial infarction in the previous six months or
   - pulmonary hypertension [grade ≥ 3 according to CTCAE] or
   - severe cardiac arrythmias [grade ≥ 3 according to CTCAE] or
   - chronic pulmonary diseases [grade ≥ 3 according to CTCAE] or
   - uncontrolled hypertension or
   - uncontrolled diabetes or
   - uncontrolled severe infections [grade ≥ 3 according to CTCAE] or
   - any other severe or uncontrolled medical illness
7. Patients with bronchial asthma with sulfite sensitivity
8. Psychiatric illness that would prevent granting of informed consent
9. Active viral infection with known human immunodeficiency virus (HIV) or viral hepatitis type B or C
10. Treatment with any of the following concomitant medications:
    - Corticosteroids, unless otherwise indicated, e.g. blood product transfusion reaction or prevention
    - Retinoids
    - Cytokines (except as outlined in Section **Fehler! Verweisquelle konnte nicht gefunden werden.**)
    - Interleukin-11
    - EPO
11. Participation in other clinical trials in the last 30 days

15 Information on the Test Product

Vidaza®/Azacitidine

Dose: 75mg/m^2/day
Mode of Administration: s.c.
Batch numbers: 12F0442, 11F0450, 13F0746, 16F2620, 16F1505, 17F0085

ARA-cell®/Cytarabine

Dose: 1 g/m^2/BID
Mode of Administration: i.v.
Batch numbers: Not applicable

Mitoxantron HEXAL®/Mitoxantrone

Dose: 75mg/m^2/day
Mode of Administration: s. c.
Batch numbers: Not applicable

Since the drugs for the induction therapy (Cytarabine, Mitoxantrone) used in this clinical trial are already approved in Germany there are no batch numbers.

The reference documents are the current SmPCs at the point of occurrence of the safety issues:

- Azacitidine:
  - Vidaza 04/2012
  - Vidaza 03/2013
  - Vidaza 11/2013
  - Vidaza 10/2014
  - Vidaza 02/2015
  - Vidaza 10/2015
  - Vidaza 03/2016

- Vidaza 06/2016
- Vidaza 03/2017
- Vidaza 05/2017

- Cytarabine:
  - Ara-Cell 06/2011
  - Ara-Cell 01/2014
  - Ara-Cell 05/2015

- Mitoxantron:
  - Mitoxantron HEXAL 10/2009
  - Mitoxantron HEXAL 09/2013

16 Duration of Treatment

A maximum of 90 days of sequential therapy followed by azacitidine maintenance therapy or follow-up was planned. Trial/Follow-up documentation ended 2 years after start of the trial therapy.

17 Reference Therapy

Not applicable

18 Criteria for Evaluation

18.1 Efficacy

The primary endpoint of the phase II part of the trial is the overall response rate on day 90. Overall response rate (ORR) includes Complete remissions (CR), Complete Remission with Incomplete Blood Count recovery (CRi) and Partial remissions (PR).
Main secondary endpoints for efficacy comprise

- Overall survival
- Event-free survival
- Days alive and out of hospital
- Number of patients undergoing hematopoietic stem cell transplantation (HCT)

18.2 Safety

CTC (common toxicity criteria) grading during any individual treatment element

19 Statistical Methods/analysis procedures

According to the trial protocol, three safety analyses were performed during phase I of the trial:

- After inclusion of three patients on dose level 1: no dose limiting toxicities were reported. The Data Monitoring Committee recommended to proceed with a second cohort on dose level 2.
- After inclusion of further four patients on dose level 2: no dose limiting toxicities were reported in three informative patients. One patient was not informative because of progression on d3 prior to start of any study therapy. The Data Monitoring Committee recommended to proceed with a third cohort on dose level 2.
- After inclusion of further three patients on dose level 2: one dose limiting toxicity was reported, resulting in 1/6 patients with dose limiting toxicities on dose level 2. The Data Monitoring Committee recommended to proceed with the phase II of the trial on dose level 2.

According to the optimal two-stage design of Simon an interim analysis for efficacy was performed as soon as 40 patients were on the MTD level of azacitidine and had their response assessment on day 90. The results of the interim analysis were presented to the DMC. The DMC recommended the continuation of the trial. The planned number of patients was recruited into the study.

All patients enrolled on the MTD level of azacitidine have been included into the final analysis. This means in particular that patients enrolled on the MTD level during the phase I part of the trial are part of the full analysis set.

The safety population includes all enrolled patients who have received at least 1 dose of the trial medication, irrespective of their belonging to the phase I or phase II part of the trial. Patients were analyzed according to the treatment actually received. The safety population was used for all safety evaluations.

The primary endpoint was analyzed according to the optimal two-stage design. In addition, the overall response rate on day 90 has been estimated, and a 95% confidence interval was calculated.

Descriptive statistics has been applied to describe the secondary endpoints. Survival and Event-free Survival was described computed using the Kaplan-Meier technique. In addition, Cox regression models were used to explore the impact of patient- and disease related factors.

Adverse events (AEs) have been summarized by worst severity grade. AEs, as well as treatment-emergent AEs, have been summarized by system organ class, and preferred term. AEs leading to death or to discontinuation from treatment, events classified as CTCAE (Version 4.03) Grade 3 or Grade 4, adverse events related to IMP, and serious adverse events were summarized separately.

20 Summary/Conclusion

The following Table 1 describes the trial population of patients included in the final analysis.

		Count	%	25% Perc	Median	75% Perc
Gender	female	51	46.8%			
	male	58	53.2%			
	Total	109	100.0%			
Age [years]		109		64	70	74
Leukocytes (Baseline) [Gpt/l]		102		1.90	4.30	24.40
ANC (Baseline) [Gpt/l]		13		0.2	0.5	0.6
Thrombocytes (Baseline) [Gpt/l]		102		38.00	64.50	114.00
Hemoglobin (Baseline) [g/dl]		102		8.4	9.0	10.2
ECOG Score (Baseline)	fully active	20	18.5%			
	able to carry out light work	71	65.7%			
	unable to carry out any work activities	17	15.7%			
	Total	108	100.0%			
AML diagnosis	primary AML	70	64.2%			
	secondary AML	38	34.9%			
	other	1	0.9%			
	Total	109	100.0%			

Table 1: Trial population

20.1 Efficacy results

The overall response rate was 64.2% (70 of 109) with a 95% confidence interval of [54.5%; 73.2%].

Median overall survival is 15.9 months, with a 95% confidence interval of [12.9; 18.9] (see figure 3).

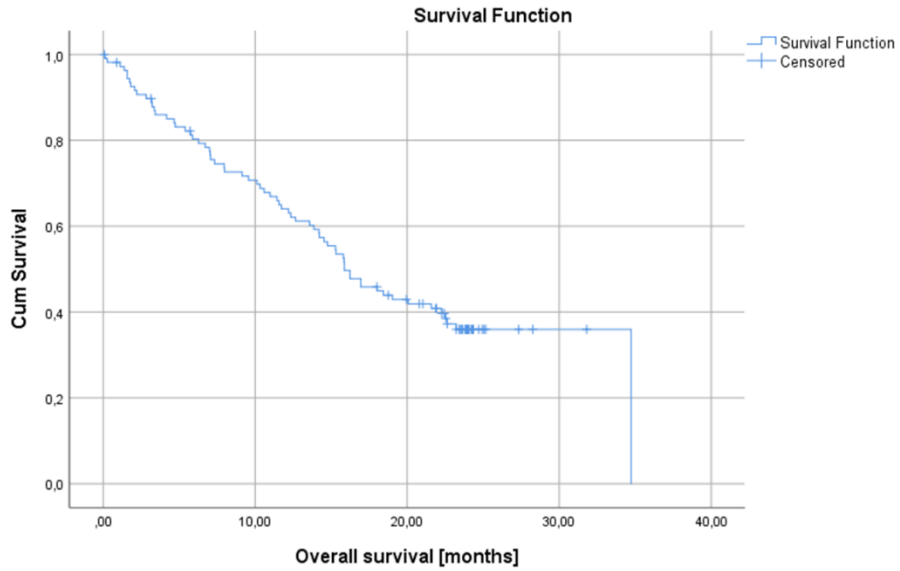


Figure 3: Overall survival.

Median event-free survival is 9.9 months, with a 95% confidence interval of [7.7; 12.0] (see figure 4).

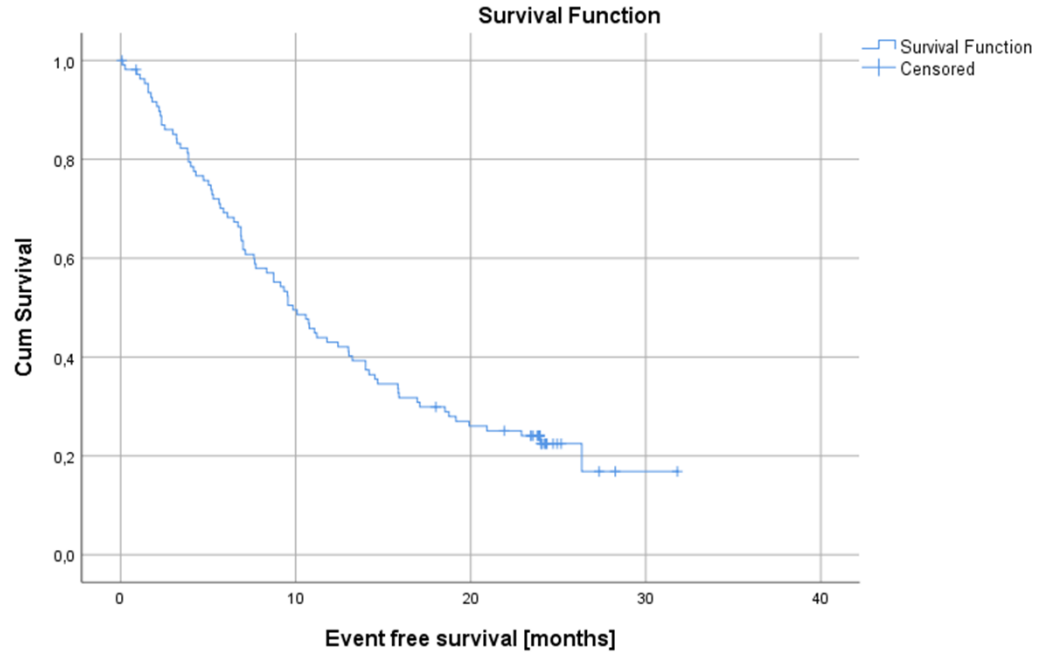


Figure 4: Event-free survival

The mean number of days alive and out of hospital up to d90 is 41.7 ± 24.5 (median 41 days, quartiles 24.5 and 59 days).

A total of 32 patients (29.4 %) underwent HCT, 20 of them during first response, and further 12 after experiencing a relapse.

20.2 Safety results

Adverse event reporting with respect to trial medication includes all patients who received at least one dose of study medication. Expected toxicities as well as any other adverse events are documented for every given cycle of induction or maintenance therapy. Regular safety documentation ends 28 days after the last application of the trial therapy.

Table 2 describes the number of cycles documented for every timepoint/cycle and the corresponding total number of adverse events, adverse events with CTCAE grade 2 – 4 and adverse events with CTCAE grade 3 - 4.
A total of 3750 adverse events occurred, from which 531 were classified as severe with CTCAE grade 3-4. During induction chemotherapy n=156 severe adverse events in 77 cycles were reported, with a mean of 2.0 ± 2.4 per cycle, while during induction therapy with azacitidine only 113 severe events in 112 cycles were reported (1.0 ± 2.1 per cycle). During maintenance therapy, toxicity was even lower, with 120 severe adverse events in 439 cycles (0.3 ± 0.8 per cycle).

Timepoint			Adverse events	Adverse events with CTCAE grade 2-4	Adverse events with CTCAE grade 3-4
Azacitidine cycle 1 (induction)	**N**	**Valid**	112	112	112
		Missing	0	0	0
	Mean		7.15	2.96	1.01
	Median		5.00	2.00	0.00
	Std. Deviation		6.791	4.014	2.146
	Sum		801	331	113
Azacitidine cycle 2 (induction)	**N**	**Valid**	54	54	54
		Missing	0	0	0
	Mean		5.65	2.33	1.02
	Median		4.00	1.00	0.00
	Std. Deviation		5.338	4.207	2.751
	Sum		305	126	55
Induction chemotherapy cycle 1	**N**	**Valid**	77	77	77
		Missing	0	0	0
	Mean		13.04	6.75	2.03
	Median		12.00	6.00	1.00
	Std. Deviation		6.447	4.332	2.401
	Sum		1004	520	156
Induction chemotherapy cycle 2	**N**	**Valid**	10	10	10
		Missing	0	0	0
	Mean		15.10	8.30	3.20
	Median		12.50	6.50	2.00
	Std. Deviation		8.103	5.618	3.084
	Sum		151	83	32
Maintenance therapy	**N**	**Valid**	439	439	439
		Missing	0	0	0
	Mean		2.70	0.84	0.27
	Median		2.00	0.00	0.00
	Std. Deviation		3.025	1.599	0.757
	Sum		1184	370	120
Follow-up	**N**	**Valid**	57	57	57
		Missing	0	0	0

Timepoint		Adverse events	Adverse events with CTCAE grade 2-4	Adverse events with CTCAE grade 3-4
	Mean	5.35	2.89	0.96
	Median	4.00	1.00	0.00
	Std. Deviation	4.897	3.788	1.476
	Sum	305	165	55

Table 2: Adverse events by cycle and severity

The following table describes the frequency of expected toxicities.

Toxicities by CTCAE grade and timepoint		Timepoint													
		Azacitidine cycle 1 (induction)		Azacitidine cycle 2 (induction)		Induction chemo-therapy cycle 1		Induction chemo-therapy cycle 2		Mainte-nance therapy		Follow-up		Total	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hypoprotein-emia	**0**	56	55%	23	49%	17	22%	1	10%	254	81%	26	51%	377	63%
	1-2	41	41%	21	45%	49	64%	5	50%	57	18%	21	41%	194	32%
	3-4	4	4%	3	6%	10	13%	4	40%	2	1%	4	8%	27	5%
Blood bilirubin increased	**0**	86	79%	42	81%	31	41%	5	50%	409	95%	43	81%	616	84%
	1-2	20	18%	8	15%	40	53%	5	50%	20	5%	9	17%	102	14%
	3-4	3	3%	2	4%	5	7%					1	2%	11	2%
ASAT / GOT increased	**0**	71	65%	42	81%	47	62%	5	50%	366	86%	41	76%	572	79%
	1-2	36	33%	10	19%	26	34%	5	50%	57	13%	10	19%	144	20%
	3-4	2	2%			3	4%			1	0%	3	6%	9	1%
ALAT / GPT increased	**0**	77	69%	45	87%	45	60%	7	70%	339	79%	41	75%	554	76%
	1-2	31	28%	7	13%	25	33%	2	20%	88	21%	11	20%	164	22%
	3-4	3	3%			5	7%	1	10%	1	0%	3	5%	13	2%
Alkaline Phosphatase (AP) increased	**0**	80	74%	39	75%	45	60%	7	70%	355	83%	38	69%	564	77%
	1-2	27	25%	13	25%	27	36%	3	30%	73	17%	16	29%	159	22%
	3-4	1	1%			3	4%					1	2%	5	1%
Creatinine increased	**0**	55	50%	33	61%	37	48%	6	60%	273	63%	30	55%	434	58%
	1-2	55	50%	21	39%	40	52%	4	40%	163	37%	25	45%	308	41%
	3-4	1	1%											1	0%
Nausea	**0**	83	74%	42	78%	35	45%	3	30%	398	93%	44	80%	605	82%
	1-2	26	23%	12	22%	41	53%	6	60%	30	7%	10	18%	125	17%
	3-4	3	3%			1	1%	1	10%			1	2%	6	1%
Vomiting	**0**	97	87%	51	94%	54	70%	3	30%	412	96%	49	89%	666	90%
	1-2	15	13%	3	6%	22	29%	6	60%	16	4%	6	11%	68	9%
	3-4					1	1%	1	10%					2	0%

Toxicities by CTCAE grade and timepoint		Timepoint													
		Azacitidine cycle 1 (induction)		Azacitidine cycle 2 (induction)		Induction chemo-therapy cycle 1		Induction chemo-therapy cycle 2		Mainte-nance therapy		Follow-up		Total	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Diarrhea	**0**	91	81%	45	83%	49	64%	5	50%	420	99%	48	87%	658	90%
	1-2	18	16%	8	15%	23	30%	4	40%	6	1%	7	13%	66	9%
	3-4	3	3%	1	2%	5	6%	1	10%					10	1%
Constipation	**0**	79	71%	43	80%	51	66%	6	60%	403	94%	51	93%	633	86%
	1-2	33	29%	11	20%	25	32%	4	40%	24	6%	2	4%	99	13%
	3-4					1	1%					2	4%	3	0%
Acute kidney injury	**0**	103	93%	51	94%	69	90%	9	90%	410	96%	49	89%	691	94%
	1-2	6	5%	3	6%	8	10%			17	4%	5	9%	39	5%
	3-4	2	2%					1	10%			1	2%	4	1%
Hematuria	**0**	107	97%	52	96%	74	96%	10	100%	380	98%	52	98%	675	98%
	1-2	3	3%	2	4%	3	4%			7	2%	1	2%	16	2%
	3-4														
Small intestinal mucositis	**0**	107	96%	53	98%	70	91%	7	70%	420	100%	52	96%	709	98%
	1-2	4	4%	1	2%	7	9%	3	30%	1	0%	2	4%	18	2%
	3-4														
Weight gain	**0**	105	94%	51	96%	69	90%	7	70%	399	95%	47	90%	678	93%
	1-2	7	6%	2	4%	8	10%	3	30%	23	5%	5	10%	48	7%
	3-4														
Weight loss	**0**	93	83%	37	70%	38	50%	6	60%	360	85%	30	58%	564	78%
	1-2	19	17%	15	28%	38	50%	4	40%	58	14%	22	42%	156	21%
	3-4			1	2%					5	1%			6	1%
Dyspnea	**0**	82	73%	43	81%	59	77%	6	60%	409	97%	45	83%	644	88%
	1-2	25	22%	6	11%	14	18%	4	40%	14	3%	7	13%	70	10%
	3-4	5	4%	4	8%	4	5%					2	4%	15	2%
Fever	**0**	69	62%	39	72%	8	10%	2	20%	411	97%	41	76%	570	78%
	1-2	42	38%	13	24%	66	86%	6	60%	12	3%	12	22%	151	21%
	3-4	1	1%	2	4%	3	4%	2	20%	1	0%	1	2%	10	1%
Cardiac arrythmia	**0**	96	86%	50	93%	66	86%	7	70%	417	99%	52	96%	688	94%
	1-2	16	14%	4	7%	11	14%	2	20%	5	1%	2	4%	40	5%
	3-4							1	10%	1	0%			2	0%
Dermatitis	**0**	108	96%	52	98%	56	73%	8	80%	415	98%	51	96%	690	95%
	1-2	4	4%	1	2%	21	27%	2	20%	7	2%	2	4%	37	5%
	3-4									1	0%			1	0%
	0	109	97%	51	96%	74	96%	10	100%	417	99%	53	100%	714	98%

Toxicities by CTCAE grade and timepoint		Timepoint													
		Azacitidine cycle 1 (induction)		Azacitidine cycle 2 (induction)		Induction chemo-therapy cycle 1		Induction chemo-therapy cycle 2		Mainte-nance therapy		Follow-up		Total	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Peripheral sensory neuropathy	**1-2**	3	3%	2	4%	3	4%			3	1%			11	2%
	3-4														
Infection	**0**	46	43%	29	57%	9	12%	2	20%	359	88%	36	67%	481	68%
	1-2	33	31%	11	22%	25	33%	2	20%	42	10%	11	20%	124	18%
	3-4	28	26%	11	22%	41	55%	6	60%	6	1%	7	13%	99	14%
Bleeding	**0**	89	91%	44	92%	33	48%	7	78%	388	97%	48	91%	609	90%
	1-2	9	9%	3	6%	34	49%	2	22%	13	3%	5	9%	66	10%
	3-4			1	2%	2	3%			1	0%			4	1%
Pain	**0**	74	70%	41	85%	28	40%	2	20%	350	87%	41	82%	536	78%
	1-2	28	26%	6	13%	38	54%	7	70%	50	12%	5	10%	134	20%
	3-4	4	4%	1	2%	4	6%	1	10%	1	0%	4	8%	15	2%

Table 3: Expected toxicities by cycle and CTCAE grade

The following table describes the occurrence of other adverse events (not captured by the list of expected toxicities).

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
Blood and lymphatic system disorders	**Anaemia**	**1-2**	0	1	0	0	32	1
		3-4	3	2	1	0	6	1
	Cytopenia	**3-4**	0	0	1	0	1	0
	Febrile neutropenia	**3-4**	1	0	1	0	1	0
	Hyperchromic anaemia	**1-2**	0	1	0	0	0	0
	Leukopenia	**1-2**	0	0	0	0	12	0
		3-4	0	0	1	0	34	3
	Lymphopenia	**1-2**	0	0	0	0	3	0
	Neutropenia	**3-4**	1	0	0	0	9	0
	Pancytopenia	**3-4**	0	0	3	0	1	0
	Splenomegaly	**1-2**	0	1	0	0	0	0
	Thrombocytopenia	**1-2**	0	0	0	0	22	0
		3-4	3	1	1	0	18	2
	Atrial fibrillation	**1-2**	1	0	1	0	0	0

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
Cardiac disorders	Atrioventricular block complete	3-4	0	0	0	0	2	0
	Atrioventricular block second degree	3-4	0	0	0	0	1	0
	Bradycardia	1-2	0	0	0	0	0	1
	Cardiac failure	1-2	0	0	1	0	5	0
		3-4	2	0	0	0	0	0
	Cardiac failure acute	3-4	0	0	1	0	0	0
	Cardiogenic shock	3-4	0	0	0	0	0	1
	Congestive cardiomyopathy	1-2	1	0	0	0	0	0
	Pericardial effusion	1-2	0	1	0	0	0	0
	Sinus tachycardia	1-2	0	0	1	0	0	0
	Supraventricular tachycardia	1-2	0	1	0	0	0	0
	Tachycardia	1-2	4	0	5	2	1	0
		3-4	0	1	0	0	0	0
Ear and labyrinth disorders	Vertigo	1-2	0	0	0	0	1	0
Endocrine disorders	Adrenal insufficiency	3-4	0	1	0	0	0	0
	Hypothyroidism	1-2	1	0	0	0	0	0
Eye disorders	Dry eye	1-2	0	0	1	0	0	0
	Eye discharge	1-2	0	0	1	0	0	0
	Keratitis	3-4	1	0	0	0	0	0
	Lacrimation increased	1-2	0	0	1	0	0	0
	Ocular hypertension	1-2	0	0	0	0	1	0
	Vision blurred	1-2	0	0	1	0	0	0
	Visual impairment	1-2	0	0	1	0	0	0
	Vitreous haemorrhage	3-4	0	0	1	0	0	0
Gastrointestinal disorders	Abdominal discomfort	1-2	1	0	0	1	1	0
	Anal incontinence	1-2	1	0	1	1	0	0
	Aphthous ulcer	1-2	1	0	0	0	4	0
	Chronic gastritis	1-2	0	0	0	0	1	0
	Constipation	1-2	2	0	1	0	9	0
	Crohn`s disease	1-2	0	0	0	0	1	0
	Diarrhoea	1-2	0	0	0	0	0	1

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Dry mouth	1-2	1	0	0	0	0	0
	Duodenal ulcer	3-4	0	1	0	0	0	0
	Dyspepsia	1-2	1	0	2	1	0	0
	Dysphagia	1-2	1	0	0	0	1	0
		3-4	0	0	0	0	1	0
	Flatulence	0	0	0	0	0	1	0
		1-2	0	1	0	0	0	0
	Gastrooesophageal reflux disease	1-2	0	1	0	0	0	0
	Gingival ulceration	1-2	1	0	0	0	0	0
	Haemorrhoids	1-2	1	0	0	0	1	0
	Large intestine perforation	3-4	0	0	0	0	0	1
	Lip ulceration	1-2	0	0	0	0	1	0
	Mouth ulceration	1-2	1	0	0	0	0	0
	Nausea	1-2	1	0	0	0	0	0
	Noninfective gingivitis	1-2	0	0	1	0	0	0
	Oral mucosal erythema	1-2	1	0	0	0	0	0
	Palatal ulcer	1-2	0	0	0	0	0	1
	Stomatitis	1-2	0	0	1	0	0	0
		3-4	0	0	0	0	0	1
	Vomiting	1-2	1	0	0	0	0	0
General disorders and administration site conditions	Asthenia	1-2	1	2	1	0	9	0
		3-4	0	1	0	0	0	0
	Device related thrombosis	1-2	0	0	0	0	1	0
	Drug intolerance	1-2	0	0	0	0	1	0
	Fatigue	1-2	1	2	1	0	18	0
		3-4	0	0	0	1	0	0
	Gait disturbance	1-2	0	0	0	0	1	0
	General physical health deterioration	1-2	0	0	0	0	1	0
		3-4	0	0	1	0	1	0
	Injection site erythema	1-2	1	0	0	0	1	0
	Injection site pruritus	1-2	0	1	0	0	0	0
	Injection site reaction	1-2	1	0	0	0	0	0
	Mucosal atrophy	1-2	1	0	0	0	0	0

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Mucosal inflammation	1-2	1	0	1	0	0	0
		3-4	0	0	1	0	0	1
	Multiple organ dysfunction syndrome	3-4	0	2	0	0	0	0
	Oedema	1-2	3	1	2	0	0	0
	Oedema peripheral	1-2	7	3	11	1	17	2
		3-4	1	1	0	0	0	0
	Peripheral swelling	1-2	1	0	0	0	2	0
	Pyrexia	3-4	0	1	0	0	0	0
	Treatment noncompliance	1-2	0	0	1	0	0	0
Hepatobiliary disorders	Hepatic failure	1-2	0	0	1	0	0	0
Immune system disorders	Anaphylactic shock	3-4	0	1	0	0	0	0
	Drug hypersensitivity	1-2	0	1	4	1	1	0
	Hypersensitivity	1-2	0	0	1	0	0	0
	Seasonal allergy	1-2	0	0	0	0	1	0
Infections and infestations	Campylobacter gastroenteritis	3-4	1	0	0	0	0	0
	Device related sepsis	3-4	0	0	1	0	0	0
	Enterococcal infection	3-4	1	0	0	0	0	0
	Erysipelas	1-2	1	0	0	0	0	0
		3-4	0	0	0	0	1	0
	Escherichia bacteraemia	1-2	0	0	0	0	0	1
	Folliculitis	1-2	0	0	2	0	0	0
	Groin abscess	1-2	0	0	1	0	0	0
	Herpes zoster	1-2	0	0	1	0	0	0
	Hordeolum	1-2	0	0	1	0	0	0
	Infection	1-2	0	0	0	1	0	0
	Infectious pleural effusion	3-4	0	0	1	0	0	0
	Nasopharyngitis	1-2	0	0	0	0	3	0
	Oral herpes	1-2	0	0	1	0	0	0
	Peritonitis	3-4	0	0	0	0	0	1
	Pneumonia	3-4	1	0	0	0	0	0
	Respiratory tract infection	1-2	0	0	0	0	1	0
	Sepsis	3-4	0	0	1	0	0	0

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Septic shock	3-4	0	0	0	0	1	1
	Sinusitis	1-2	0	0	1	0	0	0
	Soft tissue infection	1-2	1	0	0	0	0	0
	Urinary tract infection	1-2	0	0	0	0	1	0
	Urosepsis	3-4	1	0	0	0	0	0
Injury, poisoning and procedural complications	Allergic transfusion reaction	1-2	2	1	6	0	1	0
		3-4	0	0	0	0	1	0
	Cervical vertebral fracture	3-4	0	1	0	0	0	0
	Contusion	1-2	0	0	0	0	2	0
	Fall	1-2	3	1	1	1	2	0
	Limb crushing injury	1-2	0	0	0	0	0	1
	Lumbar vertebral fracture	1-2	1	1	0	0	0	0
	Procedural pneumothorax	3-4	0	0	0	0	1	0
	Refractoriness to platelet transfusion	1-2	0	0	1	0	0	0
	Skin abrasion	1-2	0	0	1	0	0	0
	Wound	1-2	0	0	1	0	0	1
Investigations	Alanine aminotransferase decreased	1-2	0	1	1	0	5	1
	Bacillus test positive	3-4	1	0	0	0	0	0
	Bacterial test positive	1-2	0	0	1	0	0	2
	Blood count abnormal	3-4	0	0	0	0	1	0
	Blood creatinine decreased	1-2	0	0	0	0	1	1
	Blood glucose abnormal	1-2	0	0	1	0	0	0
	C-reactive protein increased	1-2	2	1	2	0	3	0
	Cardiac murmur	1-2	1	0	0	0	0	0
	Enterococcus test positive	3-4	1	0	0	0	0	0
	Escherichia test positive	1-2	0	1	0	0	1	0
	Neutrophil count decreased	1-2	0	0	0	0	1	0
		3-4	0	0	0	0	4	0

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Prothrombin time prolonged	1-2	0	0	1	0	0	0
	Staphylococcus test positive	3-4	1	0	0	0	0	0
	White blood cell count decreased	1-2	0	0	0	0	4	0
Metabolism and nutrition disorders	Decreased appetite	1-2	5	0	2	1	3	0
	Dehydration	1-2	2	0	1	1	1	0
		3-4	0	0	1	0	0	0
	Diabetes mellitus	1-2	1	0	0	0	0	1
	Diabetes mellitus inadequate control	1-2	0	0	1	0	0	0
	Diabetic complication	1-2	0	0	1	1	0	1
	Folate deficiency	1-2	0	0	1	0	0	0
	Gout	1-2	2	1	0	0	4	0
	Hyperkalaemia	1-2	1	0	1	0	6	0
		3-4	0	0	2	0	0	0
	Hyperlipidaemia	1-2	0	0	0	0	1	0
	Hypernatraemia	1-2	0	0	1	0	0	0
	Hyperuricaemia	1-2	0	1	0	0	1	0
	Hypocalcaemia	1-2	0	0	0	1	0	0
	Hypokalaemia	1-2	9	2	11	2	2	1
		3-4	0	1	1	1	0	1
	Hyponatraemia	1-2	1	0	0	0	0	0
		3-4	0	0	0	0	0	1
	Iron overload	3-4	0	0	0	0	2	0
	Tumour lysis syndrome	1-2	1	0	1	0	0	0
	Type 2 diabetes mellitus	1-2	0	0	1	0	0	0
	Vitamin D deficiency	1-2	0	0	0	0	4	0
Musculoskeletal and connective tissue disorders	Arthritis reactive	1-2	0	0	1	0	0	0
	Bone disorder	1-2	0	0	0	0	1	0
	Joint swelling	1-2	0	0	0	0	1	0
	Muscle spasms	1-2	0	0	0	0	3	0
	Muscle tightness	1-2	0	0	1	0	0	0
	Muscular weakness	1-2	0	1	0	0	0	0
	Musculoskeletal pain	1-2	0	0	1	0	0	0

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Musculoskeletal stiffness	1-2	0	0	0	0	1	0
	Osteoarthritis	1-2	0	0	0	1	4	0
	Rheumatic disorder	1-2	0	1	0	0	0	0
	Rotator cuff syndrome	1-2	0	0	0	0	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	1-2	0	0	0	0	0	1
	Leukaemic infiltration extramedullary	1-2	1	0	0	0	0	0
		3-4	0	0	0	0	1	0
	Neoplasm skin	3-4	0	0	0	0	1	0
Nervous system disorders	Ageusia	1-2	1	0	0	0	0	0
	Aphasia	1-2	0	0	0	0	0	1
		3-4	0	0	0	0	1	0
	Carotid artery stenosis	1-2	0	0	0	0	1	0
	Cerebral infarction	3-4	0	0	0	0	1	0
	Cerebrovascular accident	1-2	0	0	1	0	0	0
	Dizziness	1-2	7	4	0	1	5	3
	Dysgeusia	1-2	0	1	1	0	0	0
	Headache	1-2	0	0	1	0	1	0
	Hemiplegia	1-2	0	0	0	0	1	0
	Neurological symptom	1-2	0	0	1	0	0	0
	Polyneuropathy	1-2	0	1	0	0	0	0
	Somnolence	1-2	1	1	1	0	0	0
	Syncope	1-2	0	0	1	0	0	1
		3-4	0	0	1	0	1	0
Psychiatric disorders	Anxiety	1-2	1	1	1	0	2	1
	Depression	1-2	0	0	0	0	1	1
		3-4	0	0	0	0	0	1
	Disorientation	1-2	3	0	2	0	1	0
	Hallucination, visual	1-2	1	0	0	0	0	0
	Reactive psychosis	1-2	0	0	1	0	0	0
	Sleep disorder	1-2	15	3	10	1	3	2
Renal and urinary disorders	Chronic kidney disease	3-4	1	0	0	0	0	0
	Dysuria	1-2	0	0	0	0	2	0
	Incontinence	1-2	1	0	0	0	0	0
	Nocturia	1-2	0	0	1	1	0	0

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Pollakiuria	1-2	0	1	1	0	0	0
	Polyuria	1-2	1	0	0	0	0	0
	Urinary incontinence	1-2	0	0	2	1	0	0
Respiratory, thoracic and mediastinal disorders	Bradypnoea	3-4	0	1	0	0	0	0
	Chronic obstructive pulmonary disease	1-2	0	0	1	0	0	0
	Cough	1-2	9	2	7	0	6	1
	Dysphonia	1-2	1	1	0	0	0	0
	Dyspnoea	1-2	0	0	0	0	1	0
	Dyspnoea at rest	1-2	1	0	0	0	0	0
	Hiccups	1-2	1	0	0	0	0	0
	Obstructive airways disorder	3-4	0	0	0	0	0	1
	Pleural effusion	1-2	2	2	3	0	0	1
		3-4	4	2	2	1	0	1
	Pulmonary embolism	3-4	1	0	0	0	1	1
	Pulmonary oedema	3-4	0	0	0	0	1	0
	Respiratory acidosis	3-4	0	1	0	0	0	0
	Respiratory failure	1-2	1	0	0	0	0	0
		3-4	1	3	1	0	0	1
	Sleep apnoea syndrome	1-2	0	0	0	0	1	0
	Tachypnoea	1-2	0	0	1	0	0	0
	Wheezing	3-4	0	1	0	0	0	0
Skin and subcutaneous tissue disorders	Acne	1-2	1	0	1	0	0	0
	Decubitus ulcer	1-2	2	0	1	1	0	0
		3-4	1	0	1	1	0	0
	Dermatitis allergic	1-2	0	0	1	0	1	0
	Drug eruption	1-2	0	0	5	0	0	0
	Dry skin	1-2	0	0	1	0	0	0
	Erythema	1-2	2	0	0	0	3	0
	Hyperhidrosis	1-2	1	1	0	0	0	0
	Intertrigo	1-2	0	0	1	1	0	0
	Macule	1-2	1	0	0	0	0	0
	Night sweats	1-2	0	0	1	0	1	0
	Petechiae	1-2	0	0	0	0	1	0
	Pruritus	1-2	1	1	2	0	2	1

Body system	Preferred term	CTCAE grade	Timepoint					
			Azacitidine cycle 1 (induction)	Azacitidine cycle 2 (induction)	Induction chemo-therapy cycle 1	Induction chemo-therapy cycle 2	Mainte-nance therapy	Follow-up
			Count	Count	Count	Count	Count	Count
	Pruritus generalised	1-2	0	0	1	0	0	0
	Psoriasis	1-2	1	0	0	0	0	0
	Rash	1-2	5	2	1	1	3	0
	Rash generalised	1-2	1	1	1	0	0	0
	Rash macular	1-2	0	0	2	0	0	0
	Rash maculo-papular	1-2	0	0	1	0	0	0
	Sebaceous gland disorder	1-2	0	0	0	0	1	0
Surgical and medical procedures	Tooth extraction	3-4	0	0	0	0	1	0
Vascular disorders	Flushing	1-2	0	0	0	0	2	0
	Haematoma	1-2	0	0	0	1	1	0
	Hypertension	1-2	3	0	4	0	0	0
		3-4	3	1	9	3	0	2
	Hypotension	1-2	6	1	7	1	0	1
		3-4	0	1	0	0	0	0
	Labile blood pressure	1-2	0	0	0	0	1	0
	Lymphoedema	1-2	0	0	0	0	1	0
	Phlebitis	1-2	1	0	1	0	0	1
	Thrombophlebitis	1-2	1	0	0	0	0	0
		3-4	1	0	0	0	0	0
	Thrombosis	1-2	0	0	1	0	1	0
		3-4	0	0	0	0	1	0

Table 4: Other adverse events by cycle and CTCAE grade

20.3 Conclusions

Integrating an epigenetic therapy with azacitidine and intensive induction chemotherapy (IC) in elderly patients with AML in an individualized response-based approach is feasible with a low treatment-related mortality and yields responses at least comparable to those achieved with repeated cycles of IC across all cytogenetic risk groups even in patients older than 70 years. Most importantly, response could be translated into an improved survival particularly in patients with favorable and intermediate-I risk genetics. Relapse remains high in adverse genetics.

21 Appendix

21.1 CONSORT Flow Diagram