Study Report Synopsis

Name of Sponsor: Technische Universität München (TUM), Fakultät für Medizin
Prof. Dr. med. Peter Henningsen, Dekan

Name of Finished Product: Tasigna®, Afinitor®

Name of Active Ingredient: Nilotinib (CAMN), Everolimus (RAD001)

Title of Study: An open-label phase I/II (proof of concept) trial of a combination of Nilotinib (AMN107) and RAD001 in patients with acute myeloid leukemia (AML-NiloRad)

Protocol Code: CAMN107ADE01

EudraCT: 2007-000502-70

Coordinating Investigator:
LKP (AMG): Prof. Dr. med. Justus Duyster

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Publication (reference): not published yet

Studied period (years)	**Phase:** II
first patient in: 2008	
last patient out: 2011	
The clinical study was determined prematurely in 2012 due to slower than anticipated recruitment and lack of efficacy.	

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Objectives: **Primary objective**: To determine the rate of hematological response in adult patients with c-kit + AML. **Secondary objectives**: - To determine the duration of hematological response - To evaluate overall survival - To evaluate the safety profile of a combination treatment of Nilotinib and RAD001 - To evaluate improvement of symptomatic parameters - To assess mTor, cKit and PDGF-R pathway activities during treatment as a predictive factor of response It was planned to conduct 17 visits during the first 25 weeks and follow-up visits every three months for three years to assess safety and efficacy
Methodology: prospective, multi-center, single arm, Phase II trial
Number of patients (planned and analyzed): - planned sample size: 40 patients - analyzed sample size: 19 patients (all patients who were included into the trial)
Diagnosis and criteria for inclusion: **Indication**: Acute myeloid leukemia (AML) **Inclusion criteria:** 1. Patients with: • De novo AML or secondary AML from MDS who are not candidates for myelosuppressive chemotherapy, or • De novo AML or secondary AML from MDS who have relapsed disease or are refractory to standard therapy 2. Patients at least 18 years or older 3. Patients with WHO performance status of 0 to 2 with a life expectancy under treatment of at least 3 months 4. Patients must have recovered from prior cytotoxic chemotherapy; treatment with Hydroxyurea or Ara-C is allowed until 24 hours to first administration of study drug 5. Patients must have a serum creatinine of ≤ 1.5 x ULN, SGOT/SGPT ≤ 3 x ULN and total bilirubin ≤ 2.0 x ULN 6. Female patients of childbearing potential must have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 6 months following discontinuation of study drug. A highly effective method of birth control is defined as those which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives some IUDs, sexual abstinence or vasectomised partner 7. Written informed consent obtained according to local guidelines
Diagnosis and criteria for exclusion: **Exclusion criteria:** 1. Patients with AML FAB M3 2. Patients with an expected doubling of the peripheral blast within one week 3. Patients who had prior allogeneic, syngeneic, or autologous bone marrow transplant or stem cell

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transplant less than 2 months previously 4. Impaired cardiac function, including any one of the following: • LVEF < 45% or below the institutional lower limit of the normal range (whichever is higher) as determined by MUGA scan or echocardiogram • Complete left bundle branch block • Use of a cardiac pacemaker • ST depression of > 1mm in 2 or more leads and/or T wave inversions in 2 or more contiguous leads • Congenital long QT syndrome dose levels of 400 to 1200 mg QD. Many of the common adverse events reported in the imatinib Phase II leukemia (STI0106, STI0110) studies were also reported in the nilotinib Phase I study, although a notably lower frequency of peripheral edema was identified in the nilotinib study • History of or presence of significant ventricular or atrial tachyarrhythmias • Clinically significant resting bradycardia (< 50 beats per minute) • QTc > 450 msec on screening ECG (using the QTcF formula) • QT prolonging concomitant medication • Right bundle branch block plus left anterior hemiblock, bifascicular block • Myocardial infarction within 12 months prior to starting Nilotinib • Unstable angina diagnosed or treated during the past 12 months • Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen) 5. Female patients who are pregnant or breast feeding, or adults of childbearing age not employing an effective method of birth control 6. Concurrent severe and/or uncontrolled medical or psychiatric condition which may interfere with the completion of the study 7. Patients who had more than 2 prior regimens for their current relapsed or current primary refractory disease 8. Patients with uncontrolled active infection 9. Patient with any pulmonary infiltrate on the baseline chest X-ray known to be new in the previous 4 weeks. Prior treatment with any investigational drug within the preceding 4 weeks 10. Chronic treatment with systemic steroids or another immunosuppressive agent 11. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases 12. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin. 13. Other concurrent severe and/or uncontrolled medical disease which could compromise participation in the study (i.e., uncontrolled diabetes, uncontrolled hypertension, severe infection, severe malnutrition, unstable angina, or congestive heart failure - New York Heart Association Class III or IV, ventricular arrhythmias active ischemic heart disease, myocardial infarction within six months, chronic liver or renal disease, active upper GI tract ulceration) 14. A known history of HIV seropositivity 15. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection) 16. Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumarin) 17. Hypokalemia 18. Women who are pregnant or breast feeding, or women able to conceive and unwilling to practice a highly effective method of birth control. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of RAD001). Oral, implantable, or

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injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Therefore a highly effective method of birth control in this study is defined as those, which results in a low failure rate (i.e. less than 1% per year) such as sexual abstinence or vasectomised partner
19. Patients who have received prior treatment with an mTor inhibitor
20. History of noncompliance to medical regimens
21. Patients unwilling to or unable to comply with the protocol

Test product, dose and mode of administration, batch number:
Nilotinib (CAMN; Tasigna®): orally administered, starting day 1: 2 x 400 mg/d; Batch numbers 9750 and 0087 (distributed by pharmacy of Klinikum rechts der Isar)

Everolimus (RAD001; Afinitor®): orally administered, starting day 8: 1 x 2,5 mg/d (dose escalation to 1 x 5 mg/d permitted after 4 weeks of treatment); Batch numbers 975, 9866, 9880 and 10018 (distributed by pharmacy of Klinikum rechts der Isar)

Duration of treatment / treatment schedule:
Nilotinib (CAMN; Tasigna®):
Patients started treatment on day 1 with 400 mg Nilotinib twice daily (total daily dose 800 mg).
Everolimus (RAD001; Afinitor®): after a treatment duration with Nilotinib for 1 week, patients additionally received Everolimus in a dose of 2,5 mg/day. Dose escalation to 5mg/day was permitted after a minimum of 4 weeks of treatment.
Treatment duration Nilotinib, RAD001:
Treatment duration was intended for 25 weeks or until progression of disease or unacceptable toxicity.
Treatment after completion of the study was at the discretion of the investigator. If the drug was well tolerated and the patient was benefiting according to the investigator`s assessment, the patient was eligible for an extension study. Generally patients could continue on a combination treatment of Nilotinib and RAD001 until disease progression.
Dose reductions and brief pauses of medication were experienced in 9/19 patients for various reasons (e.g. due to adverse events, serious adverse events).

Reference therapy, dose and mode of administration, batch number: n.a.

1. Reference substance: not applicable (n.a.)
2. Reference substance: n.a.

Unblinding: n.a.

Criteria for evaluation:
<u>Primary efficacy parameters</u>
Overall hematological response
For purposes of this study, hematological response included any of the following:
• complete hematological remission,
• no evidence of leukemia in peripheral blood and bone marrow, without full peripheral blood recovery,
• partial response.
Each of these response categories are described in detail below. Hematological response should have been confirmed after > 4 weeks.
Complete Remission was defined as all of the following:
• Adequate bone marrow cellularity and blast count < 5%
• No circulating peripheral blood blasts
• ANC ≥ 1.5 x 109/L
• Platelet count ≥ 100 x 109/L

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• No evidence of extramedullary involvement

No leukemic evidence (blood and marrow) but peripheral blood not recovered was defined as all of the following:

• Blast count < 5% in bone marrow
• No circulating peripheral blood blasts
• ANC > 1.0 x 109/L
• Platelet count > 20 x 109/L (platelet transfusion independent and no evidence of bleeding)
• No evidence of extramedullary involvement

Partial response

A partial response (PR) lasting ≥ 4 weeks was regarded as a response-percentage of c-kit positive blasts (as measured by FACS analysis) in bone marrow < 50% in comparison to c-kit positive blasts in FACS analysis at start of study treatment or a 50% reduction in **absolute** c-kit-positive blast count in PB (as calculated by FACS analysis and differential WBC, if available).

For the purpose of assessing hematological responses, complete blood counts including a differential count, bone marrow aspirates and biopsies and FACS analysis (if available) were performed.

Extramedullary leukemic involvement was assessed by physical examination:

• Peripheral blood (including a sample for FACS analysis if applicable) was drawn at screening, 2 times weekly during the first four weeks, every 2 weeks between weeks 5-13, and then every 4 weeks and on the last day of treatment.
• Bone marrow aspirates including a sample for FACS analysis and bone marrow biopsies were performed at screening, at weeks 4, 13 and 25 and on the last day of treatment.
• Extramedullary leukemic involvement was assessed primarily by physical examination at screening, at weeks 1, 4, 13 and 25 and on the last day of treatment.

Stable disease

Stable disease was also regarded as a response. Stable disease was defined as follows:

• Stable disease is a blast count +/- 20% in comparison to baseline over a period of at least 3 months.

<u>Secondary efficacy parameters</u>

Overall survival

Was defined as the time from first dose of Nilotinib to the death of the patient.

Duration of hematological response

Remission duration was the time from first documentation of hematological response to death or relapse, whichever comes first. Relapse was defined as the first day on which blasts in the peripheral blood and/or bone marrow measured > 30%.

Assessment of molecular target inhibition

mTor, cKit and PDGF-R pathway activities during treatment were to be determined on bone marrow biopsies.

Safety assessments

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

These assessments should have been performed within ±2 days of the scheduled day of assessment except for adverse events that were evaluated continuously throughout the study. Safety and tolerability were assessed according to NIH/NCI CTCAEv3 and 4.

Improvement in <u>symptomatic parameters</u>

AML symptoms were recorded at screening and after therapy

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Independent Safety Monitoring Board
A group of independent experts formed an independent Safety Monitoring Board (SMB).
The SMB independently reviewed the safety data during study duration. The board was to review the safety data after the enrolment of 10, 20, 30 and 40 patients and an interim analysis was to report these adverse events and assess the safety profile. In addition, the coordinating investigator was to inform the SMB about Suspected Unexpected Serious Adverse Reactions (SUSARs) with a report in written form.

Protocol amendments
There were two protocol amendments:
The first amendment comprised changes in study design as requested by the Regulatory Agency (BfArM) before first approval of the study.
The second amendment (approved by EC: 21.01.2010) comprised: a reduction in collection of certain laboratory parameters, whereas others were evaluated more often; an evaluation of the RAD001 plasma levels and documentation of functional parameters. Also the patient informed consent form was altered to reflect the fact that RAD001 had been approved in the indication of CML.

Other changes in study conduct
The patient informed consent had been changed in 2011 in order to reflect new safety information on Nilotinib (approved by EC: 21.04.2011)
In 2012 it was decided to close the clinical study prematurely, because it had been demonstrated over the course of the study, that the originally expected recruitment rate could not be kept (e.g. other competing studies, new medications slowed enrollment of the patients) and response to therapy was lacking.

Interim analyses
The SMB independently reviewed the safety data during study duration and after the enrolment of the first 13 patients an interim analysis concluded that the reported AEs were consistent in quantity and quality with the known profile of side effects of both medications and their combination and the recommendation was given to continue with the study.
An Interim Analysis was provided to the EC in July 2009 comprising these assessments on the safety.

Statistical methods
Sample size and power considerations:
Forty patients were expected to be enrolled into the trial. Given that the expected hematologic response in this patient population with standard of care is < 5% and that a response rate > 20% would indicate effectiveness of the study drugs 40 patients would be required for an alpha level of 0.05 and a power of 0.9.
Primary outcome: Hematologic response, presented as relative frequency (rate) with an exact two-sided 95% confidence interval
Secondary outcomes: Duration of hematologic response is presented with mean and standard deviation. The estimation of overall survival is given by a Kaplan-Meier curve with corresponding median survival and 95% CI. All safety and tolerability information are reported as adverse events, which are coded using MedDRA (v16.0 for AEs and v13.0 for SAEs) and assessed according to NIH/NCI CTCAE v3 and 4. AEs, SAEs, related AEs, and related SAEs are reported by MedDRA system organ class and preferred term using frequencies. Symptomatic parameters are shown as overall actual and relative incidence of AML symptoms at screening and after treatment. Assessment of molecular target inhibition: mTor, cKit and PDGF-R pathway activities during treatment were to be determined on bone marrow biopsies and presented in a by patient listing.

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Summary – Results:

Patient Demographics and Patient Disposition

In total 19 patients were included (first patient included: 29.05.2008; last patient included: 20.09.2011). The age range in this clinical trial was between 19 and 82 (median 73) years and the male/female ratio was 11/8.

Six patients were included into the study with a de novo AML, 11 patients with a secondary AML derived from MDS, and two with an AML after chemotherapy. Eight patients presented with a normal karyotype, six with a complex karyotype. In six patients deletions or aberrations could be detected in cytogenetics. In 10 patients molecular genetics showed various changes.

None of the 19 patients who received study medication are still under treatment or concluded the three year follow-up (i.e. premature discontinuation of all patients).

Twelve patients discontinued due to disease progress (1 – 26 months after inclusion into the study), four patients discontinued prematurely for various reasons (diabetes mellitus, patient request, refractory disease, no response to therapy), three patients ended the study due to death (0.5 - 4 months after inclusion into the study), fifteen patients died (0.5 – 26 months) after inclusion into the study.

Safety and Efficacy Population

Since all patients received at least one dose of Nilotinib, all patients were included into the Safety Analysable Population (SAP) and Intent To Treat Population (ITT).

For the Efficacy Analysable Population (EAP) patients with protocol deviations concerning exclusion criteria (0102-0105, 0107, 0108, 0203, and 0501) or inclusion/exclusion criteria (0101) were excluded, all other patients were included (patients who received Nilotinib for at least three weeks and patients with less than 3 weeks of treatment, since discontinuation of study medication was related to lack of efficacy (patients, who died and patients with diagnosis disease progress)).

Efficacy Results:

Response to Treatment

Primary outcome: Hematologic response:

From the 19 patients included into this clinical study no patient (in any of the study populations: SAP, ITT, or EAP) achieved overall hematological response (“Complete Response”, “No leukemic evidence, but peripheral blood not recovered”, “Partial Response”, “Stable Disease”) according to the predefined criteria of the clinical study protocol.

This equals a response rate of 0% (exact two-sided 95% confidence interval: [0%, 18%]). Appendix listing 1 shows the response criteria per patient.

Secondary outcomes:

Overall survival:

Median overall survival was 127 days for all patients in all study populations analyzed. The 95% confidence intervals for the median differed between the three populations:

Population	Total	Died	Censored	Median Survival	Lower limit of 95% CI	Upper limit of 95% CI
SAP	19	15	4	127	73	401
ITT	19	15	4	127	73	401
EAP	10	8	2	127	25	786

Duration of haematological response:

Since hematologic response was not achieved in any of the study populations, the duration of haematological response could not be assessed in any analysis set (SAP, ITT, EAP).

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However, it has been shown that in few patients, disease could be stabilized with this treatment. E.g. one patient (01/02) had received study medication for two years and survived for one more year after treatment; another patient (01/06) received study medication for about one month and survived for two more years receiving supportive medication. In other patients disease has been stable for about 2-6 months (patients 01/01, 01/04, 01/08, 01/10, 02/01) before disease progress, no response to treatment, or refractory disease was noted. One patient showed decrease of bone marrow blast infiltration after 4 weeks (04/02), but had to end treatment due to hyperglycemia; another patient (04/03) had a reduction of blasts in bone marrow by 50%, which was not confirmed after four weeks, because bone marrow was not examined at that time.

Improvement of symptomatic parameters:

None of the patients had extramedullary involvement due to AML at screening or follow-up visits. Ten Patients presented themselves with AML symptoms (e.g. bleeding, infection, elevated temperature, anaemia, neutropenia, pancytopenia, weakness dizziness, fatigue, hematoma) at screening. AML-related symptoms at the end of treatment were documented as adverse events. Each patient experienced at least one AML-related symptom at the end of treatment:

	Screening		End of treatment	
AML Symptom	N	%	N	%
Bleeding	3	15,8	3	15,8
Infection	3	15,8	7	36,8
Elevated temperature	1	5,3	6	31,6
Anaemia	2	10,5	9	47,4
Neutropenia	1	5,3	4	21,1
Pancytopenia	1	5,3	0	0,0
Weakness	1	5,3	6	31,6
Dizziness	0	0,0	1	5,3
Fatigue	3	15,8	3	15,8

mTor, cKIT and PDGF-R pathway activity

mTOR, cKIT und PDGF-R pathway activities have not been determined due to lack of response to predefined hematologic response criteria.

Safety Results:

The SMB reviewed the safety data after the enrolment of the first 13 patients and an interim analysis concluded that the reported adverse events were consistent in quantity and quality with the known profile of side effects of both medications and their combination and the recommendation was given to continue with the study. SUSARs have not been reported during the course of the study. This Interim Analysis was provided to the EC in July 2009 comprising these assessments on the safety. During the conduct of the study safety information was also compiled in four Annual Safety Reports (03.09.2007-02.09.2011), one Development Safety Report (DSUR, 03.09.2011-02.09.20012) and one Addendum to the DSUR (10.07.2013); a change in the risk-benefit evaluation of the study had not occurred from assessments of safety information or from changes in the SMPC or IB, which were deemed non-substantial.

Adverse Events (AE)

A total of 352 AEs were reported in 19 patients. Of the 350 graded AEs, 282 recovered during study, 46 did not recover, 4 were fatal, and 8 with unknown outcome. Appendix table 1 presents an overview on CTC Grade (the first 12 patients were graded according to V3, the last 7 patients according to V4)

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and appendix table 2 provides a cumulative summary tabulation of all AE according to MedDRA system organ class.

Serious AE (SAE)

A total of 40 SAEs were reported in 19 patients resulting in a total of 74 SAE terms. In most cases, serious adverse events were due to fever and infection which were associated with the underlying disease and or related to progressive disease. Appendix table 3 provides a summary of all SAEs by MedDRA organ class.

Suspected Serious Adverse Reactions (SARs)

A total of 13 SARs were reported in 10 patients resulting in 32 terms (appendix table 4). In most cases, SARs were due to fever and infection which were associated with the underlying disease and or related to progressive disease in relation to known side effects of study medication.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

The sponsor's assessment of expectedness was determined by referring to the IBs and SMPCs and no SUSARs have been reported in the study.

[The Ethics Committee was, however, informed on SUSARs in relation to Nilotinib or Everolismus which were reported to Novartis Pharma AG by other institutions during the time of the study].

Summary of Adverse Events

All reported adverse events are consistent in quantity and quality with the known profile of side effects of both medications and their combination. Taken together, the current protocol combining Nilotinib and RAD001 in AML patients was feasible according to the toxicity profile, considering the underlying disease and the stage of AML the patients presented themselves upon inclusion into the study (not candidates for myelosuppressive chemotherapy, De novo AML or secondary AML from MDS who have relapsed disease or are refractory to standard therapy).

Throughout the conduct of the study there have been various changes in SMPC and IB, which were along with new and relevant findings related to safety communicated to the study centres and the EC (in order to reflect these changes, the Patient Informed Consent had been altered once). However, it was deemed that the risk-benefit evaluation for the clinical trial was not affected.

Overall Conclusion:

In the predominately elderly population (median age of 73 years) with relapsed or refractory to standard therapy AML, where most patients included had factors commonly associated with unfavourable outcome (13/19 with AML from MDS or after chemotherapy; 10/19 with a complex karyotype and or cytogenetic aberrations; 10/19 with various changes in molecular genetics) therapeutic options are limited and to date no standardized treatment could be established. Even though some patients improved in symptoms and disease could be stabilized in others, none of the patients treated with Nilotinib and RAD001 achieved overall haematological response as defined by standard criteria in any of the study populations analysed. However, two patients survived for one or two years after start of therapy and in five patients, disease has been stable for about 2-6 months before disease progress, no response to treatment, or refractory disease was noted. The median survival was 127 days.

Even though the included number of 19 patients can only be considered as a pilot investigation without the power to draw statistical conclusions, it can be concluded that, while safety could mainly be attributed to known side effects of both medications and underlying disease, the combination therapy of Nilotinib and RAD001 does not seem to have the potential to substantially change outcome in the patient population with relapsed or refractory AML included into this clinical study.

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Date of the report:	**31.07.2013**	Date amended	Version 1.0: 21.02.2019 Version 2.0: 28.02.2019

Appendix

Listing 1: Response criteria

Month		Screen	1	1	1	1	1	1	1	1	2	2	3	3	4	5	6	7	
Week		Screen	1	1	2	2	3	3	4	4	5	7	9	11	13	17	21	25	
Visit		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13	visit 14	visit 15	visit 16	visit 17	
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13					
	FMH2/Bio																		
MRI	/FMH2/Cyto	20								25									NO CR
01-01	FLBBLAST	11	2	4	7		2	4	3	1	2	1	1	ND					NO NLE
	_ANC	0,4224	0,6384	0,6944	0,572		0,5772	0,5402	0,748	0,6204	0,6954	0,9804	1,008	0					NO PR
	FLBPLAT	93	79	100	110		52	47	78	108	94	101	109	59					NO SD
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13	visit 14	visit 15	visit 16	visit 17	
	FMH2/Bio	20								25					30			40	
MRI	/FMH2/Cyto	15								15					20			20	NO CR
01-02	FLBBLAST	0	N	ND	ND	0	0		0	ND	0	0	0	0	ND	ND	ND	0	NO NLE
	_ANC	0,682	0	0,0342	0,03135	1,2338	0,6312		1,1844	0	0,9804	1,32528	1,23216	0,738	0	0	0	0	NO PR
	FLBPLAT	64	ND	65	82	66	48		35	53	41	25	71	27	35	46	34	39	NO SD
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6												
	FMH2/Bio	10																	
MRI	/FMH2/Cyto	20																	PD
01-03	FLBBLAST	0	0				ND												
	_ANC	0,1386	0,0828				0												
	FLBPLAT	131	92				89												
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13	visit 14				
	FMH2/Bio	15								10									
MRI	/FMH2/Cyto	20								20					40				NO CR
01-04	FLBBLAST	2	2		12	11	11	9	12	10	4	9	14	8	45				NO NLE
	_ANC	0,7072	0,7072		2,7675	0,5684	0,4035	1,0136	1,792	0,9639	1,387	1,7556	1,624	1,6632	0,1124				NO PR
	FLBPLAT	9	9		21	22	19	9	20	10	23	14	25	19	10				NO SD
		visit 1	visit 2	visit 3	visit 4	visit 5													
	FMH2/Bio																		
MRI 01-0	/FMH2/Cyto	54																	PD
	FLBBLAST	0,89	1,68	1,68	5,16	3,82													
	_ANC	0,00099	0,00388	0	0,0833	0,04266													
	FLBPLAT	18	40	23	14	48													

Month		Screen	1	1	1	1	1	1	1	1	2	2	3	3	4	5	6	7	
Week		Screen	1	1	2	2	3	3	4	4	5	7	9	11	13	17	21	25	
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	*FUP1*	*FUP2*	*FUP3*	*FUP4*	*FUP5*	*FUP6*				
	FMH2/Bio	30																	PD
MRI	/FMH2/Cyto	50																	
01-06	FLBBLAST	6	10	4	2	4	5	6	7	*6*	*5*	*5*	*6*	*7*	*5*				
	_ANC	0,6125	0,4785	0,6762	0,615	0,592	0,6592	0,3465	0,4728	*0,3154*	*0,46*	*0,6031*	*0,5346*	*0,5191*	*0,4212*	*Pat stopped Study Treatment due to*			
	FLBPLAT	166	94	103	108	87	44	107	115	*91*	*85*	*95*	*77*	*60*	*86*	*disease progress after Vis 8*			
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7											
	FMH2/Bio	20																	
MRI	/FMH2/Cyto	40																	PD
01-07	FLBBLAST	66	ND	66	59	77	81	78											
	_ANC	0,4932	0	0,897	0,6589	0,345	0,6244	0,912											
	FLBPLAT	22	76	139	#NULL!	104	100	63											
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13					
	FMH2/Bio																		
MRI	/FMH2/Cyto	50								68									NO CR
01-08	FLBBLAST	68	77	75			92	86	88	83	81	86	82	75					NO NLE
	_ANC	0,096	0,0808	0,075			0,0471	0,0318	0,1221	0,0179	0,0869	0,0649	0,0439	0,0284					NO PR
	FLBPLAT	132	103	79			101	113	104	60	66	100	133	30					NO SD
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13	visit 14	visit 15			
	FMH2/Bio	10																	
MRI	/FMH2/Cyto	21																	NO CR
01-09	FLBBLAST	14		16	7	12		7	ND	11	10	12	16	21	18	18			NO NLE
	_ANC	7,242		10,6782	17,0848	15,3864		15,0984	0	17,834	24,753	14,5245	10,944	14,4478	10,3015	18,6252			NO PR
	FLBPLAT	295		242	304	279		226	181	275	467	205	129	189	307	201			NO SD
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12	visit 13	visit 14	visit 15	visit 16		
	FMH2/Bio									ND					20				
MRI	/FMH2/Cyto	20								ND					18				NO CR
01-10	FLBBLAST	3	3	2		1	4	3	4	2	7	2	8	6	2	4	5		NO NLE
	_ANC	2,328	2,8248	3,0668		2,6576	2,8982	3,339	3,4278	3,483	2,9953	1,9436	1,0661	2,8083	1,0251	2,3798	2,844		NO PR
	FLBPLAT	133	140	103		92	97	104	117	135	157	67	99	121	58	83	75		NO SD
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8										
	FMH2/Bio								30										
MRI	/FMH2/Cyto	28							80										PD
01-12	FLBBLAST	48	44	67	55	75	75	80	80										
	_ANC	2,664	3,231	3,2396	6,148	6,7046	4,746	1,0472	1,6854										
	FLBPLAT	12	16	29	15	32	21	36	23										
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	visit 9	visit 10	visit 11	visit 12						
	FMH2/Bio										0								
UL	/FMH2/Cyto	50								75	0								NO CR
02-01	FLBBLAST	0	1	2	2	0	2	0	4	0	2	2	3						NO NLE
	_ANC	0,09	0,108	0,132	0,144	0,075	0,088	0,024	0,231	0,15	0,24	0,286	0,168						NO PR
	FLBPLAT	108	131	128	124	140	98	66	69	53	50	42	24						NO SD

Table 1: Overview CTC Grade

A: CTC version 3

	CTC Grade (Version 3)											
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
SOC	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders	1	3,8%	5	19,2%	11	42,3%	8	30,8%	1	3,8%	26	100,0%
Cardiac disorders	0	0,0%	1	50,0%	1	50,0%	0	0,0%	0	0,0%	2	100,0%
Ear and labyrinth disorders	1	100,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Eye disorders	2	100,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	2	100,0%
Gastrointestinal disorders	30	63,8%	14	29,8%	1	2,1%	1	2,1%	1	2,1%	47	100,0%
General disorders and administration site conditions	18	48,6%	11	29,7%	6	16,2%	1	2,7%	1	2,7%	37	100,0%
Hepatobiliary disorders	2	50,0%	1	25,0%	1	25,0%	0	0,0%	0	0,0%	4	100,0%
Immune system disorders	0	0,0%	2	100,0%	0	0,0%	0	0,0%	0	0,0%	2	100,0%
Infections and infestations	3	18,8%	6	37,5%	7	43,8%	0	0,0%	0	0,0%	16	100,0%
Investigations	5	55,6%	3	33,3%	1	11,1%	0	0,0%	0	0,0%	9	100,0%
Metabolism and nutrition disorders	9	60,0%	2	13,3%	4	26,7%	0	0,0%	0	0,0%	15	100,0%
Musculoskeletal and connective tissue disorders	10	76,9%	2	15,4%	1	7,7%	0	0,0%	0	0,0%	13	100,0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	100,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Nervous system disorders	13	86,7%	2	13,3%	0	0,0%	0	0,0%	0	0,0%	15	100,0%
Psychiatric disorders	0	0,0%	1	100,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Renal and urinary disorders	2	50,0%	2	50,0%	0	0,0%	0	0,0%	0	0,0%	4	100,0%
Reproductive system and breast disorders	1	100,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Respiratory, thoracic and mediastinal disorders	17	70,8%	6	25,0%	1	4,2%	0	0,0%	0	0,0%	24	100,0%
Skin and subcutaneous tissue disorders	4	33,3%	4	33,3%	3	25,0%	1	8,3%	0	0,0%	12	100,0%
Vascular disorders	6	100,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	6	100,0%
Gesamt	**125**	**52,5%**	**62**	**26,1%**	**37**	**15,5%**	**11**	**4,6%**	**3**	**1,3%**	**238***	**100,0%**

B: CTC version 4

	CTC Grade (Version 4)									
	Grade 1		Grade 2		Grade 3		Grade 4		Total	
SOC	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders	1	8,3%	3	25,0%	7	58,3%	1	8,3%	12	100,0%
Cardiac disorders	1	50,0%	0	0,0%	1	50,0%	0	0,0%	2	100,0%
Eye disorders	1	100,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Gastrointestinal disorders	6	37,5%	5	31,3%	5	31,3%	0	0,0%	16	100,0%
General disorders and administration site conditions	11	45,8%	11	45,8%	2	8,3%	0	0,0%	24	100,0%
Hepatobiliary disorders	1	33,3%	2	66,7%	0	0,0%	0	0,0%	3	100,0%
Infections and infestations	2	12,5%	7	43,8%	7	43,8%	0	0,0%	16	100,0%
Injury, poisoning and procedural complications	0	0,0%	0	0,0%	1	100,0%	0	0,0%	1	100,0%
Investigations	0	0,0%	3	100,0%	0	0,0%	0	0,0%	3	100,0%
Metabolism and nutrition disorders	4	66,7%	0	0,0%	2	33,3%	0	0,0%	6	100,0%
Musculoskeletal and connective tissue disorders	3	75,0%	1	25,0%	0	0,0%	0	0,0%	4	100,0%
Nervous system disorders	4	100,0%	0	0,0%	0	0,0%	0	0,0%	4	100,0%
Renal and urinary disorders	0	0,0%	1	50,0%	1	50,0%	0	0,0%	2	100,0%
Reproductive system and breast disorders	1	100,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Respiratory, thoracic and mediastinal disorders	8	61,5%	3	23,1%	2	15,4%	0	0,0%	13	100,0%
Skin and subcutaneous tissue disorders	2	66,7%	1	33,3%	0	0,0%	0	0,0%	3	100,0%
Vascular disorders	1	100,0%	0	0,0%	0	0,0%	0	0,0%	1	100,0%
Gesamt	**46**	**41,1%**	**37**	**33,0%**	**28**	**25,0%**	**1**	**0,9%**	**112***	**100,0%**

** Two AEs were not graded (01-12, "Disease progression"; 01-04, "Dyspnea")*

Table 2: Cumulative Summary Tabulation of all AEs by system organ class (SOC) and preferred term (PT):

SOC	PT	N
Blood and lymphatic system disorders	Anaemia	19
	Febrile neutropenia	6
	Granulocytopenia	1
	Leukopenia	2
	Neutropenia	1
	Platelet disorder	1
	Thrombocytopenia	8
	Gesamt	**38**
Cardiac disorders	Cardiac failure	2
	Supraventricular tachycardia	1
	Tachycardia	1
	Gesamt	**4**
Ear and labyrinth disorders	Vertigo	1
	Gesamt	**1**
Eye disorders	Eyelid oedema	1
	Lacrimation increased	1
	Vision blurred	1
	Gesamt	**3**
Gastrointestinal disorders	Abdominal pain	2
	Aphthous stomatitis	1
	Constipation	4
	Diarrhoea	21
	Dry mouth	1
	Faecal incontinence	1
	Flatulence	1
	Gastrointestinal haemorrhage	1
	Glossitis	1
	Mouth haemorrhage	1
	Nausea	16
	Stomatitis	1
	Vomiting	12
	Gesamt	**63**
General disorders and administration site conditions	Asthenia	22
	Chest pain	2
	Death	1
	Disease progression	2
	Fatigue	7
	Mucosal haemorrhage	1
	Mucosal inflammation	1
	Oedema	1
	Oedema peripheral	7

SOC	PT	N
	Pyrexia	17
	Spinal pain	1
	Gesamt	**62**
Hepatobiliary disorders	Hyperbilirubinaemia	7
	Gesamt	**7**
Immune system disorders	Hypersensitivity	2
	Gesamt	**2**
Infections and infestations	Bronchitis	1
	Cystitis	3
	Erysipelas	3
	Escherichia infection	1
	Febrile infection	1
	Gastrointestinal infection	1
	Herpes zoster	1
	Nasopharyngitis	1
	Oral herpes	2
	Pneumonia	7
	Pneumonia herpes viral	1
	Respiratory tract infection	1
	Rhinitis	1
	Tooth infection	1
	Upper respiratory tract infection	1
	Urinary tract infection	4
	Urinary tract infection bacterial	1
	Viral pharyngitis	1
	Gesamt	**32**
Injury, poisoning and procedural complications	Thoracic vertebral fracture	1
	Gesamt	**1**
Investigations	Alanine aminotransferase increased	2
	Aspartate aminotransferase increased	1
	Blood glucose increased	1
	Blood lactate dehydrogenase increased	1
	Body temperature increased	2
	C-reactive protein increased	2
	Clostridium test positive	1
	Electrocardiogram QT prolonged	1
	Fungal test positive	1
	Gesamt	**12**
Metabolism and nutrition disorders	Decreased appetite	8
	Hypercreatininaemia	1
	Hyperglycaemia	2
	Hyperkalaemia	1
	Hypertriglyceridaemia	1

SOC	PT	N
	Hypocalcaemia	1
	Hypokalaemia	5
	Hyponatraemia	1
	Type 2 diabetes mellitus	1
	Gesamt	**21**
Musculoskeletal and connective tissue disorders	Arthralgia	3
	Back pain	4
	Bone pain	1
	Exostosis	1
	Flank pain	2
	Muscle spasms	2
	Neck pain	1
	Pain in extremity	3
	Gesamt	**17**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leukaemic infiltration	1
	Gesamt	**1**
Nervous system disorders	Dizziness	5
	Headache	12
	Hypoaesthesia	1
	Sinus headache	1
	Gesamt	**19**
Psychiatric disorders	Depression	1
	Gesamt	**1**
Renal and urinary disorders	Dysuria	1
	Nocturia	2
	Prerenal failure	1
	Renal failure acute	1
	Urinary incontinence	1
	Gesamt	**6**
Reproductive system and breast disorders	Nipple pain	1
	Vaginal inflammation	1
	Gesamt	**2**
Respiratory, thoracic and mediastinal disorders	Cough	6
	Dysphonia	1
	Dyspnoea	12
	Dyspnoea exertional	1
	Epistaxis	10
	Lung infiltration	1
	Oropharyngeal pain	4
	Pleural effusion	1
	Respiratory disorder	1
	Rhinorrhoea	1
	Gesamt	**38**
Skin and subcutaneous tissue disorders	Hyperhidrosis	1

SOC	PT	N
	Night sweats	1
	Petechiae	1
	Pruritus	6
	Rash	5
	Rash pruritic	1
	Gesamt	**15**
Vascular disorders	Haematoma	5
	Hot flush	1
	Thrombophlebitis	1
	Gesamt	**7**
Gesamt		**352**

Table 3: Cumulative summary of all SAEs by system organ class (SOC) and preferred term (PT):

SOC	PT	N*
Blood and lymphatic system disorders	Anaemia	1
	Febrile neutropenia	9
	Neutropenia	1
	Thrombocytopenia	1
	Gesamt	**12**
Cardiac disorders	Cardiac failure	2
	Gesamt	**2**
Gastrointestinal disorders	Colitis	1
	Diarrhoea	4
	Gastrointestinal haemorrhage	1
	Vomiting	1
	Gesamt	**7**
General disorders and administration site conditions	Chest pain	1
	Chills	1
	Death	7
	Fatigue	1
	General physical health deterioration	2
	Pyrexia	10
	Gesamt	**22**
Hepatobiliary disorders	Hyperbilirubinaemia	1
	Gesamt	**1**
Infections and infestations	Candidiasis	1
	Clostridium difficile colitis	1
	Erysipelas	2
	Escherichia infection	1
	Infection	1
	Neuropenic sepsis	1
	Oral herpes	1
	Pneumonia	6
	Respiratory tract infection	1
	Sepsis	1
	Urinary tract infection	1
	Gesamt	**17**
Injury, poisoning and procedural complications	Thoracic vertebral fracture	1
	Gesamt	**1**
Investigations	C-reactive protein increased	1
	Gesamt	**1**
Metabolism and nutrition disorders	Hyperglycaemia	1

SOC	PT	N*
	Hyperkalaemia	3
	Type 2 diabetes mellitus	1
	Gesamt	**5**
Musculoskeletal and connective tissue disorders	Back pain	2
	Gesamt	**2**
Renal and urinary disorders	Renal failure	1
	Renal failure acute	1
	Gesamt	**2**
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
	Pleural effusion	1
	Gesamt	**2**
Gesamt		**74**

** Anzahl bis 01.07.2013*

Table 4: Cumulative summary of all SARs by system organ class (SOC) and preferred term (PT):

SOC	PT	N*
Blood and lymphatic system disorders	Anaemia	1
	Febrile neutropenia	3
	Neutropenia	1
	Gesamt	**5**
Gastrointestinal disorders	Colitis	1
	Diarrhoea	1
	Vomiting	1
	Gesamt	**3**
General disorders and administration site conditions	Chills	1
	Death	1
	Fatigue	1
	General physical health deterioration	2
	Pyrexia	5
	Gesamt	**10**
Hepatobiliary disorders	Hyperbilirubinaemia	1
	Gesamt	**1**
Infections and infestations	Clostridium difficile colitis	1
	Infection	1
	Neuropenic sepsis	1
	Oral herpes	1
	Pneumonia	4
	Urinary tract infection	1
	Gesamt	**9**
Investigations	C-reactive protein increased	1
	Gesamt	**1**
Metabolism and nutrition disorders	Hyperglycaemia	1
	Hyperkalaemia	1
	Type 2 diabetes mellitus	1
	Gesamt	**3**
Gesamt		**32**