Study protocol

A double-blind, placebo-controlled, randomized, multi-center phase-II trial to assess the efficacy of Sorafenib added to standard primary therapy in patients with newly diagnosed AML ≤60 years of age

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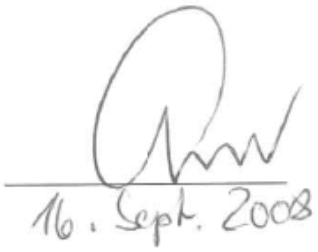

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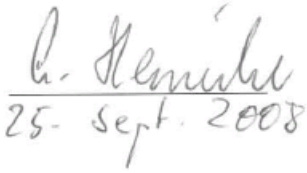

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AMG	Arzneimittelgesetz
AML	Acute Myeloid Leukemia
AMLCG	AML Cooperative Group
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APL	Acute Promyelocytic Leukemia
AR	Adverse Reaction
AraC	Cytosine Arabinoside
AST	Aspartate Transaminase
AT III	Antithrombin III
ATP	Adenosin Triphosphate
AUC	Area Under the Curve
BID	twice daily
BM	Bone Marrow
BP	Blood Pressure
BSA	Body Surface Area
CBC	Complete Blood Count
CFR	Code of Federal regulations
CNS	Central Nervous System
CR	Complete Remission
CRi	Complete Remission with incomplete regeneration of peripheral blood
CRc	Complete Cytogenetic Remission
CRm	Complete Moleculargenetic Remission
CRA	Clinical Research Associate
CrCl	Creatinin Clearance
CRF	Case Report Form
CT	Chemotherapy
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome P
DLT	Dose Limiting Toxicities
DNA	Desoxyribonucleic Acid
DSIL	Deutsche Studieninitiative Leukämie
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ED	Early Death
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid

EFS	Event Free Survival
FAB	French-American-British Cooperative Group
FDA	Food and Drug Administration
Flt	Fms like Tyrosine Kinase
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HCC	HepatoCellular Cancer
HD-AraC	High Dose-Cytarabine
HFSR	Hand-Foot Skin Reaction
HIV	Human Immunodeficiency Virus
HR	cytogenetically High Risk
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IR	cytogenetically Intermediate Risk
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
ITD	Internal Tandem Duplication
ITT	Intention To Treat analysis
LDH	Lactatedehydrogenase
LKP	Leiter der Klinischen Prüfung
LR	cytogenetically Low Risk
MAPK	mitogen-activated protein kinase
MDS	Myelodysplastic Syndrome
mg	miligram
MI	Myocardial Infarction
mm	millimeter
MRD	Minimal Residual Disease
NCI-CTC	National Cancer Institute Common Toxicity Criteria
nM	nanoMol
NPM	Nucleophosmin
OS	Overall Survival
PB	Peripheral Blood
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PE	Physical Examination
PK	Pharmacokinetic
p.o.	per os = per mouth
PR	Partial Response
PT-INR	Prothrombin Time-International Normalized Ratio

PTT	Partial Thromboplastin Time
QOD	Once Every Other Day
QD	Once Every Day
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAL	Study Alliance Leukemia
SAR	Serious Adverse Reaction
SCF	Stem Cell Factor
SOP	Standard Operating Procedure
sqm	square meters
SUSAR	Suspected Unexpected Adverse Reaction
Tx	Stem Cell Transplantation
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization
WT	Wild Type

1 BACKGROUND INFORMATION / INTRODUCTION

1.1 Condition background and current treatment

Acute Myeloid Leukemia (AML) is a clonal, malignant disorder that results from a somatic mutation in a pluripotent stem cell or a slightly more differentiated progenitor cell. The mutant cell gains a growth and/or survival advantage in relationship to the normal pool of stem cells. Fewer than 30% of adults with AML can be expected to survive three or more years and be cured[1]. Adverse prognostic factors include poor ECOG performance status prior to therapy, secondary AML, a white cell count of more than 20.000/µl or an elevated serum lactate dehydrogenase at presentation[2]. Detailed cytogenetic analysis of the leukemic blasts has also been demonstrated to provide critical prognostic information[3]. Initial AML treatment is divided into two phases: induction and consolidation. With the use of cytarabine and an anthracycline as induction therapy, complete remissions can be routinely induced in 70%-80% of patients 60 years and younger and in approximately 50% of older patients[4]. Consolidation therapy following the induction of an initial complete response is essential to prevent relapse. Three options are available: allogeneic or autologous bone marrow transplantation or chemotherapy. Transplantation is more often used in young patients with adverse karyotypes and chemotherapy in good prognosis patients[5]. Nontransplant consolidation chemotherapy regimens commonly contain cytarabine. There appears to be a clear benefit in survival to patients younger than 60 years of age that received high-dose cytarabine regimens as consolidation[6].

Generally accepted risk criteria for the assessment of prognosis are cytogenetic criteria which define either low risk or high risk (for a compilation see chapter.3.3.2). Moreover, only recently it was described that an insufficient response to induction chemotherapy is highly predictable for therapy outcome. A critical threshold for residual blast cells at the day 16 bone marrow control has been defined with ≤ 10% of marrow cellularity[7].

1.2 Molecular pathogenesis

In the last decades, significant progress has been made about the molecular events inducing leukemic transformation in AML (for review[8]). Although AML is a genetically and phenotypically heterogeneous disease, common features of the leukemic blasts include a high proliferative potential and a block in differentiation at a relatively immature state, within the mitotic pool. It is now widely accepted that AML blasts already harbor several transforming mutations when the disease becomes clinically apparent. Many AML-specific oncogenic mutations have been identified and their ability to cause leukemia has been analyzed in primary and human xenograft mouse models. A model has been suggested that at least two mutations from different

complementation classes have to accumulate in a myeloid progenitor cell to cause AML[9]. One of these mutations is thought to cause deregulation of transcriptional programs needed for the orchestration of myeloid differentiation. Thus, more than 50% of all AML cases have been shown to contain a mutation in a transcriptional regulator, often as a result from balanced reciprocal translocations.

These mutations often coincide with mutations in signal transduction mediators. Again, about 50% of AML cases have been shown to contain a mutation in a signaling mediator, most frequently in receptor tyrosine kinases or in the Ras oncogene. The receptor tyrosine kinase Flt3 has been found to be the most common target among these, in 30% of all AML cases (for review[10]). Flt3 mutations have been shown in several *in vitro* and animal models to cause malignant transformation of myeloid cells and to cooperate with other known oncogenes to cause an AML-type disease in mice.

The more common type of Flt3-mutations, so-called internal tandem duplications (ITD), are associated with a bad prognosis of AML patients, especially when the normal Flt3 allele is lost in the majority of blasts[11]. Flt3 mutations are very frequently associated with mutations in the gene for nucleophosmin (NPM), a protein with functions in organizing the traffic of proteins between the nucleus and the cytoplasm. The functional consequences of these mutations are not yet known. However, the presence of these mutations in AML blasts is a strong positive prognostic indicator. Several phase-I and phase-II trials have been reported where AML patients in later stages of the disease were treated with tyrosine kinase inhibitors that target Flt3 as single agents. In these trials, biological activity of the compounds was noted, albeit with very low complete remission rates (for review [12]). Thus, Flt3 is thought to be a promising target for the treatment of AML.

Other very common mutations in a signal transduction mediator are oncogenic N- and K-Ras mutations that have been described in AML for over 20 years, with a prevalence of slightly less than 30%. One important effector of oncogenic Ras is, among others, the Raf/MAP-kinase pathway that relays important cellular functions like proliferation, survival and differentiation (see below).

In summary, AML is thought to be the result of multiple genetic events including activating mutations in signal transduction mediators.

1.3 Investigational product background

Sorafenib is a novel RAF, Flt3, VEGFR and c-Kit kinase inhibitor that prevents tumor growth by combining two anticancer activities: inhibition of tumor cell proliferation and tumor angiogenesis.

For full details of the pre-clinical and clinical information please refer to the Nexavar® Prescribing Information (Fachinformation).

1.3.1 Pre-clinical information

General information

Bayer and Onyx developed Sorafenib (BAY-43-9006), an oral cytostatic Raf kinase inhibitor, PDGFR inhibitor and VEGFR-2 (KDR) inhibitor, for the potential treatment of various cancers[13].

Sorafenib was selected based on the inhibition of the enzyme, Raf kinase, in a battery of biochemical, cellular, and *in vivo* assays and its broad-spectrum antitumor efficacy in pre-clinical xenograft models. In other cellular assays, Sorafenib was found to be a potent inhibitor of human and mouse VEGFR-2, VEGFR-3, PDGFR-α, c-Kit and Flt3 receptor phosphorylation.

Sorafenib functions by inhibiting the Raf kinase constituent of the classical mitogen-activated protein kinase (MAPK) signaling cascade. Raf and other members (such as Ras) of this pathway are attractive targets for development of antineoplastic agents because their aberrant activity has been heavily implicated in the onset of a variety of cancers. Protein kinases possess enzymatic activity that enables intracellular signaling via a series of phosphorylation events. This intricate process is initiated upon ligand-receptor interaction at the cellular membrane. Kinase activation is then mediated through the removal of the gamma-phosphate group of ATP and subsequent transferral to a tyrosine, serine or threonine residue on its downstream substrate. Events such as these ultimately control mitogenic signals that facilitate alterations in nuclear gene expression. When properly regulated, the classical MAPK (Raf/MEK/ERK) pathway controls a variety of cellular functions such as proliferation, differentiation, and apoptosis. Genetic mutations can, however, lead to overexpression or aberrant activity of a particular MAPK. Furthermore, it is widely known that MAPK hyperactivity can lead to tumorigenesis[14].

More recently, it has also been shown that Sorafenib is a strong inhibitor of the receptor tyrosine kinase Flt3 that has been implicated in the pathogenesis of AML[15]. Also, Sorafenib inhibits the activity of VEGF receptors that have been shown to be expressed on the surface of AML blasts as well as on the surface of surrounding bone marrow microvessels. Microvessel density is greatly increased in AML bone marrow and it is possible that by inhibition of VEGF receptors, leukemia-induced neoangiogenesis is targeted, providing a further rationale for the treatment of AML with Sorafenib. Moreover, only recently it was shown that Sorafenib has a potent inhibitory activity against Kit activating mutations [16] . Although, the activity of Sorafenib against the D816 mutation is lower most of the activating mutations will be inhibited in the low nM range. Additionally it has been found that Sorafenib is able to modify the balance of pro/antiapoptotic proteins even in cells without mutations of the Flt3 or Kit kinase. Most of the effects are assumed to depend on the downregulation of the antiapoptotic proteins Mcl1 and $FLIP_L$[17].

In summary, Sorafenib targets molecular pathways that have been implicated in the pathogenesis of AML. The highest efficacy of Sorafenib is related to the inhibition of tyrosine

kinase pathways including the classical MAPK pathway, angiogenic VEGF receptors and the receptor tyrosine kinases Flt3 and c-Kit.

Combination with chemotherapeutic agents

Sorafenib can be safely combined with a variety of standard cancer chemotherapy agents, including paclitaxel, irinotecan, gemcitabine and cisplatin with no significant increase in the toxicity associated with those agents and without diminishing their antitumor efficacy in clinical investigations.

Pre-clinical pharmacokinetics

- Absorption in mice and rats was almost complete and in dogs approx. 68 %
- High bioavailability in mice and rats (approx. 80 %) and moderate in dogs (approx. 60 %)
- Slow to moderate elimination of Sorafenib from plasma with terminal halflifes of 9 h (rats), 6 h (mice), 4 h (dogs)
- Rapid and homogeneous distribution to almost all organs/tissues in rats, low penetration of blood/brain barrier
- Low residues, no evidence of irreversible binding or retention in organs or tissues of rats
- Sorafenib showed a potency to inhibit CYP isoforms *in vitro* and clinically relevant drug-drug interactions cannot be ruled out
- Excretion of the compound is primarily via the biliary/ fecal route in rats and dogs.

Pre-clinical toxicology

The pre-clinical toxicity profile of Sorafenib can be summarized as:

- Short-term high-dose treatment was well tolerated clinically by rats, mice and dogs; a plateau in systemic exposure was observed.
- Exposure-dependent mortality (mean time to death ≥3 weeks) occurred without preceding specific signs of morbidity in rats; dose-limiting toxicity in dogs was gastrointestinal (emesis, bloody diarrhea). Clinical signs of toxicity were unspecific, except for marked skin reactions in dogs. A lower threshold-dose for significant toxicities was observed with extensive duration of exposure.
- Histopathology revealed degeneration/regeneration processes in multiple organ systems including liver, kidneys, lymphoreticular/hematopoietic system, GI tract, pancreas, adrenals, reproductive organs, skin, teeth, and bone. No main target organ of toxicity could be identified; some morphological lesions were not reversible within 4 weeks (e.g., bile duct proliferation, liver fibrosis, adrenal necrosis, effects on lymphoreticular system) following a 4-week course of treatment.

- Based on genotoxicity assays conducted, Sorafenib is concluded not to exhibit a significant risk of genotoxicity to patients.
- Sorafenib was nontoxic following a single oral administration to dogs, rats or mice. Potential acutely lethal levels might not be achievable due to limited systemic exposure.

In conclusion, toxicity studies with Sorafenib in rats, mice and dogs, species considered appropriate for the pre-clinical safety evaluation, demonstrated multiple target organs, dose-limiting toxicities and clear dose and time effect relations. For further information about pre-clinical data of Sorafenib, please refer to the Nexavar® Prescribing Information (Fachinformation).

1.3.2 Clinical information

Sorafenib has been evaluated in multiple phase-1 and phase-II trials in a variety of advanced tumor types. To date, several 1000 patients have been treated with single-agent and in combination with other commonly used chemotherapeutic agents. In general, Sorafenib can be safely administered to patients on a daily base with most of the dose limiting toxicity events at 800 mg BID[18]. The majority of patients experienced adverse events at some time during the treatment with Sorafenib. Most of these events were not severe and were manageable. Typically, patients experienced skin-related symptoms, either hand-foot skin reaction (HFSR) and/or a rash. Fatigue and diarrhea were also common but usually low to moderate grade. These toxicities resolved once the drug was discontinued[19]. Mild treatment emergent hypertension (rise of 10 mmHg) was reported in about 70% of the patients. However, only the minority of patients will require antihypertensive drugs. There are some pre-clinical models suggesting a potential impact of the inhibition of proapoptotic kinases (ASK1 and MST2) by Sorafenib in drug related cardiotoxicity. Additionally, Sorafenib may interfere with the normal angiogenic response of the heart muscle to volume overload causing dilated cardiomyopathy. However, clinical observations do not support Sorafenib related cardiotoxicity[20].

Other adverse events reported as drug related include nausea, gastrointestinal symptoms, fatigue, Flu-like symptoms, fever, arthralgia, weight loss, pain, anorexia, diarrhea, dyspnea, abdominal pain, vomiting, pancreatitis, liver function test abnormalities including ALT, AST, GGT , AP and LDH increases, bilirubin increase, dermatitis, erythema, flushing, rash and pruritus, dry skin, alopecia, stomatitis, flatulance, constipation, nail changes, thrombocytopenia, headache, sensory neuropathy, myalgia, amylase elevation, lipase elevation and hypertension.

Currently data from 19 phase-I/II open-label, uncontrolled clinical trials are available for Sorafenib combinations with other anticancer agents[21]. A phase-I study (study code 10916) showed that Sorafenib is suitable for combined administration with doxorubicin in patients with advanced, refractory solid tumors. The most common drug related adverse events were: diarrhea (53%), fatigue (44%), anorexia (44%), hand-foot syndrome (40%), dyspnea (33%),

nausea (35%), rash (33%). Grade 3 and 4 drug related events included: low ANC (74%), increased partial thromboplastin time (15%), increased ALT levels (13%), lymphopenia (13%), low platelet numbers (11%), increased lipase levels (5%). Doxorubicin was given 3-weekly in a dose of 60 mg/sqm for a maximum of 6 consecutive cycles for anthracycline naive patients. Sorafenib was given from 100 mg BID to 400 mg BID. Thereby, dose limiting toxicities (DLT) were reported including HFSR and diarrhea. Less frequently observed DLTs were fatigue, hyperuricemia and asthenia. Most of the trials did not reach a maximum tolerated dose. Thus, Sorafenib is well tolerated even in combination treatment approaches.

Myelosuppression was mainly observed after combination therapy with cytotoxic agents and manifested with leukopenia, neutropenia, febrile neutropenia and thrombocytopenia.

The phase-I trial led to a recommendation of a dose of 400 mg twice daily (BID) for a continuous oral treatment in single agent therapy trials of carcinoma patients. One randomized phase-I study of Sorafenib in patients with MDS or AML examined doses at 100 mg BID, 200 mg BID and 400 mg BID and found 0/7, 2/12 and 1/17 dose-limiting toxicities at these dose levels, respectively. Since 6 patients at 400 mg BID received Sorafenib for less than 14 days due to grade 1 and 2 toxicities (abdominal pain, nausea, vomiting, rash, stroke, thrombocytopenia), subsequent patients received an intermediate dose of 300 mg BID. Recently, first results from a phase-I clinical trial have been published[22]. The trial included 16 relapsed AML patients. A clinical response was observed in 9 out of 16 patients. Whereas 6 out of 7 patients with Flt3-ITD showed a clear blast response, also 3 out 9 patients without Flt3-ITD demonstrated blast responses. No effect was observed in 3 patients carrying an Flt3-D835 mutation. In another study clinical effects (reduction in PB and BM blasts) have been seen in 4/27 evaluable pts: 2 at 200 mg BID (one 28 d, one 14 d schedule) and 2 at 400 mg BID (both on 28 d schedule). One patient at 400 mg BID with AML and a 30-base-pairs internal tandem duplication in Flt3 had a confirmed CRp lasting 3 cycles. Biologic activity (inhibition of pERK in SCF stimulated PB blasts) has been assessed in 14 pts and shows drug-related inhibition in 5/14, all at 400 mg BID. Thus, the drug has activity as single substance although the duration of response and the effect on BM blasts is limited.

Sorafenib has been combined with several chemotherapeutics in phase-I/II studies. In stage IV melanoma patients, a scheme of carboplatin (area under the curve 6) and paclitaxel (225 mg/m^2) on day 1 every 3 weeks in combination with Sorafenib 400 mg BID day 2 – 19 (2 days pause before next chemotherapy) has been established and is currently used in a phase-III trial.

Two phase-III trials have been performed in advanced renal cell cancer and advanced hepatocellular carcinoma (HCC).

In the phase-III renal cell cancer study, 903 patients resistant to standard therapy were randomized to receive either Sorafenib 400 mg BID or Placebo. Primary endpoint was overall survival (OS). A planned analysis of progression-free survival in January 2005 showed a

statistically significant improvement versus Placebo: 5.5 months and 2.8 months, respectively (HR 0.44, 95% CI 0.35-0.55, p<0.000001). Consequently, cross-over was allowed for patients on Placebo from May 2005 on. A first interim analysis for survival in May 2005 showed a significant reduction in risk of death for Sorafenib compared to Placebo. (HR 0.72, 95% CI 0.54-0.94, p=0.02). Response rates were also favorable for Sorafenib with an overall response rate (ORR) of 10% (PR) vs. 2% in the Placebo arm (p<0.001). A second analysis on survival showed a median OS of 19.3 months vs. 15.9 months (HR 0.77, 95% CI 0.63-0.95, p=0.015). These data led to registration of Sorafenib in the USA and Europe for the treatment of advanced renal cell cancer.

In the hepatocellular cancer (HCC) study, 602 previously untreated patients were randomized into an international multicenter Placebo-controlled phase-III trial and received either Sorafenib 400 mg BID or Placebo. Primary endpoint was OS. A planned interim analysis showed a significant survival benefit of Sorafenib (10.7 months vs. 7.9 months; HR 0.69, 95% CI 0.55-0.87, p=0.0006). These data led to registration of Sorafenib in the USA and Europe for the treatment of advanced hepatocellular cancer in 2007.

For further information about clinical data of Sorafenib, please refer to the current Nexavar® Prescribing Information (Fachinformation).

2 STUDY AIM AND DESIGN

2.1 Rationale for this study

Sorafenib is a potent inhibitor of wild type and mutant Raf kinases. There are abundant preclinical data suggesting that the Ras/Raf pathway may be activated and associated to pathogenesis of AML and MDS rendering Raf kinase a potentially suitable target in the treatment of these conditions. In addition, Sorafenib inhibits the MAP kinase pathway by targeting p38 kinase. Furthermore, 30% of AML patients have FLT3 activating mutations. Sorafenib is also a potent inhibitor of a mutant form of the Flt3 kinase (Flt3-ITD) and thus may be especially effective in this subgroup of AML patients. Sorafenib inhibits also c-Kit, which is present in AML blasts in 70%. Furthermore, it may be hypothesized that the angiogenesis receptor tyrosine kinases VEGFR-2 and PDGFR may play a role in the pathogenesis of AML either in regard to vascularisation of the bone marrow stroma or as growth factors on leukemic blasts. In a phase-I trial with Sorafenib as a single agent at escalating doses the drug has shown efficacy in 56% out of 16 AML patients. The response was mainly restricted to blast response in FLT3-ITD positive patients. Subsequently, it was reported that Sorafenib has inhibitory efficacy on a range of antiapoptotic molecules. This activity can lead to an enhanced antileukemic efficacy when combined with cytotoxic drugs in AML cells. Therefore, Sorafenib as a single cytostatic agent is unlikely to be a curative treatment. The present study investigates the effects of Sorafenib, when applied between and after cycles of standard chemotherapy for AML.

2.2 Benefit / risk ratio

Patients eligible for this trial have a risk of treatment failure with standard chemotherapy of 50-60% at two years. Treatment failure is an acutely life-threatening event for these patients. Included in these numbers are disease-related events (refractory disease, relapse) and treatment-related mortality that has to be expected to reach up to 10% in this patient group. The risk of this trial is that addition of Sorafenib to the standard treatment increases treatment-related toxicity. However, as pointed out above, phase-I/II trials indicate that Sorafenib can be administered safely in combination with cytotoxic drugs. Whether this is also true for the trial population is one of the objectives of this study.

The possible benefit of the trial is to decrease the rate of treatment failure in the trial population. For a single patient, this could result in increased life-span, ideally without evidence of leukemia. Given the high rate of treatment failure and the high toxicity of the currently available standard therapy, the medical need for novel, rational therapeutic approaches for this patient population is overwhelming. As pointed out above, the molecular rationale for the therapeutic

administration of Sorafenib in AML is well founded. Thus, the Benefit/Risk ratio for a patient to participate in this trial seems very favorable.

2.3 Study objectives

2.3.1 Primary

- to compare the median Event Free Survival (EFS) of AML patients in the age of ≥18 and ≤60 years between the Sorafenib and the control group (for event definition see chapter 7.2.1)

2.3.2 Secondary

- to compare the median EFS of AML patients with Flt3-ITD mutations between the Sorafenib and the control group
- to compare the median EFS of the patients in each of the six strata:
  1. HR cytogenetics: yes
  2. LR cytogenetics: yes
  3. HR and LR cytogenetics: no and NPM1-Mut: yes, Flt3 Mut: yes
  4. HR and LR cytog.: no and NPM1-Mut.: yes, Flt3 Mut.: no
  5. HR and LR cytog.: no and NPM1-Mut.: no, Flt3 Mut.: yes
  6. HR and LR cytog.: no and NPM1-Mut.: no, Flt3-Mut.: no
- to compare the median Overall Survival (OS) of AML patients with Flt3-ITD mutations between the Sorafenib and the control group
- to compare the median Overall Survival (OS) of all AML patients between the Sorafenib and the control group
- to compare the CR rate of the Sorafenib with the control group
- to compare the rate of molecular remissions of the Sorafenib with the control group
- to compare the toxicity of the Sorafenib and the control treatment
- to compare the evidence of minimal residual disease of all AML patients between the Sorafenib and the control group after induction therapy and in the course of the first remission
- to compare early treatment efficacy (day 16 bone marrow assessment) between the Sorafenib and the control group
- to compare the development of biomarkers indicating the course of disease, including genetic, epigenetic, transcriptional and protein markers in leukemic blasts, bone marrow, peripheral blood cells, serum and plasma

2.4 Study design

This is a double-blind, placebo-controlled, randomized, multi-center phase-II study. Patients aged between 18 and ≤ 60 years with newly diagnosed AML will receive an induction and consolidation chemotherapy together either with Placebo (Arm P; control arm) or with Sorafenib (Arm V; study arm). Patients will additionally receive maintenance therapy with either Placebo (Arm P) or with Sorafenib (Arm V) for one year after the start of maintenance therapy. For further details see chapter 4.3.

3 SELECTION, RANDOMIZATION AND WITHDRAWAL OF PATIENTS

3.1 Patient selection

According to the sample size calculation given in chapter 7, n = 276 patients will be included in the study with an equal allocation rate to both treatment arms.

3.1.1 Inclusion criteria

- Patients with newly diagnosed AML (except APL) according to the FAB and WHO classification, including AML evolving from MDS or other hematologic 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 ≥18 and ≤60 years
- Informed consent, personally signed and dated to participate in the study
- ECOG performance status of 0-1
- Life expectancy of at least 12 weeks
- Adequate liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:
    - Total bilirubin ≤ 1.5 times the upper limit of normal
    - ALT and AST ≤ 2.5 times upper limit of normal
    - Alkaline phosphatase < 4 x upper limit of normal
    - PT-INR/PTT < 1.5 x upper limit of normal (patients who are being therapeutically anticoagulated with an agent such as coumarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists).
- Creatinine ≤ 1.5 times upper limit of normal

3.1.2 Exclusion criteria

- Patients who are not eligible for standard chemotherapy as per discretion of the treating physician
- Central nervous system manifestation of AML
- Cardiac disease: heart failure NYHA III or IV; unstable coronary artery disease (MI 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 (creatinine clearance < 30 ml/min) (Cockcroft-Gault formula)
- Patients undergoing renal dialysis
- Chronic pulmonary disease with relevant hypoxia
- 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
- Resting blood pressure (BP) consistently higher than systolic 160 mmHg and/or diastolic 95 mmHg
- Any severe concomitant condition which makes it undesirable for the patient to participate in the study or which could jeopardize compliance of the protocol
- Patients with major surgery, open biopsy or significant traumatic injury within 4 weeks of start of first dose
- Serious, non-healing wound, ulcer or bone fracture
- Uncontrolled active infection > Grade 2 NCI-CTC version 3.0
- Concurrent malignancies other than AML
- History of organ allograft
- Allergy to study medication or excipients in study medication
- Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within 7 days prior to the start of treatment.
- Previous treatment of AML except hydoxyurea for up to 5 days
- Concomitant or previous treatment with kinase inhibitors, angiogenesis inhibitors or Mylotarg
- Investigational drug therapy outside of this trial during or within 4 weeks of study entry
- Patients unable to swallow oral medications
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results

3.2 Registration

Eligible patients will be centrally registered by the Studienzentrale SAL after the local center has faxed the patient registration form (Patientenmeldebogen) to 0351 458 4367.

Required details for registration are:

- Individual **patient number (Patientennummer)**
- Age

- Sex
- Diagnosis (according to the FAB-classification)
- Study center and name of the physician

The individual **patient number** will be specific for the local center and be assigned by the local center. **The patient number consists of three digits for the number of the local center and three digits for the individual patient.** The local center shall assign the three patient digits consecutively according to order of inclusion, starting with 001 and counting up, i.e. the first included patient of center XXX will be assigned XXX-001, the following patient will be assigned XXX-002 and so forth. The name or date of birth will not be submitted to the Studienzentrale (see chapter 9.3 Confidentiality).

A form for registration and randomization (Patientenmeldebogen) with all relevant contact information is provided in the Investigator Site File (ISF, Prüfarztordner). After registration by the center and after having obtained the molecular and cytogenetic information from the reference laboratories, the Studienzentrale SAL will perform the randomization of the patients to the two treatment arms in a stratified manner. Since treatment is homogenous in both treatment arms until day 10 randomization will be done latest at day 7. The center will be immediately informed about the randomization result in order to assure study drug supply until day 10.

3.3 Randomization Procedure and Stratification

3.3.1 Randomization

The Studienzentrale SAL is responsible for the randomization process. The central randomization process will ensure allocation concealment. The randomization will be based on a randomization list containing randomization blocks. The use of randomization blocks guarantees equal numbers of patients in each treatment arm. In order to ensure equal proportions of patients from different strata in the two treatment arms, separate randomization lists for each stratum will be used (for description of strata, see below). Eligible study patients will be randomized by consecutive inclusion in the stratum-specific randomization list according to their cytogenetically or molecular defined stratum. Patients will be assigned one of the two treatment arms according to the randomization list (A or B).

The pharmacy in Dresden (Klinikapotheke des Universitätsklinikums Dresden) will assign treatment arms A or B to individual medication bottle numbers and will send the necessary supply of bottles to each participating center (see chapter 4.1.3, Drug accountability). A copy of the list containing medication numbers per center will be deposited at the Studienzentrale SAL.

Therefore, the Studienzentrale SAL will know which individual medication number corresponds with treatment arm A or B and will accordingly select and assign a medication bottle number to the randomized patient and add this number to the pre-existing patient study number. **The patient number plus the added three digits of the medication number will form the randomization number (Randomisationsnummer).** The Studienzentrale SAL will report the number to the recruiting center by fax**.** Figure 1 illustrates the general composition of the randomization number.

CCC – PPP – MMM

CCC = three digits for local trial center (Kliniknummer)

PPP = three digits for patient inclusion number

MMM = three digits for medication number

Figure 1: Composition of the randomization number (Randomisationsnummer)

In order to ensure double blinding, the pharmacy will assign treatment arm A and B to Sorafenib or Placebo and neither the Studienzentrale SAL nor the investigators will know which treatment arm corresponds to Sorafenib and Placebo, respectively. The closed envelops concealing the allocation of the individual patients will be deposited at the Dresden pharmacy and the local trial site only and not at the Studienzentrale. The Studienzentrale SAL will keep the randomization lists confidential and will not report the treatment arm to the investigators in order to ensure that in case of unblinding of one patient the investigator remains blinded for all other included and randomized patients. In case of unblinding, the investigators will have to contact the Safety Board which is separated from the randomization department at the Studienzentrale SAL. Even if the investigator reports the result of the unblinding to the Safety board, the results will not be reported to the randomization department. Therefore, in case of unblinding of an individual patient, the randomization department at SAL will still not be able to know which treatment arm corresponds with Placebo or Sorafenib and blinding throughout the whole trial period is guaranteed.

The centers will be supplied with starter medication kits after initiation of the study in the individual center. The center will report the eligible patient to the Studienzentrale SAL by faxing the patient registration form (Patientenmeldebogen) and send the required bone marrow and blood probes (Table 16, page 29) to the central laboratories (Table 17, page 29). After the Studienzentrale SAL has received the molecular and cytogenetic test results from the reference laboratories, the Studienzentrale SAL will perform the randomization as described above and

report the **randomization number** to the trial site via fax response. The number will be noted in the patient file and in the trial documentation forms. **The last three digits of the randomization number correspond with the number of the individual medication bottles available at the trial center.** The patient will then receive the medication bottles labeled with her/his individual **randomization number** (center number plus patient number plus number of individual medication bottle). Since treatment is homogenous in both treatment arms until day 10, randomization will be done latest at day 7. The center will be immediately informed about the randomization result in order to assure study drug supply until day 10.

3.3.2 Stratification

Drug assignment will be performed in a balanced way according to the individual patient risk. Cytogenetic risk definition will be done according to Bloomfield et al.[23]. This definition includes:

- **low risk (LR):** t(8;21)(q22;q22) ;inv(16)(p13q22)/t(16;16)(p13;q22)
- **intermediate risk (IR):** normal karyotype, balanced structural rearrangement: t(9;11)(p22;q23), unbalanced structural rearrangements: del(7q), del(9q), del(11q), del(20q), numerical aberrations:–Y, +8, +11, +13, +21 and all other patients who do not fulfil low or high risk criteria
- **high risk (HR):** complex karyotype, balanced structural rearrangement inv(3)(q21q26), t(3;3)(q21;q26), t(6;9)(p23;q34) t(6;11)(q27;q23), t(11;19)(q23;p13.1), unbalanced structural rearrangement: del(5q), numerical aberrations: –5; –7
- additionally **high risk (HR)** criteria will be fulfilled if a blast count ≥10% at the day 16 bone marrow control is evident, however no stratification will be done based on this analysis

On the basis of the known prognostic significance of the Flt3 and NPM status, the IR group will be subdivided into four different strata. This results in six distinct risk strata which will be used for stratification in this trial. The composition of the strata is shown in Table 1.

Since stratification is necessary for a well balanced trial, an urgent definition of molecular markers of the patients will be done. The results of the analysis have to be obtained latest by day 7 of the chemotherapy protocol to ensure drug order until day 10.

Definition of Strata						
S	HR cyto-genetics: yes	HR cyto-genetics: no LR cyto-genetics: yes	HR cyto-genetics: no LR cyto-genetics: no NPM1-Mut: yes FLT3-Mut: no	HR cyto-genetics: no LR cyto-genetics: no NPM1-Mut: yes FLT3-Mut:yes	HR cyto-genetics: no LR cyto-genetics: no NPM1-Mut: no FLT3-Mut: yes	HR cyto-genetics: no LR cyto-genetics: no NPM1-Mut: no FLT3-Mut: no
1	x					
2		x				
3			x			
4				x		
5					x	
6						x

Table 1: Definition of Strata

3.4 Removal of patients from study

A patient who withdraws is one who discontinues participation in a clinical study for any reason.

Patients may be withdrawn from the trial for the following reasons:

- At their own request or at the request of their legally acceptable representative
- If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the sponsor

Patients must be withdrawn also for the following reasons:

- In case of unacceptable toxicity or progressive disease
- In case of substantial non-compliance with the requirements of the study
- Positive beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same time lines as a serious adverse event

- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing results
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree
- Development of a second cancer that requires treatment
- Patient is lost to follow-up
- Interruption in study drug administration for a period longer than 28 consecutive days
- Patient death

Relevant visit data will be entered into the CRF, and any unused study medication will be accounted for and returned for all subjects entered into the trial even if for a brief period of time. Subjects who discontinue study treatment will have relevant information completed and recorded in the CRF and medical record. All subjects who discontinue because of adverse events or clinical laboratory abnormalities should be followed up until they recover or stabilize and the subsequent outcome recorded.

In case of premature withdrawal of any cause, all data documented up to the date of withdrawal will be entered into the study analysis.

3.5 Unblinding

The pharmacy Dresden will provide a closed envelope for each medication number containing the information whether a patient is in the Sorafenib or in the Placebo group. The closed envelopes will be deposited at the Dresden pharmacy and at the local center treating the patients. In case of an adverse event that makes it necessary for the treating physician to obtain this information, the envelope can be opened (unblinding). In case of unblinding the Safety Desk should be informed immediately via fax.

After the end of the trial, the envelopes have to be given back to the Studienzentrale via the visiting monitor. The event of obtaining the information on the nature of the investigational drug has to be documented in the file and in the CRF.

4 STUDY, STANDARD AND CONCOMITANT TREATMENTS

4.1 Investigational product and Placebo

Sorafenib (BAY-43-9006) is an oral cytostatic Raf kinase inhibitor, PDGFR inhibitor, VEGFR-2 (KDR) inhibitor, Flt3 and c-Kit inhibitor. For more details of the preclinical and clinical information please refer to chapter 1.3.1 and to the current Nexavar® Prescribing Information (Fachinformation).

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4.1.1 Relevant physical, chemical and pharmaceutical properties

The drug product for supply of clinical trials is a 200 mg coated tablet (calculated as free base Sorafenib). The formulation is presented as an immediate release dosage form, i.e. the active ingredient is completely dissolved under in-vitro test conditions within a short period of time. The tablet cores contain Sorafenib tosylate and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethyl cellulose, sodium lauryl sulfate and magnesium stearate. The film-coat consists of hydroxypropylmethyl cellulose, polyethylene glycole, tiranium dioxide and red iron oxide. The tablets have a red color in appearance, a weight of 350 mg, and a 10 mm round shape. For blinding purpose in clinical trials, corresponding Placebo tablets are available.

4.1.2 Instructions for storage and handling

The stability profile of the drug substance is good. The current retest period for storage at room temperature is 30 months. In addition, the drug substance is insensitive to the influence of light. The tablets are packaged in HDPE bottles. They should only be stored in the pack provided. The storage temperature should not exceed 25°C.

4.1.3 Interactions with concomitant medications

Sorafenib has the ability to inhibit a variety of liver metabolic enzymes in vitro. The clinical impact of this inhibition in humans taking drugs metabolized by these enzymes is unknown. Therefore, all patients enrolled onto this trial who are taking concomitant medications that are known to be metabolized by the liver should be closely observed for side effects of these concomitant medications. Furthermore, patients taking narrow therapeutic index medications, including the following should be monitored proactively:

- Warfarin
- Quinidine
- Digoxin

4.1.4 Effect of food

When given with a high-fat meal, Sorafenib absorption was reduced. Therefore, Sorafenib/ Placebo should be administered fasting or with a moderate-fat meal.

4.1.5 Dose modification and delays of Sorafenib or Placebo

The modifications of Sorafenib or Placebo will follow the following pre-defined dose levels:

Dose level 1 (starting dose):	400 mg BID (2 tablets twice a day)
Dose level 2:	400 mg QD (2 tablets once a day)
Dose level 3:	400 mg QOD (2 tablets every second day)

Table 2: Sorafenib dose levels

Please note that the dose of 400 mg BID (total daily dose 800 mg) is the standard dose. If a dose reduction below 400 mg QOD (2 tablets every other day) is required, the patient should be discontinued from the study treatment. After resolution of the adverse event, the dose may be re-escalated from dose level 2 or 3 to the starting dose (see table) at the discretion of the investigator. As a general rule, grade 3 toxicity should be followed by permanent dose reduction. Exceptions are skin toxicities as defined below.

Resolution of an adverse event is defined as disappearance or reduction of the adverse event to below grade 3 toxicity. For patients with toxicities ≥grade 2 present at baseline (before start of Sorafenib/ Placebo treatment), resolution to maximum grade 1 level will apply.

4.1.5.1 Dose modification for hematological toxicity

Hematological toxicities will be considered not relevant for dose modification during the period of chemotherapy and the expected subsequent myelosuppression. However, these criteria will apply after hematopoietic recovery from the last chemotherapy course during the subsequent maintenance therapy.

Toxicity	**Grade 1**	**Grade 2**	**Grade 3***	**Grade 4***
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade <2, then resume treatment at the same dose level. If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade <2, then reduce dose to 400 mg p.o. QD and resume treatment.	Withhold dose until toxicity is grade <2, then reduce dose to 400 mg p.o. QD and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor (safety desk at SAL).
*Patients who develop grade 3 leukopenia, or grade 3/ grade 4 lymphopenia may continue Sorafenib/ Placebo treatment without interruption at the discretion of the investigator.				

Table 3: Dose modifications and delays for hematologic toxicities of Sorafenib/ Placebo

Table 4 summarizes the recommendations for dose delays and modifications for all non-hematologic adverse events, except for skin toxicities and hypertension, which will be detailed separately (Table 5, Table 6, Table 7). These recommendations pertain, if the adverse event is considered to be related to Sorafenib/ Placebo, but not to the chemotherapy.

Toxicity	**Grade 1**	**Grade 2**	**Grade 3***	**Grade 4***
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade <1, then resume treatment at the same dose level. If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade <1, then reduce dose to 400 mg p.o. QD and resume treatment.	Withhold dose until toxicity is grade <1, then reduce dose to 400 mg p.o. QD. and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.
*Patients who develop grade 3 fever/ chills, grade 3 elevation of hepatic transaminases with ALT and AST <10x ULN, grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis may continue Sorafenib/ Placebo treatment without interruption at the discretion of the investigator. Also excludes nausea/ vomiting that has not been premedicated, and diarrhea. If no recovery after 30 day delay, treatment will be discontinued unless patient is deriving clinical benefit. If more than 2 dose reductions are required, treatment will be discontinued.				

Table 4: Dose modifications for Sorafenib-associated non hematological toxicity except hand-foot skin reactions and hypertension

4.1.5.2 Dose modifications for skin toxicity

Only for the purpose of dose delays and modifications, patients experiencing Hand-Foot syndrome should have their signs and symptoms graded according to the following system (see Table 5). Other skin toxicities will be graded according to CTCAE Version 3.0. Please note that Hand Foot Syndrome will be graded and recorded as an adverse event according to CTCAE Version 3.0 in the CRF. These recommendations pertain, if the adverse event is considered to be related to Sorafenib/ Placebo, but not to the chemotherapy.

Grade 1	Numbness, dysesthesia/ paresthesia, tingling, painless swelling or erythema of the hands and/ or feet and/ or discomfort, which does not disrupt normal activities
Grade 2	Painful erythema and swelling of the hands and/ or feet and/or discomfort affecting the patient's activities
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

Table 5: Grading for Hand-Foot Syndrome

According to the grade and incidence of skin toxicity (including rash and hand-foot syndrome) for a given patient, the following dose modification schedule will be followed.

Skin toxicity grade	Occurrence	Suggested Dose modification
Grade 1: Numbness, dysethesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patients normal activity	Any occurrence	Institute supportive measures immediately and continue Sorafenib/Placebo treatment
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Institute supportive measures and consider a decrease of Sorafenib/Placebo dose to 400mg daily for 28 days If toxicity resolves or returns to grade 0–1 after dose reduction, increase Sorafenib/Placebo to full dose after 28 days If toxicity does not resolve or return to grade 0-1 despite dose reduction, interrupt Sorafenib/Placebo treatment for a minimum of 7 days, until toxicity has resolved or returned to grade 0–1. When resuming treatment after dose interruption, re-start Sorafenib/Placebo at reduced dose of 400mg daily for 28 days If toxicity remains absent or at grade 0–1 at reduced dose, increase Sorafenib/ Placebo to full dose after 28 days
	2nd or 3rd occurrence	Decrease dose to 400mg daily for the study period, do not re-escalate the dose
	4th occurrence	Decision whether to discontinue Sorafenib/ Placebo treatment should be made based on clinical judgment and patient preference
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes inability to work or perform activities of daily living	1st occurrence	Institute supportive measures and interrupt Sorafenib/ Placebo treatment for a minimum of 7 days and until toxicity has resolved or is reduced to grade 0–1 When resuming treatment after dose interruption, re-start Sorafenib/Placebo at reduced dose of 400mg daily for 28 days If toxicity remains absent or at grade 0–1 at reduced dose, increase Sorafenib/ Placebo to full dose after 28 days
	2nd occurrence	Decrease dose to 400 mg daily for the study period, do not re-escalate the dose
	3rd occurrence	Decision whether to discontinue Sorafenib/ Placebo treatment should be made based on clinical judgment and patient preference

Table 6: Suggested Dose Modifications for Sorafenib/ Placebo for Hand-Foot Skin Reaction

4.1.5.3 Dose modifications for hypertension

An increased incidence of hypertension was observed in Sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation of Sorafenib/ Placebo should be considered. In general, hypertension should be treated according to Table 7.

Management of treatment-emergent hypertension	
Grade of Event (CTCAE v3)	**Management / next dose**
Grade 1: asymptomatic and transient	Consider increased BP monitoring
Grade 2: asymptomatic and diastolic BP < 110 mmHg	Begin anti-hypertensive therapy and continue Sorafenib/ Placebo
Grade 2: symptomatic / persistent OR Diastolic BP ≥ 110 mmHg OR Grade 3	Sorafenib/ Placebo should be stopped* until symptoms resolve and diastolic BP returns to ≤ 100 mmHg. Treat subject with anti-hypertensives. When Sorafenib/ Placebo is re-started, reduce to 400 mg p.o. QD and possibly re-escalate dose later at the discretion of treating physician. If diastolic BP is not controlled to ≤ 100 mmHg on therapy, reduce Sorafenib/ Placebo to 400 mg p.o. every other day (QOD) and monitor BP closely If BP is not controlled on Sorafenib/ Placebo 400 mg p.o. QOD, study treatment should be discontinued
Grade 4: life-threatening	Discontinue Sorafenib/ Placebo permanently (end of study)
Please note the distinction between asymptomatic and symptomatic grade 2 hypertension. * Subjects requiring a delay of > 28 days should go off protocol therapy (end of study).	

Table 7: Suggested dose modifications for Sorafenib/ Placebo-associated hypertension

4.1.5.4 Dose modifications for surgery

Temporary interruption of Sorafenib/ Placebo is recommended in patients undergoing major surgical procedures. In advance of elective procedures, it is recommended that Sorafenib/ Placebo is interrupted for 5-7 days. There is limited clinical experience regarding the timing of re-initiation of Sorafenib/ Placebo therapy following major surgical intervention. Therefore, the decision to resume Sorafenib/ Placebo therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

4.1.6 Drug accountability

Packaging, labeling and distribution will be performed by the Dresden pharmacy (Klinikapotheke des Universitätsklinikums Dresden) on behalf of the sponsor.

The drug will be distributed to the center pharmacies or to the responsible investigator in the center in plastic bottles containing an approximately 1 month drug supply (140 tablets of 200 mg Sorafenib each or Placebo), labeled according to the scheme described above (see chapter 3.3.1). The centers will be supplied with 18 bottles of medication for the initial treatment of 6 patients (3 x 3 bottles for treatment arm A and 3 x 3 bottles for treatment arm B) immediately after initiation. Three bottles contain 420 tablets (140 tablets per bottle) and are sufficient for a minimum treatment with study medication of 105 days, i.e. covering at least the first two courses of induction therapy and the first and second course of consolidation depending on daily dose and time interval between consolidations (see chapter 4.3).

The delivery of the initial three bottles per patient will be part of the starter kit and new starter kits will be organized by the Studienzentrale SAL when needed. Each local center is responsible for ordering more supply for each patient after use of the first three bottles. Each center will have to reorder when the patient starts to use the first tablets from the last remaining bottle. The reorder has to be done via the Studienzentrale SAL. Here the order will be documented and the pharmacy will be informed immediately.

With the first re-order (Erste Nachbestellung), the pharmacy will send 5 bottles sufficient for a minimum of 175 days, i.e. covering at least 5.5 months of maintenance therapy (maintenance therapy starts at day 8 of the third course of consolidation).

With the second re-order (Zweite Nachbestellung), the pharmacy will send 6 bottles sufficient for a minimum of 210 days, i.e. covering the remaining 6.5 months of maintenance therapy.

Each center has to document in a list, when which drug was given to whom. This list has to contain the date, the patient number, the batch number, the use-by date and the number of tablets dispensed. All empty medication bottles and left-over tablets have to be returned to the center investigator by the patients and have to be stored by the center investigator for documentation. The number of bottles and tablets for each individual patient will be registered by the documentation assistant. Medication documentation will be checked during the monitoring visits and empty bottles and unused medication will be returned to the pharmacy of Universitätsklinikum Dresden for disposal.

4.2 Standard cytotoxic therapy

Cytarabine (AraC)

Cytarabine belongs to the group of chemotherapeutic agents called antimetabolites. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported.

Cytarabine is not active orally. It may be given by intravenous infusion or injection, subcutaneously, or intrathecally. When large intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours post injection. This problem tends to be less severe when the drug is infused.

A cytarabine syndrome has been reported to occur in patients. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, the use of corticosteroids should be considered as well as continuation of therapy with cytarabine.

Like other cytotoxic drugs, cytarabine may induce anemia, leukopenia, thrombocytopenia and hyperuricemia secondary to rapid lysis of neoplastic cells.

Acute pancreatitis has been reported to occur in patients being treated with cytarabine who have had prior treatment with L-asparaginase.

Severe and at times fatal CNS, GI and pulmonary toxicity has been reported following high dose schedules of cytarabine. These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, pulmonary edema, liver damage with hyperbilirubinemia. Rarely, severe skin rash, leading to desquamation has been reported.

For full details of the drug information please refer to the "Fachinformationsverzeichnis Deutschland" in its latest version.

Daunorubicin

Daunorubicin has antimitotic and cytotoxic activity through a number of proposed mechanisms of action. It forms complexes with DNA by intercalation between base pairs. It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the religation portion of the ligation-religation reaction which topoisomerase II catalyzes. Single strand and double strand DNA breaks result. Daunorubicin may also inhibit polymerase activity, affect regulation of gene expression, and produce free radical damage to DNA.

Daunorubicin must be given into a rapidly flowing intravenous infusion. It must *never* be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.

Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m^2 in adults.

Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or hemorrhage.

Dosage should be reduced in patients with impaired hepatic or renal function.

Daunorubicin may transiently impart a red coloration to the urine after administration, and patients should be advised to expect this.

For full details of the drug information please refer to the "Fachinformationsverzeichnis Deutschland" in its latest version.

4.3 Treatment plan for study and control arm

4.3.1 Study design and flow chart

This is a double-blind, Placebo-controlled trial. All patients randomized into the control arm (called Arm P for Placebo in this chapter for descriptive purposes only) will receive Placebo tablets after chemotherapy and during maintenance. All patients randomized into the interventional arm (called Arm V for Verum in this chapter for descriptive purposes only) will receive Sorafenib after chemotherapy and during maintenance. The principal treatment strategy is given in the accompanying Figure 2.

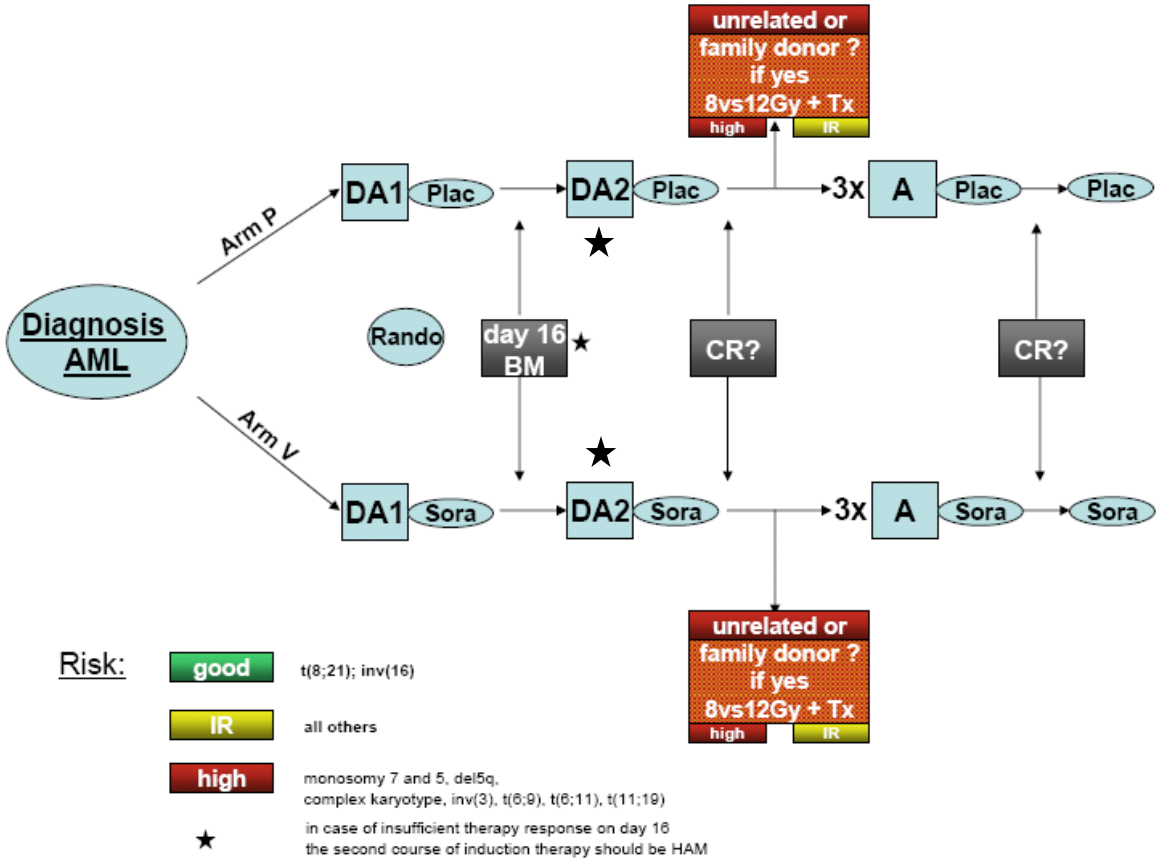

Figure 2: Flow chart of treatment plan for study and control arm; "P" stands for Placebo, "V" stands for Verum (Sorafenib)

4.3.2 Induction therapy

4.3.2.1 Arm P (Standard cytotoxic therapy plus Placebo)

AraC	100 mg/ m^2/ day	continuous infusion over 24 hours	days 1-7
Daunorubicin	60 mg/ m^2/ day	infusion over 2 hours	days 3, 4 and 5
Placebo		2 tablets twice a day	from day 10 continuously until day 19

Table 8: Standard induction therapy plus Placebo

Patients will receive an identical second course of induction therapy starting earliest day 22 if the blast count in the bone marrow at day 16 is reduced. If there is no reduction in the blast count at day 16 or if there is even evidence of increased blast counts the patient should receive an alternative second induction therapy based on a high dose AraC application[24] (HAM).

Alternative induction therapy - HAM (in the case of insufficient response to induction therapy I)

AraC	3g/ m^2/ 12hrs	infusion of 3 g/m^2 over 3 hours BID every 12 hours	days 1, 2 and 3
Mitoxantrone	10 mg/ m^2/ day	60 minutes infusion	days 3, 4 and 5
Placebo	2 tablets	twice daily	from day 10 continuously until day 19

Table 9: Alternative induction therapy plus Placebo

It is allowed to postpone the second course if the patient has an uncontrolled infection or transitory contraindications against chemotherapy. The second course can be started once these problems have been resolved.

4.3.2.2 Arm V (Standard cytotoxic therapy plus Sorafenib)

AraC	100 mg/ m^2/ day	continuous infusion over 24 hours	Days 1-7
Daunorubicin	60 mg/ m^2/ day	infusion over 2 hours	days 3, 4 and 5
Sorafenib	800 mg/ day	2 tablets twice a day	from day 10 continuously until day 19

Table 10: Standard induction therapy plus Sorafenib

Patients will receive an identical second course of induction therapy starting earliest day 22 if the blast count in the bone marrow at day 16 is reduced. If there is no reduction in the blast

count at day 16 or if there is even evidence of increased blast counts the patient should receive an alternative second induction therapy based on a high dose AraC application[25] (HAM).

Alternative induction therapy– HAM (in the case of insufficient response to induction therapy I)

AraC	3g/ m^2/ 12hrs	infusion of 3 g/m^2 over 3 hours BID every 12 hours	days 1, 2 and 3
Mitoxantrone	10 mg/ m^2/ day	60 minutes infusion	days 3, 4 and 5
Placebo	2 tablets	twice daily	from day 10 continuously until day 19

Table 11: Alternative induction therapy plus Sorafenib

It is allowed to postpone the second course if the patient has an uncontrolled infection or transitory contraindications against chemotherapy.

4.3.3 Consolidation therapy

4.3.3.1 Consolidation therapy for LR patients as defined by cytogenetics and for IR patients without an HLA-identical sibling

All patients in CR/ CR_i after induction therapy should receive three courses of HD-AraC consolidation therapy not earlier than one week after attaining CR/ CR_i. If, in the opinion of the treating physician, the patient's condition does not allow for consolidation therapy, consolidation therapy can be postponed for up to 4 weeks after a CR/ CR_i is reached. However, if the patient is not attaining CR/ CR_i 5 weeks after the beginning of the second induction therapy course he/she should be classified as treatment failure (definition of event and EFS see chapter 7) and study treatment should be terminated .

Criteria for the beginning of each consolidation course: platelets > 70.000/µl and neutrophils > 1.000/µl.

Arm P (Standard cytotoxic therapy plus Placebo)

AraC	3g/ m^2/ 12hrs	infusion of 3 g/m^2 over 3 hours BID every 12 hours	days 1,3 and 5
Placebo		2 tablets twice a day	from day 8 continuously until 3 days before first day of next chemotherapy course

Table 12: Consolidation therapy plus Placebo

Each consolidation course will start at least 1 week after regeneration of peripheral blood counts (platelets ≥ 70.000/µl, neutrophils ≥ 1.000/µl), but not earlier than day 28 of the first cycle

Arm V (Standard cytotoxic therapy plus Sorafenib)

AraC	3g/ m^2/ 12hrs	infusion of 3 g/ m^2 over 3 hours BID every 12 hours	days 1, 3 and 5
Sorafenib	800 mg/ day	2 tablets twice a day	from day 8 continuously until 3 days before first day of next chemotherapy course

Table 13: Consolidation therapy plus Sorafenib

Each consolidation course will start at least 1 week after regeneration of peripheral blood counts (platelets ≥ 70000/µl, neutrophils ≥ 1000/µl), but not earlier than day 28 of the first cycle

If there is no full regeneration of peripheral blood counts at day 35 after high dose cytosinarabinosid chemotherapy the study medication should be reduced according to Table 3. If more than 2 levels of dose reduction are required, the patient will be excluded from the study.

4.3.3.2 Consolidation therapy for IR patients with an HLA identical sibling:

Patients in CR/ CR_i after induction therapy should receive a consolidation therapy based on allogeneic transplantation from an HLA identical sibling. The patients will be censored for outcome analysis at the beginning of conditioning chemotherapy for transplantation and will not receive any further treatment with Sorafenib. If there is no family donor availability, patients proceed with treatment as described under 4.3.3.1.

4.3.3.3 Consolidation therapy for HR patients:

All patients in CR/ CR_i after induction therapy should receive a consolidation therapy based on allogeneic stem cell transplantation. This may involve transplantation procedures from either an HLA identical sibling or an unrelated HLA-matched donor. The patients will be censored for outcome analysis at the beginning of conditioning chemotherapy for transplantation and will not receive any further treatment with Sorafenib. If there is no donor availability, patients proceed with treatment as described under 4.3.3.1.

4.3.4 Maintenance therapy

Maintenance therapy will be given to patients who received 3 courses of consolidation therapy with high dose AraC and Sorafenib/ Placebo.

4.3.4.1 Arm P

Patients will not receive any maintenance therapy, but Placebo (2 tablets) twice daily, starting on day 8 of the last consolidation cycle. Maintenance therapy will be administered continuously until one year after start of maintenance therapy.

4.3.4.2 Arm V

All patients in CR after consolidation therapy will receive a maintenance therapy with Sorafenib 400 mg twice daily (2 tablets twice a day = 800 mg/day). Maintenance therapy will start on day 8 of the last consolidation cycle. Maintenance therapy will be administered continuously until one year after start of maintenance therapy.

4.3.5 Concomitant medications/ therapy

All appropriate palliative and supportive care for disease-related symptoms will be provided to all patients. This includes anti-emetics and other symptomatic treatments, which should be used as needed and may be given prophylactically in subsequent cycles.

Patients may receive anti-microbial prophylaxis in the presence of myelosuppression at the investigator's discretion.

G-CSF will be given at a dose or doses in accordance with the institution's standard practice regarding the use of growth factors. It is also to the discretion of the participating centers, which type of G-CSF preparation they choose to treat their patients. Available preparations are filgrastim (Neupogen®), lenograstim (Granocyte®) and the pegylated form of pegfilgrastim (Neulasta®)

5 STUDY PROCEDURES

5.1 Study evaluations

Most procedures for patient evaluation listed below are considered by the investigators to be necessary according to the standard of good clinical practice for the diagnosis and treatment monitoring of AML patients.

5.1.1 Evaluations before treatment

(for full details about time points of evaluations please refer to the “schedule of evaluations”)

- Complete blood count (CBC) with differential and platelets
- Serum chemistries: electrolytes, creatinine, urea, uric acid, bilirubin, AP, AST, ALT, LDH, amylase, lipase, phosphate
- Coagulation: PTT, quick, INR, fibrinogen, ATIII
- Blood type
- Full history and clinical examination
- Serum pregnancy test for women of child bearing potential
- Vital signs, incl. blood pressure measurement
- Body height and body weight
- Performance status (ECOG)
- Electrocardiogram
- Echocardiography
- Chest X-ray
- Sonography of the abdomen
- Bone marrow aspirate and biopsy, peripheral blood cell, serum and plasma:
    - Cytomorphological examination incl. cytochemistry
    - Immunophenotyping
    - Cytogenetics
    - Molecular genetic analyses for the presence of Flt3-ITD and Flt3 point mutations, genomic ratio of Flt3-ITD vs. Flt3-WT, for NPM1 mutations, for the presence of Bcr-Abl, PML-RARalpha, AML1-ETO, inv(16), CEBP□, WT-1 and CBFß-MYH11.
    - Asservation of vital bone marrow cells (Ficoll-treated bone marrow), RNA, DNA and protein lysates, serum and plasma in a central tissue repository.
    - Determination of mutations in other kinases than FLT3 (e.g. Kit, JAK2, RAF) and transcription factors (e.g. CEBPα, WT1)
    - Determination of methylation status of genes like p15 or p16
    - Determination of SNP´s in metabolizing enzymes like e.g. of the CYP family*

*These analyses will be performed for exploratory research purposes and are optional.

Evaluations during treatment

(for full details about timepoints of evaluations please refer to the “schedule of evaluations”)

- Bone marrow aspirate (and biopsy)
- Asservation of vital bone marrow cells (Ficoll-treated bone marrow), bone marrow RNA, DNA and protein lysates, serum and plasma in a central tissue repository
- Control of CBC (with differential and platelets), coagulation and serum chemistries (including amylase, lipase and phosphate)
- Performance status
- Physical examination
- Body weight
- Diagnostic procedures i.e. in case of severe infections will follow standard procedures and should include diagnostic measures such as chest x-ray, ultrasound, urinanalysis
- Evaluations performed before the first course of induction therapy will be repeated prior to each following course if necessary in the investigator’s opinion
- ECG and echocardiography as often as necessary in the investigator’s opinion
- Daily measurement of blood pressure during the first three weeks of Sorafenib/ Placebo treatment and weekly for the following three weeks Sorafenib/ Placebo treatment

5.1.2 Evaluations during and/ or at the end of maintenance therapy

(for full details about timepoints of evaluations please refer to the “schedule of evaluations”)

Performance status

Physical examination

Vital signs

- CBC (with differential and platelets), coagulation and serum chemistries (including amylase, lipase and phosphate)
- Bone marrow aspirate (and biopsy)
- Asservation of vital bone marrow cells (Ficoll-treated bone marrow), bone marrow RNA, DNA and protein lysates, serum and plasma in a central tissue repository

5.1.3 Evaluations during follow up (standard routine parameters)

- Bone marrow aspirate in case of suspected relapse
- CBC with differential every 3 months
- Performance status every 3 months

5.1.4 Evaluations in case of relapse

CBC with differential and platelets

- Bone marrow aspirate
- Asservation of vital bone marrow cells (Ficoll-treated bone marrow), bone marrow RNA, DNA and protein lysates, serum and plasma in a central tissue repository

5.2 Schedule of evaluations

	Within 10 days prior to the first course of induction therapy	Between day 1 and day 22 of first course of induction chemo-therapy	Early response evaluation (d 16)	Before the second course of induction therapy	From day 1 of second course of induction chemo-therapy until start of consolidation therapy	Remission control – latest 35 days after the beginning of second induction	Before each course of consolidation therapy	From the beginning of first course of consolidation until the end of third course of consoli-dation = beginning of maintenance therapy	Postremis-sion control latest day 35 after begin of each course of consoli-dation therapy
Informed consent	X								
Medical history	X								
Performance status and physical examination	X			X			X		
Vital Signs (blood pressure and pulse)[a]	X	Daily measurement of blood pressure		X	weekly		X	weekly	
Body weight and height	X			X			X		
CBC (with differential and platelets)[a]	X	3 times / week		X	weekly	X	X	weekly	X
Chemistry and coagulation[a]	X	3 times / week		X	weekly		X	weekly	

	Within 10 days prior to the first course of induction therapy	Between day 1 and day 22 of first course of induction chemo-therapy	Early response evaluation (d 16)	Before the second course of induction therapy	From day 1 of second course of induction chemo-therapy until start of consolidation therapy	Remission control – latest 35 days after the beginning of second induction	Before each course of consolidation therapy	From the beginning of first course of consolidation until the end of third course of consoli-dation = beginning of maintenance therapy	Postremis-sion control latest day 35 after begin of each course of consoli-dation therapy
ECG and echocardiography[a]	X			X			X		
Pregnancy test[e]	X								
Bone marrow aspirate	X		X			X			X[b]
Bone marrow biopsy	X								
Bone marrow and blood samples for exploratory research	X		X			X			X[b]

Table 14: Schedule of evaluation I (prior to and during induction/ consolidation therapy)

	Start of maintenance therapy	During maintenance therapy	End of maintenance therapy	Follow-up 3, 6, 9, 12, 15 and 18 months after end of maintenance therapy	Relapse (during study treatment or follow-up)
Performance status and physical examination	X	monthly	X	X	
Vital Signs (blood pressure and pulse)[a]	X	monthly	X		
CBC (with differential and platelets)[a]	X	monthly	X	X	X
Chemistry and coagulation[a]	X	monthly	X		
ECG and echocardiography[a]	X				
Bone marrow aspirate		X[c]	X	X[d]	X
Bone marrow and blood samples for exploratory research		X[c]	X	X[d]	X

Table 15: Schedule of evaluation II maintenance therapy + follow-up)

[a] These evaluations should be repeated as often as necessary in the opinion of the treating physician
[b] For patients who are in a morphologic leukemia-free state (until relapse or CR) or suspected relapse
[c] One month after beginning of maintenance therapy and then every 3 months or at suspected relapse
[d] For patients with suspected relapse
[e] Pregnancy tests are to be performed for woman with child-bearing potential only.

5.3 Duration of the study and the follow up period

Accrual time: 24 months	Treatment: 18 months	Follow-up: 18 months

Assuming an accrual time of 24 months and duration of treatment (of the last included patient) of approximately 18 months the duration of the study will be approximately 42 months. The duration of the follow up period will be 18 months.

End of study

The study will end one month after the end of therapy of last patient.

5.4 Central bone marrow diagnostics and shipment modalities

The diagnosis of AML will be performed at the participating centers. In order to assure highest quality standards a central review of the cytomorphological diagnosis will be performed. Molecular genetic analyses that are either required for risk stratification (Flt3-ITD and Flt3 point mutations, NPM1 mutations, AML1-ETO, inv(16), or necessary to exclude leukemia entities not covered by the protocol (Bcr-Abl, PML-RARalpha) will be done in a centralized way. Additionally, karyotype analyses should be done centrally. In any case, karyotype analyses must be both shared for central review and for risk stratification purpose by the Studienzentrale latest at day 7 after treatment start.

5.4.1 Requested material and shipment modalities

Immediately at diagnosis, please collect for central diagnostics
15 ml heparinized bone marrow
5 ml bone marrow aspirate in EDTA
20 ml heparinized peripheral blood (if blasts are present)
at least 10 unstained bone marrow smears
2 unstained peripheral blood smears

Table 16: Bone marrow diagnostics: requested material

Shipment is recommended from Monday through Friday and will be organized by the Studienzentrale SAL after the center has faxed the patient registration form (Patientenmeldebogen) to 0351/ 458-4367. Material will be picked up until the afternoon from Monday to Friday and be delivered by overnight express to the following addresses:

Universitätsklinikum Carl Gustav Carus Med. Klinik und Poliklinik I Hämatologisches Labor Haus 65 a Fetscherstr. 74 01307 Dresden Tel.: 0351/ 458-4251 Fax: 0351/ 458-4367 For information on results, please contact: Prof. Dr. C. Thiede Tel.: 0351/ 458-5628

Table 17: Material shipment address

5.4.2 Molecular genetic analyses

For the central cell repository and the central molecular genetic analyses bone marrow aspirate and peripheral blood of each patient has to be sent to Dresden at diagnosis.

For further investigations the remaining material will be cryo-preserved at the central study office. Upon consultation with the study group it will be at the disposal of interested working groups for scientific investigations.

5.4.3 Cytomorphologic examination and cytochemistry

Initial leukemia diagnostics and differentiation are based on the morphology of peripheral blood and bone marrow smears as well as on cytochemical examinations. If the bone marrow aspirate is not available, diagnosis will be based on the bone marrow biopsy.

A Pappenheim staining, a peroxidase reaction and an esterase reaction are performed. Diagnosis and classification of the AML will be performed according to FAB criteria as well as according to the WHO classification. These analyses will be performed in the local participating centers. The central study offices participate in round robin tests within the scope of the network of excellence for acute and chronic leukemias and offer reference laboratory diagnostics for discussion of questionable cases. To be able to quickly assess the diagnostic material, bone

marrow and peripheral blood smears are requested for all patients at diagnosis (for shipping modalities, see above). Discrepancies between diagnostic results between the local participating center and the central cytomorphology will be resolved by discussion. For discussion of cytomorphology, one of the persons below can be contacted.

PD Dr. F. Kroschinsky, Dr. S. Parmentier
Medizinische Klinik und Poliklinik I
Universitätsklinikum Carl Gustav Carus an der
Technischen Universität Dresden
Hämatologisches Labor Haus 65a
Fetscherstr. 74
01307 Dresden
Tel.: 0351/458-3412
Fax: 0351/458-4367

5.4.4 Immunophenotyping

An immunologic typing of the leukemia cells will be performed for all patients. These analyses are performed centrally. The immunophenotyping should contain the antigen CD56 and should be performed according to the proposals by the network of excellence “Acute and chronic leukemias”. For discussion of flow cytometry data can be contacted:

Dr. U. Oelschlägel
Medizinische Klinik und Poliklinik I
Universitätsklinikum Carl Gustav Carus an der
Technischen Universität Dresden
Hämatologisches Labor Haus 65a
Fetscherstr. 74
01307 Dresden
Tel.: 0351/458-4473 resp. -5621
Fax: 0351/458-4367

For shipment modalities and required material see chapter 5.4.

5.4.5 Cytogenetics

For each patient a cytogenetic examination has to be immediately performed at diagnosis. Chromosomal G-Banding will be performed. Molecular genetic analyses and fluorescent-in-situ-hybridizations will be performed if necessary. There is a centralized cytogenetic analysis conducted in the SAL study center Dresden. If in exceptional cases centers are not able to participate in the centralized cytogenetic analysis, the center that work together with local cytogenetic laboratory have to ensure that karyotype analysis will be completed at day 7 in order to provide the requested information for stratification of the patients. Cytogenetic laboratories should fax the study center and the “Studienzentrale” the results of the analysis as soon as the analysis is completed. For discussion of cytogenetic data can be contacted:

Dr. B. Mohr

Medizinische Klinik und Poliklinik I

Universitätsklinikum Carl Gustav Carus an der

Technischen Universität Dresden

Hämatologisches Labor Haus 65a

Fetscherstr. 74

01307 Dresden

Tel.: 0351/458-5619 resp. -2517

Fax: 0351/458-4367

6 ASSESSMENT OF SAFETY

6.1 Adverse Event definitions

Adverse Events and Serious Adverse Events will be graded according to the National Cancer Institute Common Toxicity Criteria (CTC) 3.0 for Cancer Clinical Trials.

Definition of Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign, symptom, disease or exacerbation of a preexisting condition temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal product.

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease.

The reporting of abnormal laboratory values should be avoided unless they lead to clinical consequences that are not routine.

Definition of Adverse Reaction (AR)

An adverse reaction (AR) is an AE, which is judged by the investigator as having a reasonable suspected causal relationship to an investigational medicinal product. For regulatory purposes an AR is an AE judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Definition of Unexpected Adverse Reaction (UAR)

An unexpected adverse reaction (UAR) is an AR, the nature and severity of which is not consistent with the applicable Nexavar® (Sorafenib) product information.

Examples of UAR include:

- An expected/ labeled AR with an unexpected outcome (e.g. a fatal outcome).
- A more specific reaction than labeled (“acute renal failure” is a labeled AR, a new report of “interstitial nephritis” is more specific and therefore unexpected).
- An increase in the rate of occurrence of an expected AR, which is judged to be clinically important, is considered as unexpected.

Definition of Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to study drug or not) that occurs at any dose and:

- Results in death or
- Is life-threatening (at the time of the event; does not refer to an event which hypothetically might have caused death if it were more severe) or
- Requires in-patient hospitalization or prolongation of existing hospitalization (elective hospitalizations/procedures for preexisting conditions that have not worsened or for preplanned treatment are excluded) or
- Results in persistent or significant disability/incapacity or
- Is a congenital abnormality/birth defect.

Significant medical events that may or may not result in death, be life threatening, or require hospitalization, may also be considered as a serious adverse event when they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes in the definitions listed above.

All deaths including death to disease progression during protocol treatment and for 30 days after the last protocol treatment have to be reported immediately on an SAE form, although death is an outcome per definition, not an adverse event per se.

Definition of Serious Adverse Reaction (SAR)

A serious adverse reaction (SAR) is an SAE, which is judged by the investigator as having a reasonable suspected causal relationship to an investigational medicinal product. For regulatory purposes an SAR is an SAE judged by the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction is an SAE, which is both judged by the investigator as having a reasonable suspected causal relationship to an investigational medicinal product (SAR) and the nature and severity of which is not consistent with the applicable Nexavar® (Sorafenib) product information. It is the duty of the sponsor to review all reported SAEs/ SARs for unexpectedness.

Study specific exceptions

Leukemia-associated serious adverse events do not have to be reported as serious adverse events on this protocol. Myelosuppression, thrombocytopenia, anemia and associated complications are expected events during leukemia therapy and are part of the treatment success (marrow emptying of leukemia cells). Therefore, myelosuppression-associated complications such as fever, infections, bleeding, and related hospitalization will be reported on appropriate pages of the CRF as an adverse event. In this context only prolonged myelosuppression, i.e. pancytopenia with marrow hypocellularity on day 40 or later from start of last cytotoxic therapy without evidence of leukemia, will require immediate reporting on an SAE form.

6.2 Safety monitoring and reporting of AEs

AEs and SAEs will be recorded from the time the informed consent is signed, up to and including 30 days following last administration of study drug.

Severity of adverse events and serious adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) 3.0 for Cancer Clinical Trials.

All adverse events have to be recorded on the appropriate adverse event pages in the CRF.

The National Coordinating Investigator (LKP) is responsible for central safety monitoring and reporting on behalf of the sponsor and has installed a central safety desk located at the Studienzentrale SAL. The investigator must fax all serious adverse events (SAEs) identified by the protocol as requiring immediate reporting on an SAE form to the safety desk within 1 working day.

This applies regardless of severity (CTCAE 3.0 grade) and whether or not the SAE is considered related to the use of study drug by the investigator. Where possible, a diagnosis rather than a list of symptoms should be given. The investigator should complete all the details requested including dates of onset, severity, corrective therapies given, outcome and opinion as to whether the adverse event is likely to be drug-related. The investigator should not wait for full details before making the initial report. Personal data have to be replaced by the trial patient number before forwarding any information.

If the event is fatal or life threatening, the investigator must fax any relevant follow-up information of the reported SAE to the safety desk within additional 8 days. If the reported SAE is not fatal or life threatening, the investigator must fax follow-up information as soon as possible.

Via the central safety desk, the National Coordinating Investivator (LKP) will review the SAE again for seriousness and relatedness and assess the SAR for expectedness according to Summary of Product Characteristics Nexavar® Prescribing Information (Fachinformation).

Via the safety desk, the LKP will ensure that the Ethics Committee, competent authority and participating investigators will be informed of all suspected unexpected serious adverse reactions (SUSARs) and all other relevant safety information in accordance with legal requirements.

It is the duty of the safety desk to inform the marketing authorization holder of Sorafenib according to stipulation.

Safety Desk

Studienzentrale SAL

Fetscherstr. 74

Universitätsklinikum Dresden

01307 Dresden

Phone: 0351/ 458-2633

Fax: 0351/ 458-7326

6.3 Warnings and Precautions

6.3.1 Investigational product (Sorafenib)

For the most recent safety update, please refer to the current Nexavar® Prescribing Information (Fachinformation).

6.3.1.1 Contraindications

Sorafenib is contraindicated in patients with known severe hypersensitivity to Sorafenib or any of the excipients.

6.3.1.2 Special Warnings and Precautions for Use

Nexavar® (Sorafenib) is approved for treatment of patients with hepatocellular carcinoma and advanced renal cell cancer. Because this is a novel agent, current knowledge of the adverse events associated with this compound is limited. As with any new chemical entity, there is always potential for unexpected adverse events.

Pregnancy: Women should avoid becoming pregnant while on therapy.

Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).

Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, Sorafenib should be assumed to cause fetal harm when administered to a pregnant woman.

Breastfeeding should be discontinued during Sorafenib therapy.

Dermatological Toxicities: Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with Sorafenib. Rash and hand-foot skin reaction are usually CTC (National Cancer Institute Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with Sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of Sorafenib, or in severe or persistent cases, permanent discontinuation of Sorafenib.

Hypertension: An increased incidence of hypertension was observed in Sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation of Sorafenib should be considered.

Hemorrhage: An increase in the risk of bleeding may occur following Sorafenib administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of Sorafenib be considered.

Wound healing complications: No formal studies of the effect of Sorafenib on wound healing have been conducted. In patients undergoing major surgical procedures, temporary interruption of Sorafenib therapy is recommended for precautionary reasons. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume Sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Cardiac Ischemia and/or Infarction: In the phase-III advanced RCC study (TARGETS), the incidence of treatment-emergent cardiac ischemia/infarction events was higher in the Sorafenib group (2.9%) compared with the Placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of Sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

Gastrointestinal perforation: Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking Sorafenib. In some cases this was not associated with apparent intra-abdominal tumor. Sorafenib therapy should be discontinued in patients with GI perforation.

Effects on ability to drive and use machines: No studies on the effects of Sorafenib on the ability to drive or use machines have been performed. There is no evidence that Sorafenib affects the ability to drive or operate machinery.

Patients with Hepatic Impairment: *In vitro* and *in vivo* data indicate that Sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering Sorafenib to patients with Child-Pugh A and B hepatic impairment.

Patients with Renal Impairment: Sorafenib has not been studied in patients with severe renal impairment (CrCl <30 ml/min) or in patients undergoing dialysis.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been performed with Sorafenib. Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently. No specific studies with Sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for Sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in

rats consisted of testicular atrophy or degeneration, degeneration of epidymidis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥30 mg/m^2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m^2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m^2/day of Sorafenib. Adequate contraception should be used during therapy and for at least 3 months after completing therapy.

Pediatric Use: The safety and effectiveness of Sorafenib in pediatric patients have not been studied. Repeat dosing of Sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily Sorafenib doses ≥600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

Geriatric Use: In total, 32% of RCC patients treated with Sorafenib were age 65 years or older and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

6.3.1.3 Interaction with Other Medications

Drug-Drug Interactions: Caution is recommended when administering Sorafenib together with compounds that are metabolized/ eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan)

Metabolism enzyme inducers - A five-day application of rifampicin before taking a single dose of Sorafenib lead to a mean 37% decrease of the AUC of Sorafenib. Other inducers of CYP3A4 activity and/or glururonidation (e.g. Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may increase metabolism of Sorafenib and thus decrease Sorafenib plasma concentrations.

CYP3A4 Inducers - Continuous concomitant administration of Sorafenib and rifampicin resulted in an average 37% reduction of Sorafenib AUC. Other inducers of CYP3A4 activity (e.g.

Hypericum perforatum also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of Sorafenib and thus decrease Sorafenib concentrations.

CYP3A4 inhibitors - Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of Sorafenib. Therefore, clinical pharmacokinetic interactions of Sorafenib with CYP3A4 inhibitors are unlikely.

CYP2C9 substrates - The possible effect of Sorafenib on warfarin, a CYP2C9 substrate, was assessed in Sorafenib-treated patients compared to Placebo treated patients. The concomitant treatment with Sorafenib and warfarin did not result in changes in mean PT-INR compared to Placebo. However, patients taking warfarin should have their INR checked regularly (see section Warnings and Precautions for use).

CYP isoform-selective substrates - Concomitant administration of midazolam, dextromethorphan and omeprazole, which are substrates of cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, following 4 weeks of Sorafenib administration did not alter the exposure of these agents. This indicates that Sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes.

Combination with other anti-neoplastic agents - In clinical studies, Sorafenib has been administered together with a variety of other anti-neoplastic agents at their commonly used dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant use of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6) with Sorafenib (100, 200 or 400 mg twice daily), administered with a 3-day break in dosing around administration of paclitaxel/carboplatin, resulted in no significant effect on the pharmacokinetics of paclitaxel. Concomitant treatment with Sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. Docetaxel (75 or 100 mg/m^2 administered once every 21 days) when co-administered with Sorafenib (200 mg twice daily or 400 mg twice daily administered on Day 2 through 19 of a 21-day cycle), with a 3-day break in dosing, around administration of docetaxel, resulted in a 36-80% increase in docetaxel AUC and a 16-32%

increase in docetaxel C_{max}. Caution is recommended when Sorafenib is co-administered with docetaxel.

Warfarin/ Phenprocoumon: Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on Sorafenib therapy. Patients taking warfarin concomitantly should be monitored regularly for changes in prothrombin time, INR and for clinical bleeding episodes.

6.3.1.4 Pregnancy and Lactation

Pregnancy: It should be avoided becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity). Sorafenib should not be used during pregnancy. Prescribers may only consider it to be used, if the potential benefits justify the potential risks to the fetus.

- There are no adequate and well-controlled studies in pregnant women using Sorafenib. Studies in animals have shown reproductive toxicity including malformations. In rats, Sorafenib and its metabolites were demonstrated to cross the placenta and Sorafenib is anticipated to inhibit angiogenesis in the fetus.
- Women should avoid becoming pregnant while on therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity). Women should use one save method - like intrauterinepessar, hormonal treatment or vasoresection of the man + one additional method like diaphragmapessar or usage of condoms for birth control.
- In animals, Sorafenib has been shown to be teratogenic and embryotoxic. Adequate contraception should be used during therapy and for at least 3 months after completion of therapy.

Breastfeeding should be discontinued during Sorafenib therapy.

- It is not known whether Sorafenib is excreted in human milk. In animals, Sorafenib and/or its metabolites were excreted in milk. Because many drugs are excreted in human milk and because the effects of Sorafenib on infants have not been studied, woman should discontinue breastfeeding during Sorafenib treatment.

Effects on fertility: Results from animal studies indicate that Sorafenib can impair male and female fertility.

6.3.1.5 Adverse Reactions

The overall safety profile of Sorafenib is based on 1286 cancer patients, who received Sorafenib as single agent. This table will be used to determine the “expectedness” of ADRs used for reporting of adverse events to Regulatory Agencies from clinical studies. It is not a complete list of adverse events reported in clinical trials.

System Organ Class	**Very Common > 10%**	**Common > 1% to < 10%**	**Uncommon > 0.1% to < 1%**
Infections and infestations			Folliculitis infection
Blood and lymphatic system disorders	Lymphopenia	Leucopenia Neutropenia Anemia Thrombocytopenia	
Immune system disorders			Hypersensitivity reactions (including skin reactions and urticaria)
Endocrine disorders			Hypothyroidism
Metabolism and nutrition disorders	Hypophosphatemia	Anorexia	Hyponatremia Dehydration
Psychiatric disorders		Depression	
Nervous system disorders		Peripheral sensory neuropathy	Reversible posterior leukoencephalopathy*
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders			Myocardial ischemia and infarction* Congestive heart failure*
Vascular disorders	Hemorrhage (including gastrointestinal* and respiratory tract* and cerebral hemorrhage*) Hypertension		Hypertensive crisis*
Respiratory, thoracic and mediastinal disorders		Hoarseness	Rhinorrhea
Gastrointestinal disorders	Diarrhea Nausea Vomiting	Constipation Stomatitis (including dry mouth and glossodynea) Dyspepsia Dysphagia	Gastro esophageal reflux disease Pancreatitis Gastritis Gastrointestinal perforation*
Hepato-biliary disorders			Increase in bilirubin and jaundice
Skin and subcutaneous tissue disorders	Rash Alopecia Hand-foot reaction** Pruritus Erythema	Dry skin Dermatitis exfoliativa Acne Skin desquamation	Eczema Erythema multiforme minor
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	
Reproductive system and breast disorders		Erectile dysfunction	Gynaecomastia

General disorders and administration site conditions	Fatigue Pain (incl. mouth, abdominal, bone pain, headache and tumor pain)	Asthenia Fever Influenza-like illness	
Investigations	Increased amylase Increased lipase	Weight decreased Transient increase in transaminases	Transient increase in blood alkaline phosphatase INR abnormal, prothrombin level abnormal
* Events may have a life-threatening or fatal outcome. Such events are uncommon. ** Palmar plantar erythrodysaesthesia syndrome in MedDRA			

Table 18: Adverse Drug Reactions in patients in multiple clinical trials (MedDRA coded)

In combination with cytotoxic agents, myelosuppression leading to febrile neutropenia has also been observed. Such events may have a life-threatening or fatal outcome.

The percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received Sorafenib versus Placebo on the phase- III RCC trial is shown in Table 19. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving Sorafenib compared to 22% of patients receiving Placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving Sorafenib compared to 6% of patients receiving Placebo.

Adverse Event NCI-CTCAE v3 Category/Term	**NEXAVAR N=451**			**Placebo N=451**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Any Event	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/ skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand-foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0

Adverse Event NCI-CTCAE v3 Category/Term	NEXAVAR N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hemorrhage/ bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

Table 19: Treatment-Emergent Adverse Events Reported in at Least 10% of Sorafenib-Treated patients – Phase III Advanced RCC Study

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the Sorafenib and Placebo groups (10% of Sorafenib patients and 8% of Placebo patients).

Adverse Event* NCI- CTCAE v3 Category/Term	NEXAVAR N=297			Placebo N=302		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Event	98	39	6	96	24	8
Constitutional symptoms						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Dermatology/ Skin						
Rash/ desquamation	19	1	0	14	0	0
Pruritus	14	<1	0	11	<1	0
Hand-foot skin reaction	21	8	0	3	<1	0
Dry skin	10	0	0	6	0	0
Alopecia	14	0	0	2	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	29	3	0	18	3	<1
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	14	0	0	10	0	0
Hepatobiliary/ pancreas						
Liver dysfunction	11	2	1	8	2	1
Pain						

	NEXAVAR N=297			Placebo N=302		
Adverse Event* NCI- CTCAE v3 Category/Term	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Pain, abdomen	31	9	0	26	5	1
*In study 100554 (HCC), the rate of ascites was similar in both NEXAVAR and Placebo groups.						

Table 20: Adverse Events Reported in at least 10% of patients and at a higher rate in NEXAVAR-Arm than the Placebo Arm – Study 100554 (HCC)

Hypertension was reported in 9% of patients treated with NEXAVAR and 4% of those treated with Placebo. CTCAE grade 3 hypertension was reported in 4% of NEXAVAR treated patients and 1% of Placebo treated patients. No patients were reported with CTCAE grade 4 events in either treatment group.

Hemorrhage/ bleeding was reported in 20% of Placebo patients and 18% of those receiving NEXAVAR. The rates of CTCAE grade 3 and 4 bleeding was also higher in the Placebo group (CTCAE grade 3 in 5% Placebo and 3% NEXAVAR and CTCAE grade 4 in 4% Placebo and 2% NEXAVAR). Bleeding from esophageal varices was reported in 4% of Placebo treated patients and 2.4% in NEXAVAR treated patients.

Renal failure was reported in 2.6% of Placebo patients and 0.3% of those receiving NEXAVAR.

6.3.1.6 Laboratory Abnormalities

The following laboratory abnormalities were observed in the phase III advanced RCC (TARGETS) trial:

Elevated lipase and amylase: Elevated lipase and amylase levels were very commonly reported. CTC Grade 3 or 4 lipase elevations occurred in 12% of patients in the Sorafenib group compared to 7% of patients in the Placebo group. CTC Grade 3 or 4 amylase elevations were reported in 1% of patients in the Sorafenib group compared to 3% of patients in the Placebo group. Clinical pancreatitis was reported in 2 of 451 Sorafenib treated patients (CTC Grade 4) and 1 of 451 patients (CTC Grade 2) in the Placebo group.

Hypophosphatemia: Hypophosphataemia was a common laboratory finding, observed in 45% of Sorafenib treated patients compared to 12% of Placebo patients. CTC Grade 3 hypophosphataemia (1–2 mg/dl) occurred in 13% on Sorafenib treated patients and 3% of patients in the Placebo group. There were no cases of CTC Grade 4 hypophosphataemia (< 1 mg/dl) reported in either Sorafenib or Placebo patients. The etiology of hypophosphataemia associated with Sorafenib is not known.

Lymphopenia: CTC Grade 3 or 4 were reported for lymphopenia in 13% of Sorafenib treated patients and 7% of Placebo patients, for neutropenia in 5% of Sorafenib treated patients and 2% of Placebo patients, for anemia in 2% of Sorafenib treated patients and 4% of Placebo patients and for thrombocytopenia in 1% of Sorafenib treated patients and 0% of Placebo.

Anemia: Observed in 44% of Sorafenib-treated patients and 49% of Placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of Sorafenib-treated patients and 4% of Placebo patients.

Thrombocytopenia: Observed in 12% of Sorafenib-treated patients and 5% of Placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of Sorafenib-treated patients and 0% of Placebo patients.

Further details of the side effect profile of Sorafenib can be found in the current Nexavar® Prescribing Information (Fachinformation).

6.3.2 Standard cytotoxic therapy (Cytarabine and Daunorubicin)

For information of all known adverse drug reactions please refer to the "Fachinformationsverzeichnis Deutschland" in its latest version.

7 STUDY OUTCOME AND STATISTICAL ANALYSIS

7.1 Power and Sample Size Calculation, Interim Analysis

Power calculations are based on the following assumptions:

Control group:	median event free survival (EFS) 9 months
Sorafenib group:	median event free survival (EFS) 13.5 months (improvement of 50%)
Error of first kind:	α =0.05 (two sided)
Power:	80%
Accrual time:	24 months
Follow up:	18 months
Randomization:	1/1 allocation

To detect an improvement of median EFS from 9 months to at least 13.5 months, we need 125 evaluable patients per group i.e. a total of 250 patients to yield the necessary number of approximately 191 events.

Although all efferts will be taken to avoid patient loss to follow up, there might be a rate of loss due to various possible reasons. Censoring by transplantation in first remission will leadi to an additional loss.The rate of allogeneic transplantation is assumed with about 10% of the patients. Patients receiving allogeneic stem cell transplantation will be censored for analysis at the time point of transplant. In order to account for this, exponential hazard of 0.0074 is incorporated in the sample size calculation.

Within 24 months the participating centers are able to recruit up to 300 patients fulfilling the inclusion and exclusion criteria. Taking into account a drop out rate of about 10 % the study-centers will recruit the necessary number of patients (n=276) within 24 months.

All calculations are done using SAS-Software (PROC POWER) licensed to the University of Münster.

One interim analysis and the final analysis are planned for the intent-to-treat EFS endpoint such that the overall type I error is controlled at a two-sided 0.05 level. Interim analysis will be done according to the Obrien/Flemming approach. When 50% of the expected intent-to-treat EFS events (191 events x 0.5 = 95) are attained the first interim analysis on the intent-to-treat EFS endpoint will be conducted.

The (unblinded) interim analysis will be performed by the Studienzentrale SAL in cooperation with Institut für Medizinische Informatik und Biometrie, Münster.

Number of patients

There is an assumption that about 10 % of the patients will receive post remission therapy with allogeneic stem cell transplantation. Those patients will be censored in the analysis at the time point of transplantation. Further under the assumption of loss to follow-up or alternate post-remission treatment, or protocol violation in up to 25 patients, total accrual to this trial is planned for 276 patients (138 per arm).

7.2 Statistical Analysis Plan

We assume an accrual time of 24 months and a follow-up time of 18 months.

The statistical analysis will be performed according to the intention to treat principle (ITT analysis). This means that every patient included into the study and randomized to one treatment arm will be evaluated in that arm, even if he does not receive study-medication, or if any other violations of the study protocol occur.

- The primary endpoint (median EFS) will be compared between both treatment arms using two-sided stratified log-rank test as described in detail. This part of the analysis is considered as confirmatory.
- Analyses of secondary endpoints will include morphologic CR-rate, overall survival, leukemia free interval and leukemia free survival.
- In an exploratory approach EFS and OS will be analyzed using stratified Cox-regression. Treatment arm and cytogenetic findings will be included as independent variables. The results of these analyses will be considered as exploratory. No α-adjustment will be performed.
- In addition to the ITT-analysis a per protocol analysis (PP-analysis) will be performed. This analysis will include only those patients who could be treated with full adherence to the protocol. Besides this, the PP-analysis will parallel the ITT-analysis.

7.2.1 Response criteria and outcome measures

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.

Efficacy

Evaluation of bone marrow aspirate, peripheral blood counts and differentials are used to assess the efficacy of the study medication.

Responding Patients:

Early treatment assessment:

- 16 days after therapy
- blast reduction

Morphologic Complete Response (CR):

- Platelet count >100.000/µl
- Granulocyte count of >1.000/µl
- Bone marrow (aspirate with marrow spicules): < 5% blasts, Absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (Sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent stable hemoglobin value

Complete Remission with incomplete regeneration of peripheral blood (CRi)

- Bone marrow (aspirate with marrow spicules): < 5% blasts, Absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (sensitivity: 5%)
- Absence of extramedullary leukemia
- Peripheral blood with no blast cells and either less than 1.000/µl granulocytes and/or less than 100.000/µl platelets

Cytogenetic Complete Response (CRc):

- Platelet count >100.000/µl
- Granulocyte count of >1.000/µl
- Bone marrow (aspirate with marrow spicules): < 5% blasts, Absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (Sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent stable hemoglobin value
- Normal cytogenetics (based on conventional banded studies and FISH)

Molecular Complete Response (CRm):

- Platelet count >100.000/µl
- Granulocyte count of >1.000/µl
- Bone marrow (aspirate with marrow spicules): <5% blasts, Absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent stable hemoglobin value
- Normal cytogenetics (based on conventional banded studies and FISH)

- Molecularly negative (no detection of pretreatment genetic markers with a methodology providing a sensitivity of at least $1:10^3$)

Treatment failure:

Partial Remission (PR):

- Platelet count >100.000/µl
- Granulocyte count of >1.000/µl
- Bone marrow (aspirate with marrow spicules): Decrease of at least 50% in the percentage of blasts to 5% - 25%

Resistant disease:

- Patient survives ≥ 7 days post Chemotherapy (CT); persistent AML in blood or bone marrow

Death in Aplasia:

- Patient survives ≥ 7 days post Chemotherapy (CT); death while cytopenic, with aplastic bone marrow

Indeterminate cause:

- Patients who die < 7 days post CT; Patients who die > 7 days post CT with no PB blasts, but no bone marrow examination; Patients who do not complete the first course of therapy

Morphologic relapse:

- Reappearance of blasts post CT in PB or bone marrow

Definition of Study Endpoints

Complete remission rate (CR rate):

Proportion of patients in complete remission (CR, as defined above) after induction chemotherapy.

Event free survival (EFS):

Time interval from day 1 of study treatment until

- treatment failure (no CR/ CRi 5 weeks after the beginning of the second induction therapy course),
- relapse from CR
- relapse from morphologic leukemia-free state (CR_i)
- death from any cause

whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR or Morphologic leukemia-free state will be noted. For a patient with none of these events before the end of study follow-up, observation of EFS will be censored at the date of his or her last follow-up examination.

Overall survival (OS):

Time interval from day 1 of study treatment to the day of death. For a patient who is not known to have died by the end of follow-up, observation of OS will be censored on the date the patient was last known to be alive.

8 QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Data Safety Monitoring Board (DSMB)

The Safety Committee of this trial will consist of three members of the scientific community not involved in this trial. The committee will meet quarterly (usually by phone conference) with the National Coordinating Investigator (LKP) of the trial and review all serious adverse events (SAE), suspected unexpected severe adverse reactions (SUSARS) and will be informed about statistically significant differences between the treatment arms. The Safety committee will give recommendations about the continuation of the trial and/or about necessary trial amendments.

8.2 Monitoring

Before the beginning of the study there will be a central meeting for all investigators from all participating centers (initiation meeting). At this meeting there will be a central training concerning all the relevant details of the study.

The National Coordinating Investigator (LKP) is responsible for data monitoring on behalf of the sponsor and has installed a central data monitoring located at the Studienzentrale SAL. During the course of the study each participating center will be visited by a monitor as often as necessary according to the number of patients enrolled. During each of these visits, source data verification will be performed on the basis of a pre-specified monitoring plan generated by the central data monitoring at the Studienzentrale SAL. Discrepancies between documented and source data will lead to queries and will have to be resolved by the investigator. Queries will be documented in a monitoring report and stored in the central data monitoring at the Studienzentrale SAL. Furthermore, at monitoring visits problematic cases as specified by the National Coordinating Investigator (LKP) will be discussed.

At the end of the study there will be a special close out visit for each center.

8.3 Data Management

The National Coordinating Investigator (LKP) is responsible for the data management on behalf of the sponsor. The LKP will make a contract for the central data management with the Koordinierungszentrum für Klinische Studien Dresden (KKS) The KKS provides a validated and certified database, which will be equipped with an audit trail which allows for a full follow-up of the history of each item.

Data capture of the study is partly paper based and partly electronically using pre-specified case report forms (CRF). The documentation of basic patient characteristics required for registration and randomization will be done by the participating investigators. The further

documentation process will be facilitated by a documentation assistant sent by the Studienzentrale SAL. Completed CRFs will be checked and paper CRFs will be collected and delivered to the Studienzentrale SAL by the monitor as soon as the requested data are available.

8.4 Reference Laboratories

Central diagnostics for molecular genetic analyses, cytogenetic analysis and flow cytometry

All diagnostic procedures will be performed centrally in Dresden.

Molecular cytogenetic analyses:

Prof. Dr. C. Thiede

Medizinische Klinik und Poliklinik I

Universitätsklinikum Carl Gustav Carus an der

Technischen Universität Dresden

Hämatologisches Labor Haus 65a

Fetscherstr. 74

01307 Dresden

Tel.: 0351/458-5627 resp. -4251

Fax: 0351/458-4367

Cytogenetic analyses:

Dr. B. Mohr

Medizinische Klinik und Poliklinik I

Universitätsklinikum Carl Gustav Carus an der

Technischen Universität Dresden

Hämatologisches Labor Haus 65a

Fetscherstr. 74

01307 Dresden

Tel.: 0351/458-5619 resp. -2517

Fax: 0351/458-4367

Immunphenotyping:

Dr. U. Oelschlägel

Medizinische Klinik und Poliklinik I

Universitätsklinikum Carl Gustav Carus an der

Technischen Universität Dresden

Hämatologisches Labor Haus 65a

Fetscherstr. 74

01307 Dresden

Tel.: 0351/458-4473 resp. -5621

Fax: 0351/458-4367

For shipment modalities and required material see chapter 5.4.

Reference diagnostics for cytomorphology

As stated above, a central review of selected cases will be performed in the diagnostic reference center:

PD Dr. F. Kroschinsky, Dr. S. Parmentier

Medizinische Klinik und Poliklinik I

Universitätsklinikum Carl Gustav Carus an der

Technischen Universität Dresden

Hämatologisches Labor Haus 65a

Fetscherstr. 74

01307 Dresden

Tel.: 0351/458-3412

Fax: 0351/458-4367

9 INVESTIGATOR'S RESPONSIBILITIES, ETHICAL CONSIDERATIONS, CONFIDENTIALITY, INSURANCE

9.1 Investigator's responsibilities

The Principal Investigators have more than two years experience in the conductance of clinical trials.

9.1.1 Declaration of Helsinki and GCP compliance

On behalf of the sponsor, the National Coordinating Investigator (LKP) ensures that this trial will be conducted in accordance with the Declaration of Helsinki (in its latest version, Seoul 2008) and the ICH Guidelines in Good Clinical Practice as well as with the applicable regulatory requirements.

9.1.2 Protocol adherence

All investigators must adhere to the protocol as detailed in this document. The investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria.

9.1.3 Documentation and retention of records

Case Report Forms (CRFs)

The investigator is responsible for maintaining adequate and accurate CRFs which have been designed to record all observations and other data pertinent to the clinical investigation. CRFs should be filled out completely by the investigator or delegate as stated in the Site Delegation List. The documentation of basic patient characteristics required for registration and randomization will be done by the participating investigators. The further documentation process will be facilitated by a documentation assistant sent by the Studienzentrale SAL. All paper CRFs should be completed in a neat, legible manner to ensure accurate interpretation of the data; a black ball-point pen should be used to ensure the clarity of reproduced copies of all CRFs.

As described in the ICH GCP Guidelines (E6), 'essential documents', including CRFs, source documents, consent forms, laboratory test results, and medication inventory records, will be archived by the investigator according to the current rules and regulations.

Recording, access and retention of Source Data

Source documents are defined as any document where the information is collected during the study procedures for a specific subject. Source documents can be patient's medical file, appointment books, original laboratory reports, X-rays, investigator or nurses notes, etc. Source

data to be collected during this study will include, but are not restricted to: patient's medical file, original laboratory reports, histology, and pathology reports.

9.1.4 Competent local authorities

It is the responsibility of the National Coordinating Investigator (LKP) on behalf of the sponsor to notify the competent local authority of all study centers about the conduct of this trial before starting recruitment. The LKP shall inform the competent local authority within 90 days of termination of the clinical trial. Where the clinical trial has been suspended or interrupted by the LKP, notification shall take place within 15 days, giving the reasons for suspension or interruption.

9.2 Ethical considerations

9.2.1 Institutional Review Board / Independent Ethics Committee approval

It is the responsibility of the principal investigator of each trial site to provide all requested information about qualification of the respective trial site and trial staff to the National Coordinating Investigator (LKP)/ sponsor. The LKP will submit the application for favorable opinion to the IRB/IEC.

The trial may only be conducted as approved by the Ethics committee and the competent authority. Substantial amendments may only be implemented after approval. Additional trial sites may only recruit patients, if the LKP/sponsor already obtained approval for the site.

9.2.2 Audits and Inspections

In compliance with European regulations/ ICH-GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the National Coordinating Investigator (LKP; Studienzentrale SAL) and the regulatory agency(s) direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is responsible for giving any requested support for any monitoring, inspection or audit visit. The investigator has to be available during these visits.

9.2.3 Informed Consent

It is the responsibility of the investigator to obtain written Informed Consent from patients and keep it in the Investigator Site File (ISF). Each patient or the patient's legal guardian is requested to sign the Patient Information and Consent Form after the patient has received

written information and an explanation of what the study involves (i.e., the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities). A copy of the Patient Information and signed Consent Form must be given to the patient or the patient's legal guardian.

9.3 Confidentiality

The investigator must ensure that the patient's encryption is maintained. On the CRFs or other documents submitted to the Studienzentrale SAL, subjects should be identified by a patient number/ randomization number only. The name or date of birth will not be submitted to the Studienzentrale. The investigator at the local trial site will record the name, date of birth and other patient characteristics together with the patient study/ randomization number on the patient identification list, which is part of the Investigator Site File. The site investigator only will be able to identify the patient by patient study number/ randomization number. Documents that are not for submission to the study central office (e.g. signed informed consent forms) should be kept in strict confidence by the investigator.

The investigator may label the specimens for central diagnostics with the patient name and patient study number, because they will not be available of the Studienzentrale SAL. The results of central diagnostics will be reported to the Studienzentrale SAL using the patient study number/randomization number, age and sex only. The name and date of birth of the patients must not be submitted to the Studienzentrale.

9.4 Insurance

According to § 40 AMG, the sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The insurance was taken out at

Allianz Versicherungs-Aktiengesellschaft

10900 Berlin

Fax: 01802 / 400 102

Versicherungsscheinnummer: GHA 30/0446/3357761/490

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The subject is responsible for notification. The insured

person will be agreed to all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject

9.5 Report

After conclusion of the trial, a report shall be written by the National Coordinating Investigator (LKP) on behalf of the sponsor. The report will include a statistical analysis, an appraisal of the results from a medical viewpoint and a safety evaluation. It will be based on the items listed in this trial protocol.

REFERENCES

1. Buchner T, Hiddemann W, Wormann B et al. Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. Blood 1999;93:4116-4124.

2. Buchner T, Berdel WE, Schoch C et al. Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia. J.Clin.Oncol. 2006;24:2480-2489.

3. Mrozek K, Bloomfield CD. Chromosome Aberrations, Gene Mutations and Expression Changes, and Prognosis in Adult Acute Myeloid Leukemia. Hematology 2006;2006:169-177.

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