An Investigator-Initiated Study To Evaluate Ara-C and Idarubicin in Combination with the Selective Inhibitor Of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Relapsed Or Refractory AML

Protocol code	**SAIL**
EudraCT Number	2014-000526-37
Sponsor:	GSO Global Clinical Research B.V.
LKP according to §4 Abs. 25 and §40 Abs. 1 Nr. 5 AMG:	Professor Dr. Michael Heuser, Hannover

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APPROVAL OF THE PROTOCOL BY SPONSOR

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Version	Version 3.1, 13.01.2017

Dr. Anne L. Kranich
CEO, GSO Global Clinical Research B.V.

V. Kranich
Signature

16.01.2017
Date (DD Month YYYY)

APPROVAL OF THE PROTOCOL BY LKP ACCORDING TO §4 ABS. 25 AND §40 ABS. 1 NR. 5 AMG

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Version	Version 3.1, 13.01.2017

Michael Heuser, MD, PhD

Physician, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation (Hannover Medical School)

Signature

Date (DD Month YYYY)

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled:

"An Investigator-Initiated Study to Evaluate Ara-C and Idarubicin in Combination with the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with relapsed or refractory AML", version 3.1 dated 13.01.2017.

and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice, all applicable national regulations as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

Signature	Date (DD Month YYYY)
Investigator	Investigator's Institution

SYNOPSIS

Protocol code.	**SAIL**
Protocol version (Date)	Version 3.1, dated 13.01.2017
Detailed title	Evaluation of Ara-C and Idarubicin in Combination with the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with relapsed or refractory AML
EudraCT no.	2014-000526-37
LKP according to §4 Abs. 25 and §40 Abs. 1 Nr. 5 AMG	Professor Dr. Michael Heuser, Hannover
Sponsor	GSO Global Clinical Research B.V. EBC Amsterdam Keizersgracht 62-64 1015CS Amsterdam The Netherlands
Study design	Multi center, open-label, non-randomized Phase 2 trial. Patients with relapsed/refractory Acute Myeloid Leukemia (AML) will receive standard chemotherapy cytosine arabinose (Ara-C) 100mg/m² days 1-7 and Idarubicin 10 mg/m² days 1, 3, 5 every 4 weeks (max. 2 cycles) and Selinexor as a flat dose of 60 mg twice weekly during weeks 1-3 of a 4-week cycle starting on Day 2 of week 1 (total of 6 doses per induction cycle). If a bone marrow CR or CRi was achieved the patient will be recommended for stem cell transplantation, which represents the end of study treatment. If a partial remission was achieved an additional induction cycle will be initiated. Patients achieving CR or CRi, who are not eligible for SCT will receive consolidation therapy with AraC (3 cycles) in parallel to maintenance with Selinexor until relapse. Patients with >50% blast reduction after 2 cycles will continue maintenance with Selinexor until PD. Patients will be evaluated for disease status at the end of each 4-weeks induction cycle and approximately every 3 months after allogeneic SCT or CR (or CRi) has been achieved until relapse or death, whichever is first.
Duration of study	The planned number of 40 patients was reached. End of enrolment period: June 2016. End of study is defined as 2 years after registration of last patient
Total number of sites	6-8

Study population	Patients with relapsed/refractory Acute Myeloid Leukemia (AML) according to the inclusion and exclusion criteria will be enrolled in this study trial.
Objectives	
Primary objective	• To determine the efficacy of Selinexor in combination with standard chemotherapy in patients with relapsed/ refractory AML by determination of rate of complete remission (CR) or morphologic complete remission with incomplete blood count recovery (CRi), as defined by the recommendations on diagnosis and management of AML in adults from an international expert panel, on behalf of the European LeukemiaNet[(1)]
Secondary objectives	• To determine the efficacy of Selinexor in combination with standard chemotherapy in patients with relapsed/ refractory AML by o Rate of partial remissions o Percentage of patients being transplanted after induction therapy o Early death rate o Overall survival (OS) o Event-free survival • To evaluate overall safety and tolerability of Selinexor characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03), timing and relatedness of adverse events (AEs) and laboratory abnormalities observed during the treatment within this study.
Exploratory objectives	To identify the Pharmacokinetics and Pharmacodynamics of Selinexor in patients with relapsed/refractory AML
Planned sample size	A sample size of 40 patients is planned and all patients receive standard chemotherapy with Selinexor. If a CR is achieved patients are intended to receive stem cell transplantation.
Inclusion criteria	To be eligible for this trial, patients must meet the following criteria: 1. Cytological or histological diagnosis of AML with the exception of promyelocytic leukemia (AML M3) 2. Patients must have relapsed/refractory disease (relapse after stem cell transplantation is permitted) as defined as: patients with <PR after first cycle of induction chemotherapy, or b. patients with <CR(i) after second cycle of induction chemotherapy, or c. patients who relapse after conventional chemotherapy or d. patients who have undergone a single stem cell transplantation and who have relapse of their AML.

	3. Men and women aged ≥18 years and eligible for standard dose of chemotherapy (7+3); 4. A period of at least 3 weeks needs to have elapsed since last treatment (with the exception of hydroxyurea) before participating in this study. Hydroxyurea induction therapy to reduce peripheral blast counts is permitted prior to initiation of treatment on protocol. Treatment may begin in <3 weeks from last treatment if deemed in the best interest of the patient after discussion with the PI of the study; 5. ECOG performance status ≤ 2 6. Serum biochemical values with the following limits unless considered due to leukemia: creatinine ≤2 mg/dl; total bilirubin ≤2x ULN, unless increase is due to hemolysis or congenital disorder; transaminases (SGPT or SGOT) ≤2.5x ULN. 7. Ability to swallow and retain oral medication 8. Ability to understand and provide signed informed consent; 9. Cardiac ejection fraction must be >/=50% (by echocardiography). 10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
Exclusion criteria	Patients with any of the following will not be eligible for participation: 1. Treatment with any investigational agent within four weeks. 2. Cumulative anthracycline dose (daunorubicin or equivalent) >360 mg/m² 3. HIV infection 4. Presence of any medical or psychiatric condition which may limit full compliance with the study, including but not limited to: 5. Presence of CNS leukemia 6. Unresolved toxicity from previous anti-cancer therapy or incomplete recovery from surgery. 7. For patients after SCT as part of prior treatment: a. Necessity of immunosuppressive drugs b. GvHD > grade 1 8. Any of the following within the 12 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis, or other thromboembolic event. 9. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2. 10. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study. 11. Clinically significant bleeding within 1 month

Treatment scheme	All enrolled patients may participate in an optional baseline translational research study. Patients will receive single dose of Selinexor (60 mg) after registration and before first induction cycle. Bone marrow aspirate samples will be collected pre-dose and 24 hour post-dose. All enrolled patients will be treated with Ara-C at a dose of 100 mg/m² continuous infusion (day 1-7) and idarubicin at a dose of 10 mg/m² iv (day 1,3,5) every 4 weeks and Selinexor. If a second cycles is applied idarubicin is only given on day 1 and 3). Selinexor will be administered at a dose of 60 mg twice weekly orally during weeks 1-3 of a 4-week cycle (day 2,4,9,11,16,18) (total of 6 doses per induction cycle). If a CR was achieved the patient will be recommended for stem cell transplantation and will have his/her end of treatment and will be followed for event-free and overall survival. If patient has achieved a PR an additional cycle (4 weeks) will be initiated. If a CR was achieved the patient will be recommended for stem cell transplantation and will be followed for event-free and overall survival. In patients achieving CR or CRi after 1 or 2 4-week cycles who are not eligible or do not undergo additional stem cell transplantation, but, in the opinion of the investigator, are benefiting from Selinexor, then oral Selinexor dosed twice weekly may be continued parallel to consolidation therapy with Ara-C until relapse or toxicity develops. The dose of Ara-C is 3 g/m² IV for 2h every 12 hours at 3 consecutive days for patients with good performance status and younger than 60 years (in total 6 doses). If patients are older than 60 years the dose is 1 g/m² IV for 2h every 12 hours at 3 consecutive days. Consolidation with AraC will consist of 3 4-week cycles. During consolidation Selinexor dosing (60 mg) will start on day 2 and continue twice weekly in weeks 1-3 of a 4-week cycle (total of 6 doses per cycle). Selinexor twice weekly (with ~48 hours between two consecutive doses) in weeks 1-3 of a 4-week cycle at a dose of 60 mg (total of 6 doses per 4-week cycle) may continue until relapse or for maximally 1 year of treatment. Patients achieving a > 50% blast reduction after the end of 2 induction cycles, not candidates for SCT, and in the opinion of the investigator, are benefiting from Selinexor, oral Selinexor dosed twice weekly may be continued until PD or for maximally 1 year of treatment. Drug administration will occur twice weekly with ~48 hours between two consecutive doses at a dose of 60 mg. One cycle is 4 weeks with 6 doses of Selinexor during weeks 1-3. (e.g.

	on Monday and Wednesday or on Tuesday and Thursday or on Wednesday and Friday). Treatment will continue until progression of disease (PD) or unacceptable toxicity, withdrawal of consent by the patients, or non-compliance by the patient with protocol requirements. Patients for whom none of the above mentioned is achieved after 2 4-week induction cycles will have their end of treatment and will be followed for overall survival.
Primary Endpoint	Percentage of patients achieving a complete response (CR) or CRi (complete remission without normalization of peripheral blood counts)
Secondary Endpoints	• Partial response rate • Percentage of patients undergoing subsequent allogeneic stem cell transplant • Early death rate • Overall survival (OS) • Event-free survival (Events are defined as Death, not achieving a CR or CRi, Relapse after CR or CRi) • Toxicity (acc. to NCI CTC AE v4.03)
Exploratory Endpoints (Optional Studies)	• Limited pharmacokinetics to measure plasma concentration of Selinexor • Selinexor-induced changes in mRNA levels of XPO1 and tumor suppressor markers • Selinexor-induced changes in plasma cytokine levels • Selinexor-induced changes in gene expression profiling of leukemic blasts isolated from patients • Expansion of leukemic blasts in mice for therapeutic studies
Efficacy assessment	Clinical and Bone Marrow Aspirate examinations and safety assessments are performed at baseline, at the End of induction cycles and if applicable at the end of each consolidation cycle. Disease status during maintenance will be evaluated at the end of each cycle and Follow-up after SCT every 3 months ± 28 days If a patient discontinues treatment due to any other reason than disease progression/ death/ withdrawal of informed consent, the disease evaluations shall continue until definition of relapse-free survival are met. This includes patients who wish to discontinue treatment, but agree that further data is captured for the purpose of the study (partial withdrawal).
Safety assessment	All adverse events occurring during the course of the trial and for up to 30 days after the last dose of study medication will be captured, documented and reported. Toxicity will be graded twice weekly during treatment.

	Until recovery of platelets and ANC, hematology assessments are done as often as necessary to determine the exact date of recovery of platelets and ANC. Safety laboratory assessments include complete blood count, time to recovery of platelets ≥ 50x 10^9/L and ≥ 100x 10^9/L, ANC recovery ≥ 0.5x 10^9/L and ≥ 1.0x 10^9/L, clinical chemistry, including liver function test, coagulation, and 12-lead electrocardiogram as well as cardiac ultrasound.
Statistical considerations	**Primary Efficacy Parameter** The primary efficacy measure will be the rate of complete responders (CR). **Secondary Efficacy Parameters** The secondary efficacy measures: • Rate of partial remissions • Percentage of patients being transplanted after induction therapy • Early death rate will be analyzed as rates. • Overall survival (OS); • Event-free survival (Events are defined as Death, not achieving a CR or CRi, Relapse after CR or CRi) will be described by median survival time and respective 95%-confidence intervals.
Sample size calculation	The sample size calculation is based on the evaluation of response rates according to Fleming for single-stage phase II designs. For the Fleming's procedure the two response levels p0 (expected CR rate) and p1 (meaningful increase in CR rate) are specified as p0=30% and p1=60%: N=25 patients should participate in the study to ensure a power of $1-\beta=0.90$ for the discrimination of p0 and p1. According to Fleming the null hypothesis should be rejected if at least $r = \left[Np_0 + Z_{1-\alpha}\sqrt{Np_0(1-p_0)} \right]_{*}+1$ responses are observed (x* denotes the nearest integer to). With p0 and N defined as above and $Z1-\alpha = (1-\alpha)$-quantile of the normal distribution = 1.645 at least 12 responders should be observed to show the efficacy as postulated. Using the same approach in the 15 additional patients, submitted to an adapted drug regimen, the power will be 80% to discriminate a p0=30% (expected CR rate) from a p1=65% (meaningful increase in CR rate), if 8 out of 14 completed patients are considered as responders, with a one-tailed alpha error of 5%. Alternatively, the power will be 90% to discriminate a p0=30% from a p1=70% again if 8 out of 14 completed patients are considered as responders, with a one-tailed alpha error of 5%.

Accompanying baseline translational study (optional)	Leukemic blast cells will be isolated pre- and 24 hr post- a single Selinexor dose (60 mg) given at baseline (after registration and before first induction cycle). Blast cells will be used for leukemic stem cell gene expression profiling and in mouse model studies to define parameters associated with clinical responsiveness to Selinexor.
Data Monitoring Committee	An independent Data Monitoring Committee (DMC) will be implemented that reviews accumulating data of the clinical trial with respect to any potential safety issues, study progress and critical efficacy endpoints. The DMC will be an independent board consisting of 2-3 physicians with special expertise in AML. A physician is not allowed to participate in this clinical trial while serving on the DMC. The DMC will be supported by an independent statistician, if necessary. The DMC will review safety data, recovery times and efficacy of the clinical trial and support the interpretation of clinical trial results.

INFORMATION TO BE PROVIDED REGARDING SAES/PREGNANCY

In the case of a serious adverse event (SAE) or pregnancy, the following person must be contacted by fax within 24 hours:

Clinical Trial Manager	**Dr. Anne L. Kranich**
Address:	**GSO mbH** **Gesellschaft für Studienmanagement und Onkologie mbH** **Harvestehuder Weg 21** **20148 Hamburg**
Phone:	**+49 40 44 19 54 60**
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List of Abbreviations

β-HCG	Beta human chorionic gonadotropin
AE	Adverse event
AESI	Adverse event of special interest
ACS	Acute Cerebellar Syndrome
ALT (SGPT)	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolut Neutrophil Count
aPTT	Activated partial thromboplastin time
AraC	Cytarabin
AST (SGOT)	Aspartate aminotransferase
BP	Blood pressure
BSA	Body surface area
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract research organisation
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
D	Day
DLBCL	Diffuse large B-Cell lymphoma
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FU	Follow-Up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
GRP	Growth regulatory protein
GvHD	Graft-versus-Host Disease
h	Hour
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
ITT	Intent to treat
IV	Intravenous
LCS	Leucemia stem cells
LDH	Lactate dehydrogenase
LIC	Leucemia-initiating cells
LVEF	Left ventricular ejection fraction

m^2	Square metre (body surface area)
MCL	Mantle cell lymphoma
mg	Milligram
MI	Myocardial infarction
min	Minute
mL	Millilitre
mRNA	Messenger Ribonucleic acid
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
PT	Prothrombin time
RBC	Red blood count
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Stable disease
SINE	Selective inhibitor of nuclear export
SADR	Serious adverse drug reaction
SUSAR	Suspected unexpected serious adverse reaction
T-ALL	T- Acute lymphoblastic leukemia
TSP	Tumor suppressor protein
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
XPO1	Exportin 1

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Acute myeloid leukemia

Acute myeloid leukemia (AML) is a malignancy of hematopoietic progenitor cells [2]. Patients below an age of 60 years are treated with 1-2 cycles of standard chemotherapy usually with cytosine arabinoside (Ara-C) and daunorubicin according to the 7 + 3 schedule. Between 70-80% of patients achieve a complete remission. Both American [3, 4] and European [5] cooperative group studies have found that the choice of anthracycline (daunorubicin or idarubicin, or the anthracenedione mitoxantrone) is of little consequence, assuming equitoxic doses are administered. Thereafter, patients receive consolidation therapy which is guided by the European LeukemiaNet (ELN) risk criteria [6, 7]. Patients with good risk receive several cycles high dose Ara-C[8, 9], patients with intermediary risk I and II and patients with unfavorable prognosis are transplanted in first CR if a suitable donor is available and no contraindications to stem cell transplant exist. In Germany, up to two thirds of patients receive an allotransplant in first remission. With this strategy 70-80% of patients are cured in the good risk category [10, 11], 50% in the intermediary risk and 20-40% in the high risk category [12].

Recurrent/ Relapsed AML

Patients with relapsed AML usually have a dismal prognosis[13]. The best outcome is achieved in patients who receive an allotransplanting with about 20% - 40% of patients being long term survivors [14]. The best results with allografting are achieved in patients who have achieved a second remission [15]. The chance of a second CR depends of the duration of the first remission, the karyotype and the performance status of the patient.

No standard regimen exists for the treatment of patients with relapsed acute myeloid leukemia (AML), particularly in patients with a first remission duration of less than 1 year [16]. A number of agents have activity in recurrent/relapsed with an overall response rate of 20-80%, depending on study design and treatment (see Table 1, Appendix 1). Re-induction with Ara-C and daunorubicin will result in a 50% CR rate in patients who had a first remission lasting longer than 1 year [17-19]. In a trial of mitoxantrone in combination with Ara-C in patients with refractory or relapsed AML with 49 patients 62.5% with first relapse AML achieved complete remission while none of the four patients with more than one prior remission responded [20]. A triple combination of mitoxantrone, etoposide, and cytarabine (MEC) demonstrated a CR induction rate of 55% in a population including 30 patients with relapsed AML, 28 patients with primary refractory AML, and 16 patients with secondary AML[21]. A phase 1-2 study of clofarabine plus Ara-C in 25 patients with relapsed acute myeloid leukemia 7 (22%) achieved complete remission (CR), and 5 (16%) achieved CR with incomplete platelet recovery (CRi), for an overall response rate of 38%[22]. For patients not achieving a complete remission the only potentially curative treatment option is allogeneic transplantation with up to 20% of patients being long term survivors[14].

Therefore, the combination of Ara-C and idarubicin was chosen for standard induction therapy and if the patient receives complete remission transplantation is recommended.

In the light of a dismal prognosis for patients with relapsed/rectory AML a great clinical need exists for new treatment options.

1.1.2 Selinexor

Over 10 major tumor suppressor pathways have evolved in order to prevent the development and progression of neoplasia. Because the vast majority of tumor suppressor (TSP) and growth regulatory (GRP) proteins require nuclear localization in order to carry out their antineoplastic activities, enhancing their nuclear export leads to their functional inactivation. The major TSP/GRP are exported exclusively by the protein CRM1 (also called XPO1), and tumors showing elevated CRM1 levels with cytoplasmic mislocalization of TSP/GRP.

Additional detailed information is provided in the Investigator's Brochure.

Selinexor is an orally available, irreversible, potent and Selective Inhibitor of Nuclear Export (SINE) that specifically blocks XPO1. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. Normal cells, with minimal or no DNA damage, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE compounds are not intrinsically cytotoxic; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

1.1.2.1 Preclinical Efficacy

In vitro experiments with continuous (~72 hour) exposure to Selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture including multiply-resistant cancers, with the majority of IC50s for cytotoxicity <800 nM and most hematologic tumor lines having IC50s of 20-400 nM for Selinexor. In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC50s were typically >5 µM. Efficacy was demonstrated in mouse models of myeloma, mantle cell lymphoma (MCL), and T-cell acute lymphocytic leukemia (T-ALL) xenografts. Moreover, efficacy including significant survival advantages was demonstrated in acute myeloid leukemia (AML) [MV4-11 (FLT3-ITD)] [23, 24] and chronic lymphocytic leukemia (CLL) (TCL-1) leukemografts. Efficacy was also demonstrated in solid tumor xenografts including prostate, breast, liver, glioblastoma, kidney and colon cancers. KPT-276 and KPT-335, SINEs closely related to Selinexor, have been given orally to several dogs with various cancers in ongoing pilot studies, and clear evidence of antitumor activity with acceptable tolerability has been obtained in dogs with both *de novo* newly diagnosed and chemotherapy (e.g. CHOP- (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone-resistant diffuse large B cell non-Hodgkin's lymphoma (DLBCL) in dogs. In a Phase 2b study of newly diagnosed or first relapsed NHL (mainly DLBCL) in dogs, KPT-335 induced a 34% objective response rate (≥50% tumor shrinkage) as a single agent. Reduced food intake, which can be accompanied by weight loss, was observed; food supplementation can largely overcome this and dosing has been maintained for over 6 months in dogs with cancer.

1.1.2.1.1 Preclinical Efficacy: AML

AML cells overexpress the nuclear exporter, Exportin 1 (XPO1/CRM1) and higher XPO1 levels correlate with poor outcome [28]. The novel selective inhibitor of nuclear transport (SINE), Selinexor, antagonizes XPO1 and shows potent cytotoxicity for AML and ALL cells in vitro, independent of genotype.

Selinexor show potent antiproliferative effect and induced apoptosis, cell cycle arrest and myeloid differentiation in AML cell lines and patient blasts, including those from patients with NPM1 and FLT3-ITD mutations [23].

Mechanistic studies show that SINE induces nuclear localization and activation of multiple tumor suppressor proteins (TSPs), leading to rapid apoptosis of AML cells. In addition, a strong down-regulation of the oncogenes FLT3 and c-KIT were observed after SINE treatment in both FLT3-ITD and wild-type cell lines [23]. Selinexor treatment also restored the localization of cytoplasmic mutant NPM1 into the nucleus.

In murine AML and ALL models, Selinexor showed potent antileukemic activity without toxicity to normal hematopoietic cells [23,24,29].

1.1.2.2 Preclinical Safety

In the Selenixor nonclinical safety program in Spegue-Dawley rats and cynomolgus monkeys, the primary effects of oral Selinexor were dose-dependent reductions in food intake and body weight (or reductions in body weight gain), with minimal clinical symptoms (no or mild non-bloody diarrhea), associated primarily with gastrointestinal atrophy. Similar effects are observed in mice and dogs. At high repeated doses of Selinexor associated with marked weight loss, there were changes in cerebellar granular layer neurons in both rats (≥300 mg/m²) and monkeys (≥72 mg/m²), but only monkeys showed any CNS symptoms. No central nervous system (CNS)-related adverse side effects were observed in the GLP, rat and monkey 4-cycle toxicity studies. A GLP, rat neurofunctional study (Irwin test) has also been performed at dose levels of 12, 60, or 300 mg/m² (2, 10, and 50 mg/kg). No behavioral changes were observed at all doses tested.

In the pivotal, GLP, 4-week monkey study, there was no evidence of a direct or indirect effect of Selinexor on the morphology and intervals of the ECG at up to 36 mg/m² (3 mg/kg). Based on these results, QT prolongation or other cardiac effect does not appear to be a safety concern for Selinexor.

In summary, dose limiting toxicity (DLT)/mortality in both rats and monkeys is related primarily to marked weight loss with atrophy of the gastrointestinal (GI) tract and noncritical effects on other major organs.

Further detailed information is provided in the Investigator's Brochure.

1.1.2.3 Clinical Efficacy

Karyopharm Therapeutics is currently conducting three open label Phase 1 clinical trials to assess the safety, tolerability and efficacy of Selinexor given orally 2-3 times per week. The first study (KCP-330-001) is a dose escalation study in patients with advanced hematological malignancies, the second (KCP-330-002) is a dose escalating study in patients with advanced or metastatic solid tumor malignancies and the third (KCP-330-003), a food effect study, is in patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. All patients entering these single-agent phase 1 studies have relapsed after available therapies and have objectively progressing tumors at time of study drug initiation. To date Selinexor has been administered to over 130 patients. The food effect study was initiated in July 2013, so preliminary safety or efficacy data are not yet available.

In the Phase 1 study (KCP-330-001) a total of 39 patients with relapsed AML have been enrolled. As of December 4, of 33 pts who were evaluable for response, complete response (CR) with full hematological recovery was achieved in 4 patients (11%), and CR without hematological recovery (CRi) in 1 patient (3%). Partial Response (PR) was achieved in 2 patients (6%). Morphological leukemia free state was achieved in 1 patient (3%). Ten (29%) of the remaining patients have had stable disease for > 30 days, and 13 (34%) have had progressive disease.

Table 1: Responses in Arm 2 (AML) [16.8 mg/m² to 40 mg/m²] (Study KCP-330-001) as of December 4, 2013

Responses in Arm 2 Acute Myeloid Leukemia Patients as 4-Dec-2013								
Number of Pts Evaluated	Total CRs, CR(i)s, PRs, and SD (%)	CR (%)	CR (i) (%)	PR (%)	MLFS (%)	SD (%)	PD	WC
33	18 (55%)	4 (12%)	1 (3%)	2 (6%)	1 (3%)	10 (30%)	11 (33%)	4 (12%)

Abbreviations: N=number of patients, CR=complete remission, CRi=complete remission without platelet recovery, PR=partial response, MLFS=morphological leukemia free state, SD=stable disease, PD=progressive disease, NE=not evaluable, WC=withdrew consent.

1.1.2.4 Clinical Safety

Gastrointestinal adverse events and fatigue are the most common types of AEs seen in Arm 2 (AML) patients. As of 8 November 2013, Karyopharm has reports of AEs in 36 of the 38 patients enrolled in this arm and the AE prevalence percentages below are based upon 38 patients. As of 8 November 2013, the gastrointestinal adverse events typically consist of nausea in 22 patients (58%), anorexia in 17 patients (45%), vomiting in 13 patients (34%) and weight loss in 10 patients (26%). The gastrointestinal events are primarily Grade 1 or Grade 2 events that are generally responsive to standard supportive care. Fatigue was observed in 18 patients in this arm (47%) as of 8 November 2013, including Grade 3 fatigue in three patients (8%) and Grade 1 or Grade 2 fatigue in 15 patients (39%). Karyopharm has also observed Grade 4 thrombocytopenia in three patients (8%) in this arm as of 8 November 2013. Karyopharm expects that the thrombocytopenia is primarily a result of patients entering this arm with marked bone marrow suppression due to both disease and prior therapies.

It is anticipated that fewer and more mild gastrointestinal events and reduced fatigue will be observed in the future as a result of the initiation of supportive care and medications prior to beginning Selinexor therapy.

To date, over 1,800 patients have received Selinexor in clinical studies. Of these, 1,175 patients were evaluable for safety as of 31 May 2016.

Since the beginning of this study new safety data were revealed from other ongoing clinical trials with Selinexor. Four cases of Nervous System Disorders are described below. The necessity to report all cases of cerebellar toxicity ≥ 3 as SAE is included in the Safety Reporting Procedures in chapter 7.

One patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome (ACS) following 3 doses of selinexor at 85 mg/m^2 twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Selinexor was permanently discontinued, and the patient recovered to near baseline over ~6 weeks.

A five-year-old male patient with refractory AML and prior stem cell transplant (SCT) had severe body pain, followed the next day by irritability, aphasia, and lower extremity weakness after receiving 4 doses of selinexorr (70 mg/m^2) and 5 days fludarabine and cytarabine. The event was considered to be ACS. Selinexor was permanently discontinued and the patient recovered completely after 6 weeks.

A 19-month-old patient with relapsed AML and without prior SCT was unable to hold his trunk or head straight and demonstrated erratic use of his hands on study day 13, after receiving 4 doses

of Selinexor (70 mg/m^2) and prior to receiving fludarabine or cytarabine. The event was considered to be ACS. Selinexor dosing was permanently discontinued and his ataxia improved over the course of two weeks.

An 18-year old female patient with heavily pre-treated, refractory AML developed cognitive disturbance Grade 3 after receiving 4 doses of Selinexor 56 mg/m² twice weekly. Symptoms included flat affect and brief episodes of non-responsiveness, but not focal or gait disturbances. Selinexor was held and the symptoms resolved within one week,however, after restarting treatment and receiving two additional doses , the symptoms returned and selinexor was permanently discontinued. The symptoms returned to near baseline. The event differs from ACS seen in the other patients, as the patient had pre-existing MRI abnormalities, including cerebellar disease, but did not develop focal abnormalities or gait disturbances.

ACS is defined as Adverse Event of Special Interest (AESI), see section 7.1.5. A further AESI is the development of (or worsening of existing) cataracts during treatment with Selinexor. In 30 patients (3%), a cataract (or worsening of existing cataract) occurred, but in all cases, prior or ongoing use of other drugs associated with cataracts, diabetes or age-related progression have been implicated in cataract worsening. Most of the cases were worsening of existing cataracts.

1.2 Study Rationale

Selective inhibition of nuclear export (SINE) is a novel therapeutic strategy that could potentially be applicable to many cancers. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared. *In vivo* efficacy was observed with Selinexor treatment groups in mouse models of different types of cancer. Moreover, efficacy including significant survival advantages was demonstrated in acute myeloid leukemia (AML) [MV4-11 (FLT3-ITD)] [23, 24], and chronic lymphocytic leukemia (CLL) (TCL-1) leukemografts. These studies demonstrate potent *in vitro* and *in vivo* efficacy of Selinexor against a variety of cancer tumor models as a standalone agent or in combination with a variety of anti-cancer modalities.

In a recent study the safety and efficacy of Selinexor and Ara-C as single agent or in combination was tested in vivo. Treatment with AraC or Selinexor alone significantly prolonged the survival of leukemic mice from a median survival of 24 days (APL + vehicle) to 33 days or 39 days, respectively (P < 0.0001). Encouragingly, combination therapy with AraC + KPT-330 further prolonged survival compared to monotherapy (P < 0.0001), with some mice being cured of the disease.

In the Phase 1 study (KTP-330-001) 5 out of the 33 AML patients (15%) have experienced a complete remission (CR)/ complete remission without platelet recovery (CRi).

Because of the encouraging efficacy, unique mechanism of action and clinical safety, it is considered to be a suitable agent to study in the combination with Ara-C and Idarubicin.

2 OBJECTIVES OF THE STUDY

2.1 Primary Objective

The primary objective is to determine the efficacy of Selinexor in patients with relapsed/ refractory AML by complete response rate (CR) or CRi), as defined by the recommendations on diagnosis and management of AML in adults from an international expert panel, on behalf of the European LeukemiaNet[(1)].

2.2 Secondary Objectives

Secondary objectives of the study are:

- To determine the efficacy of Selinexor in combination with standard chemotherapy in patients with relapsed/ refractory AML by:
    - Rate of partial remissions
    - Percentage of patients being transplanted after induction therapy
    - Early death rate
    - Overall survival (OS)
    - Event-free survival (Events are defined as Death, not achieving a CR or CRi, Relapse after CR or CRi)
- To evaluate overall safety and tolerability of Selinexor characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03), timing and relatedness of adverse events (AEs) and laboratory abnormalities observed during the treatment within this study

2.3 Exploratory Objectives (Optional Studies)

- Translational Research on Patient Leukemic Blast Cells
    - Selinexor-induced changes in gene expression profile of leukemic blasts isolated from patients
    - Expansion of leukemic blasts in mice for therapeutic studies
- Pharmacokinetics and Pharmacodynamics of Selinexor in patients with relapsed/refractory AML will be assessed in an explorative manner.
    - Limited PK to assess Selinexor plasma level
    - Pharmacodynamic assessments
        - Selinexor-induced changes in mRNA levels of XPO1 and tumor suppressor markers from leukocytes
        - Selinexor-induced changes in plasma cytokine levels

3 STUDY DESIGN

3.1 Overview of Study Design and Dosing Regimen

This is a multi center, open-label, non-randomized phase II trial study.

Patients are informed, screened and enrolled in the study at the time of progression of disease on prior chemotherapy documented by Bone Marrow Aspirate. Treatment should start within two weeks after enrolment.

The study design is displayed in Figure 1.

3.1.1 Baseline Translational Research Study (optional)

All enrolled patients may participate in an optional baseline translational research study. Patients will receive single dose of Selinexor (60 mg) after registration and before first induction cycle. Bone marrow aspirate samples will be collected pre-dose and 24 hour post-dose. Blast cells will be used for leukemic stem cell gene expression profiling and in mouse model studies to define parameters associated with clinical responsiveness to Selinexor. See 5.1.2.1 for more details.

3.1.2 Definition of Treatment Cycle

All enrolled patients will be treated with cytosine arabinoside (Ara-C) at a dose of 100 mg/m² continuous infusion (day 1-7) and idarubicin at a dose of 10 mg/m² i.v. (days 1,3,5) every 4 weeks and Selinexor for a maximum of 2 cycles. During the second cycle the idarubicin dose is restricted to 2 administrations on day 1 and 3.

Patients will receive oral Selinexor 60 mg twice weekly in weeks 1-3 of a 4-week cycle (Monday/ Wednesday or Tuesday/ Thursday or Wednesday/Friday) starting on day 2 of week 1 (total of 6doses per induction cycle).

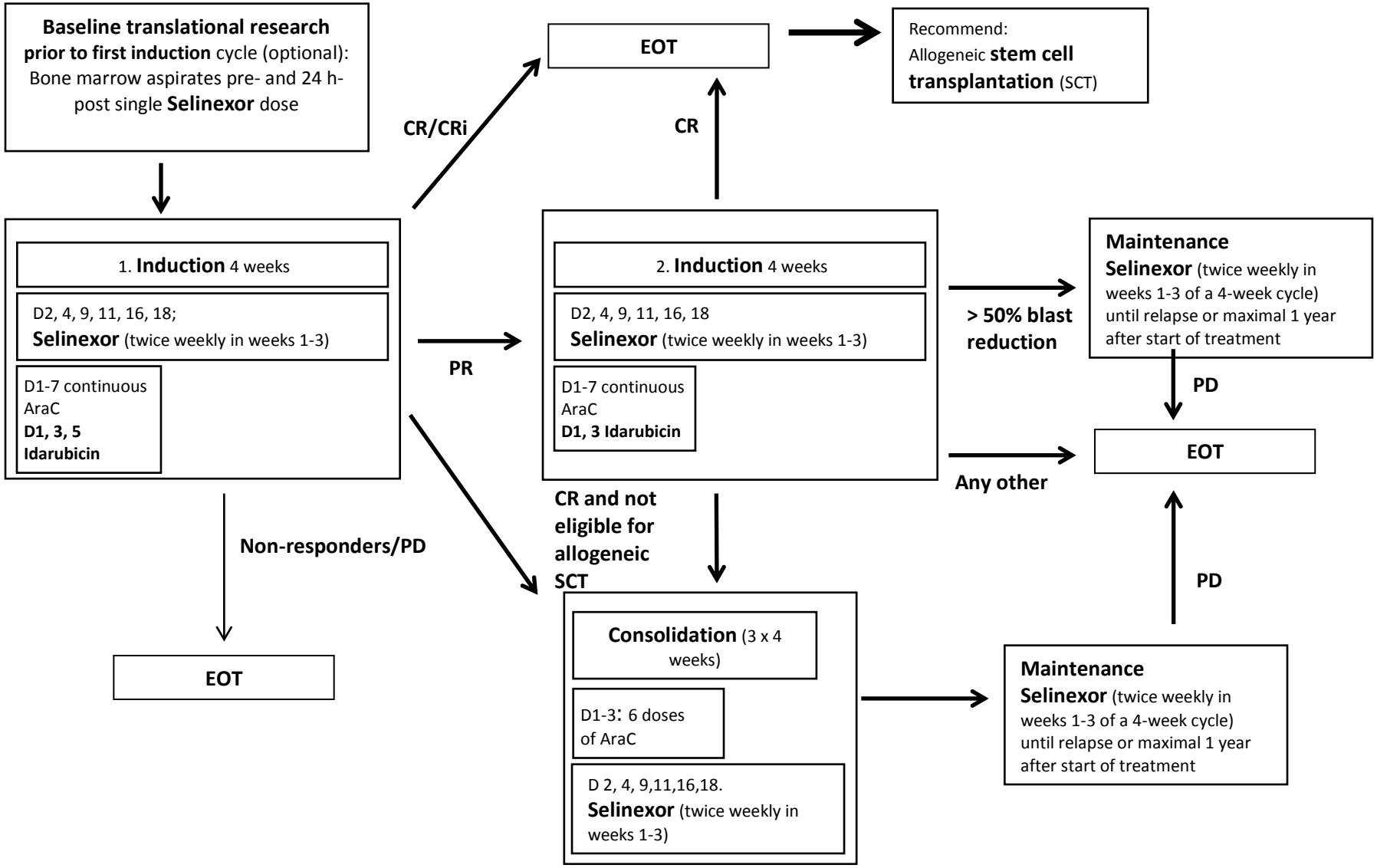
If a CR or CRi was achieved, patients will be recommended for stem cell transplantation. If a PR is achieved patients can undergo a second, identical treatment cycle.

In patients who are not eligible or do not undergo additional stem cell transplantation, but, in the opinion of the investigator, are benefiting from Selinexor, then oral Selinexor dosed twice weekly in weeks 1-3 of a 4-week cycle may be continued parallel to 3 cycles of consolidation therapy with Ara-C until relapse or toxicity develops. The dose of Ara-C is 3 g/m² IV for 2h every 12 hours at 3 consecutive days for patients with good performance status and younger than 60 years (in total 6 doses). If patients are older than 60 years the dose is 1 g/m² IV for 2h every 12 hours at 3 consecutive days. During consolidation Selinexor dosing (60 mg) will start on day 2 of week 1 of a 4-week cycle and will be continued twice weekly during weeks 1-3 of a 4-week cycle (total of 6 doses per cycle). Selinexor twice weekly (Monday/ Wednesday or Tuesday/ Thursday or Wednesday/Friday) in weeks 1-3 at a dose of 60 mg (total of 6 doses per 4-week cycle) may continue until relapse or for maximally 1 year of treatment.

Patients achieving a > 50% blast reduction after the end of 2 induction cycles and in the opinion of the investigator, are benefiting from Selinexor and are not candidates for Stem cell transplantation, oral Selinexor dosed twice weekly in weeks 1-3 may be continued. Drug administration will occur twice weekly, on days 1 and 3 of weeks 1-3 of a 4-week cycle at a dose of 60 mg (e.g. on Monday and Wednesday or on Tuesday and Thursday or on Wednesday and Friday). One cycle is 4 weeks with 6 doses of Selinexor.

Safety assessments are performed at baseline visit, twice weekly during induction treatment, at the End of Cycle and at the End of Treatment visit. Clinical and Bone Marrow Aspirate for disease status are performed at baseline, at the end of the cycle during induction and consolidation. During maintenance and follow-up after SCT bone marrow aspirate is required in case of suspicious blood counts. If a patient discontinues treatment due to any other reason than disease progression/ death/ withdrawal of informed consent, the disease evaluations shall continue until disease progression. This includes patients who wish to discontinue treatment, but agree that further data is captured for the purpose of the study (partial withdrawal).

Figure 1: Study Flow Chart



3.1.3 Treatment Duration

Treatment duration for patients achieving CR or CRi during induction will be 1 or 2 cycles of 4 weeks each. These patients will be recommended for stem cell transplantation and have their end of treatment prior to SCT and will be followed for event-free and overall survival.

For patients achieving CR or CRi but who are not eligible or do not undergo additional stem cell transplantation, will continue in consolidation/maintenance therapy with 3 cycle of AraC combined with 4-week cycles with twice-weekly Selinexor during weeks 1 and 3 until relapse (for maximally 1 year of treatment).

Patients with a > 50% blast reduction at the end of 2 induction cycles and in the opinion of the investigator, are benefiting from Selinexor, will in maintenance therapy with 4-week cycles with twice-weekly Selinexor in weeks 1-3 until progression of disease (for maximally 1 year of treatment).

For patients for whom none of the above mentioned is achieved after 2 4-week induction cycles will discontinue study and will be followed for overall survival.

In any case, treatment will be discontinued upon progression of disease (PD) or unacceptable toxicity, withdrawal of consent by the patients, or non-compliance by the patient with protocol requirements.

3.1.4 End of treatment Visit

Patients that discontinue from treatment will undergo an end of treatment visit, regardless of the reason of discontinuation, approximately 30 days (±7 days) after the last dose of study medication. In case of allogeneic SCT the end of treatment visit should be performed prior to SCT.

3.1.5 Follow-up Phase

Patients who discontinued for reasons other withdrawal of consent for participation in the trial will be followed every 3 months ± 28 days for event free- and/or overall survival.

A patient may decide to discontinue study treatment. This is not the same as fully withdrawal of consent to participate in the trial and these patients should be encouraged to continue to be followed for event-free and overall survival. If a patient chooses to have no further interaction regarding the study (fully withdrawal of consent), the investigator must provide written documentation of the patient’s decision to fully withdraw from the study.

3.2 Study timelines

The planned number of 40 patients was reached. The end of the enrolment period was June 2016. End of study will be defined 2 years after registration of the last patient.

4 SELECTION OF THE STUDY POPULATION

4.1 Target Population

Patients with relapsed/refractory Acute Myeloid Leukemia (AML) according to the inclusion and exclusion criteria below will be enrolled in this study trial. Both male and female patients are enrolled.

The baseline leukemia assessment must have taken place within 2 weeks prior to start of treatment. Under no circumstances are patients, who were once enrolled in this study, permitted to be re-enrolled into the same study.

4.2 Inclusion Criteria

To be eligible for this trial, patients must meet the following criteria:

1. Cytological or histological diagnosis of AML with the exception of promyelocytic leukemia (AML M3)
2. Patients must have relapsed/refractory disease (relapse after stem cell transplantation is permitted) as defined as: patients with <PR after first cycle of induction chemotherapy, or
   b. patients with <CR(i) after second cycle of induction chemotherapy, or
   c. patients who relapse after conventional chemotherapy or
   d. patients who have undergone a single stem cell transplantation and who have relapse of their AML.
3. Men and women aged ≥18 years and eligible for standard dose of chemotherapy (7+3);
4. A period of at least 3 weeks needs to have elapsed since last treatment (with the exception of hydroxyurea) before participating in this study. Hydroxyurea induction therapy to reduce peripheral blast counts is permitted prior to initiation of treatment on protocol. Treatment may begin in <3 weeks from last treatment if deemed in the best interest of the patient after discussion with the PI of the study;
5. ECOG performance status ≤ 2
6. Serum biochemical values with the following limits unless considered due to leukemia: creatinine ≤2 mg/dl; total bilirubin ≤2x ULN, unless increase is due to hemolysis or congenital disorder; transaminases (SGPT or SGOT) ≤2.5x ULN
7. Ability to swallow and retain oral medication
8. Ability to understand and provide signed informed consent;
9. Cardiac ejection fraction must be >/=50% (by echocardiography).
10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

4.3 Exclusion Criteria

Patients with any of the following will not be eligible for participation:

1. Treatment with any investigational agent within four weeks.
2. Cumulative anthracycline dose (daunorubicin or equivalent) >360 mg/m²
3. HIV infection
4. Presence of any medical or psychiatric condition which may limit full compliance with the study, including but not limited to:
5. Presence of CNS leukemia

6. Unresolved toxicity from previous anti-cancer therapy or incomplete recovery from surgery.
7. For patients after SCT as part of prior treatment:
    a. Necessity of immunosuppressive drugs
    b. GvHD > grade 1
8. Any of the following within the 12 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis, or other thromboembolic event.
9. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2.
10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.
11. Clinically significant bleeding within 1 month

4.4 Registration of Patients

Patients will be screened for eligibility and eligibility check form/Patient Registration Form will be sent to **GSO** mbH, Hamburg.

Patient eligibility will be reviewed by GSO mbH for all patients participating in the study prior to receiving study treatment.

PROTOCOL SPECIFIC QUESTIONS:

- All eligibility criteria will be checked one by one
- Actual values for the eligibility parameters will be requested when applicable
- Date of written informed consent (day/month/year)

Patient eligibility will be checked by GSO mbH once all screening procedures are completed. There will be no exceptions. Any questions should be addressed to GSO mbH prior to registration.

The eligibility check form/Patient Registration Form will be sent from the site to GSO mbH by email or by fax for evaluation at the following:

GSO mbH

Email: kranich@gsoglobal.com

Telephone: +49 40 44 19 54 60

Fax: +49 40 44 19 54 78

Upon confirmation of eligibility, GSO mbH will assign a patient number and return the signed eligibility check form/Patient Registration Form via fax or email to the site. The Patient Registration Form will confirm the treatment arm in which the patient will participate.

The first planned dose of study drug will be administered within 2 weeks after bone marrow aspirate verification of disease progression.

5 SCHEDULE OF ASSESSMENT AND PROCEDURES

5.1 Study Assessments

5.1.1 Response Assessments

Disease status will be assessed by bone marrow and peripheral blood analysis at the end of each 4-weeks induction and consolidation cycle. Disease status during maintenance will be evaluated by peripheral blood analysis at the end of each cycle and during follow-up after SCT every 3 months ± 28 days. Bone marrow aspirate during maintenance and FU is required in case peripheral blood analysis is suspicious for progression of disease/relapse. Response is evaluated according to Döhner et al. criteria[1].

5.1.2 Translational, Pharmacodynamic and Pharmacokinetic Analyses (Optional)

5.1.2.1 Baseline Translational Studies

5.1.2.1.1 Leukemic Blast Cell Expansion in Mice

The leukemic blasts isolated from bone marrow aspirates of patients will be expanded in 2-3 NSG mice and then retransplanted into 20 NSG mice for therapeutic experiments. The resulting mouse models of patient leukemias will be used to determine the activity of Selinexor against both the bulk leukemia population and leukemia-initiating cells (LICs) of patient AML cells. Mice transplanted with patient AML cells will be treated with either vehicle control or Selinexor to assess the drug response of the bulk AML population and will then re-transplant at limiting cell dilutions the bone marrow AML cells of the vehicle and Selinexor treated mice into new recipient mice in order to calculate the fold reduction of LICs in response to therapy. The therapeutic response of mouse primagrafts of patient leukemias will be correlated with clinical outcomes of patients enrolled in the trial.

5.1.2.1.2 Leukemic Stem Cell Gene Expression

Recent studies by Eppert et al., 2011 and Metzeler et al., 2013 identified AML stem cell prognostic (42 gene) signature by correlating enrichment for the leukemia stem cell (LCS) expression signature with the clinical outcome.[25, 26] To analyze the extent of “stemness” of patient AML blasts in response to treatment with Selinexor, we will perform gene expression profiling of leukemic blasts isolated from patients before the start of therapy and 24 hour after the first drug dose. The LSC scores will be calculated based on the extent of the enrichment in the 42 LSC-specific gene signature for patient leukemias and will be used to predict clinical outcome. These experiments will be critical for defining the anti-leukemic activity of Selinexor against LICs of specific patient AML cells and predicting patients’ long-term response to the Selinexor therapy.

5.1.2.2 Pharmacodynamic Studies

5.1.2.2.1 XPO1 Inhibition

Leukocytes will be isolated from patient blood samples collected pre- and post-dosing (≥ 4hr) and total RNA will be isolated to study changes in gene expression before and after exposure to Selinexor. Inhibition of XPO1 (Selinexor target) will be assessed by qRT-PCR of XPO1 and other genes, which are upregulated once XPO1 is inactivated (based on Karyopharm gene chip studies)(e.g., ARRDC3, NGFR, SLC family, PCLO).

5.1.2.2.2 Cytokines

Blood samples will be collected pre- and post-dosing and analyzed for plasma cytokine concentrations. Cytokines include: interleukin 1 alpha (IL1α), tumor necrosis factor alpha (TNFα), interleukin 6(IL-6), MCP1, interferon gamma (IFNγ), vascular endothelial growth factor alpha (VEGFα), interleukin 8 (IL-8), interferon alpha (IFNα), interleukin 10 (IL-10).

5.1.2.3 Pharmacokinetics of Selinexor

Blood samples will be obtained pre- and post-first Selinexor dose of induction cycle 1 to determine Selinexor plasma concentrations.

5.1.3 Safety Assessments

Throughout the treatment period until one month after the last dose of study medication, patients will be assessed for all adverse events. Common terminology criteria for adverse events (CTCAE v4.03, see Appendix 7) will be used for grading. If necessary, the patient may be withdrawn from the study treatment.

Medical history including leukaemia and treatment history will be reviewed and recorded at the screening visit.

Concomitant medications will be documented throughout treatment phase until the EOT visit.

Adverse events (see also Section 7.1): All patients will be closely monitored for adverse events from start of treatment, i.e. cycle 1 day 1, until 30 days after the last dose of study medication. Adverse events for which the relationship to test drug is not “unrelated” should be followed up until they have returned to baseline status or stabilised. Adverse events will be recorded at each visit.

5.1.4 Laboratory Assessments

Safety blood samples include complete blood count, time of recovery of platelets ≥ 50x 10^9/L and ≥ 100x 10^9/L, ANC recovery ≥ 0.5x 10^9/L and ≥ 1.0x 10^9/L, clinical chemistry, including liver function test and coagulation.

5.2 Study Procedures

The Schedule of Study Events is displayed in tabular form as Table 2.

Table 2: Schedule of Assessments during the study

Assessments by Visit	**Screening**	**Baseline**	**Induction cycle(s)**		**Consolidation (if applicable)**	**Maintenance (if applicable)**	**End of treatment**	**Follow-up**[19]
Time window	Within 14 days prior to registration	After registration, before Day1 of induction	During Treatment Twice weekly	End of Cycles	weekly (D2,8,15,21 ± 2 days)	Twice per cycle D1,15 ± 2 days)	30-days after last dose/prior to SCT	Every 3 months ± 28 days
Informed consent [1]	X							
Inclusion and exclusion criteria	X							
Demographics	X							
Medical history [2]	X							
Pregnancy test (if applicable) [3]	X							
Physical examination and ECOG[4]	X		X	X	X	X	X	
Body height and weight [5]	X			X	X	X	X	
BSA	X							
Vital signs [6]	X		X	X	X	X	X	
Standard clinical neurologic examination	X							
12-lead ECG	X			X	X	X		
Cardiac ultrasound[7]	X			X			X	
Hematology [8]	X		X	X	X	X	X	X
Hematological Recovery status [21]			X[21]	X[21]	X[21]	X[21]	X[21]	X[21]

Assessments by Visit	Screening	Baseline	Induction cycle(s)		Consolidation (if applicable)	Maintenance (if applicable)	End of treatment	Follow-up[19]
Calculation [9] (or measurement) of GFR	X			X	X		X	
Clinical Chemistry [10]	X			X	X	X	X	
Urine analysis [11]	X			X	X[11]	X[11]		
Coagulation test [12]	X		X	X	X[12]	X[12]		
HIV testing[13]	X							
Assessment of signs and symptoms, AE	X		X	X	X		X	
CTCAE v 4.03 scale toxicity			X	X	X	X	X	
Concomitant medication	X		X	X	X	X	X	
Bone Marrow Aspirate[14]	X			X	X	X[14]		X[14]
Survival								X
Selinexor baseline dose[15]		X						
Bone Marrow aspirates for translational research[16](optional)		X						
Blood draws for translational research[17](optional)			X		X			
Blood draws for Pharmacokinetics[18](optional)			X					
Ophthalmological examination[20]	X							

Notes

[1] Prior to the first study-specific measures

[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, response of prior cancer therapies, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[3] Applicable for women of childbearing potential. Serum β-HCG test within 7 days before the first dose of study drug. To be repeated by urine test, if date of first result exceeds the 7-day window

[4] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom directed.

[5] Body height will be measured at screening only.

[6] Vital signs: blood pressure, pulse and temperature
[7] Echocardiography of left ventricular ejection fraction (LVEF) to observe cardiac toxic city of idarubicin**.** at baseline, before a second facultative induction course and before first consolidation therapy. Maybe repeated if clinically indicated.
[8] Hematology: hemoglobin,red blood cell (RBC) count, platelets, white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes), leukemic blasts.
[9] Calculated GFR according to the formula of Cockroft and Gault.
[10] Clinical chemistry: Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
[11] Urine analysis will include urine bilirubin, glucose, hemoglobin, ketones, pH, protein (once per cycle in consolidation/maintenance)
[12] Coagulation test include prothrombin time (PT) and activated partial thromboplastin time (aPTT) (once per cycle in consolidation/maintenance)
[13] If not performed within the last 6 months
[14] Including cytogenetic, flow cytometry and molecular analysis (FLT3 ITD or TKD mutation or NPM-1 mutation, FLT3 ITD at baseline only) at baseline, end of each induction and consolidation cycle. In maintenance and FU after SCT if blood count is suspicious for progression of disease/relapse.
[15] Baseline Selinexor dosing: single dose given after registration but before beginning of first induction cycle.
[16] Bone marrow aspirates for translational research will be taken prior to baseline Selinexor dose and 24 hour post-baseline dose. 2 ml of each aspirate will be used to isolate viable cells for mouse studies; 2 ml of each aspirate will be processed to isolate RNA for stem cell expression array analysis.
[17] Blood draws for translational research (exploratory pharmacodynamic analysis): (2 x 2.5 ml for XPO1 inhibition in leukocytes, 2 ml for cytokines) will be collected on day of first in-clinic dose of Selinexor during each induction and consolidation cycle. 2 x 2.5 ml, plus 2 ml blood will be collected pre-dose and 2 x 2.5 ml will be collected 4 hr post-dose.
[18]Blood draws (2 ml) for PK analysis will be performed during first induction cycle on day of first in-clinic dose of Selinexor: pre-dose, 2 hr and 4 hr post-dose.
[19] Follow-up is to include all patients, including those having undergone SCT
[20] required at screening and if clinically indicated during the treatment phase. Ophthalmologic examination includes:

- prior to dilation: best corrected visual acuity and slit lamp examination including tonometry
- following dilation: fundoscopy and a slit lamp exam to document lens clarity. If a cataract is seen during the exam, cataract will be graded according to the Lens Opacities Classification System III (LOCS III)

[21] Hematological Recovery status: platelet recovery ≥ 50x 10^9/L and ≥ 100x 10^9/L, ANC recovery ≥ 0.5x 10^9/L and ≥ 1.0x 10^9/L reached and date of recovery. Until recovery of platelets and ANC, hematology assessments are done as often as necessary to determine the exact date of recovery of platelets and ANC

5.2.1 Prophylactic Therapy for All Patients

Patients may receive prophylactic treatment to prevent anorexia and nausea, which includes:

- Megesterol acetate 160-400 mg daily, 0-3 days before the first dosing day of Selinexor

  AND

- Olanzapine 5.0 mg qhs or 2.5 mg bid, 0-3 days before the first dosing day of Selinexor

OR

- Mirtazapine 15 mg qd (qpm/qhs), 0-3 days before the first dosing day of Selinexor

If the patient is on steroids coming on the study, megesterol acetate should be added prophylactically to prevent anorexia. If an increased risk of adverse effects due to olanzapine is anticipated, olanzapine can be omitted. However, it is recommended that mirtazapine or other appetite stimulating serotonergic agent be used. Additional standard supportive care agents may be used as needed (prn).

Supportive care may be tapered or discontinued in Cycle 2 or later in patients who tolerate Selinexor well in Cycle 1.

5.2.2 Screening Procedures

All patients will be screened and screening procedures performed within 14 days prior to the start of induction treatment unless specified otherwise below. These include the following:

Signed written informed consent	Obtained prior to any study specific assessments
Demographics and medical history	• Age, gender, ethnic background • Details on leukemia diagnosis including WHO subtype, cytogenetics and molecular investigations such as FLT3 and NPM-1 mutations • Details on prior therapy, including start and stop dates, response of prior cancer therapies, disease progression during or after therapy, as well as discontinuation due to toxicities • Previous and concurrent relevant diseases • Current symptoms and/ or residual toxicities from prior therapies
Pregnancy test (if applicable)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years. In case the sampling date for the serum pregnancy test exceeds 7 days before treatment start, a urine test is required for confirmation
Physical examination and vital signs	• Body height and weight • BSA • Blood pressure, pulse, temperature • Physical examination

ECOG performance status	Please refer to 17.4
Standard clinical neurological examination	A neurological exam will be performed to assess motor, sensory and balance functions
Cardiac evaluation	12-lead ECG, cardiac ultrasound
Calculation (or measurement) of GFR	Please refer to Appendix 6
Urine analysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, red blood cell (RBC) count, platelets, white blood cell (WBC) count, WBC differential (neutrophils, lymphocytes), leukemic blasts
Clinical chemistry	Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
Coagulation tests	prothrombin time (PT) and activated partial thromboplastin time (aPTT)
Ophthalmological examination	Required at screening and if clinically indicated during the treatment phase. Ophthalmologic examination includes: • prior to dilation: best corrected visual acuity and slit lamp examination including tonometry • following dilation: fundoscopy and a slit lamp exam to document lens clarity. If a cataract is seen during the exam, cataract will be graded according to the Lens Opacities Classification System III (LOCS III)
HIV testing	Required, if not done within 6 months prior to study.
Assessment of disease status	Bone Marrow Aspirate including cytogenetic, flow cytometry and molecular analysis (FLT3 ITD or TKD mutation or NPM-1 mutation)
Concomitant medication	Concomitant medication currently used

5.2.3 Baseline Procedures (after registration but before Day 1 of first induction cycle, optional)

Selinexor dose :	Single Selinexor (60 mg)
Bone Marrow aspirates for translational research:	Aspirate collected pre- and 24 hour post-Selinexor dose, for isolation of live cells and RNA

5.2.4 Treatment Phase

During the treatment phase the following assessments are to be performed according to the study flow chart within the allowed visit windows:

Physical examination and vital signs	• Body weight • BSA • Blood pressure, pulse, temperature • Physical examination (symptom directed)
ECOG performance status	Please refer to Appendix 4
Cardiac evaluation	12-lead ECG, cardiac ultrasound
Urine analysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, white blood cell (WBC) count, neutrophils, lymphocytes, platelets, leukemic blasts
Clinical chemistry	Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
Coagulation tests	prothrombin time (PT) and activated partial thromboplastin time (aPTT)
Assessment of disease status	Bone Marrow Aspirate, peripheral blood analysis as above
Assessment of hematological recovery status	Platelet recovery ≥ 50x 10^9/L and ≥ 100x 10^9/L, ANC recovery ≥ 0.5x 10^9/L and ≥ 1.0x 10^9/L reached and date of recovery
Adverse events and concomitant medication	Assessed on an ongoing basis.
Blood draws for translational research (optional)	2 x 2.5 ml for XPO1 inhibition in leukocyte assays and 1 ml for cytokine assays will be collected on day of first in-clinic dose of Selinexor during each induction and consolidation cycle. 2 x 2.5 ml, plus 1 ml blood will be collected pre-dose and 2 x 2.5 ml will be collected 4 hr post-dose
Blood draws for pharmacokinetics (PK, optional)	Blood draws (2 ml) for PK analysis will be performed during first induction cycle on day of first in-clinic dose of Selinexor: pre-dose, 2 hr and 4 hr post-dose.

5.2.5 End of Treatment

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 7 days) after the last application of study drug. In case of allogeneic SCT the end of treatment visit should be performed prior to SCT.

At the EOT visit, the patients will undergo the following assessments:

Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination
ECOG performance status	Please refer to Appendix 4
Standard clinical neurological examination	A neurological exam will be performed to assess motor, sensory and balance functions
Cardiac evaluation	cardiac ultrasound
Hematology	Hemoglobin, white blood cell (WBC) count, neutrophils, lymphocytes, platelets, leukemic blasts
Assessment of hematological recovery status	Platelet recovery ≥ 50x 10^9/L and ≥ 100x 10^9/L, ANC recovery ≥ 0.5x 10^9/L and ≥ 1.0x 10^9/L reached and date of recovery
Clinical chemistry	Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Total Protein, Albumin, LDH
Coagulation tests	prothrombin time (PT) and activated partial thromboplastin time (aPTT)
Adverse events and concomitant medication	Assessed on an ongoing basis

5.2.6 Follow-Up

Patients who discontinued for reasons other withdrawal of consent for participation in the trial will be followed every 3 months ± 28 days event free and overall survival to assess the following:

- Relapse after CR or CRi
- Progression of disease in case of PR and non-responders
- Death
- Assessment of hematological recovery status until Platelet recovery ≥ 50x 10^9/L and ≥ 100x 10^9/L, ANC recovery ≥ 0.5x 10^9/L and ≥ 1.0x 10^9/L is reached and date of recovery.

Follow-Up will be continued for maximum of 24 months per patient or end of study as defined below, whichever is first.

5.2.7 End of Study

The primary statistical analysis will be performed when all patients have discontinued treatment with study medication, i.e. 30 days after the last patient last dose. End of study will be defined 2 years after registration of last patient.

5.3 Planned Treatment of the Patient after End of Treatment Phase

After completion of the study at routine follow-up (EOT), patients will generally be treated at the discretion of the investigator according to medical routine, although stem cell transplantation is recommended if a donor is available and no contra-indications exist.

5.4 Removal of Patients from Treatment

Subjects will be free to discontinue treatment or withdraw from the study at any time, for any reason. Or they may be withdrawn/ removed if necessary in order to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. Patients who are withdrawn from the study will not be replaced.

Patients will be removed from further treatment for the following reasons:

- Disease progression
- Non-compliance
- Need of treatment with medications not allowed by the study protocol
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator discretion
- Pregnancy
- Termination of the study by the sponsor

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT and the follow-up visits should be performed, if possible. The CRF section entitled “End of Treatment” must be completed in all cases. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made, with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the case report form.

If a patient withdraws consent for further study treatment, the patient should still be followed for disease progression and overall survival. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

5.5 Study Discontinuation

The whole study may be discontinued at the discretion of the sponsor in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients

6 TREATMENT

6.1 Investigational medicinal product (IMP)

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

The IMP in this study is Selinexor. AraC and Idarubicin are not considered IMP as the treatment is according standard of care. Any AraC or Idarubicin with marketing authorisation in the member state can be administered according to protocol.

The investigator or other appropriate individual, who is designated by the local principal investigator, should maintain records of the inventory at the site, the use for each patient and delivery, storage and destruction. Investigators should maintain records that adequately document that patients were provided the doses specified in the protocol and reconcile all investigational product(s) received from the sponsor.

6.2 Preparation and Administration of Selinexor

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Tablets, including instructions for administration, are dispensed by study personnel on an outpatient or inpatient basis.

Patients will be provided with an adequate supply of study drug for self-administration at home until at least their next scheduled study visit.

6.2.1 Drug Name, Formulation and Storage

INN: Selinexor

Company´s Drug ID	KPT-330
Chemical name:	(Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)-*N*′-(pyrazin-2-yl)acrylohydrazide
Classification:	Cell biological modifier: Apoptosis inducing agent
Mechanism of action:	Selinexor is a **S**elective **I**nhibitor of **N**uclear **E**xport (**SINE**) that specifically blocks nuclear export by binding irreversibly to XPO1 protein.
Molecular formula:	$C_{17}H_{11}F_6N_7O$
Molecular weight:	443.31
Approx. solubility:	<0.03 mg/mL in water (pH 2-8) >10 mg/mL in dimethylsulfoxide <2 mg/mL in 40% v/v PEG-400/H_2O <2 mg/mL in 15% v/v EtOH/H_2O

6.2.1.1 Tablets

Selinexor (KPT-330) for oral administration will be supplied as 10 mg tablets. Bottles of 50 tablets per bottle will be supplied.

6.2.1.2 Labelling

Each bottle of Selinexor tablets will be labelled in accordance with current ICH GCP and specific national requirements.

6.2.1.3 Storage

Selinexor tablets will be stored at ambient temperatures between 5 –30 °C in a locked and secured area with restricted access to study staff. The tablets should not be stored at freezer temperatures or allowed to freeze. Tablets will be supplied in white high density polyethylene (HDPE) bottles.

6.2.2 Route of Administration

Selinexor tablets will be taken orally twice weekly during weeks 1-3 of a 4-week cycle, either on Monday and Wednesday or on Tuesday and Thursday or on Wednesday and Friday.

Selinexor is to be taken within approximately 30-minutes of solid food consumption together with 240 mL (8 ounces) of water.

Each dose will consist of Selinexor for oral administration with a dose of 60 mg.

6.2.3 Compliance

The investigator should ensure that the investigational product is used only in accordance with the protocol. All doses given are to be documented in the CRF, including exact dose, number of tablets, time and date administered. The principal investigator or the designee will account for the number of tablets dispensed against those stored at the site. Any deviations and missed doses will be recorded in the CRF and drug accountability logs for verification with the reasons for missed doses. The investigator/ designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. It will be requested from patients to document intake of Selinexor in a patient diary.

The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.

6.3 Dose modification of Selinexor

Toxicity will be graded according to NCI CTCAE, version 4.03; the therapy modifications described below are applied according to this severity grading.

Each dose modification or treatment delay has to be documented in the CRF, including the respective reason.

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, Selinexor (KPT-330) shows a wide therapeutic range, with documented anti-leukemic activity from ~17mg/m² to ≥55mg/m² orally twice weekly. At the present time, we cannot predict which patient's leukemia will respond to lower doses, nor can tolerability be predicted. Therefore, in order to individualize and optimize therapeutic benefit with this oral SINE XPO1 antagonist, initiation of study therapy will be with a relatively high dose (60 mg twice weekly in weeks 1-3 of a 4-week cycle by mouth) of Selinexor. Although this is a high dose, it is below the MTD of oral Selinexor, and we believe will maximize early disease control with good tolerability in the majority of patients. Flexible dose reductions and/or schedule modifications will be permitted. In patients with tolerability issues on Selinexor, it is recommended either: (1) reducing Selinexor dose by 30% or (2) reducing Selinexor dosing frequency to once weekly.

6.3.1 Dose Adjustment Guidelines for Selinexor Related Toxicities

Toxicity will be graded according to NCI CTCAE, version 4.03; the therapy modifications described below are applied according to this severity grading.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

Re-escalation of the study drug is allowed as outlined in the sections that apply for the specific toxicity. If drug-related toxicity requires a treatment delay of more than 28 days the patient is taken off protocol treatment.

Each dose modification or treatment delay has to be documented, including the respective reason.

Table 2: Prespecified dose/schedule modifications for adverse events related to study drug

Dose level	Dose of Selinexor
Dose level 0	60 mg twice weekly (D1, D3)
Dose level -1	50 mg twice weekly (D1, D3)
Dose level -2	40 mg once weekly (D1)
Dose level -3	30 mg once weekly (D1)
Dose level -4	Discontinue dosing

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, we note that selinexor shows a reasonably wide therapeutic range, with activities from ~10mg/m2 to ≥50mg/m2. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, we will allow for dose and/or schedule modifications as described below. Patients should also be treated aggressively with supportive care to reduce toxicities.

Table 3: Criteria for dose adjustments of Selinexor-related toxicities

Toxicity and Intensity	Dose Modification
Fatigue (common)	
Grade 1	Insure adequate caloric intake and assess volume status. Adjust other medications. Consider addition of low dose corticosteroids (e.g., 4 mg dexamethasone with each dose of Selinexor or 10 mg prednisone per day every day). Rule out other causes of fatigue such as adrenal insufficiency.
Grade 2	Insure adequate caloric and fluid intake and assess volume status. Add corticosteroids on day of Selinexor (e.g., 4 mg dexamethasone), or give or 10-15mg prednisone every other day. If fatigue dose not resolve to Grade 1, increase corticosteroids to the day of and the day after Selinexor dosing, and/or reduce dose of Selinexor by one level (Table 2).
Grade 2 lasting ≥7 days and Grade 3	Insure adequate caloric and fluid intake and assess volume status. Interrupt Selinexor dosing until resolved to Grade ≤ 1, reduce dose of Selinexor by 1 level (Table 2), and add corticosteroids on day of (± day after) Selinexor dosing.
Anorexia or weight loss (common)	
Grade 1	Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). If fatigue or nausea also present, consider low doses of corticosteroids (as for fatigue) on day of ± day after Selinexor dosing.
Grade 2	Add high-calorie supplements (e.g., Ensure®). Consider olanzapine 2.5-5 mg po qhs (especially if nausea or sleep disturbance present). Consider megesterol acetate 400-800 mg daily. Consider low dose corticosteroids (see fatigue). Consider anabolic steroids such as oxandrolone. Consider dronabinol (Marinol®). Skip intermittent doses of Selinexor while supportive medications are instituted. If Grade 2 anorexia does not resolve after institution of supportive medications, reduce Selinexor dose by 1 level (Table 2).
Grade 3	Interrupt dosing with Selinexor. Add high calorie supplements. Use supportive medications alone or in combinations. Restart Selinexor at 1 dose level reduction (Table 2) once anorexia resolves to Grade ≤ 2 and weight stabilized. If Grade 2 anorexia persists with supportive medications, reduce dose of Selinexor another level (Table 2).
Nausea/Emesis (common)	
Grade 1	5-HT3 antagonists, D2 antagonists, olanzapine 5mg qhs or 2.5mg bid, corticosteroids (e.g., 4-10 mg dexamethasone with each dose of Selinexor ± the day after dosing), NK1 antagonists, or dronabinol (Marinol) or combinations can prevent nausea in the majority of patients.
Grade 2	Implement one or more combinations of anti-nausea medications. If nausea does not resolve to Grade ≤ 1, reduce dose of Selinexor by one dose level (Table 2).

Toxicity and Intensity	Dose Modification
Grade 3	Implement one or more combinations of anti-nausea medications and interrupt dosing of Selinexor. Selinexor may be restarted with one dose level reduction (Table 2) when nausea is Grade ≤ 2 and adequate caloric and fluid intake have been achieved.
Hyponatremia (common)	
Grade 1 (Lower Limit of Normal to 130 nM)	Maintain dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation, rule out other causes. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150mg/dL).
Grade 3 (120-130 nM) without symptoms	First Occurrence: Discontinue Selinexor until resolved to Grade ≤ 1 then reinstate starting dose. Check renal function, serum and urinary electrolytes, and rule out other causes. Reinforce patient education regarding fluid intake. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150mg/dL). Subsequent Occurences: Discontinue Selinexor until resolved to Grade ≤ 1 then reduce dose by 1 level (Table 2). Check renal function, serum and urinary electrolytes, and rule out other causes.
Grade 3 (120-130 nM with symptoms) or Grade 4 (<120 nM)	Check renal function, serum and urinary electrolytes, and rule out other causes. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150mg/dL). Discontinue Selinexor until resolved to Grade ≤ 1 then reduce dose by 1 level (Table 2). Check renal function, serum and urinary electrolytes, and rule out other causes.
Renal (rare)	
Serum creatinine	
Calculated or measured creatinine clearance ≥ 20 cc/min	Maintain dose level
Calculated or measured creatinine clearance < 20 cc/min	Maintain dose level as Selinexor is not eliminated by the kidney.
Hepatic (rare)	
Bilirubin	
Total bilirubin < 1.5 x ULN	Maintain dose level
Total bilirubin 1.5-3 x ULN	Reduce Selinexor to once weekly dosing at the same dose until resolved to ≤ Grade 1, then restart twice weekly dosing

Toxicity and Intensity	Dose Modification
Grade 3 (> 3.0-10.0 x ULN) Grade 4 (> 10.0 x ULN)	Discontinue Selinexor until resolved to Grade ≤ 2, then follow guidelines above. Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then reduce Selinexor dose by 1 level (Table 2) and continue treatment at the discretion of the investigator. Discontinuation of Selinexor is required if concurrent elevations of total bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed and other causes have been ruled out. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE Grade 2, respectively.
AST or ALT (rare)	
Grade 1 (> ULN-2.5 x ULN)	Maintain dose level
Grade 2 (> 2.5-5.0 x ULN)	Delay Selinexor until resolved to Grade ≤ 1, then maintain dose level. Consider addition of S-adenosylmethionine (SAM) 400mg qd-bid.
Grade 3 (> 5.0-20.0 x ULN)	Delay Selinexor until resolved to ≤ Grade 2, then reduce by 1 dose level (Table 2). Consider addition of S-adenosylmethionine (SAM) 400mg qd-qid. If no further AST or ALT elevations occur during one cycle (4 weeks) at the reduced dose level, then dose may be continued at the reduced dose. Discontinuation of Selinexor is required if concurrent elevations of direct bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE Grade 2, respectively.
Grade 4 (> 20.0 x ULN)	Delay Selinexor until resolved to ≤ Grade 2, then reduce by 2 dose levels (Table 2).
Cardiac (rare)	
Hypertension	Treatment-emergent hypertension should be treated as per standard cardiology practice. Recommended agents for the management of blood pressure elevations on Selinexor include angiotensin-converting enzyme inhibitors and calcium channel blockers.
Grade 1	Maintain dose level

Toxicity and Intensity	Dose Modification
Grade 2 / 3	Delay Selinexor and initiate/intensify antihypertensive therapy. Selinexor may be restarted in conjunction with standard anti-hypertensive medication if BP is controlled (i.e., BP ≤ 150/100 mmHg). If BP is controlled ≤ 7 days after suspending Selinexor, maintain dose level If BP is controlled > 7 days after suspending Selinexor , then reduce by 1 dose level (Table 2).
Grade 4	Delay the Selinexor and initiate/intensify antihypertensive therapy, then reduce by 1 dose level (Table 2). Selinexor may be restarted in conjunction with anti-hypertensive medication if BP is controlled (i.e., BP ≤ 150/100 mmHg).
Cardiac – Other (rare)	
Grade 1 or 2	Maintain dose level
Grade 3	Delay Selinexor until resolved to ≤ Grade 1, then reduce by 1 dose level (Table 2).
Grade 4	Discontinue study treatment
Diarrhea (common)	
Grade 1 (despite maximal anti-diarrheal medication)	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care. Maintain dose level of Selinexor.
Grade 2 (despite maximal anti-diarrheal medication)	Reduce to Selinexor to one weekly until resolved to ≤ Grade 1, then re-start twice weekly at the current dose level. If diarrhea returns as ≥ Grade 2, then reduce Selinexor dose by one dose level and dose once weekly until resolved to ≤ Grade 1, then re-start twice weekly at reduced dose level
Grade 3/4 (despite maximal anti-diarrheal medication)	Delay Selinexor until resolved to ≤ Grade 1 or baseline and patient is clinically stable, then follow guidelines above.
Neurotoxicity (not observed to date)	
≥ 1 CTCAE grade level increase	Grade 0 → Grade 1: maintain dose level Grade 0 or 1 → Grade 2: delay study treatment until resolved to ≤ Grade 1, then reduce by 1 dose level (Table 2).
≥ CTCAE Grade 3	Discontinue study treatment until resolved to Grade ≤ 1 then reduce by 2 dose levels (Table 2).
Amylase and/or lipase elevations (rare)	
Grade 1 or 2	Maintain dose level
Asymptomatic Grade 3 or 4	Delay Selinexor until ≤ Grade 2, then restart at 1 dose level reduction (Table 2). Rule out other causes of amylase/lipase elevation. If levels have not returned to ≤ Grade 2 within 3 weeks then no further Selinexor may be given and the patient should discontinue permanently from the study. A computed tomography (CT) scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any Grade 3 elevation of amylase and/or lipase.

Toxicity and Intensity	Dose Modification
Symptomatic Grade 3 or 4	Selinexor must be stopped immediately and proper supportive care provided. Evaluate enzyme levels at least twice weekly until resolution to ≤ Grade 1. Clinical manifestations should be monitored as needed until resolution or stabilization of the disease condition. Selinexor may be re-started at 2 dose levels below (Table 2) after resolution to ≤ Grade 1.
Pancreatitis (not observed to date)	
Grade 1	Maintain dose level
Grade 2, 3 or 4	Discontinue study treatment.
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Rule out other causes including drug effects. For first occurrence: continue dosing without interruption: however, reduce Selinexor by 1 dose level. For ≥ second occurrence: interrupt selinexor and check platelet counts weekly until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. If the occurrence falls on a Day 1 of a cycle: delay start of cycle, check platelet counts weekly until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level when resuming.
Grade 4 without bleeding	Rule out other causes including drug effects. Interrupt Selinexor until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. If the occurrence falls on a Day 1 of a cycle: delay start of cycle, check platelet counts weekly until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level when resuming.
≥ Grade 3 with bleeding	Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable and the platelets have recovered to Grade 2 or baseline. When resuming selinexor, reduce by 1 dose level. If the occurrence falls on a Day 1 of a cycle: delay start of cycle, check platelet counts weekly until the bleeding has stopped, patient is clinically stable and the platelets have recovered to Grade 2 or baseline. Reduce selinexor by 1 dose level when resuming.
Neutropenia	
Grade 3 or 4 Neutropenia With (febrile neutropenia) OR Without fever	Institute prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils weekly until recovers to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming. If the occurrence falls on a Day 1 of a cycle: delay start of cycle, check neutrophils weekly until recovers to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming.
Anemia	
Treat per institutional guidelines including blood transfusion. Consider transfusing for haemoglobin < 8 g/dL. If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Medical Monitor.	

Toxicity and Intensity	Dose Modification
Other Selinexor-related adverse events	
Grade 1 or 2	Maintain dose level and initiate standard supportive care.
Grade 3	Delay dose until resolved to ≤ Grade 1, then reduce by 1 dose level (Table 2).
Grade 4	Discontinue Selinexor and rule out other causes. If other causes of Grade 4 adverse event are uncovered, Selinexor may be re-initiated at 1 dose level reduction (Table 2).
All dose modifications should be based on the worst preceding toxicity. Isolated values of ≥ Grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed. Patients are allowed dose reductions to a minimum dose of 15 mg/m^2 as described in Table 2. **If a patient requires a dose interruption of > 28 days, then the patient must be discontinued from the study.** Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals until resolution or stabilization of the event, whichever comes first. a. Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) otherwise specified values.	

For all ≥ Grade 3 hematological or non-hematological AEs that are NOT Selinexor related:

After consultation with the Medical Monitor and at the discretion of the treating physician, Selinexor dosing may be maintained provided that the patient can continue to take the agent by mouth, or via other enteral route.

6.3.2 Selinexor Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney. Therefore, no dose alteration of Selinexor is required with renal dysfunction.

6.3.3 Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have Selinexor treatment withheld until infection has clinically resolved or the patient is clinically stabilized. After the infection has resolved clinically or the patient's clinical condition has stabilized, treatment with Selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics for prolonged periods while re-initiating their Selinexor regimen at the discretion of the investigator. Note: Over 1,175 patients receiving selinexor were evaluated for safety as of 31 May 2016 in clinical studies. Opportunistic infections attributed to selinexor were not observed, even with long-term (> 6-month) dosing.

6.3.4 Conditions not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the above guidelines. Selinexor does not need to be held in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions

6.3.5 Missed doses

A maximum of three doses may be given per week. If the dose was missed for more than 24 hours, the dose will be skipped and the next dose will be taken as per schedule. If the dose was missed within 24 hours, then it will be replaced. Doses should not be administered in less than 36 hours apart and all missed doses should be documented in the patient diary and the CRF.

6.3.6 Vomited doses

If a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

6.4 Concomitant Medication and Treatment

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the case report form (CRF). Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s) and any clinical findings. Patients should minimize the use of products containing acetaminophen to less than 1000 mg acetaminophen on dosing days. Acetaminophen can interfere with the metabolism of Selinexor. For combination painkillers containing acetaminophen it is recommended that single agent opiates or aspirin combinations (when clinically acceptable) be substituted.

6.4.1 Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, adverse events and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.

6.4.1.1 Prevention of Pregnancy

Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

6.4.1.2 Use of Blood Products

During the administration of Selinexor, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Appropriate anti-coagulation is allowed during the study (eg: LMW heparin, direct factor Xa inhibitors, etc).

6.4.2 Prohibited Medications

Patients should minimize the use of products containing acetaminophen. For combination painkillers containing acetaminophen it is recommended that single agent opiates or metamizol combinations (when clinically acceptable) be substituted, particularly on the days of Selinexor dosing.

Concurrent therapy with an approved or investigational anticancer therapeutic, other than Ara-C, Idarubicin and glucocorticoids as specified herein, is not allowed.

Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

Other investigational agents should not be used during the study.

Inactivation of Selinexor by glutathione conjugation is a significant metabolic pathway *in vitro* and *in vivo*, including in humans. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. *In vitro* studies using human liver microsomes confirm *in vivo* findings that Selinexor undergoes minimal CYP450 metabolism. Therefore, administration of Selinexor with drugs which undergo substantial glutathione conjugation should be minimized or avoided. These drugs include acetaminophen (paracetamol) and ethyl alcohol. It should be noted that studies of Selinexor in combination with acetaminophen are to begin in late 2013 and therefore that these recommendations are empirical. It should also be noted that recreational ethanol ingestion is associated with glutathione depletion; therefore, the use of products containing ethanol should be minimized or avoided on Selinexor dosing days.

6.5 Supportive Care Guidelines

Supportive measures for optimal medical care shall be provided during participation in this clinical trial. Supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers), glucocorticoids, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. As needed and per individual study site institutional guidelines, prophylactic therapies, including antivirals, antifungals, and antibiotics, may be administered to ameliorate risks associated with non-malignant disorders or of immune system compromise.

All patients are required to receive prophylactic anti-emetics ondansetron 8 mg (or similar 5-HT3 antagonist) before their first dose of Selinexor and continued two or three times daily, as needed.

6.5.1 Anorexia

Based on clinical observations in over 1,175 adult patients treated with selinexor as of 31 May 2016, one of the most frequent treatment-emergent adverse event is anorexia (50%) with poor caloric and fluid intake leading to weight loss, fatigue and nausea. Therefore, it is strongly recommended that patients at risk for anorexia, weight loss, and/or fatigue receive strong nutritional counseling, high caloric beverages with adequate electrolyte levels (e.g., Ensure®), prophylaxis with appetite-stimulating agent(s), and anti-emetic agents. Patients with proper nutritional support and counseling have remained on Selinexor for >11 months. There is no correlation between initial BMI or weight and the development of anorexia.

In patients with problematic food/liquid/caloric intake, a patient log of food and drink should be considered and monitored by the treatment team.

Fresh juices, simple carbohydrates, as well as ginger can improve appetite before the meal; ginger may also improve dysgeusia.

Since the duration of treatment is short and most of the patients are hospitalized during induction treatment patients with anorexia nutrition is usually provided by infusion directly into the circulatory system

If constipation occurs, then laxatives should be given as constipation can contribute to anorexia and loss of appetite.

6.5.2 Fatigue

Fatigue may be related to underlying malignancy, Selinexor side effects, side effects of other agents or concurrent morbidities. Fatigue may also be related to anorexia and/or dehydration, so caloric and fluid intake should be optimized in all patients (please see above aggressive guidelines for maintenance of food and fluid intake). Acid suppression (proton pump inhibitors and/or H2-blockers) may be beneficial in some patients with fatigue.

6.5.3 Emesis

Supportive care for nausea and vomiting should be given promptly. The site can consider prophylactic treatment in case of previous side effect of nausea and vomiting with prior anti-cancer therapy. The treatment should start with the first sign of nausea. Standard anti-emetics are allowed and strongly recommended.

6.5.4 Acute Emesis

Acute emesis is not a major observation with Selinexor but has been reported. Selinexor associated nausea/emesis generally responds to D2-antagonists, 5-HT3 antagonists, or combinations of agents.

5-HT3 receptor antagonists (Zofran® 8 mg on days of dosing) — First-generation 5-HT3 receptor antagonists all appear equally effective at preventing nausea/emesis at the recommended doses. A single dose of a 5-HT3 receptor antagonist prior to therapy is equivalent to a multiple dose schedule. The efficacy of 5-HT3 receptor antagonists is significantly improved when they are combined with glucocorticoids. As QTc prolongation is the main side effect, magnesium and potassium should be corrected prior to use. If first-generation 5-HT3 receptor antagonists+dexamethasone do not adequately control emesis, second generation 5-HT3 receptor antagonists (e.g., palonosetron) should be considered. Second generation 5-HT3 receptor antagonists also improve delayed nausea/emetic response.

Neurokinin-1 receptor antagonists (e.g., aprepitant or fosaprepitant, Emend®) – should be considered in case of uncontrolled emesis with standard treatments as described above. Neurokinin-1 receptor antagonists should be given with combination of dexamethasone and first or second generation 5-HT3 receptor antagonists.

Additional treatment: Metoclopramide Hydrochloride 10mg, 30 min before meal (up to 4 time a day) or prochlorperazine (standard doses) have been effective in many patients. Dronabinol (Marinol) has shown some activity in both nauea/emesis and anorexia in patients treated with Selinexor. Lorazapeam can be added to the combination treatment of 5-HT3 receptor antagonists +dexamethasone, e.g., at night, but has been less effective in Selinexor associated nausea/emesis.

6.5.5 Delayed Emesis - > 24h after treatment

Management — Selinexor is infrequently associated with delayed, resistant emesis. Many of the regimens associated with delayed emesis are classified as high-emetic risk, and professional guidelines recommend the use of an NK1 receptor antagonist (either NK-1 blockers e.g., aprepitant on days 1 to 3 or fosaprepitant on day 1 only), plus a glucocorticoids on days 1 to 4, along with a 5-HT3 receptor antagonist (particularly second generation agents) on day 1. This regimen is effective against both acute and delayed emesis. The data supporting the individual components of this regimen are reviewed below.

Olanzapine — Conventional antiemetics are more successful at preventing emesis than in preventing nausea, particularly delayed nausea. Olanzapine at the dose of 2.5 to 5 mg once daily (typically given at night to mitigate sedative effects) was proven effective in both anti emesis and nausea control. It may also be useful for management of breakthrough emesis, and to improve food intake in patients with anorexia.

Glucocorticoids are also consistently useful and should be administered as described above.

Granisetron transdermal patch — A transdermal preparation of granisetron should be consider in patients that have uncontrolled emesis/nausea >grade 2 under best supportive treatment

Ginger — Supplemental ginger added to foods or at doses of 0.5, 1.0gm powder daily total dose, usually in divided doses. Ginger may also improve dysgeusia.

Additional agents can be added, including lorazepam or alprazolam, a dopaminergic D2-antagonist (eg, prochlorperazine, thiethylperazine, haloperidol), or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist.

6.5.6 Diarrhea

Diarrhea is common at up to 27 % as of 31 May 2016 (mostly Grade 1), which responds to standard anti-diarrheal agents. Fluid replacement is important to prevent dehydration, fatigue and electrolyte abnormalities (e.g., hyponatremia).

6.5.7 Hyponatremia

Hyponatremia Grade 3 (plasma sodium < 130 nM) has been reported in 283 patients (24%) of patients treated with selinexor as of 31 May 2016: (please note that Grade 2 hyponatremia is not recognized in the CTCAE, v. 4.03; Grade 1 hyponatremia includes any plasma level between normal and 130 nM). None of the cases of Grade 3 hyponatremia was symptomatic and all were rapidly correctable with standard measures. No instances of Grade 4 hyponatremia have been seen. One case was pseudohyponatremia due to hyperglycemia (not associated with Selinexor). Most of the patients had anorexia, nausea, vomiting and/or diarrhea. Two of the patients with Grade 3 hyponatremia had third-space fluid accumulation or resolution (e.g., ascites, edema). Adequate fluid and caloric intake, including electrolyte rich beverages rather than free water, has led to reversal of the hyponatremia.

6.5.8 Liver enzyme increase

Liver toxicities in rodents and monkeys were not observed in the GLP toxicology studies. To date, significant liver toxicity has not been reported in patients treated with Selinexor. Patients should minimize their use of alcohol and acetaminophen as these drugs may deplete hepatic glutathione which could alter Selinexor metabolism. Studies of low dose acetaminophen administered just prior to Selinexor (in order to boost hepatic and gastrointestinal levels of Selinexor as demonstrated in rat nonclinical studies) are ongoing and will clarify any potential drug-drug interactions and/or liver toxicities of this combination. The secondary goal of these studies is to boost hepatic Selinexor levels in order to enhance hepatic anti-tumor activity. Glutathione (GSH) replacing agents such as N-acetylcysteine or S-adenosylmethionine may be considered if Selinexor induced liver dysfunction is suspected.

7 SAFETY REPORTING

The Investigator's Brochure will be used as reference document for KPT-330 (selinexor) and will be provided to the investigators in the investigator's file.

7.1 Adverse Events and Laboratory Abnormalities Reporting

7.1.1 Adverse Event

An adverse event is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (ICH E6:1.2).

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

7.1.2 Adverse Drug Reaction

All untoward and unintended responses to a medicinal product related to any dose administered.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

A serious ADR (SADR) is an ADR that meets the definition of serious (provided below).

7.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that meets one or more of the following:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other important medical events
- A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility. Any adverse event that does not meet one of the definitions of serious (e.g. visit to A&E, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the "other significant medical hazard" criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether such an AE should be considered serious.

7.1.4 NOT to be reported as SAEs

For this study, the following is **not** classified as serious adverse event:

- Progression or deterioration of the malignancy under study (including new metastatic lesions) or death due to progression.
- Hospitalization for the performance of protocol-required procedures or administration of study treatment. However, hospitalization or a prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Hospitalization or procedures planned prior to study start. A pre-planned procedure must be documented in the source documents. However, hospitalization or prolonged hospitalization for a complication remains to be reported as an SAE.
- An elective hospitalization for a pre-existing condition unrelated to the studied indication.
- Hospital admission that is not associated with an adverse event (e.g. social hospitalization for purpose of respite care).
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusions remains to be reported as an SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

7.1.5 Adverse events of special interest (AESI)

The occurrence of acute cerebellar syndrome (ACS) and development of (or worsening of existing) cataracts during treatment with Selinexor are closely monitored as AESIs.
All cases of cerebellar toxicity ≥ Grade 3 must be captured as an SAE and reported in an expedited Safety Report within 24 hours of awareness of the event.

7.1.6 SUSAR/ Unexpected Serious ADR

A SUSAR/ Unexpected Serious ADR is a suspected unexpected serious adverse reaction. A suspected adverse reaction is an adverse event for which there is a reasonable possibility that the drug caused the event. An unexpected adverse reaction is any adverse reaction with a reasonable possibility that the study drug caused the event and the specificity or severity is not consistent with the current investigator's brochure for Selinexor. Also, reports that provide significant information on the specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the investigator's brochure would be considered "unexpected". All suspected adverse reactions related to Selinexor which occur in the trial and that are both unexpected and serious (SUSARs/ Unexpected Serious ADR) are subject to expedited reporting.

7.2 Reporting of SAEs

Any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the study from the date of signing the informed consent, irrespective of the treatment received by the patient, must be reported to the sponsor (via coordinating CRO) within 24 hours (expedited reporting). For each patient, all serious adverse events must be reported up to 30 days after the last dose of investigational product. Serious adverse events occurring more than 30 days after a patient is discontinued from the study treatment may be reported at the discretion of the investigator.

The completed SAE form must be faxed to:

GSO mbH

Fax: +49 40 44 19 54 78

The following detailed information must be recorded for each serious adverse event in the SAE report form:

- A description of the AE in medical terms according to NCI-CTC Version 4.03, not as reported by the subject
- The severity grade as assessed by the investigator according to the definitions in NCI-CTC Version 4.03
- The date of becoming serious and the date of becoming known (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and chemotherapy and any action taken
- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history

  If in any one subject the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time.

  The investigator is required to submit SAE Follow-up reports until the SAE has resolved or stabilized and all queries have been answered.

7.3 Reporting of SUSARs/ Expedited Reporting of Unexpected Serious ADRs

The sponsor will via coordinating CRO ensure the notification of the appropriate ethics committees, competent authorities and participating investigators of all SUSARs events occurring at the sites in accordance with local legal requirements, statutes and the European Clinical Trial Directive as follows:

- Reporting of the SUSAR to the Competent Authorities and Ethics Committees within 15 days (or within 7 days for fatal and life-threatening events)
- Sending the event to all participating Investigators for information (with confirmation of receipt).
- In addition, all events that require a new assessment of the risk-benefit ratio will be reported to the Ethics Committee and the Competent Authority of each concerned Member State within 15 days. This includes:
- Single reports of expected serious adverse reactions with unexpected outcome.
- An increase in the rate of occurrence of expected serious adverse reactions which is judged to be clinically relevant
- Post-study SUSARs that occur after the patient has completed a clinical trial
- New events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects

The sponsor is responsible to ensure that the latest investigator's brochure is used as the source document for determining the expectedness of an SAE.

7.4 Recording of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly recorded in the subjects' medical records and the electronic case report form.

The following adverse event attributes must be assigned by the investigator:

- Adverse event term according to the NCI-CTC criteria Version 4.03
- Severity grade according to the NCI-CTC criteria Version 4.03
- Start date and stop date (or date of last assessment)
- Outcome
- Causality to study drug and chemotherapy (to be assessed as either related or unrelated)
- Any action taken

Adverse events will be followed until they resolve to baseline or considered stable. It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if the meet the criteria described in section 7.1.3.

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. If an adverse event occurs which is not described in the CTCAE version 4.03, the four-point scale below will be used.

Mild	Discomfort noticed but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect daily activity
Severe	Inability to work or perform normal daily activity
Life-threatening	Represents an immediate threat to life

7.5 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the CRF. In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Laboratory test value abnormalities as such should not be reported on the AE page of the CRF as adverse events unless they are judged clinical significant by the investigator.

7.6 Pregnancy

Female patients must be instructed to immediately inform the investigator if they become pregnant during the study. The study treatment must immediately be stopped and the patient must be withdrawn from the study. Pregnancies occurring up to 6 months after the completion of the last treatment cycle must also be reported to the investigator. The investigator must report all pregnancies within 24 hours to GSO mbH. GSO mbH will forward all pregnancy reports to the sponsor within 24 hours. The investigator should counsel the patient; discuss the risks of continuing the pregnancy and the possible effects on the fetus. The patient should be monitored until the conclusion of the pregnancy.

Pregnancy occurring in the partner of a patient participating in the study should also be reported to the investigator, the sponsor and the CRO. The partner should be counseled and followed as described above.

7.7 Adverse Drug Reactions with Concomitant Medication

The investigators must be aware that for all concomitant medications the regulations of post-marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

8 BIOSTATISTICS

8.1 Trial Design and Hypotheses

This is a single-arm trial to evaluate efficacy of Selinexor in patients with relapsed/ refractory AML by complete response rate (CR) or CRi), as defined by the revised recommendations of the International Working Group for diagnosis, standardization of response criteria in Acute Myeloid Leukemia for AML.

The trial tests the null hypothesis that the observed response rate is less or equal than the predefined limit of 30% versus the alternative hypothesis that the response rate is at least 60%.:

H0 : $p \leq p0$ against the alternative hypothesis H1 : $p \geq p1$.

8.2 Sample Size Calculation

The sample size calculation is based on the evaluation of response rates according to Fleming using the A'Hern (Sample size tables for exact single-stage phase II designs. Statist. Med. 2001;20:859-866.) extension.

In Fleming's procedure two response levels p0 and p1 are specified:

- the largest response proportion p0 which, if true, would clearly imply that the treatment does not warrant further investigations (except for other types of administration, e.g. in standardized combinations); and
- the minimum required response level p1 that would imply the treatment warrants further investigations.

The following characteristics were specified

- p0= 0.30
- p1= 0.60
- α = 0.05 (one-tailed) and
- β = 0.10

N=25 patients should participate in the study to ensure a power of $1-\beta=0.90$ for the discrimination of p0 and p1. According to Fleming the null hypothesis should be rejected if at least

$$r = \left[Np_0 + Z_{1-\alpha}\sqrt{Np_0(1-p_0)} \right]_{*}+1$$

responses are observed (x* denotes the nearest integer to). With p0 and N defined as above and $Z1-\alpha = (1-\alpha)$-quantile of the normal distribution = 1.645 at least 12 responders should be observed to show the efficacy as postulated.

Using the same approach in the 15 additional patients, submitted to an adapted drug regimen, the power will be 80% to discriminate a p0=30% (expected CR rate) from a p1=65% (meaningful increase in CR rate), if 8 out of 14 completed patients are considered as responders, with a one-tailed alpha error of 5%.

Alternatively, the power will be 90% to discriminate a p0=30% from a p1=70% again if 8 out of 14 completed patients are considered as responders, with a one-tailed alpha error of 5%.

8.3 Evaluation Categories for Patients

A Data Review will be performed prior to the data base lock. In this meeting the patients will be assigned to the respective analysis set depending on the observed protocol deviations..

8.3.1 Intent-to-Treat Population

Intent-to-Treat Analysis Set (ITT): The ITT-population includes all subjects who have received study medication at least once and for whom efficacy data upon treatment are available.

8.3.2 Per Protocol Population

Per Protocol Set (PP): The PP population includes all patients who completed the treatment section (up to Visit 9) without any major protocol deviation.

8.3.3 Safety Population

Safety Analysis Set (SAS): The SAS- Set will comprise all subjects who received at least one administration of study medication at any dosage and for any period of time.

8.4 Methods of Statistical Analysis

8.4.1 General Statistical Considerations

All statistical analyses will be performed and all summary tables and data listings will be prepared using the most recently installed version of the Statistical Analysis System® (SAS) software at the time of statistical analysis. For continuous variables, summary statistics (mean, standard deviation, median, minimum and maximum values) will be tabulated. For discrete variables, the frequency distribution will be tabulated. Statistical tests will be of descriptive nature only except for the analysis of the responder rate.
The following chapter describes the planned statistical analyses at the time of writing the study protocol. More details about the statistical analyses will be provided in the separate Statistical Analysis Plan (SAP), which will be finalized before enrolment of the first subject. Any changes in the statistical methods compared to the final SAP will be documented in the integrated Clinical Study Report.

8.4.2 Demographics and Baseline Characteristics

The following baseline conditions will be analyzed and described:

- Age, gender, ethnic background
- Details on leukemia diagnosis including WHO subtype, cytogenetics and molecular investigations such as FLT3 and NPM-1 mutations
- Details on prior therapy, including start and stop dates, disease progression during or after therapy, as well as discontinuation due to toxicities
- Previous and concurrent relevant diseases
- Current symptoms and/ or residual toxicities from prior therapies
- Body height and weight, BSA
- ECOG performance status
- Standard clinical neurological examination
- Cardiac evaluation
- Calculation (or measurement) of GFR
- HIV testing
- Assessment of disease status
- Concomitant medication

8.4.3 Efficacy Evaluation

Primary Efficacy Parameter
The primary efficacy measure will be the rate of complete responders (CR). Disease status will be assessed by bone marrow and peripheral blood analysis at the end of each 4-weeks induction and consolidation cycle. Disease status during maintenance will be evaluated by peripheral blood analysis at the end of each cycle and during follow-up after SCT every 3 months ± 28 days. Bone marrow aspirate during maintenance and FU is required in case peripheral blood analysis is suspicious for progression of disease/relapse. Response is evaluated according to Döhner et al. criteria[1].

Secondary Efficacy Parameters
The secondary efficacy measures will be:

- Rate of partial remissions
- Percentage of patients being transplanted after induction therapy
- Early death rate
- Overall survival (OS)
- Event-free survival (Events are defined as Death, not achieving a CR or CRi, Relapse after CR or CRi)

8.4.4 Safety Evaluation

Safety evaluation will comprise the following variable and their change from baseline:

- Blood pressure, pulse, temperature
- Physical examination
- Urine analysis
- Hematology
- Clinical chemistry
- Time of recovery of platelets and ANC
- Coagulation tests

The number of patients developing adverse experiences will be tabulated [NCI CTCAE] Version 4.03. The CTC v4.03 will be the basis for grading the laboratory changes. Additionally, the subset of adverse experiences considered treatment-related will be summarized. Listings of adverse experiences leading to treatment discontinuation and those identified as 'severe' or of 'maximal' severity will be provided.

8.5 Interim and Final Analysis

No formal interim analyses are planned.

9 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross–check of the CRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator. Data for this study will be recorded via CRF. It will be transcribed by the site from the source documents onto the CRF. Data are reviewed and checked for omissions, apparent errors, and values requiring further clarifications using computerized and manual procedures. Data queries requiring clarification are communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database and an audit trail will document all corrections.

10 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be implemented that reviews accumulating data of the clinical trial with respect to any potential safety issues, study progress and critical efficacy endpoints. The DMC will function in accordance with the principles of the following documents: EMA guideline on data monitoring committees (EMEA/CHMP/EWP/5872/03 Corr), ICH Note for guidance E3 (structure and content of clinical study reports), ICH Note for guidance E6 (Good Clinical Practice), ICH Note for Guidance E9 (Statistical Principles for Clinical Trials) and Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medical products for human use.

The DMC will be an independent board consisting of 2-3 physicians with special expertise in AML. A physician is not allowed to participate in this clinical trial while serving on the DMC. The DMC will be supported by an independent statistician, if necessary.

The DMC will review safety data, recovery times and efficacy of the clinical trial and support the interpretation of clinical trial results.

A DMC charter will be set up which defines the roles and responsibilities of the DMC.

11 ETHICAL ASPECTS

11.1 Declaration of Helsinki / Good Clinical Practice

The Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all those engaged in research on human beings. Any exceptions must be justified and stated in the protocol. The latest version of the Declaration of Helsinki is available at www.wma.net.

Additionally it is the responsibility of all those engaged in research on human beings to ensure that the study is performed in accordance with the international standards of Good Clinical Practice and according to all local laws and regulations concerning clinical studies.

11.2 Patient Information and Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after an adequate explanation of the aims, importance, anticipated benefits, potential hazards and consequences of the study according to applicable local laws. Written informed consent must be obtained before any study-specific procedures are performed. It must be also explained to the patient that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason, without incurring any penalty or withholding of treatment on the part of the investigator.

With the declaration of consent, the patient agrees to data about his/ her disease being recorded within the context of the clinical trial and that it may be transferred to the sponsor in pseudonymized form.

The subject/ patient also agrees to allow the monitor/ auditor/ health authorities to verify the patient data collected against the subject's/ patient's original medical records for the purpose of source data verification.

The informed consent form personally signed and dated by the patient must be kept on file by the investigator(s) and documented in the CRF and the subject's medical records. The investigator must confirm with the sponsor/coordinating CRO that he/ she has obtained written informed consent.

If new safety information results in significant changes to the risk/ benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue in the study.

If family doctors are to be informed of their patients' participation in the clinical study, this should be mentioned in the consent form.

11.3 Independent Ethics Committees and Regulatory Authorities

11.3.1 Approval of the Study by the Regulatory Authority and Independent Ethics Committees

It is the responsibility of the sponsor to obtain and maintain independent approval from the applicable regulatory authority and a positive opinion from the competent ethics committees to conduct the study in accordance with local legal requirements and statutes.

Indemnity insurance will be arranged for the trial subjects in accordance with the applicable local law.

11.3.2 Notification of the Study

The sponsor is responsible for notifying the competent regional authority about the study and all principal investigators at the participating investigational sites, if applicable by local law.

11.3.3 Obligation to Report and Document

The sponsor and the investigator are responsible for complying with the requirements for reporting and documentation in accordance with local legal requirements and statutes.

12 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made via amendment. The sponsor is responsible for obtaining independent approval for substantial amendments from the applicable regulatory authority and a positive opinion from the competent ethics committees in accordance with local legal requirements, statutes and the European Clinical Trial Directive. Approval must be obtained before any changes can be implemented, except for changes necessary in order to eliminate an immediate hazard to trial subjects or when the changes are non-substantial and involve only logistical or administrative aspects of the trial (e.g. change of telephone numbers).

13 STUDY DOCUMENTATION, CRFS AND RECORD-KEEPING

13.1 Investigator's Files / Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: investigator's study file and subject/ patient data.

The investigator's study file will contain all essential documents such as the protocol/ amendments, case report and query forms, patient information and informed consent form, ethics committee and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities (if applicable), drug records, staff curriculum vitae and authorisation forms, and other appropriate documents/correspondence, etc.

Patient data includes patient hospital/clinic records (e.g. medical reports, surgery reports appointment book, medical records, pathology and laboratory reports, ECG, EEG, X-ray, etc.), signed informed consent forms and patient screening and eligibility screening forms.

The investigator must keep these two categories of documents on file for at least 15 years (or longer, as legally required) after completion or discontinuation of the study. The documents must be archived in a secure place and treated as confidential material.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in the event of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

All documents must be archived in a secure place and treated as confidential material.

13.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when case report forms are illegible or when errors in data transcription are suspected. In the event of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected. According to the standards of the data protection law, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy.

13.3 Audits and Inspections

This study may be audited by the sponsor, any person authorised by the sponsor, or the competent health authority in order to determine the authenticity of the recorded data and compliance with the study protocol.

The investigator must be aware that source documents for this trial should be made available to appropriately qualified personnel working on behalf of the sponsor/monitor/auditor/health authority inspectors after appropriate notification for the purposes of source data verification and proper review of the study progress. The verification of the case report form data must be done via direct inspection of the source documents. The investigator agrees to comply with the sponsor and regulatory authority requirements regarding the auditing of the study.

All materials used in clinical studies are subjected to quality control.

13.4 Case Report Forms

For each patient enrolled, acase report form must be completed and signed by the principal investigator or an authorised delegate from the study team. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted in the CRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to document the outcome clearly.

14 MONITORING THE STUDY

The monitor is responsible for familiarising the investigator(s) and the entire centre staff involved in the study with all study procedures, including the administration of the study drug.

The monitor will visit the clinical study centre before the first patient has been enrolled (initiation visit). During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs (source data verification), the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

Key study personnel must be available to assist the monitor during these visits. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15 CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator and the sponsor (or designated person) must ensure that all data obtained in the course of a clinical study is treated with discretion in order to guarantee the rights of the patient's privacy, according to the standards of the data protection law. CRFs or other documents should be submitted to the sponsor in pseudonymised form. The investigator should keep a patient identification log showing codes and names. The investigator should maintain documents not intended for submission to the sponsor, e.g. patients' written consent forms, in the strictest confidence.

16 STUDY REPORT AND PUBLICATION POLICY

This study will be entered into a clinical trial protocol registry and clinical results database. The sponsor is responsible for the timely reporting of study data. An integrated clinical study report (CSR) has to be completed one year after the end of the study (whether completed or prematurely terminated). The report has to be approved by the responsible specialist chosen by the sponsor, the project manager of the CRO, the statistician and the coordinating investigator by provision of their signatures. In this multi-centre study, the main publication will be a full publication of all data from all sites. Any publication of the results, either in part or in whole (abstracts in journals, oral presentations, etc.) by investigators or their representatives will require a pre-submission review by the sponsor and the coordinating investigator. This requirement only serves the information of the sponsor and does not imply any claim to any editing or restriction of the content of publications and presentations. The coordinating investigator will be the first author. The senior author of the study will be the last author. The remaining positions will be based on recruitment, good data quality and scientific input to the study. The final author list will be a joint agreement between the coordinating investigator and the sponsor. For all other publications, the order of the authors will be determined according to recruitment, data quality and significant scientific input to the study, after consulting the coordinating investigator.

17 APPENDICES

Appendix 1	Overview of current relapsed/refractory AML treatment studies
Appendix 2	Adverse Event Categories for Determining Relationship to Test Drug
Appendix 3	Definitions According to ICH Topic E2A Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, (CPMP/ICH/377/95)
Appendix 4	ECOG Performance Status
Appendix 5	Cockroft-Gault Formula
Appendix 6	National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
Appendix 7	RESPONSE CRITERIA IN AML

17.1 Appendix 1 – Overview of current relapsed/refractory AML treatment studies

Table 4: Overview of current relapsed/refractory AML treatment studies

Source	Indication	No of patients enrolled (evaluable)	Drug	Dose	ORR (CR / PR)	SD	PFS (months)	OS (months)
Breems et al[17]	Relapsed/ refractory AML	667	Cytarabine + daunorubicin or idarubicin	200 mg/m² 7 days +	46%			
Paciucci et al. [20]	Relapsed/ refractory AML	49	Cytorabine + mitoxanthine	100 mg/m² 7 days + 10 mg/m² 3 days	50-60%		8	
Haroussea et al.[19]	Relapsed/ refractory AML	35	Cytorabine + Idarubicine	1 mg/m² + 8 mg/m² 2 days every 12h 6 doses	50-60%		16	
Spadea et al. [21]	Relapsed/ refractory AML	44	Cytorabine + Mitoxanthrone + Etopsid (MEC)	1 g/m² + 6 mg/m² + 80 mg/m² days 1 to 6	55%			
Greenberg et al. [27]	Relapsed/ refractory AML	63	MEC		17%		10	
		66	MEC + valspodar (PSC388)		25%		9	
Faderl et al. [22]	Relapsed/ refractory AML	32	Cytarabine + Clofarabine	1 g/m² + 40 mg/m² 5 days	48%			

17.2 Appendix 2 - Adverse Event Categories for Determining Relationship to Test Drug

Related (must have one of them)

- This category applies to those adverse events that are considered to be related to the test drug. An adverse event may be considered related if:
- It follows a reasonable temporal sequence from administration of the drug
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject
- It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists: e.g. (1) bone marrow depression, (2) tardive dyskinesias.)
- It follows a known pattern of response to the suspected drug
- It reappears upon rechallenge

Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under related.

17.3 Appendix 3 – Definitions According to ICH Topic E2A Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, (CPMP/ICH/377/95)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment.

Adverse reactions are defined as all untoward and unintended responses to an investigational medicinal product related to any dose administered. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

A serious adverse event or serious adverse reaction is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfils at least one of the following criteria:

- is fatal (results in death) (NOTE: Death is an outcome, not an event)
- is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- required in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgement should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in A&E or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

An unexpected adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product)

Causality is initially assessed by the investigator. With respect to the obligation to report and document (regulatory authorities, ethics committees and other investigators) serious adverse events, causality can be one of two possibilities:

- No (unrelated; equals not drug-related)
- Yes (remotely, possibly or probably drug-related)

All adverse events not assessed as definitively “not drug-related” by the investigator will be considered as adverse drug reactions.

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction whose nature or severity is not consistent with the applicable product information.

It is important that the severity of an adverse event is not confused with the seriousness of the event. For example, vomiting which persists for many hours may be severe, but is not necessarily a serious adverse event. On the other hand, stroke which results in only a limited degree of disability may be considered a mild stroke, but would be a serious adverse event.

A serious adverse event occurring during the study or which comes to the attention of the investigator within three weeks of stopping the treatment or during the protocol-defined follow-up period, if this is longer, must be reported, whether considered treatment-related or not. In addition, serious adverse events occurring after this time should be reported if considered related to test “drug”.

Such preliminary reports will be followed by detailed descriptions later that will include copies of hospital case reports, autopsy reports and other documents.

For serious adverse events, the following must be assessed and recorded on the adverse events page of the case report form: intensity, relationship to test substance, action taken, and outcome to date.

The obligation to document and report must be adhered to according to the national and international laws and regulations.

For contact details and fax no. for SAE and pregnancy reporting, please refer to Section 7.2.

17.4 Appendix 4 – ECOG Performance Status

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead

17.5 Appendix 5 – Cockroft-Gault Formula

Calculated CL_{CR} (ml/min) = $\frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}]}{72 \times \text{subject's serum creatinine (in mg/dL)}}$ *

*: x 0.85 for females

Calculated CL_{CR} (ml/min) = $\frac{[(140 - \text{subject's age in years}) \times \text{subject's actual body weight in kilograms}] \times K^*}{\text{subject's serum creatinine (in µmol/L)}}$

K*: 1.23 for males, 1.05 for females

17.6 Appendix 6 – NCI-CTCAE version 4.03

17.7 Appendix 7- Response criteria in AML

Definitions of response criteria are based primarily on those given by Döhner et al.[1]

Response criteria	Absolute Neutrophil count	Absolute Platelets count	Bone marrow Blasts (%)	Comments
Complete remission (CR)*	>1.0 x 10^9/L (1000/µL)	>100 x 10^9/L (100.000/µL)	<5	Absence of blasts with Auer rods; Absence of EMD; independence of red cell transfusion
CR with incomplete recovery (CRi)†	<1.0 x 10^9/L (1000/µL)	<100 x 10^9/L (100.000/µL)	<5	All CR criteria except for residual neutropenia or thrombocytopenia.
Morphologic leukemia-free state‡	NA	NA	<5	Absence of blasts with Auer rods; Absence of EMD; no hematologic recovery required
Partial remission (PR)	>1.0 x 10^9/L (1000/µL)	>100 x 10^9/L (100.000/µL)	5 to 25	Relevant in the setting of phase 1 and 2 clinical trials only; decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)§	>1.0 x 10^9/L (1000/µL) or <1.0 x 10^9/L (1000/µL)	>100 x 10^9/L (100.000/µL) or <100 x 10^9/L (100.000/µL)	<5	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)i	No standard definition; depends on molecular target			

Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials); or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination

Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy; or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

EMD extamedullary disease

* All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

† The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

‡ This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

§ Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.

i As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 10^4 copies of *ABL1* in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission.

¶ In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AµL.

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