A randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral selinexor (KPT-330) to standard induction chemotherapy in AML and high risk myelodysplasia (MDS) (IPSS-R > 4.5) in patients aged ≥ 66 years .

A study in the frame of the masterprotocol of parallel randomized phase II studies in elderly AML

PROTOCOL

Principal Investigators: G.J. Ossenkoppele, B. Löwenberg

Sponsor **:** HOVON

EudraCT number **:** 2014-001876-75

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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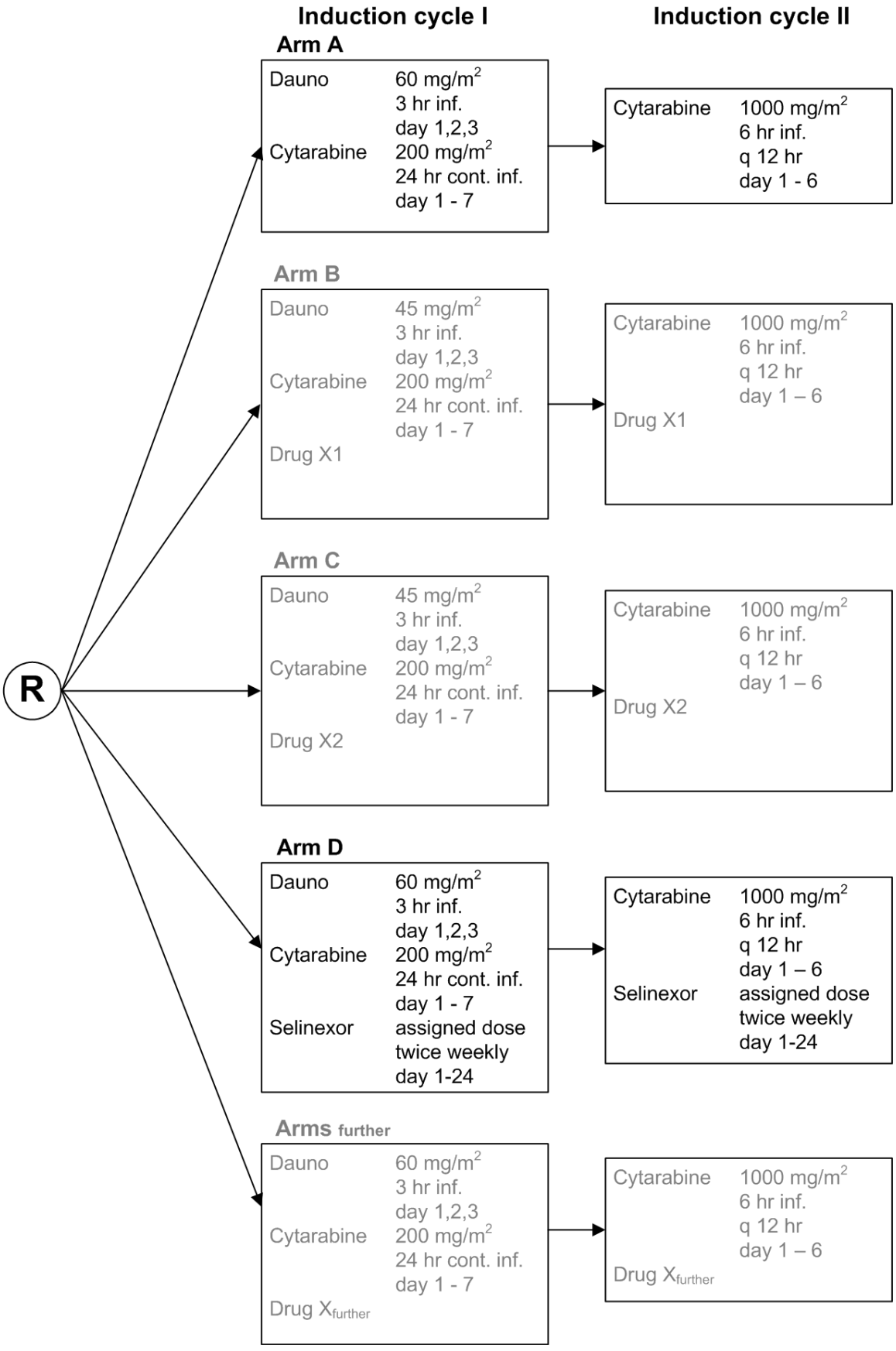
By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.

Scheme of study



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3 Synopsis

Study phase	Randomized phase II
Study objectives	Primary objectives Part A of the study (if applicable): 1. To assess the safety and tolerability of selinexor added to standard induction chemotherapy for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia) and select the feasible dose level for part B of the study 2. To assess in a randomized comparison the effect of selinexor on the CR rate. Part B of the study: 1. To assess the safety and tolerability of selinexor added to standard induction chemotherapy for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia) as regards the selected dose level of selinexor 2. To assess in a randomized comparison the effect of the in Part A selected dose of selinexor on the CR rate. Secondary objectives For part B: 1. To determine the efficacy profile (event free survival (EFS), disease free survival (DFS) and overall survival (OS)) associated with the two therapy regimens. 2. To measure MRD by immunophenotyping in relation to clinical response parameters. 3. To identify potential biomarkers predictive of response, EFS, DFS and OS by exploratory genomic analysis (microarray, gene mutations)
Patient population	Patients with AML (except FAB M3) or high risk MDS (IPSS-R > 4.5), previously untreated, age ≥ 66 yrs
Study design	This is a prospective, open label, multicenter study that is conducted in the frame of a masterprotocol with multiple parallel randomized phase II studies. The scheme of this

	design consists of one arm with the standard treatment for AML as compared to various arms with experimental treatments. Patients in this study are treated with standard induction chemotherapy with or without selinexor. During part A of the study the feasibility of combining selinexor with DNR/Cytarabine will be evaluated and the dose of selinexor will be selected. Decisions regarding dose escalation, continuation with starting dose level or stopping, are based on the incidence of DLT (dose limiting toxicity: see 17.1) During part B of the study that will be conducted with the selected dose of selinexor , the CR rate (primary endpoint) and secondary endpoints (EFS, DFS, OS, as well as MRD and genomic profiling) will be assessed.
Duration of treatment	Expected duration of 2 cycles of induction chemotherapy with or without selinexor including evaluation is about 3 months.
Number of patients	Per treatment arm a maximum of 100 patients at the final dose level
Adverse events	Adverse events will be documented if observed and serious adverse events will be reported immediately
Planned start of recruitment	Q4-2016
Planned end of recruitment	Q1-2019
End of trial	Last patient, last visit

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
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Monitoring	HOVON Data Center	Erasmus MC Cancer Institute Clinical Trial Center
Cytogenetics review	B. Beverloo E. van den Berg-de Ruiter	Erasmus MC, Rotterdam University Medical Center, Groningen
Cytological and immunophenotype review		Hematocytology Review Committee, Erasmus MC, Rotterdam
GEP and molecular diagnostics coordinator	P. Valk	Erasmus MC, Rotterdam
MRD coordinator	G.J. Schuurhuis	VU University Medical Center, Amsterdam
Statistician	Y. van Norden	HOVON Data Center, Erasmus MC Cancer Institute, Clinical Trial Center
Steering committee	Principal investigators Study coordinators Statisticians	
Datamanagement	HOVON Data Center	Erasmus MC Cancer Institute Clinical Trial Center
Serious Adverse Events (SAEs) notification	HOVON Data Center	Erasmus MC Cancer Institute Clinical Trial Center E-mail: saereports@erasmusmc.nl

4.1 Cytological and immunophenotype review

Review of bone marrow aspirate at diagnosis by the Hematocytology Review Committee (HRC) is required.

Four unstained blood and 6 unstained bone marrow smears should be sent together with a filled out cytology form and a copy of the report of the immunological marker analysis to

HOVON Hematocytology Review Committee (HRC)
T. de Jong, room Nc-828
Department of Hematology
's Gravendijkwal 230
3015 CE Rotterdam
The Netherlands

Confirmation of diagnosis is not necessary for randomization and start of treatment.

4.2 Cytogenetic review

Central review will be performed for cytogenetic analysis at diagnosis.

Each cytogeneticist, responsible for the cytogenetic analysis of the patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study. A filled out cytogenetic form together with 2 representative karyotypes and a copy of the original cytogenetic report should be sent within 5 weeks after registration to the HOVON Data Center for central review.

If additional FISH analysis was performed, a filled out FISH form together with a copy of the original FISH report should be sent with the cytogenetic data for central review.

5 Introduction

5.1 AML

Acute myeloid leukemia is a clonal hematopoietic stem cell disorder characterised by an accumulation of immature progenitor cells by a block in differentiation resulting in the suppression of normal hematopoiesis**.** The disease is heterogeneous with respect to morphology, immunophenotype, cytogenetics and molecular and gene expression signature as well as in outcome(1).

Treatment for AML is intensive consisting mostly on 3-4 courses of an anthracycline and Cytosine-arabinoside (cytarabine) based cytostatic therapy resulting in a CR rate of 70-80% in patients below 60 years and about a 40% long term survival (2). Outcome in older patients is much less satisfactory falling to a 2 years survival of 10% due to overrepresentation of prognostic factors determining poorer outcome and the unability to deliver very intensive therapy in these older patients (3).

Relapses are emerging from residual disease present after chemotherapy that easily can be detected by multicolour flowcytometry in the majority of cases and is correlated with outcome (4). Although therapy has been intensified in elderly patients by increasing the doses of existing drugs there is no evidence of improvement of survival (5). However, HOVON recently showed that doubling of the daunomycin dose produces faster and more CRs (64% vs 54%, p=0.002) with no apparent enhanced hematological or other organ toxicity nor an increase in the 30-day mortality (average 11%). This increased CR rate in the escalated arm was restricted to the patients in the age range 60-65, and in this age range the increased CR rate is also reflected in a better event free and overall survival. These findings lead to the conclusion that patients between 60-65 years will have to be treated according more intensive treatment protocols (6).

So there is an urgent need for new treatment modalities in the elderly AML patient group (≥ 66 years).
The improvement in understanding the biology of AML has identified new targets which have been used for new drug development. There are now a wide range of these new molecular targeted treatments waiting for clinical application (8).

5.2 Study Design

HOVON/SAKK Cooperative groups concentrate their developmental therapeutic efforts for the 66+ yrs age segment of AML patients, on developing effective treatments for these patients, for whom current treatment in spite of active clinical research has remained highly unsatisfactory. Therefore new treatment modalities are introduced and evaluated in combination with standard chemotherapy. For this an approach is chosen with multiple parallel randomized phase II studies that will be conducted within the frame of a master protocol. The scheme of this new design consist of one arm with the standard treatment for AML as compared to various arms with experimental treatments. The design is flexible in the sense that one of the study arms with investigational drugs can be closed as soon as indicated by toxicity or lack of efficacy (according to predefined stopping rules). On the other hand another study arm with a new investigational agent can be added to the program at any time. The design is based upon a phase II strategy but it allows for adding a phase III part in case the results of the phase II part are positive and indicate promising antileukemic activity. Thus, each new investigational treatment arm is first tested in a randomized phase II setting and based on the results of the phase II study, the study can be followed by a phase III study. If applicable an initial feasibility phase will precede the phase II.
In the statistical analysis, for the final analysis as well as for the interim analysis, pairwise comparisons of one of the investigational treatments and the standard treatment are planned. In these comparisons, only the results for the patients which are randomised over at least the two compared treatments are used. So, in the statistical analyses for investigational arm investigating

selinexor we compare the results of the patients allocated to treatment of that arm with the patients that were allocated to the standard arm but who could have been allocated to treatment arm investigating selinexor. Participating hospitals are free to participate with randomization to the standard arm and a subset of the investigational treatment arms. Another advantage of the design is that if one of the investigational arms is on hold e.g. because of an interim analysis, the trial remains open for the other investigational treatments.

Example Assume three hospitals participate in the trial which consists of the standard arm A and three experimental arms B, C, D. Furthermore we assume that hospital 1 randomizes patients over arms A, B and D, hospital 2 randomizes over arms A, B and C and hospital 3 randomizes over arms A, B, C and D.

	Arm A	Arm B	Arm C	Arm D
Hospital 1	X	X		X
Hospital 2	X	X	X	
Hospital 3	X	X	X	X

Then, for the analyses of treatment B the results of all patients allocated to arm A and arm B are taken into account. For the analyses of treatment C only the results of patients from hospital 2 and 3 allocated to arm A and arm C are taken into account and for treatment D the results of patients from hospitals 1 and 3 allocated to arm A and arm D are taken into account. In Figure 1 below, we give a graphical representation of a trial over time. It is shown that the standard arm A is open throughout the trial. At T0 at the start of this trial, three arms are open for inclusion of patients: the standard arm A, investigational arm B and experimental arm C. Arm B starts as phase II, whereas arm C starts in a dose finding phase. Arm D opens at time T2, and is open until T4. At T3, it is decided to stop accrual in phase II for investigational arm B (according to predefined stopping rules). A phase III study for investigational arm B is developed and at T5 this phase III study is opened for inclusion. From this moment on no new investigational treatments arms are added to the protocol, but also no other investigational treatment arms will continue as a phase III study until arm B is closed. So, every investigational treatment follows the same scheme: a feasibility part if necessary, phase II and phase III if continuation of the arm is implied by the stopping rules at the interim analysis, under the condition that only one investigational treatment can be investigated in a phase III. (The phase III will be investigated in a separate study.)

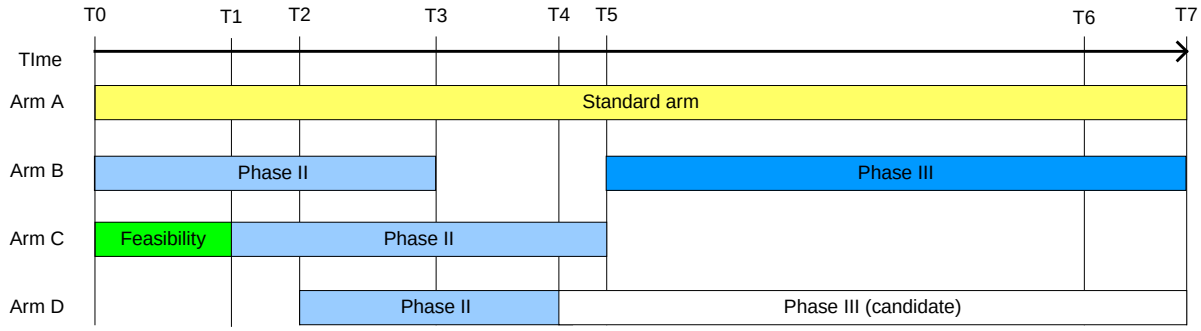


Figure. Example of study progress in time

The master protocol of this clinical trial that will serve as a template will contain all general information necessary for a clinical study according EU directives, in which e.g. the endpoints and objectives as well as the statistical considerations are described. For any new drug treatment investigated in this trial the study specific information will be added to the masterprotocol resulting in a complete protocol consisting of the masterprotocol plus information about this particular new drug. This protocol also includes the stopping rules for the feasibility part. Thus, the primary endpoint(s) for the phase II analysis are the same for each of the investigational treatments, and so is the sample size justification for the efficacy part. The Study coordinators are involved in the decision to continue or stop an investigational treatment at the interim analysis.

Randomisation

All patients are randomized between the standard treatment and one or more investigational treatments. Each hospital chooses to which set of investigational treatments it participates in the trial. Thus, all patients of a hospital are randomized over the same set of treatments; of course this elected set can change in time. To keep the number of patients who are treated with the standard treatment as small as possible we intend to randomize patients concurrently over more than one investigational treatment and the standard treatment.

Feasibility Part

In this part of the trial, if necessary, the feasibility of the treatment is determined using predefined stopping rules depending on toxicity and death. Using stopping rules we decide if the dose level has to be reduced (or if the investigational arm has to be stopped) or can be escalated or we continue the investigational arm at the present dose level. For the stopping rules we take into account the number of dose limiting toxicities (DLT) in the investigational arm. The DLT can be defined differently for every investigational treatment and will involve mortality as well as those severe adverse events (CTC grade 3 and/or 4) that are expected and considered relevant for the specific investigational treatment. We expect to include about 15-20 patients per dose level per arm. This part of the trial is also performed randomized, in such a way that the trial can directly be continued

at the selected dose level while the results of the patients treated at the selected dose level can be taken into account for the efficacy analyses in the phase II part of the investigational arm of the trial, since the stopping rules are only based on mortality and/or toxicity. The choice can be made to perform a dose finding phase only in a small number of hospitals.

Phase II

In the phase II part of the trial the efficacy of the investigational treatments is studied, to determine if it is promising enough to continue to phase III. If applicable, the investigational arm will continue as a phase III study without a large time gap. The primary endpoint of this phase II part is the CR rate, so that the decision whether or not to continue as phase III is made on the basis of the % of CR in the standard arm and the investigational arm which is analysed. The same set of decision rules and target number of patients applies to any investigational treatment. We expect to include (maximum) about 100 patients at the maximum dose level in each investigational arm, with one interim analysis.

Phase III

The phase III investigation will be examined in a different trial.
The primary endpoint of the phase III part of investigation of a new drug will be event free survival (EFS). One of the main secondary endpoints will be overall survival. In the final analysis also the results of the patients treated in phase II will be taken into account, in the sample size computations the phase II analyses are taken into account as interim analysis. From the moment one of the experimental arms is planned to be continued as a phase III study, no new experimental treatments will be included in the trial and no other experimental treatment will be continued in a phase III study. All arms which are already open will continue and be analysed according to the rules as defined in the protocol. The sample size has to be decided by simulations.
The motivation of this new treatment design is that:

- Current treatment strategies are disappointing, with little or no progress in the last 15 years
- This approach makes it possible to preliminary assess various promising new agents
- A number of promising new drugs are now available
- More progress could be made in a shorter time frame.
- If one of the experimental arms is on hold or closed, the trial remains open for the other investigational treatments.
- New promising drugs can be implemented more efficiently

At the present time HOVON/SAKK intends to investigate a number of potentially interesting antileukemic agents. According to the design outlined above, more than one investigational study arm can run in parallel to a standard treatment arm so that new study arms may be opened in due course or active study arms may be closed as indicated by the evaluation of the results of the randomized phase II. Such changes will be implemented through development of new studies, that

will consist of this master protocol with addition of a new drug to be evaluated.

5.3 Selinexor

5.3.1 Mechanism of Action of Selinexor

Neoplasms must inactivate most or all of the >10 major tumor suppressor pathways in order to perpetuate their phenotypes [9]. 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[10].

Selinexor is an oral, first in class, slowly reversible, potent and Selective Inhibitor of Nuclear Export (SINE) that specifically blocks chromosomal region maintenance 1 (CRM1). Selinexor restores many of the tumor suppressor (TSP) and growth regulatory (GRP) proteins to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. All cell types exposed to SINE in vitro undergo G1/S±G2/M cell cycle arrest, followed by a 'genomic fidelity' review, and cells with damaged genomes are induced to undergo apoptosis.[11] Normal cells, with an intact genome, 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.[12] Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by CRM1 inhibition; normal hematopoietic cells and their functions are largely spared[11]

In vitro experiments with continuous (~72 hour) exposure to selinexor demonstrated potent proapoptotic 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. Moreover, selinexor demonstrated cytotoxicity in multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) cells in the absence or presence of bone marrow stroma cells (BMSC). In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC50s were typically >5 µM. As noted above, selinexor had little effect on normal (nonmalignant) lymphocytes or other nontransformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction.

AML cells overexpress the nuclear exporter, Exportin 1 (XPO1/CRM1) and higher XPO1 levels correlate with poor outcome (Kojima 2013). 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 [Ranganathan 2012].

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 [Ranganathan 2012]. 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 (Etchin 2013a,b, Ranganathan 2012).

5.3.2. Clinical Experience of Selinexor in AML

KCP-330-001: A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced Hematological Malignancies

Study KCP-330-001 is a Phase 1, open-label, dose-escalation study to evaluate the safety and tolerability of oral selinexor and determine the RP2D in patients with hematological malignancies with three arms. Arm 1 includes patients with “chronic” hematological malignancies multiple myeloma (MM), Waldenström’s Macroglobulinemia (WM), Non-Hodgkin’s Lymphoma (NHL) and chronic lymphocytic leukemia (CLL). This trial enrolled 2 patients in cohort 1 with dose escalation of 100% increase from cohort 1 to 2. Cohort 2 enrolled at least 3 patients with dose escalation of 100% increase from cohort 2 to 3. For cohorts 3 and beyond, the standard 3+3 design was used with dose escalation increase of 30-40% from previous cohort. Arm 2 includes patients with acute myeloid leukemia (AML) of any subtype except M3. Because of the rapidly progressive nature of AML, Arm 2 began dosing at 16.8 mg/m2 after dose limiting toxicity (DLT) clearance in cohort 3 (12 mg/m2) and initiation of 16.8 mg/m2, corresponding to cohort 4 of the Chronic Hematological Malignancies portion of the study. The standard 3+3 design was used with dose escalation increase of 30-40% from previous cohort. Arm 3 includes up to 12 patients with relapsed/refractory Peripheral T-cell lymphoma (PTCL) or Cutaneous T-cell lymphoma (CTCL) treated at a dose of 30 mg/m2 twice weekly.

As of 31 December 2013, a total of 119 patients have been enrolled in this study, with 48 patients on Arm 2 (AML) enrolled at ten clinical centers in the USA, Canada, and Denmark, and treated at

doses ranging from 3 mg/m2 to 60 mg/m2 on Schedule 2 or Schedule 3 (10 or 8 doses/cycle). As of 31 December 2013, 9 AML patients remain on study treatment

Overview of Clinical Efficacy in AML In the Phase 1 study (KTP-330-001), 21 of the 35 patients (60%) evaluated as of 28 February 2014 have experienced a complete remission (CR), complete remission without platelet recovery (CRi), partial response, morphologic leukemia free state or stable disease (SD). Six patients experienced a CR or CR(i). Five of these patients experienced a CR, while the other patient experienced a CR(i). As of 28 February 2014, 2 patients have experienced a partial response, one of these patients showed a morphologic leukemia free state, 12 patients are showing SD. Eleven patients were deemed non evaluable for response (these patients did not have a post treatment biopsy). Responses for the 34 patients who had been evaluated as of 28 February 2014, each of whom received a dose between 16.8 mg/m^2 to 55 mg/m^2 per cycle, are shown in Table 1.

Table 1: Responses in Arm 2 (AML) [16.8 mg/m^2 to 55 mg/m^2] as of 28 February 2014 (Study KCP-330-001)

Number of Patients Evaluated	Total CRs, CR(i)s, PR and SD (%)	CR (%)	CR(i) (%)	PR (%)	MLFS (%)	SD (%)	PD (%)
35	21 (60%)	5 (15%)	1 (3%)	2 (6%)	1 (3%)	12 (34%)	14 (40%)

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,

Overview of Clinical Safety in AML Gastrointestinal adverse events and fatigue are the most common types of AEs seen in Arm 2 (AML) patients. As of 17 January 2014, AE prevalence percentages were based on 48 AML patients in the Arm. The gastrointestinal adverse events typically consist of nausea in 26 patients (54%), anorexia in 21 patients (44%), vomiting in 14 patients (29%) and weight loss in 10 patients (21%). The gastrointestinal events are primarily Grade 1 or Grade 2 events that are generally responsive to standard supportive care. Fatigue was observed in 22 patients in this arm (46%), including Grade 3 fatigue in four patients (8%) and Grade 1 or Grade 2 fatigue in 18 patients (37%). Karyopharm has also observed Grade 4 thrombocytopenia in two patients (4%). 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. Blurred vision (Grade 1 and 2) was reported n 19 patients (40%); in some cases vision changes appear to be related to pre-existing conditions detected during pre-study ophthalmologic exams.

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.

5.3.3. Rationale for the Selinexor Doses and Dosing Regiment in AML

More than 200 patients with advanced cancers have received selinexor orally in three Phase 1 studies of selinexor. KCP-330-001 is a dose escalation study in patients with advanced hematologic malignancies including AML. KCP-330-002 is a dose escalation study in patients with advanced solid tumors. KCP-330-003 is a food effect study in patients with advanced sarcomas. Initially, 10 doses per 4-week cycle of selinexor was evaluated. The DLTs were anorexia/nausea and fatigue at 40 mg/m2 in KCP-330-002 and the maximum tolerated dose (MTD) was 30mg/m2 on this regimen. The recommended phase 2 dose (RP2D) for 10 times per cycle dosing is 30mg/m2 in both solid and hematologic malignancies.

However, pharmcoadynamics' analyses suggest that that at doses > 12 mg/m2, selinexor inhibits XPO1 activity for >48 hrs. Therefore, reduced intensity dosing at twice weekly (8 times per 4-week cycle) was evaluated and has shown improved tolerability with observed anti-cancer activity. Dose escalation on this twice-weekly schedule in KCP-330-001 in patients with chronic B-cell malignancies is currently proceeding at 60 mg/m2 and in patients with rel/ref AML at 70 mg/m^2. Recent analysis of the existing PK data from Phase 1 trials KCP-330-001 and KCP-330-002 supports the use of fixed rather than BSA-based dosing.The 5th and 95th percentile for BSA values encountered to date in Phase 1 trials KCP-330-001 and KCP-330-002 are 1.5 and 2.3 m2, respectively (N=331). PK values (Cmaxand AUC(0-f)) for a given flat (fixed) dose of selinexor were similar across this typical BSA range, indicating that exposure is not strongly correlated with BSA. This implies that we can switch to flat dosing rather than rely on a BSA based dosing scheme.

6 Study objective

6.1 Primary objectives

For part A of the study (if applicable):

1. To assess the safety and tolerability of selinexor added to standard induction chemotherapy for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia) and select the feasible dose level for part B
2. To assess in a randomized comparison the effect of selinexor on the CR rate.

For part B:

1. To assess the safety and tolerability of selinexor added to standard induction chemotherapy for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia) as regards the selected dose level of selinexor

2. To assess in a randomized comparison the effect of selinexor on the CR rate.

6.2 Secondary objectives

For part B:

1. To determine the efficacy profile (event free survival (EFS) disease free survival (DFS) and overall survival (OS)) associated with the two therapy regimens.
2. To measure MRD by immunophenotyping in relation to clinical response parameters.
3. To identify potential biomarkers predictive of response, EFS, DFS and OS by exploratory genomic analysis (microarray, gene mutations)

7 Study design

This is a multicenter study that is conducted in the frame of a masterprotocol with multiple parallel randomized phase II studies that will be conducted within the frame of a master protocol. The scheme of this design consists of one arm with the standard treatment for AML as compared to various arms with experimental treatments (see section 5.2 for further information). In this trial, elderly patients (aged ≥ 66 years) with AML (except those with FAB M3) and high risk MDS (IPSS-R > 4.5) fit for standard chemotherapy will be treated with two cycles of chemotherapy with or without selinexor). During the first part A of the study the feasible dose level of selinexor will be selected according DLTs. Part B of the randomized study will continue with the selected dose level of selinexor.

Arm A: Cycle I: Daunomycin/cytarabine (3/7 days)
Cycle II: Intermediate dose cytarabine

Arm D: Cycle I: Daunomycin/cytarabine (3/7 days) + selinexor (twice weekly starting day 1)
Cycle II: Intermediate dose cytarabine + selinexor (twice weekly starting day 1)

The initial dose of selinexor in the first cohort of patients is 60 mg twice weekly (see 9.1.1.). Decisions regarding dose escalation are based on the incidence of DLT (Dose Limiting Toxicity: death within 31 days of start cycle I and before start cycle II), and will be made according the rules defined in chapter 17.
All patients will be evaluated for response after cycle I and II. Patients in CR after cycle II with an HLA identical sibling donor can be offered an allograft with non-myeloablative conditioning.

8 Study population

8.1 Eligibility for registration

8.1.1 Inclusion criteria

- Patients eligible for standard chemotherapy.
- Patients 66 years and older
- Patients with:
    - a diagnosis of AML and related precursor neoplasms according to WHO 2008 classification (excluding acute promyelocytic leukemia) including secondary AML (after an antecedent hematological disease (e.g. MDS) and therapy-related AML, **or**
    - acute leukemia's of ambiguous lineage according to WHO 2008 **or**
    - a diagnosis of refractory anemia with excess of blasts (MDS) and IPSS-R > 4.5
- Adequate renal and hepatic functions unless clearly disease related as indicated by the following laboratory values:
    - Serum creatinine ≤1.0 mg/dL (≤88.7 µmol/L); if serum creatinine >1.0 mg/dL (>88.7 µmol/L), then the estimated glomerular filtration rate (GFR) must be >60 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation where the Predicted GFR (ml/min/1.73 m^2) = 186 x (Serum Creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if patient is female) x (1.212 if patient is black) NOTE: if serum creatinine is measured in µmol/L, recalculate it in mg/dL according to the equation: 1 mg/dL = 88.7 µmol/L and use the above mentioned formula.
    - Serum bilirubin ≤ 2.5 x upper limit of normal (ULN)
    - Aspartate transaminase (AST) ≤ 2.5 x ULN
    - Alanine transaminase (ALT) ≤ 2.5 x ULN
    - Alkaline phosphatase ≤ 2.5 x ULN
- WHO performance status 0, 1 or 2 (see Appendix F)
- Written informed consent.
- Male and female patients must use an effective contraceptive method if relevant during the study and for a minimum of 6 months after study treatment.

8.1.2 Exclusion criteria

- Acute promyelocytic leukemia
- Patients previously treated for AML (any antileukemic therapy including investigational agents), a short treatment period (< 2 weeks) with Hydroxyurea is allowed
- Concurrent history of active malignancy in the two past years prior to diagnosis except for:
    - Basal and squamous cell carcinoma of the skin

  - in situ carcinoma of the cervix
- Blast crisis of chronic myeloid leukemia
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etcetera)
- Cardiac dysfunction as defined by:
  - Myocardial infarction within the last 6 months of study entry, **or**
  - Reduced left ventricular function with an ejection fraction < 50% ad measured by MUG scan or echocardiogram **or**
  - Unstable angina **or**
  - New York Heart Association (NYHA) grade II or greater congestive heart failure (see Appendix I) **or**
  - Unstable cardiac arrthythmias
- Patients with a history of non-compliance to medical regimens or who are considered unreliable with respect to compliance
- Patients with any serious concomitant medical condition which could, in the opinion of the investigator, compromise participation in the study.
- Patients who have senile dementia, mental impairment or any other psychiatric disorder that prohibits the patient from understanding and giving informed consent.
- Current concomitant chemotherapy, radiation therapy, or immunotherapy other than as specified in the protocol.
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

9 Treatments

9.1 Dose level of Selinexor

9.1.1 Part A

Patients will receive the induction treatment cycles as described in section 9.2 and 9.3. In part A of the study selinexor is started at a dose level of 60 mg twice weekly orally. Decisions regarding dose escalation to 80 mg twice weekly of each cycle, continuation with current dose level or reducing the dose is based on the incidence of DLT (dose limiting toxicity: death within 30 days of start cycle I and before start of cycle II) and will be performed according to the rules defined in section 17. If the decision is made to escalate to 80mg, a discussion with the Selinexor drug provider must occur first in order to evaluate the decision based on the most current safety data.

9.1.2 Part B

The selinexor dose level for part B is selected in part A

9.2 Treatment schedules

9.2.1 Remission induction treatment Cycle I

Table 2 Standard arm A :

Agent	Dose/Day	Route	Days
Daunomycin	60mg/m^2	3hr infusion	1,2,3
Cytarabine	200mg/m^2	continuous infusion(24hrs)	1 thru 7

Table 3 Investigational arm D :

Agent	Dose/Day	Route	Days
Daunomycin	60mg/m^2	3hr infusion	1,2,3
Cytarabine	200mg/m^2	continuous infusion(24hrs)	1 thru 7
Selinexor	60 or 80 mg twice weekly	orally	1,3,8,10,15,17,22,24

9.2.2 Remission induction treatment Cycle II

Table 4 Standard Arm A:

Agent	Dose/Day	Route	Days
Cytarabine	1000mg/m^2 q 12 hrs	6 hr infusion	1 thru 6 (12 doses)

Table 5 Investigational arm D:

Agent	Dose/Day	Route	Days
Cytarabine	1000mg/m^2 q 12 hrs	6 hr infusion	1 thru 6 (12 doses)
Selinexor	60 or 80 mg twice weekly	orally	1,3,8,10,15,17,22,24

Cycle II will be given as soon as possible after cycle I but at least within 8 weeks after start of cycle I. If after cycle I the bone marrow shows persistence of leukemia it is recommended that patients proceed to cycle II immediately. Otherwise cycle II will be started as soon as there is evidence of haematological regeneration. No dose reduction is allowed.

9.3 Method of administration of Selinexor

Selinexor will be administered orally and is to be taken within 30-minutes of solid food consumption together with at least 120 mL of water.

Each dose will consist of selinexor for oral administration on an mg basis, irrespective of the patient's actual calculated body surface area (BSA) at baseline.

9.4 Dose modification for Selinexor

Treatment with selinexor is required to be discontinued at occurrence of any grade 3-4 non-hematological toxicity attributable to selinexor. If toxicity resolves to ≤ grade 1 within 4 weeks, treatment will be restarted (on scheduled days). No dose modifiations of selinexor are permitted. Selinexor does **not** need to be held **attributable to** the following cases :

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with adequate treatment of anti-emetics or anti-diarrheals –
- Alopecia of any grade
- Weight loss of less than 20%
- Electrolytes abnormalities that are reversible with standard interventions

9.5 Further information on study medication

Selinexor will be supplied and administered as coated, immediate-release oral tablets in strengths of 20 mg tablets in wallet-sized blister packs.

Selinexor tablets (20 mg) are currently in ongoing stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

All selinexor tablets must be kept in an appropriate, limited access, secure place until dispensed, destroyed or returned to Karyopharm Therapeutics, Inc. or designee for destruction.

Selinexor tablets can be stored at room temperature or refrigerated, at or below 86 ˚F or 30 ˚C, do not freeze. Room temperature storage is recommended. The study site will be required to maintain a log of the temperature where the study medication is stored.

. The tablets are clear coated with Opadry II clear and prepared from a common blend prepared from a wet granulation of active compound (KPT-330, selinexor), Kollidon® 30 (polyvinyl pyrrolidone), sodium lauryl sulfate, croscarmellose sodium, and Avicel PH-101 (Microcrystalline cellulose). The granulation is adjusted to final compression blend with Avicel PH-102 (Microcrystalline cellulose), Aerosil® (colloidal silicon dioxide), magnesium stearate, and additional croscarmellose sodium. All tablet excipients are GRAS and suitable for use in pharmaceuticals.

9.6 Provision of study medication

Karyopharm Therapeutics will supply Selinexor. Medication labels will comply with the legal requirements of each country and will be printed in the local language. The storage conditions for study drug will be described on the medication label. Bottles must be stored in a safe, secure location. The investigator must maintain an overall drug accountability log for the study, as well as individual records for each patient. The drug formulation, dose, number of blisters/tablets dispensed, received and returned must be recorded for each patient.

9.7 Therapy for adverse events associated with study medication

Supportive measures for optimal medical care according to local guidelines should be provided during participation in this clinical trial. Based on clinical observations in over 170 adult patients treated with selinexor, the dose limiting toxicities (DLTs) are primarily related to anorexia with poor caloric and fluid intake leading to weight loss, fatigue and nausea. Supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers), and other standard treatments may be administered as per institutional guidelines for symptomatic patients.

Supportive care recommendations based on the experience of the adult Phase I clinical trials are presented below.

9.7.1 Recommended prophylactic therapy to reduce anorexia, nausea and fatigue associated with selinexor

Three prophylactic medications (one from group A, one from group B, and ondansetron) are recommended during cycle 1 to minimize anorexia and nausea, and may be tapered or discontinued after cycle 2 as tolerated. If there is an adverse reaction to one of the prophylactic medications it may be discontinued or omitted.

A. Either **dexamethasone** (preferred) 2-4 mg (or equivalent glucocorticoid given on the day of ± the day after selinexor dosing; continuous dosing also permitted; maximum 30mg dexamethasone or equivalent per week) –or– **megesterol** 80-400 mg daily, starting 0-3 days before the first dosing day of selinexor on days of dosing.

B. Either **olanzapine (preferred)** 5.0 mg qhs or 2.5 mg bid, starting 0-3 days before the first dosing day of selinexor –or– **mirtazapine** 7.5-15 mg daily (qpm or qhs), starting 0-3 days before the first dosing day of selinexor.

C. **Ondansetron** 8 mg starting before the first dose of selinexor and continued bid – tid prn. Other standard 5-HT3 antagonists may be substituted for ondansetron.

A sample weekly schedule for prophylactic therapy is noted below and may be adjusted according to patient tolerance.

Compound	Day Prior to first Selinexor Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Selinexor		X		X				
Dexamethasone	X	X	X	X	X			
Megesterol	X	X	X	X	X	X	X	X
Olanzapine (or mirtazapine)	X	X	X	X	X	X	X	X
Ondansetron		X	BID-TID prn					

9.7.2 Nausea and Emesis

Supportive care for nausea and vomiting should be given promptly (see 9.7.1 for treatment recommendations to begin prior to first dose and/or during Cycle 1). Standard anti-emetics are allowed and strongly recommended. The treatment should start with the first sign of nausea, particularly with olanzapine 2.5-5.0 mg po qhs, that has been shown in the Phase I studies to prevent much of the nausea and emesis associated with selinexor. Patients can be initiated on olanzapine prior to initiating therapy with selinexor. These may be tapered after Cycle 1 in patients with good tolerability

Acute Emesis (occurring within 24 hours of administration of selinexor)

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.

Standard D2-receptor antagonists are often quite effective in preventing selinexor induced nausea.

5-HT3 receptor antagonists all appear equally effective at preventing nausea/emesis at the recommended doses. As QTc prolongation is the main side effect, magnesium and potassium should be corrected prior to use.

Neurokinin-1 receptor antagonists (e.g., aprepitant) should be considered in case of uncontrolled emesis with standard treatments as described above. Neurokinin-1 receptor antagonists can be given with combination of 5-HT3 receptor antagonists.

Additional treatment: Metoclopramide hydrochloride prior to meals (up to 4 times a day) has been effective in many adult patients. Lorazepam can be added to the combination treatment of 5-HT3 receptor antagonists, e.g. at night, but has been less effective in selinexor associated nausea and

emesis.

Delayed Emesis (occurring greater than 24 hours after administration of selinexor)
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), along with a 5-HT3 receptor antagonist on day 1. This regimen is effective against both acute and delayed emesis.
Conventional antiemetics are more successful at preventing emesis than in preventing nausea, particularly delayed nausea. In adult studies, olanzapine once daily (typically given at night to mitigate sedative effects) was proven effective in both antiemetic and nausea control.
In adults, additional agents have been administered including: lorazepam, alprazolam, dopaminergic D2-antagonists (eg, prochlorperazine, thiethylperazine, haloperidol), or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist.

9.7.3 Anorexia

Selinexor treatment can cause anorexia, reduced food intake and weight loss. In the phase I studies it has been shown that patients receiving prophylactic treatment to prevent anorexia, fatigue and nausea as described in 9.7.1 have benefitted. Additional standard supportive care agents may be used as needed..

9.7.4 Diarrhea

Diarrhea is common at up to 32% (mostly Grade 1), which responds to standard anti-diarrheal agents.

9.7.5 Liver enzyme increase

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 that could alter selinexor metabolism. Glutathione (GSH) replacing agents such as N-acetylcysteine or S-adenosylmethionine may be considered if selinexor induced liver dysfunction is suspected.

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

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

9.7.7 Missed or Vomited Doses

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 hrs, then it will be replaced. Doses should not be administered in less than 36 hrs apart and all missed doses should be documented.

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.

If a patient missed a full week of dosing for non-study drug related events (eg. a required medical procedure or an unanticipated personal emergency), the days missed will not be replaced.

9.7.8 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.

9.7.8.1 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.

9.7.8.2 Prevention of pregnancy

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 male patients, effective methods of contraception must be used throughout the study and for six months following the last dose.

9.7.8.3 Prohibited medication

Patients should minimize the use of products containing acetaminophen, which can interfere with the metabolism of selinexor, on the days of selinexor dosing. Acetaminophen should not be taken within 4 hours before or after selinexor dosing. For combination painkillers containing acetaminophen it is recommended that single agent opiates or aspirin combinations (when clinically acceptable) be substituted, particularly on the days of selinexor dosing within 2 hours before or after selinexor dosing.

Concurrent therapy with another investigational anticancer therapeutic, is not allowed.

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

The primary metabolism of selinexor in humans is through glucuronidation. Inactivation of selinexor by glutathione conjugation is a secondary metabolic pathway in vitro and in viv, 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 underway and preliminary data suggest the combination of low dose acetaminophen and selinexor is not toxic. 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.

10 End of protocol treatment

A patient may discontinue participation in the study for any one of the following reasons (categorized on the Off Treatment Form of the CRF as one of the following):

1. Normal completion of protocol treatment (i.e. cycles I + II)
2. Excessive extramedullary drug toxicity preventing continuation of treatment
3. Hypoplastic bone marrow abnormalities preventing continuation of treatment
4. Delay of start cycle II for >8 weeks after start cycle I (for any reason except the two reasons mentioned before (2 and 3))
5. Relapse
6. Adverse event preventing further treatment
7. Lack of patient compliance (especially refusal to continue treatment)
8. Death
9. Major protocol violation

All relevant information related to the reason for treatment discontinuation, including contributory factors, must be included in the Off Treatment Form of the CRF and recorded in the patient medical records.

11 Required clinical evaluations

11.1 Table 5 Required investigations

	At entry	After Cycle I and II	FU
Medical history/daily status	X	daily until discharge o.i.	X
Check of inclusion/exclusion criteria	X		
Collection of informed consent	X		
Adverse events		X	
Physical examination	X	daily until discharge o.i.	X o.i.
Hematology	X	every other day until PBR	X
Blood chemistry	X	X[1)]	X[4)]
Bone marrow aspirate			
Morphology	X	X	X[5)]
BM immunophenotyping	X		
Cytogenetics	X	X[2)]	X[2)]
Molecular diagnostics	X		
Gene expression profiling	X		
MRD assessment	define LAP(s)[6]	day 28-35[6]	X[6]
Bone marrow biopsy			
Histopathology	X		
Specific investigations			
Coagulation tests	X	only PTT, weekly until discharge	
Chest X-ray	X	o.i.	
ECG	X	o.i.	
Cardiac ejection fraction	o.i.		
Dental examination	X		
Ophthalmologic examination	o.i.	o.i.	
Virological tests	X		
Microbiological tests	X	X[3)]	

o.i. on indication

1) - every other day until discharge: Creatinine, Na, K, Glucose.
- weekly until discharge: Ca, P, Mg, Cl, AST, ALT, Alk. Phos., γ-GT, bilirubine (direct+indirect), LDH, albumin

2) only when cytogenetic abnormalities were evident: to document remission after protocol treatment or when relapse is supected

3) according to local bacteriology guidelines

4) only creatinine, AST, ALT, Alk. Phos., γ-GT, bilirubin

5) o.i. and if patient in first CR: at 4, 8, 12, 18, 24, 36, 48 months

6) Immunological examination for MRD detection at diagnosis, in case of CR at day 28-35 after cycle I as well as after cycle II, and at relapse (further details will be provided to the participating centers in a laboratory manual)

11.2 Observations prior to start of treatment

- History, including exposure to insecticides, previous chemotherapy or radiotherapy, antecedent hematological diseases (≥ 3 months duration prior to diagnosis AML or high risk

MDS, record AML, subtype and type of prior other antecedent hematological disease) or antecedent oncological diseases

- Physical examination including body weight, height, vital signs, performance status (see Appendix F), splenomegaly, hepatomegaly, signs of extramedullary leukemia (if signs, record site, and level of evidence (physical examination, radiologically confirmed, pathologically confirmed))
- Hemoglobin, hematocrit, reticulocytes, platelets, WBC and WBC differential
- Blood chemistry, including serum creatinin, Na, K, Ca, uric acid, glucose, albumin, bilirubin, AST, ALT, alkaline phosphatase, gamma GT, LDH
- Surveillance cultures of throat, stools and urine (according to local microbiology guidelines)
- Chest X-ray
- Cardiac ejection fraction, measured by MUGA or echocardiogram if clinically indicated.
- ECG
- Dental examination
- Full ophthalmological examinationif clinically indicated during study. Prior to dilaton; best corrected visual acuity, visual field examination via automated perimetry, tonometry, and color vision test. Dilated fundoscopy and slit lamp exam including anterior segment photos to document lens clarity
- Serology for cytomegalovirus (CMV) infection, HIV (human immunodeficiency virus), hepatitis A, B and C
- Coagulation studies including fibrinogen, APTT, PTT
- Bone marrow aspiration for:
    - cytology and cytochemistry to establish WHO and FAB subtype of AML or MDS
    - cytogenetics (cell culture and banding analysis)
    - immunological phenotyping to verify myeloid leukemia, determination of leukemia associated phenotype (LAP),
    - molecular analysis for *AML1/ETO, CBFβ/MYH11, BCR/ABL, Flt3-ITD, CEBPA* and *NPM1* gene mutations and *EVI1* expression and if possible other available or emerging interesting genetic markers (mutations of *KIT*, *WT1*, *FLT3*-point mutations, gene expression markers *ERG, BAALC* and other potentially relevant markers),

      - whole genome transcriptional profiling (further details will be provided to the participating sites in a laboratory manual)
- Bone marrow biopsy for histopathology o.i.
- Consider donor search

11.3 Observations during and following induction treatment cycle I and II

- Daily status and physical examination (including vital signs) if clinically indicated
- Blood cell count, quantitative platelets, WBC count and differential at least every other day when hospitalized until PBR, thereafter as clinically indicated.
- X-chest, ECG as clinically indicated
- Creatinin, Na, K, glucose every other day until discharge
- Ca, Mg, phosphate, AST, ALT, alkaline phosphatase, gamma GT, bilirubin (direct and indirect), LDH , albumin, PTT as clinically indicated and at least weekly until discharge
- Surveillance cultures according to local bacteriology guidelines
- Following each cycle, at day 18-21, the response will be assessed by bone marrow aspiration, blood evaluation and extramedullary disease status evaluation (see Appendix C). If and as long as the marrow is not conclusive a new marrow will be taken as clinically indicated, but at least at weekly intervals.
- Marrow sampling for minimal residual disease assessments prior to cycle II, and after cycle II in case of CR or relapse.

11.3.1 Toxicity assessment

During and following each cycle, toxicity has to be carefully examined and evaluated. During the clinical phase a daily assessment of toxicities will be performed. After discharge patients will be followed weekly and the same investigations will be performed. The toxicity assesment includes the following:

- Complete history of symptoms and complaints
- Complete physical examination, with special emphasis on neurological symptoms
- Laboratory examination of hemogram, electrolytes, liver enzymes and kidney parameters
- Chest X-ray as clinically indicated
- Electrocardiography when indicated
- DLT assessment at day 31 after induction cycle I (see 17.1)

Toxicities will be scored according to the most recent version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 (see Appendix E).

11.3.2 Response assessment after Cycle I and Cycle II

Following each cycle, at day 18-21, the response will be assessed by bone marrow aspiration, blood evaluation and extramedullary disease status evaluation (see Appendix C). If and as long as the marrow is not conclusive a new marrow will be taken as clinically indicated, but at least at weekly intervals. If the marrow shows evidence of resistant disease after Cycle I, Cycle II may be started as soon as possible without waiting for PBR. In all other cases blood evaluation will be repeated until

PBR.Cytogenetic analysis may be used to document remission in patients when abnormalities were evident. The response after cycle 2 will be assessed at day 28 and as long as the marrow is not conclusive a new marrow will be taken as clinically indicated, but at least at weekly intervals.

11.4 Observations during follow up

Outpatient visits to the clinic are planned twice weekly until full hematological recovery or CR:
Thereafter visits are planned as follows:
Outpatient visits to the clinic are planned according to the following schedule:

- Year 1: Subjects will be seen at least every 6 weeks.
- Years 2 and 3: Subjects will be seen at least at 3 months intervals.
- Years 4 and 5: Subjects will be seen once every 6 months.

In this schedule time is measured from the date of completion of protocol treatment.
At each clinical visit the following examinations will be done:

- Interim history and physical examination if clinically indicated
- Hemoglobin, WBC count and differential, platelet count, erythrocyte count, reticulocyte count
- Creatinin, AST, ALT, alkaline phosphatase, γGT, bilirubin
- Chest X-ray when clinically indicated
- Cytogenetic analysis will be included when cytogenetic abnormalities were evident and when leukemic relapse is suggested.

11.5 MRD assessment

Definition of MRD: malignant blasts as a percentage of the stem/progenitor compartment and as a percentage of the whole white blood cell compartment. These percentages are calculated based on the frequency of cells with an aberrant phenotype.

Immunological examination for MRD detection at diagnosis, in case of CR at day 28-35 after cycle I as well as after cycle II, and at relapse (a laboratory manual with details will be provided to the participating centers)

12 Toxicities

Daunomycin

Congestive heart failure is a major complication of anthracyclins, frequently observed after high cumulative doses. The total dose of daunomycin in this study is 180 mg/m². This dose is below the levels associated with congestive heart failure. Daunomycin causes pancytopenia and can induce

septic or hemorrhagic complications. Other side effects are hair loss, mucositis, cardiomyopathy, nausea, vomiting, colitis.

Cytarabine (Ara-C)

Cytarabine causes pancytopenia and can induce septic or hemorrhagic complications.

Cytarabine at a dose of 200 mg/m² may cause anorexia, nausea, vomiting, hepatic dysfunction, skin rash, pneumonitis, fever.

Intermediate dose cytarabine (1000 mg/m^2) may cause nausea, vomiting, stomatitis, skin rash, fever, conjunctivitis (prevented by the use of methylcellulose or steroid eye drops), somnolence, and in few cases cerebellar toxicity. Cytarabine must be stopped immediately in case of nystagmus or dysarthria.

Selinexor

Selinexor is currently in clinical development and has not been approved by the Food and Drug Administration (FDA) for commercial use. Human experience with selinexor is currently limited and the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicities will be scored according to the most recent version of the NCI Common Terminology Criteria of Adverse Events, version 4 (Appendix E).

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

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

Side effects observed in patients include:

Very common side effects (≥10%):

In 100 people receiving selinexor more than 10 people may have:

- Nausea
- Vomiting
- Diarrhea
- Anorexia – loss of appetite
- Hyponatremia – low sodium
- Dehydration
- Blurred vision
- Thrombocytopenia – decrease in platelets, which help your blood clot

- Anemia – decrease in red blood cells
- Neutropenia - decrease in neutrophils – a specific type of white blood cell that helps fight infectionsLeucopenia – decrease in white blood cells

- Fatigue
-
- Weight loss
- Dygeusia - change in taste
- Dizziness
-

Common side effects (≥1-10%):

In 100 people receiving selinexor about 1 to 10 people may have:

- Constipation
- Dry mouth
- Creatinine increased - increase in creatinine in the blood due to a reduction in kidney function, often related to dehydration
- Worsening of pre-existing cataracts
- Febrile neutropenia – fever, in the absence of a normal white blood cell response that may mean you have an infection
- Dyspnea – shortness of breath
- Syncope - fainting
- Confusion
- Pneumonia
- Sepsis – potentially life-threatening complication of an infection

Uncommon side effects (>0.1-1%):

In 1000 people receiving selinexor about 1 to 10 people may have:

- Cognitive disturbance
- Altered balance

Rare side effects (>0.01-0.1%):

In 10 000 people receiving selinexor about 1 to 10 people may have:

- Acute cerebellar syndrome (symptoms can include a sudden loss of coordination, balance or slurred speech)

Reproductive risks

Patients should not become pregnant or father a child while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study. It is not anticipated that female patients enrolling in this study will be able to conceive. However, in the rare event that this is possible, 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 six months following the last dose.

13 Reporting serious adverse events and SUSARS

13.1 Definitions

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject during protocol treatment. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse reaction (AR)

Adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected

Serious Adverse Events (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose results in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- severe/permanent disability
- a congenital anomaly
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

Note that any death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Unexpected Serious Adverse Events

Unexpected Serious Adverse Events are those SAEs of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as a source document in that country.

Suspected unexpected serious adverse reaction (SUSAR)

All suspected serious ARs which occur in the trial and that are both unexpected and serious.

13.2 Reporting of (Serious) Adverse Events

Adverse event

All AEs of CTCAE grade 2 or higher have to be reported on the Adverse Events CRF, with the exception of alopecia, nausea/vomiting and progression of the disease under study, a pre-existing condition that does not increase in severity (the pre-existing condition should be reported on the baseline concomitant diseases CRF) and abnormal laboratory values that have been recorded as being not clinically significant by the (sub)investigator in the source documents.

Adverse events will be reported from the first study-related procedure until 30 days following the last protocol treatment or until the start of subsequent systemic therapy for the disease under study, if earlier.

Adverse events occurring after 30 days should also be reported if considered related to study drug.

Grade 3 or 4 adverse events considered related to study drug must be followed until recovery or until 6 months after the last protocol treatment, whichever comes first.

All other adverse events must be followed until recovery or until 30 days after the last protocol treatment, whichever comes first.

Serious Adverse Events

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last protocol treatment or until the start of subsequent systemic therapy for the disease under study, if earlier.

Serious adverse events occurring after 30 days should also be reported if considered to be at least suspected to be related to the study drug.

All SAEs must be reported to the HOVON Data Center by e-mail within 24 hours of the initial observation of the event, except hospitalizations for:

- a standard procedure for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- a procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse

event.

- ♦ prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- ♦ a procedure that is planned (i.e., planned prior to starting of treatment on study; must be documented in the source document and the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study drug remains a reportable serious adverse event.

All details should be documented on the Serious Adverse Event Report. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 2 working days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the Serious Adverse Event Form. The assessment of causality is made by the investigator using the following table:

Table 7 Assessment of causality:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT	There is insufficient or incomplete evidence to make a clinical

ASSESSABLE	judgement of the causal relationship.

13.3 Processing of serious adverse event reports

The HOVON Data Center will forward all SAE reports within 24 hours of receipt to the prinicipal investigator and Karyopharm Therapeutics. The HDC safety desk will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR).
The IB will be used as a reference document for expectedness assessment.
The HOVON Data Center will provide to the Ethics Committee(s) a six-monthly line listing of all reported SAE's if this is required by national laws or regulations or by the procedures of the Ethics Committee.

13.4 Reporting Suspected Unexpected Serious Adverse Reactions

The HDC Safety Desk, on behalf of the sponsor, will ensure the reporting of any SUSAR to the Ethics Committees (EC), the Competent Authority (CA), Karyopharm Therapeutics and the investigators in compliance with applicable law and regulations, and in accordance with any trial specific agreements between the sponsor and a co-sponsor or Karyopharm Therapeutics.

Expedited reporting of SUSARs will occur no later than 15 days after the HOVON Data Center had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

13.5 Pregnancies

Male subject:
Female partners of males taking investigational product should be advised to call their healthcare provider immediately if they get pregnant. The male subject should notify the investigator of this partner's pregnancy and her healthcare provider information. The investigator will then provide this information to the sponsor for follow-up as necessary. All details should be documented on the pregnancy form.

The sponsor will forward immediately any information regarding pregnancies and foetal exposure described above to Karyopharm Therapeutics.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the investigator(s)

13.5 Data Safety and Monitoring Board

The DSMB will advise the Principal Investigator, co-investigators and the chair of the working group in writing about the continuation of the trial. The DSMB will review the general progress and feasibility of the trial, the quality and completeness of the data, adverse events and safety, and differences in results between the arms of a randomized trial. The DSMB will consider if there is any concern regarding the safety and well-being of trial subjects or regarding the scientific validity of the trial results. The DSMB will give recommendations about dose escalations, dose reductions, continuation at a dose level or stopping because of inefficacy on the basis of interim reports at specific time points (see section 17 for more details on the interim analyses). The DSMB will base her advice on the reports provided by the trial statistician. The DSMB is free to take into consideration external information, such as the (interim) results of other trials or literature reports.
The DSMB consists of at least three members, with at least one independent statistician and two international clinical hematologists with a broad background in AML therapeutics.
Details of the DSMB constitution and tasks are documented in the trial specific DSMB charter.
The DSMB will receive at least the following reports from the trial statistician for review:

- Interim analysis reports (as described in chapter 17)
- Annual safety data listing the incidence of (serious) adverse events, (serious) adverse reactions and SUSARs
- Annual progress data listing the number of enrolled patients and the status of data collection

14 Endpoints

14.1 Primary endpoint

- Incidence of DLT (part A)
- The effect of selinexor on the CR rate (part B of study)

14.2 Secondary endpoints

- Overall survival (time from registration till the death of the patient.)
- Event free survival (i.e., time from registration to induction failure (i.e. no CR on induction), death or relapse whichever occurs first)
- Disease free survival (time from CR on protocol treatment until relapse or death, whichever

comes first)

- Prognostic value of molecular markers and gene expression profiles of the leukemia assessed at diagnosis
- Prognostic value of minimal residual disease (MRD) measurements following therapy by standardized sampling of marrow/blood

15 Registration and Randomization

15.1 Regulatory Documentation

The following documents must be provided to the HOVON Data Center before shipment of the study drug to the investigational site and before enrollment of the first patient.

By the principal investigator or study coordinator for all sites within their country:

- name and address of the (central) Ethical Committee including a current list of the members and their function;
- any other documentation required by local regulations.

15.2 Randomization

Eligible patients who have given written informed consent must be registered and randomised before start of treatment. For registration and randomization of patients we use TOP, all patients are randomized between the standard treatment and one or more experimental treatments. Each hospital chooses to which set of experimental treatments it participates in the trial. So, all patients of an hospital are randomized over the same set of treatments, of course this set can change in time. To keep the number of patients who are treated with the standard treatment as small as possible we intend to randomize patients over more than one experimental treatment and the standard treatment.

Patients can be registered and randomised at the HOVON Data Center of the Erasmus MC Cancer Institute, Clinical Trial Center via the Internet through TOP (Trial Online Process; https://www.hdc.hovon.nl/top) or by phone call: +31.10.7041560 or fax +31.10.7041028 Monday through Friday, from 09:00 to 17:00. A logon to TOP for participants can be requested at the HOVON Data Center.

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Local patient code (optional)
- Sex

- Date of birth
- Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number. Patients will be randomized, stratified by center. Patient study number, result of randomization, and dose level of selinexor (if applicable) will be given immediately by TOP or phone and confirmed by fax or email.
Local Patient Code is a code assigned to the patient by the investigational site for local administrative purposes. The code may be up to 8 characters long (letters and numbers allowed). The code should be in compliance with privacy regulations. It should not contain identifying data, such as patient initials or the complete hospital record number. The local code will be visible in the confirmation messages sent by TOP to local participants after registration of the patient. The key to this local patient code should only be accessible by the local investigator and the local trial staff. Using or entering a local patient code is not obligatory.

16 Data collection

Data will be collected on electronic Case Report Forms (e-CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- inclusion and exclusion criteria;
- baseline status of patient including medical history and stage of disease;
- timing and dosage of protocol treatment;
- adverse events;
- parameters for response evaluation;
- any other parameters necessary to evaluate the study endpoints;
- survival status of patient;
- reason for end of protocol treatment.

Each CRF page will be identified by a trial number, and a combination of patient study number (assigned at registration) and hospital name.
The e-CRF will be completed on site by the local investigator or an authorized staff member. Each page must be signed by the local investigator upon completion by means of an electronic signature. All CRF entries must be based on source documents.
Written instructions for completing the CRF will be provided by the HOVON Data Center. Access to the e-CRF will be provided by the HOVON Data Center only to authorized site staff members who have completed a training course on the use of the e-CRF. Training materials will be provided by the HOVON Data Center.

16.1 Reporting DLT information

To monitor the incidence of dose limiting toxicity (DLT) a separate CRF (DLT-form) will be send to the local investigator after randomization.
This DLT-form must be filled out for every patient, independent of randomization result. The form should be dated, signed by the responsible investigator and returned to the HOVON Data Center by fax within 48 hours after DLT-occurrence, or 31 days after start of cycle I if no DLT occurred.

17 Statistical considerations

The aim of this study is to decide whether the addition of selinexor to standard induction treatment could be sufficiently effective to warrant a continuation to a phase III study. The target number of patients for this phase II study is 100 in the standard treatment arm and 100 in the investigational arm for each experimental drug at the final dose level.
All analyses will be according to the intention to treat principle, i.e. patients will be analyzed according to the treatment arms they were assigned to. However, patients initially randomized but considered ineligible afterwards based on information that should have been available before randomization, will be excluded from all analyses. The final analysis will be done one year after last patient is registered in the selinexor arm.

17.1 Part A: Toxicity of Selinexor

Decisions regarding dose escalation, dose reduction or continuation with the initial or current dose of selinexor, will be based on the incidence of dose limiting toxicity (DLT) in the investigational arm. A DLT is defined as death within 31 days of start of cycle I and before initiation of start of cycle II, irrespective of the cause of death. In the HOVON/SAKK AML 43 the incidence of DLT defined in this way was 13%. A patient is evaluable for the DLT analysis if the patient has experienced a DLT or if the patient is still alive at day 31 after start of cycle I.

The following Table shows the decision rules that will be applied at a certain dose level during part A of the study. In this Table, the definition of DLT was restricted to death within 31 days following the start of cycle I and the decision rules are based on the comparison of the observed incidence with the incidence of DLT in the HOVON/SAKK AML 43 (13%).

Table 8. Decision rules for dose selection

Note. The actual decision to stop, reduce, escalate or continue at the final dose level will be made by the steering committee with these decision rules as guidelines. The actual decision may deviate

from the decision proposed by the rules. The steering committee may take other information from this trial and from other trials into account, including feedback from the drug providers. When according to the decision rules a decision can be made, a report will be made with the DLT information, but also with all available information concerning SAE incidence, haematological recovery and overall survival, including the cycle II data.

Number of evaluable patients in Arm D at the current dose level	Criterium	Decision
N < 15	D ≥ 3 and P1(D) <10%	Trial on hold or go to lower dose level
	Otherwise	Continue
N ≥ 15 and < 20	D ≥ 3 and P1(D) <10%	Trial on hold or go to lower dose level
	P2(D) <10%	Escalate or final dose level reached
	Otherwise	Continue
N ≥ 20 and <25	P1(D)<5%	Trial on hold or go to lower dose level
	P2(D) <10%	Escalate or final dose level reached
	Otherwise	Continue
N ≥ 25 and < 30	P1(D)<5%	Trial on hold or go to lower dose level
	D ≤ 0.13*N +1	Escalate or final dose level reached
	Otherwise	Continue
N = 30	P1(D)<5%	Trial on hold or go to lower dose level
	D ≤ 0.13*N +1	Escalate or final dose level reached
	Otherwise	Continue: final dose level reached

Explanation

N the number of evaluable patients in the experimental arm at the current dose level. Each time that a decision of reducing or escalating is reached, counting the number of evaluable patients starts again at '1' until the next dose cohort of (a maximum of) 30 evaluable patients has been included.

D the observed number of DLTs among the N patients in the current dose cohort

P1(D) the probability that **D or more** DLTs is observed among N patients when the true risk of DLT at this dose level would be -as in the HOVON AML 43 elderly study- 13%. A small value for P1 indicates that the observed number of DLTs is high and that it is likely that the true risk of DLT is considerably higher than 13%.

P2(D) the probability that **D or less** DLTs is observed among N patients when the true risk of DLT at this dose level would be twice as high as in the HOVON AML 43 elderly study, i.e. 2x13=26%. A small value for P2 indicates that the observed number of DLTs is comparatively low and that it is likely that the true risk of DLT is considerably smaller than 26%.

The trial will be continued at the current dose level as long as no decision for reducing, stopping or escalating can be made until 30 evaluable patients in the experimental arm are present. Then, according to the decision rules, the decision will be: continue at the current dose level (i.e. the final dose level). Once a decision has been reached, data from patients at this dose level who were not evaluable at the time of decision will not influence this decision at a later time point. Trial on hold means that the recruitment in the study will be stopped and decisions to stop or amend the trial need to be made.

In the next table, the characteristics of the decision rules have been evaluated with 1000 simulations (each simulation representing one trial) for hypothesized true probabilities for DLT incidence of 13% and 26% and with a target number of patients equal to a maximum of 30 per dose cohort.

Table 9 Impact of decision rules in 1000 simulated trials

	Dose level at which escalation is possible			Dose level at which no escalation is possible		
Decision	perc [%]	npat [n]	pdlt [%]	perc [%]	npat [n]	pdlt [%]
True probability of DLT=13%						
Stop/reduce dose	15.9	11.1	39.1	15.9	11.1	39.1
Continue	7.6	30	18.7	84.1	19.4	9.3
Escalate	76.5	18.3	8.4	-	-	-
True probability of DLT=26%						
Stop/reduce dose	71.6	11.3	40.8	71.6	11.3	40.8

Continue	9.1	30	21.0	28.4	23.1	13.8
Escalate	19.3	19.9	10.4	-	-	-

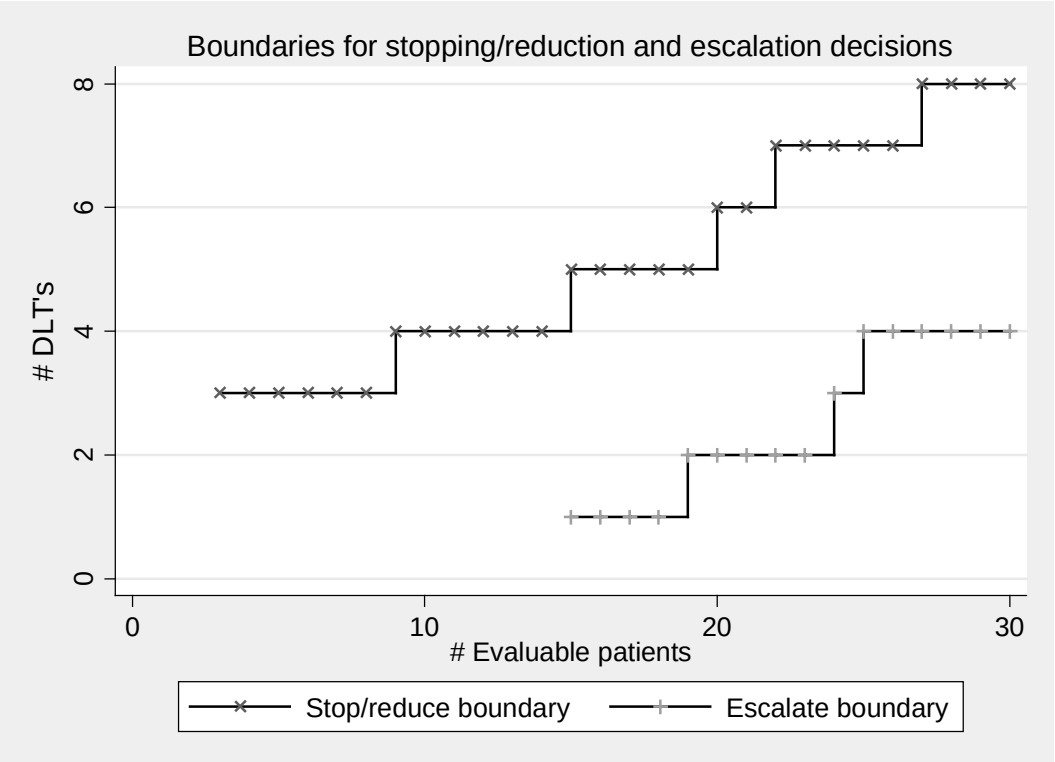
perc:	% times this decision is made in 1000 simulated trials
npat:	mean # evaluable pts (at time of the decision)
pdlt:	mean % pts with DLT (at time of the decision)

Thus, if the true probability of DLT is 13%, the appropriate decision to escalate to the higher dose level will be made in 76.5% of the 1000 simulated trials after on average 18.3 evaluable patients. In 15.9% of the simulated trials, the study will be wrongly put on hold after on average 11.1 patients. This is because at the moment this decision is made the observed incidence of DLT is high (on average 39.1%) due to stochastic variation.

If the true probability of DLT is 26%, the inappropriate decision to escalate to the higher dose level will be made in 19.3% of the 1000 simulated trials after on average 19.9 patients. This is because at the moment this decision is made the observed incidence of DLT is low (on average 10.4%) due to stochastic variation. In 71.6% of the trials, the correct decision to put the trial on hold will be made.

The stopping and escalation boundaries until a maximum of 30 evaluable patients are shown in the figure below.

Figure



An experimental arm will be put on hold when the number of DLTs exceeds the upper boundary of x-signs (including the boundary itself, e.g. after 3 DLTs / 3 patients or 8/30). Escalation is possible when the number of DLTs is below the lower boundary of +-signs, e.g. if ≤ 1/15, 2/19, 3/24 or 4 DLTs /25 patients.

17.2 Part B: Efficacy:

17.2.1 Design

Only if the trial will not be stopped because of too many DLTs in the investigational arm an analysis of efficacy is relevant. Primary endpoint for efficacy is the CR rate on protocol after induction treatment. The observed difference in CR rates (Dcr) between the investigational arm D at the final dose level and the Standard arm A will be used as criterion in the decision rules. One interim analysis regarding efficacy will be performed when 50 patients will be evaluable for CR in each arm (ie, at N=50/ 50). The following decision rules will be used as guidelines.

Table 10 Decision algorithm

Decisions	Conditions
At interim analysis (N=50/50)	
Stop because of inefficacy	Upper Limit of 80%-Confidence Interval for Dcr <15%, which is the case if the observed Dcr≤2%
Consider to continue as phase III	Lower Limit of 95%-Confidence Interval for Dcr >0%, which is the case if the observed Dcr≥19%
Continue as phase II	Otherwise
At final analysis (N=100/100) (if not stopped before)	
Stop because of inefficacy	The Upper Limit of 80%-Confidence Interval for Dcr <15%, which is the case if the observed Dcr < 6%
Consider to continue as phase III	Otherwise

The decision algorithm indicates that, assuming that the observed CR in the standard arm is 50% (as in the HOVON 43 AML[elderly]), an observed Dcr of at least 6% at the final analysis is required to fulfill the above criterion for “Consider to continue as Phase III” (ie, Upper Limit of 80%-Confidence Interval ≥15%). However, when the found Dcr is in the range of 6-15% and statistically non-significant (ie, lower limit of 95%-CI <0), evidence from other studies (eg, abstracts presented at conferences) could be used to support the eventual decision to continue as Phase III. A statistically significant Dcr in the range 10-15% (or higher) may be regarded as evidence enough to warrant

continuation as Phase III without evidence from other studies.

Assuming that the true CR rate in the standard arm is around 50% (as in the HOVON 43 AML), and that a total of 50 patients in arm D will be treated at the final dose level until the interim analysis and a total of 100 patients in arm D will be treated in arm D at the final dose level until the final analysis, then the application of the above decision rules lead to the following probability predictions at various levels of the true difference in response rates. These predictions were derived from series of 10,000 simulations.

The example in this Table shows that at a true existing difference of -10% (ie, in favor of the standard arm) the probability to continue as Phase III, either conditionally on evidence from other studies or without restrictions, either at interim or at the final analysis, is only 1.3%. This probability increases to 20.5% at a true difference of 0% to 96.9% at a true difference of 20%.

Table 11 Probability to continue as candidate Phase III given a true difference in CR rates (CR rate in standard arm = 50%)

	At interim (N=50)		At final analysis (N=100)	
	Probability to stop	Probability to continue as (conditional) Phase III	Probability to stop	Probability to continue as (conditional) Phase III
True difference in CR rates: arm B minus arm A				
-10%	82.3	0.2	16.4	1.1
0%	46.3	2.8	33.2	17.7
10%	12.9	18.4	17.1	51.6
20%	1.4	54.9	1.7	42.0

Above considerations apply if the decisions would be purely based on the primary endpoint only. In reality, the actual decisions at the final analysis will also take into account outcomes with respect to secondary endpoints in addition to information from other studies.

17.2.2. Statistical analyses

CR rate: primary analysis

Patients with CR(i) on cycle I/II (i.e. best response after cycle I/II) are considered as responders for the primary endpoint. All eligible patients registered and randomized for or against Selinexor at the final dose level will be included in the primary analysis of part B (i.e. including patients which were also part of the dose finding phase). The primary endpoint of the study is the difference in CR rate between Selinexor at the final dose level and patient in the standard treatment arm who were randomized against Selinexor at the final dose level. Also the 80% and 95% confidence interval of this difference will be computed. The decision rules as described in section 17.2.1 will serve as a guideline to decide if the treatment will be valuable to continue to a Phase III setting.

Other efficacy endpoints

Actuarial estimates of the survival endpoints DFS, EFS and OS at convenient time points (at least at 6 and 12 months) will be estimated using the Kaplan-Meier method. An comparison of these endpoints between treatment arms will performed using Cox regression analysis, which will give estimates of the hazard ratio with 95% confidence intervals (CIs). For EFS and DFS actuarial estimates will also be given for the competing risks. The CR rate will be compared between the two treatment arms using logistic regression, which will give an estimate of the odds ratio with 95% CI.

Toxicity analyses

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of adverse events CTCAE grade 2 or more, by treatment arm and cycle. Adverse events will be summarized by maximum CTCAE grade.

18 Ethics

18.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP Guidelines. The local investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

18.3 Patient information and consent

Written informed consent of patients is required before registration, randomization and any other

study specific procedure.

19 Trial insurance

The HOVON insurance program covers all patients from participating centres in The Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site www.hovon.nl.
Individual participating centers from outside the Netherlands have to inform the HOVON about the risk insurance of patients participating in a study.

Intergroup studies.
The HOVON insurance program does not automatically cover the risk insurance of patients from centres participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered/randomised through their offices.

20 Publication policy

Trial results will always be submitted for publication in a peer reviewed scientific journal regardless of the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for a publication.
The final publication of the trial results will be written by the Principal Investigator, the Study Coordinator(s) and the trial statistician on the basis of the statistical analysis performed by the trial statistician. A draft manuscript will be submitted for review to:

- All co-authors
- The chair of the relevant HOVON working group, who is entitled to share and discuss the manuscript with working group members
- An industry partner if so agreed in the contract between HOVON and company

After revision the final manuscript is submitted to the HOVON secretary for review of compliance with this policy.

After approval by the HOVON board the manuscript will be sent to a peer reviewed scientific journal. Authors of the main manuscript will include the Principal Investigator, the Study Coordinator(s), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion rate), the trial statistician and the trial manager. Others who have made a significant contribution to the trial may also be included as author, or otherwise will be included in the acknowledgement.
Authors of correlative manuscripts (e.g. results of side studies) will include the Principal Investigator,

the Study Coordinator(s), and those persons who have made a significant contribution to the published results.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, results for secondary endpoints, but no comparisons between randomized treatment arms for the primary endpoint may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the Principal Investigator, the Study Coordinator(s) and the trial statistician. This is applicable to any individual patient or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study endpoints unless the final results of the trial have already been published.

21 Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
ALT	Alanine Amino Transferase (SGPT)
ANC	Absolute Neutrophil Count
AR	Adverse reaction
Ara-C	Cytarabine, cytosine arabinoside
AST	Aspartate Amino Transferase (SGOT)
bid	Twice a day
BM	Bone Marrow
CBF	Core binding factor
CI	Confidence interval
CMV	Cytomegalo virus
CR	Complete Remission
CRi	Complete Remission with incomplete blood count
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
DFS	Disease free Survival
DLT	Dose Limiting Toxicity
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EFS	Event Free Survival
EMD	Extra medullary disease
FISH	Fluorescent In Situ Hybridization
FU	Follow up
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HOVON	Dutch/Belgian Hemato-Oncology Cooperative Group
HRC	Hematocytology Review Committee
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IM	Intramuscular
IPSS	International Prognostic Score System (for MDS)
IV	Intravenous
LAP	Leukemia Associated Phenotype
MDS	Myelodysplasia

METC	Medical Ethical review committee
MK	monosomal karyotype
MRD	Minimal Residual Disease
MUGA	Multiple Gated Acquisition Scan
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PBR	Peripheral Blood Recovery
PR	Partial Response
prn	As needed
qhs	Every night at bedtime
qpm	Every day after noon or every evening
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
tid	Three times a day
ULN	Upper Limit of the Normal range
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen
WBC	White Blood Cell

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A1. WHO 2008 classification for Acute Myeloid Leukemias (AML) and related precursor neoplasms

- Definition AML: ≥ 20% myeloblasts in blood or bone marrow
- Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryoblastic leukemia are considered blast equivalents

Table 12. WHO 2008 classification for AML and related precursor neoplasm

WHO code	Category	Subcategory and short description
9896	AML with recurrent genetic abnormalities	AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1**
9871		AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFß-MYH11**
9866		Acute promyelocytic leukemia; AML with t(15;17)(q22;q12); *PML-RARA* and cytogenetic variants
9897		AML with t(9;11)(p22;q23); *MLLT3-MLL*
9865		AML with t(6;9)(p23;q34);*DEK-NUP214*
9869		AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
9911		AML (megakaryoblastic) with t(1;22)(p13;q13);*RBM15-MKL1*
9861		Provisional entity: AML with mutated *NPM1*
9861		Provisional entity: AML with mutated *CEBPA*
9895	AML with myelodysplasia related changes	Previous history of myelodysplastic syndrome **or** Myelodysplastic syndrome-related cytogenetic abnormality **or** Dysplasia present in > 50% of 2 or more cell lineages **Absence of both** Prior cytotoxic therapy for an unrelated disease Recurring cytogenetic abnormality as described in AML with recurrent genetic abnormalities
9920	Therapy-related myeloid neoplasms	Includes t-AML, t-MDS and t-MDS/MPN
9861	**Acute myeloid leukemia, NOS**	
9872	AML with minimal differentiation	<3% of blasts positive for Sudan Black B or MPO. Blasts usually express CD13 and/or CD117, with or without CD33 in absence of lymphoid markers cCD3, cCD22 and cCD79a
9873	AML without maturation	Blasts ≥90% of bone marrow non-erythroid cells (i.e. excluding also lymphocytes, plasmacells, macrophages and mast cells) ≥3% of blasts positive for Sudan Black B or MPO Blasts express MPO and one or more of myeloid-associated antigens such as CD13, CD33 or CD117
9874	AML with maturation	≥10% maturing cells of neutrophil lineage <20% bone marrow monocytes
9867	Acute myelomonocytic leukemia	>20% neutrophils and precursors of marrow cells

		>20% monocytes and precursors of marrow cells
9891	Acute monoblastic and monocytic leukemia	≥80% of the leukemic cells are monoblasts, promonocytes and monocytes
9840	Acute erytroid leukemia	Erythroleukemia (erythroid/myeloid) Presence of medium to large size erythroblasts: ≥ 50% of bone marrow cells Blasts: ≥ 20% of the bone marrow nonerythroid cells
		Pure erythroid leukemia Presence of medium to large size erythroblasts
9910	Acute megakaryoblastic leukemia	>50% of the blasts are of megakaryocytic lineage Blasts express CD41 and/or CD61
9870	Acute basophilic leukemia	Primary differentiation to basophils; mature basophils are usually sparse
9931	Acute panmyelosis with myelofibrosis	Acute panmyeloid proliferation with accompanying fibrosis
9930	Myeloid sarcoma	Tumor mass of myeloblasts or immature myeloid cells occurring in an anatomical site other than the bone marrow
Myeloid proliferations related to Down syndrome (DS)		
9898	Transient abnormal myelopoiesis (TAM)	Morphologic and immunophemotypic features are similar to the blasts in most cases of DS AML
9898	Myeloid leukemia associated with Down syndrome	Usually an acute megakaryoblastic leukemia
9727	**Blastic plasmacytoid dendritic cell neoplasm (BPDC)**	
		Blastic NK-cell lymphoma

*Rare cases show < 20% myeloblasts; these should be classified as AML

A2. WHO 2008 classification for myelodysplastic syndromes

Table 13. WHO 2008 classification for myelodysplastic syndromes

WHO code	Disease	Blood findings	Bone marrow findings
9980 *9991* *9992*	Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anemia (RA); Refractory neutropenia (RN); Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia[1] No or rare blasts (<1%)[2]	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage <5% blasts <15% of erythroid precursors are ring sideroblasts
9982	Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only <5% blasts
9985	Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%)[2] No Auer rods <1 x 10^9/l monocytes	Dysplasia in ≥10% of the cells in ≥ two myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts in marrow No Auer Rods ±15% ring sideroblasts
9983	Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) <5% blasts[2] No Auer rods <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 5-9% blasts[2] No Auer rods
9983	Refractory anemia with excess blasts-1 (RAEB-2)	Cytopenia(s) 5-19% blast Auer rods ± <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 10-19% blasts[2] Auer rods ±
9989	Myelodysplastic syndrome-unclassified (MDS-U)	Cytopenias ≤1% blasts[2]	Unequivocal dysplasia in less than 10% of the cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS < 5% blasts
9986	MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts No Auer rods Isolated del(5q) cytogenetic abnormality
9985	Refractory cytopenia of childhood		

[1]Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U

[2]If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB 1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

[3] Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2

A3. WHO 2008 Acute leukemia's of ambiguous lineage

Table 14. WHO 2008 Acute leukemia's of ambiguous lineage

WHO code	Category	Short description
9801	Acute undifferentiated leukemia	Expresses no markers considered specific for either lymphoid or myeloid lineage
9806	MPAL, with t(9;22)(q34;q11.2); *BCR-ABL1*	
9807	MPAL, with t(v;11q23); *MLL* rearranged	
9808	MPAL, B/myeloid, NOS	
9809	MPAL, T/myeloid, NOS	
	MPAL, NOS-rare types	
	Other ambiguous lineage leukemia's	A combination of markers is expressed that does not allow classification as either AUL or MPAL

MPAL= mixed phenotype acute leukemia

Table 15. Requirements for assessing more than one lineage to a single blast population (mixed phenotype)

Myeloid lineage Myeloperoxidase (flow cytometry, immunohistochemistry or cytochemistry) Or Mononcytic differentiation (at least 2 of the following: NSE, CD11c, CD14, CD64, lysozyme)
T lineage Cytoplasmic CD3 (flow cytometry with antibodies to CD3 epsilon chain; immunohistochemistry using polyclonal anti-CD3 antibody may detect CD3 zeta chain, which is not T-cell specific) Or Surface CD3 (rare in mixed phenotype acute leukemia's)
B lineage (multiple antigens required) Strong CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10 Or Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10

A4. FAB classification of AML

Table 16. Cytological criteria for the diagnosis of acute myeloid leukemia: French-American-British-(FAB) classification

FAB subtype	
	For all AML subtypes the following criteria apply: ♦ Blasts ≥ 30% of bone marrow nucleated cells, except for M3 ♦ ≥ 3% of blasts positive for Sudan BlackB or Myeloperoxidase, except for M0 and M7
M0	♦ < 3% of blasts positive for Sudan Black B or Myeloperoxidase ♦ at least one of the following myeloid markers present: CD13,CD33, CD15, CDw65 ♦ in absence of lymphoid markers CD3 and CD22
M1	♦ Blasts ≥ 90% of bone marrow nonerythroid cells (i.e. excluding also lymphocytes, plasma cells, macrophages and mast cells) ♦ Maturing granulocytic cells (i.e. promyelocytes towards polymorphonuclear cells ≤ 10% of nonerythroid cells ♦ (pro)monocytes ≤ 10% of nonerythroid marrow cells
M2	♦ Blasts 30-89% of bone marrow nonerythroid cells ♦ Maturing granulocytic cells (i.e. promyelocytes to polymorphonuclear cells) > 10% of nonerythroid cells ♦ Monocytic cells (i.e. monoblasts to monocytes) < 20% of nonerythroid cells
M2E	♦ Analogous to M4E, but lacking clear monocytic differentiation
M3	♦ Promyelocytes (most hypergranular) > 30% of bone marrow nucleated cells
M3V	♦ Promyelocytes (hypogranular or microgranular) > 30% of bone marrow nucleated cells
M4	♦ Granulocytic cells (myeloblasts to polymorphonuclear cells) ≥ 20% of nonerythroid cells plus one of the following criteria • Monocytic cells (monoblasts to monocytes) ≥ 20% of nonerythroid cells Or • Peripheral blood monocytes ≥ 5 x 10^9/l Or • Elevated urinary lysozymes ≥ 3 x normal value
M4E	♦ Same as M4, but with ≥ 5% abnormal eosinophils (basophilic granulae)
M5A	♦ Blasts ≥ 30% of bone marrow nonerythroid cells ♦ Bone marrow monocytic component ≥ 80% of nonerythroid cells ♦ Monoblasts ≥ 80% of bone marrow monocytic component
M5B	♦ Blasts ≥ 30% of bone marrow nonerythroid cells ♦ Bone marrow monocytic component ≥ 80% of nonerythroid cells ♦ Monoblasts < 80% of bone marrow monocytic component
M6	♦ Erythroblasts ≥ 50% of bone marrow nucleated cells ♦ Blasts ≥ 30% of bone marrow nonerythroid cells
M7	♦ > 30% of bone marrow nucleated cells are megakaryoblasts CD41 or CD61 positive or ♦ Platelet specific peroxidase reaction (electron microscopy) ♦ < 3% of blasts positive for Sudan Black B or Myeloperoxidase

B. Revised International Prognostic Score System (IPSS-R) for MDS

Table 17. Risk categories

Risk category	IPSS-R score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

Table 18. IPSS-R prognostic score values

Prognostic score value	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blast, %	≤2	-	>2- <5	-	5-10	>10	-
Hemoglobin mmol/l	≥6.2	-	5.0- <6.2	<5.0	-	-	-
Platelets $x10^9$/l	≥100	50- 100	<50	-	-	-	-
ANC $x10^9$/l	≥0.8	<0.8	-	-	-	-	-

-indicates not applicable

Table 19. Cytogenetic scoring system for IPSS-R

Prognostic subgroups	Cytogenetic abnormalities
Very good	-Y,del(11q)
Good	Normal, del(5q),del(12p),del(20q), double including del(5q)
Intermediate	del(7q),+8,+19,i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q),del(3q), double including -7/del(7q), complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

Greenberg PL et al., Blood, 120;(12): 2454-2465

C. AML Response criteria

These response criteria were published in the 2009 paper, "Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet" [(12)], and are based on International Working Group recommendations published in 2003 [(**Error! Reference source not found.**)].

Table 20 Response Criteria

CATEGORY	DEFINITION
Complete remission (CR) [1]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L; platelet count >100 x 10^9/L; independence of red cell transfusions
CR with incomplete recovery (CRi) [2]	All CR criteria except for residual neutropenia (<1.0 x 10^9/L) or thrombocytopenia (<100 x 10^9/L)
Morphologic leukemia-free state [3]	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc) [4]	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) [5]	No standard definition; depends on molecular target
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase II/III trials), or failure to achieve CR, CRi or PR (phase I 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 [6]	Bone marrow blasts > 5%; or reappearance of blasts in the blood; or development of extramedullary disease

[1] 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 5-7 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.

[2] 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.

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

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

[5] As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 104 copies of ABL1 in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission.

[6] 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/AML.

D Risk group definition

Patients are classified in 4 risk groups according to the table below.

Table 21

Risk		Definition	% pts at baseline	% pts with CR & consolidation
Good	GR1	t(8;21) or *AML1-ETO*, WBC≤20	5 %	7 %
	GR2	inv(16)/t(16;16) or *CBFB-MYH11* gene	6 %	7 %
	GR3	MK-, *CEBPA*+	7 %	8 %
	GR4	MK-, *FLT3ITD-/NMP1+,* CRe	11 %	13 %
Intermediate	IR1	t(8;21) or *AML1-ETO*, WBC>20	2 %	2 %
	IR2	CN –X –Y, WBC≤100, CRe	17 %	21 %
Poor	PR1	CN –X –Y, WBC≤100, not CRe	10 %	8 %
	PR2	CN –X –Y, WBC>100	5 %	4 %
	PR3	CA, non CBF, MK-, no abn3q26, EVI1-	16 %	15 %
Very Poor	VPR1	Non CBF, MK+	9 %	5 %
	VPR2	Non CBF, abn3q26	2 %	1 %
	VPR3	Non CBF, EVI1+	9 %	9 %

The table gives the % distribution of each risk subgroup of all patients at diagnosis and of all patients that have reached CR and have received consolidation treatment.

- The core-binding factor (CBF) leukemias involve AML's with cytogenetic abnormality t(8;21)(q22;q22) or the *AML1-ETO* fusion gene and the cytogenetic abnormalities inv(16)(p13q22) or t(16;16)(p13;q22) or the related fusion gene *CBFB-MYH11*.
- If cytogenetics unknown, consider as CN
- Monosomal karyotype (MK) refers to AML with two or more autosomal monosomies or a single autosomal monosomy in the presence of one or more structural cytogenetic abnormalities
- MK-: monosomal karyotype negative
- MK+: monosomal karyotype positive
- CN –X-Y: cytogenetically normal or only loss of X or Y chromosome
- CA: cytogenetically abnormal
- CRe: attainment of early CR, ie after cycle I
- EVI1+ refers to high EVI1 mRNA expression
- FLT3-ITD-/NMP1+ : FLT3-ITD mutant negative (FLT3ITD-) but NPM1-mutant positive (NPM1+): Fms-like tyrosine kinase receptor-3 internal tandem duplications (FLT3-ITD) and nucleophosmin-1 (NPM!) mutations often go together as dual genetic anomalies in the same AML.

To exclude ambiguities in the classification patients should be classified in the following hierarchical order: first patients with CBF abnormalities in GR1, GR2 or IR1, of the remaining patients the MK+ patients in VPR1, followed by the abn3q26 patients in VPR2 subsequently the CEBPA+ patients in GR3 and the FLT3ITD-/NPM1+ patients in GR4, subsequently the EVI1+ patients in VPR3. The remaining patients are classified in PR1, IR2, PR2 and PR3.

The above risk classification is based on

(a) an analysis of the data of 1975 patients from the previous HOVON/SAKK AML studies for patients up to 60 years of age (4, 4A, 29 and 42), registered before January 1, 2004 and with successful cytogenetic analysis

(b) an analysis of the data of a subset of 424 patients for which also marker information and microarray expression data were available.

E. Common Terminology Criteria for Adverse Events

The grading of toxicity and adverse events will be done using the most recent version of the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4. A complete document may be downloaded from the following sites:

http://ctep.cancer.gov/reporting/ctc.html
http://www.hovon.nl (under Trials > General information about studies)

F. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

G. NYHA* scoring list

Grade 1 No breathlessness

Grade 2 Breathlessness on severe exertion

Grade 3 Breathlessness on mild exertion

Grade 4 Breathlessness at rest

The *New York Heart Association functional and therapeutic classification applied to dyspnoea