A Randomized Phase II Study of Oral Sapacitabine in Elderly Patients with Acute Myeloid Leukemia Previously Untreated or in First Relapse, or Previously Treated Myelodysplastic Syndromes

Protocol Number:	CYC682 - 06 (A6)
Study Drug:	Sapacitabine (CYC682)
IND Number:	#53748
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Sponsor:	Cyclacel Ltd 1 James Lindsay Place Dundee DD1 5JJ, UK.

Compliance: This study will be performed according to Good Clinical Practice (GCP)

INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

The list of investigators is contained in the Study Master File. The function and responsibility of individuals and companies involved in the conduct of this study are listed in Table 1.

Table 1 Study Administration Structure

Function	**Responsible Person**
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Study Monitor	Details will be provided in the Operations Manual.
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SIGNATURE PAGE FOR PRINCIPAL INVESTIGATOR

Clinical Study No.: CYC682-06 (A6)

Title: A Randomized Phase II Study of Oral Sapacitabine in Elderly Patients with Acute Myeloid Leukemia Previously Untreated or in First Relapse or Previously Treated Myelodysplatic Syndromes

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices (GCP) in the tripartite harmonized guidelines of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki (2000 Edinburgh), and applicable legal and regulatory requirements.

Principal Investigator (Study Site)	Signature	Date

SIGNATURE PAGE FOR CYCLACEL LTD

Clinical Study No.: CYC682-06 (A6)

Title: A Randomized Phase II Study of Oral Sapacitabine in Elderly Patients with Acute Myeloid Leukemia Previously Untreated or in First Relapse or Previously Treated Myelodysplastic Syndromes

Approved by the following:

Judy H. Chiao		June 8, 2010
Judy H. Chiao, MD	Signature	Date

Vice President
Clinical Development
and Regulatory Affairs
Cyclacel Ltd.

STUDY SYNOPSIS

Title of Study	A Randomized Phase II Study of Oral Sapacitabine in Elderly Patients with Acute Myeloid Leukemia Previously Untreated or in First Relapse or Previously Treated Myelodysplastic Syndromes
Protocol Number	CYC682-06 (A6)
Number of Study Sites	Approximately 25
Number of Patients	Approximately 325
Investigational Drug	Sapacitabine capsules (25, 50 and 75 mg)
Study Design	Open label, phase II, randomized (Part 1, 3 and 4); open-label, phase II, non-randomized (Part 2)
Objectives	The primary objective of Part 1 of this study is to evaluate 1-year survival rate of 3 dosing schedules in elderly patients with previously untreated or first relapsed acute myeloid leukemia (AML) or previously treated myelodysplastic syndromes (MDS); the secondary objectives are to assess the number of patients who have achieved a CR, CRp, PR, CRi or hematological improvement (HI) and their corresponding durations, transfusion requirements, number of hospitalized days and safety. The primary objective of Part 2 of this study is to evaluate the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and the rate of complete response (CR or CRp) in elderly patients with previously untreated AML and significant concomitant medical illnesses defined as having a hematopoietic cell transplantation comorbidity index score (HCTCI) of 2 or higher; the secondary objectives are to assess response duration, transfusion requirements, number of hospitalized days, overall survival, and safety. The primary objective of Part 3 of this study is to evaluate 1-year survival rate of 3 dosing schedules in elderly patients with previously untreated AML that evolved from MDS after receiving hypomethylating agents for the preceding MDS; the secondary objectives are to assess the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and their corresponding durations, transfusion requirements, number of hospitalized days and safety. The primary objective of Part 4 of this study is to evaluate 1-year survival rate of 3 dosing schedules in older patients with MDS previously treated with hypomethylating agents; the secondary objectives are to assess the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and their corresponding durations, transfusion requirements, number of hospitalized days and safety.
Main Criteria for Inclusion	Part 1: Elderly patients $\geq$ 70 years of age with histologically or pathologically confirmed AML who have not received any systemic therapy for AML or who are in first relapse after achieving a CR to initial induction, consolidation and/or maintenance therapy; MDS patients must be $\geq$ 60 years of age with histologically or pathologically confirmed MDS (intermediate-2 or higher risk) and have been previously treated with hypomethylating agents. Part 2: Elderly patients $\geq$ 70 years of age with histologically or pathologically confirmed AML who have not received any systemic therapy for AML; HCTCI of 2 and higher. Part 3: Elderly patients $\geq$ 70 years of age with histologically or pathologically confirmed AML preceded by MDS after receiving hypomethylating agents for the preceding MDS but the newly diagnosed AML has not been treated with systemic

	anti-leukemic therapy. Part 4: older patients ≥ 60 years of age with histologically or pathologically confirmed MDS (intermediate -2 or higher risk and 6 - < 20% blasts in bone marrow) that has been previously treated with hypomethylating agents.
Treatment	Part 1: Eligible patients will be randomized to receive one of the following dosing schedule: Arm A: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks Arm B: 300 mg *b.i.d.* x 7 consecutive days every 4 weeks Arm C: 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks Part 2: Eligible patients will receive sapacitabine at 300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks. Part 3: Eligible patients will be randomized to receive one of the following dosing schedule: Arm D: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks Arm E: 300 mg *q.d.* x 7 consecutive days every 4 weeks Arm F: 300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks Part 4: Eligible patients will be randomized to receive one of the following dosing schedule: Arm G: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks Arm H: 300 mg *q.d.* x 7 consecutive days every 4 weeks Arm I: 100 mg *q.d.* x 5 consecutive days per week for 2 weeks every 4 weeks Treatment will continue until: clinically significant progressive disease; lack of efficacy; unacceptable toxicity; patient withdrawal of consent; investigator's discretion that it is in the best interest of the patient to withdraw; intercurrent illness or changes in patient's condition that renders patient ineligible, or continuing treatment of sapacitabine unsafe, or regular follow-up impossible; non-compliance with study medication or protocol-required evaluations and follow-up; or termination of the clinical trial by the sponsor.
Efficacy Assessment	The primary efficacy endpoint of Part 1, 3 and 4 is the rate of 1-year survival; the primary efficacy endpoints of Part 2 are the rate of clinical benefit (CR, CRp, PR major HI or SD) and the rate of complete response (CR or CRp).
Safety Assessment	Patients will be seen in the clinic prior to each treatment cycle and monitored by physical exams, laboratory tests, and other appropriate studies. A post-treatment follow-up visit in clinic or by phone will be conducted within 4 weeks after the last dose of the study drug, or prior to the initiation of new cancer treatment if possible.
Study Period	December 2007 to November 2011

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ara-C	Cytarabine
AST	Aspartate aminotransferase
AUC	Area under the curve
b.i.d.	Twice daily; every 12 hours
BSA	Body surface area
CBC	Complete blood count
CFR	Code of Federal Regulations
C_{max}	Peak plasma concentration
CNDAC	1-(2-C-cyano-2-deoxy-(-D-arabino-pentafuranosyl) cytosine
CNDACTP	CNDAC-tri phosphate
CS-682	Sapacitabine
CYC682	Sapacitabine
CR	Complete remission
CRp	Complete remission with incomplete platelet count recovery
CRi	Complete remission without blood count recovery
CRA	Clinical research associate
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
dL	Deciliter
dFdC	Gemcitabine
DI	Dose intensity
5'DFUR	Doxifluridine, furtulon
DAR	Drug accountability record
DL	Dose level
DLco	Lung diffusion capacity of carbon monoxide
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Federal Drug Administration
FEV1	Forced expiratory volume in one second
5-FU	5-fluorouracil
GMP	Good manufacturing practice
HBV	Hepatitis B virus
HCTCI	Hematopoietic cell transplantation comorbidity index
HCV	Hepatitis C virus
HI	Hematological improvement
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
hr	Hour
IC_{50}	Drug concentration necessary to inhibit cell growth by 50%
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
ILS	Increased life span

IRB	Institutional review board
IND	Investigational New Drug Application
INR	International normalized ratio
i.p.	Intraperitoneal
i.v.	Intravenously
JP	Japanese Pharmacopoeia
Ki	Inhibitory constant
LFT	Liver function tests
mg	Milligrams
min	minute
ml	Milliliters
MDS	Myelodysplastic syndromes
MPD	Myeloproliferative disorders
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MW	Molecular weight
n	Number of patients
NCI	National Cancer Institute
ND	Not detected
No.	Number
5'nuc	5'nucleotidase
Ph.Eur	European Pharmacopoeia
PK	Pharmacokinetics
PO	Oral or orally
PS	Performance status
PLT	Platelet count
PT	Prothrombin time
PTT	Partial thromboplastin time
q	Every
q.d.	Once a day
q12hrs	Every 12 hours
RBC	Red blood cell
RD	Recommended phase II dose
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
$T_{1/2}$	Half-life
TGI	Tumor growth inhibition
TI	Therapeutic index
ULN	Upper limit of normal of the laboratory where the testing is performed
UV	Ultraviolet
USP	United States Pharmacopoeia
w	Week
WBC	White blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Nucleoside analogues represent a major group of antitumor cytotoxic drugs. Cytarabine (ara-C) and fludarabine are the two most active drugs against leukemias; whereas, gemcitabine and 5-fluorouracil are active against a wide range of solid tumors.

The nucleoside analogues currently available for use in clinic are prodrugs which are not active by themselves. Upon entering cells, these nucleoside analogues are phosphorylated by nucleoside kinases and the phosphorylated metabolites are incorporated into DNA causing a pause in or termination of DNA synthesis. The close correlation between the degree of drug-induced cell death and the amount of incorporated analogue molecules in cellular DNA strongly suggests that the incorporation of these molecules into DNA is a key cytotoxic event.[1]

The clinical effectiveness of nucleoside analogues appears to be influenced by multiple factors including the substrate specificities of nucleoside kinases, the expression levels of kinases in tumor tissues, and the rate of metabolic elimination by inactivating enzymes.[1, 2] Rationally designed nucleoside analogues with improved biochemical properties may be more effective antitumor agents.

1.2. Investigational Product - Sapacitabine

2'-*C*-Cyano-2'-deoxy-β-D-*arabino*-pentafuranosylcytosine (CNDAC) is a rationally designed analogue of deoxycytidine. It causes single-strand DNA breakage that cannot be repaired by ligation. This type of DNA damage is different from that caused by other nucleoside analogues such as ara-C and gemcitabine, which terminate or pause DNA synthesis at the site of incorporation.[1] This unique strand-breaking action seems to be the basis of CNDAC's ability to induce cell cycle arrest at the G2 phase, as distinct from the S-phase block seen with ara-C or gemcitabine. During the drug discovery phase, many derivatives of CNDAC were synthesized and investigated for stronger antitumor activity than CNDAC. Sapacitabine (also known as CYC682, formerly CS-682), is a N4-palmitoyl compound that has been chosen for clinical development because of its broad range of antitumor activity in preclinical studies.

Following oral administration, sapacitabine [1-(2-C-cyano-2-deoxy-β-D-*arabino*-pentafuranosyl)-N^4-palmitoylcytosine] is converted to CNDAC by amidases and esterases in the gut, plasma, and liver. CNDAC can be converted to CNDAC-mono phosphate by deoxycytidine kinase which is thought to be the rate-limiting step in the formation of CNDAC-triphosphate (CNDACTP). CNDACTP is the active metabolite of sapacitabine and exerts its cytotoxic effects via the following mechanisms: a) potent inhibition of DNA polymerase, b) cessation of DNA strand elongation by incorporation into DNA strands, and c) breakage of DNA strands at the 3'-diester bond of CNDAC after its incorporation into the DNA. This latter mechanism is considered to be a novel effect that is not exhibited by other

nucleoside analogues. CNDAC-phosphates can be degraded by cytidine deaminase and 5'nucleotidase. However, compared with ara-C, CNDAC is a weak substrate of cytidine deaminase.

In addition to the antitumor activity of its metabolite, the parent drug sapacitabine itself is cytotoxic against a variety of cancer cell lines, including those lacking deoxycytidine kinase. This suggests that the antitumor activity of sapacitabine *in vivo* is likely to be mediated by both the parent drug as well as its active metabolite, CNDAC. The cellular pharmacology of sapacitabine is currently under investigation.

Sapacitabine and its active metabolite, CNDAC, showed a broad spectrum of activity against human tumor cells from various organs. In human tumor xenograft models, sapacitabine was active against a variety of tumors, and was especially effective against gastric, mammary, lung, colorectal, and hepatic tumor xenografts where tumor regressions were observed. Although sapacitabine showed a partial cross-resistance to ara-C-resistant tumor cell lines, it was active *in vivo* against P388 leukemia cell lines resistant to mitomycin C, vincristine, 5-FU, or cisplatin. In a mouse P388 leukemia model and in human xenografts of poorly differentiated gastric adenocarcinoma, sapacitabine exhibited much more potent antitumor activity than 5'-DFUR and gemcitabine. The antitumor effect of sapacitabine was maintained for a long period by a treatment schedule including drug-free intervals. Re-grown tumors responded to sapacitabine despite previous treatment with this drug. Summaries of these studies are provided in the Sapacitabine Investigator's Brochure.[3]

In summary, sapacitabine, a rationally designed nucleoside analogue, may be a more efficacious antitumor agent than other nucleoside analogues. Its oral route of administration is more convenient for patients as compared with the intravenous administration route required by other nucleoside analogues.

1.3. Preclinical Toxicology Studies

Single-dose toxicity studies in rodents, and repeat dose studies of up to 3 months duration in mice and dogs have been completed. Summaries of toxicology studies are provided in the Sapacitabine Investigator's Brochure.[3] Sapacitabine has a direct toxic effect on rapidly proliferating cells, which is consistent with the known side effects of cytotoxic drugs. The major toxicities are hematopoietic, gastrointestinal, and testicular. The toxicities appear to be similar between single and repeat dosing, as well as between species.

In genotoxicity studies, sapacitabine was positive in the chromosome aberration and mouse micronucleus tests, although it was negative in the Ames reverse bacterial mutation test. It was also positive in rat teratogenicity studies.

1.4. Clinical Studies

Sapacitabine monotherapy has been evaluated in six phase I clinical trials (see Table 2) in cancer patients with the primary objective of determining the recommended phase II doses

(RD) of a number of dosing schedules.

Table 2 Clinical Trials of Sapacitabine

Protocol Number	Study Design	Dosing Schedule	Recommended Phase II Dose (RD)	Status (Enrolled/ Treated)
CYC682-99-01 (S97-1241)	Phase I (Solid tumors)	*q.d.* x 5 consecutive days per week for 4 weeks out of 6 weeks	40 mg/m^2/day *q.d.* for 5 consecutive days for 4 weeks out of 6 weeks (Sankyo formulation)	Completed (n=48/47)
CYC682-99-02 (S97-2241)	Phase I (Solid tumors)	*q.d.* x 3 days per week (Monday, Wednesday, Friday) for 4 weeks out of 6 weeks	160 mg/m^2 *q.d.* x 3 days per week (Monday, Wednesday, Friday) for 4 weeks out of 6 weeks (Sankyo formulation)	Completed (n=40/40)
CYC682-03-03	Phase I (solid tumors, lymphomas)	*b.i.d.* for 14 days every 3 weeks or *b.i.d.* for 7 days every 3 weeks	33 mg/m^2 *b.i.d.* x 14 days every 3 weeks (Sankyo formulation) or 50 mg *b.i.d.* x 14 days every 3 weeks (Encap formulation)* or 75 mg *b.i.d.* x 7 days every 3 weeks (Encap formulation)*	Closed to accrual (n=38/37)
CYC682-05-04	Phase I (Leukemias and MDS)	*b.i.d.* for 7 days every 3 weeks or *b.i.d.* for 3 days per week for 2 weeks every 3 weeks	325 mg *b.i.d.* x 7 days every 3 weeks or 425 mg *b.i.d.* x 3 days per week x 2 weeks every 3 weeks	Ongoing (n=48/47)
CYC682-06-05	Phase II (cutaneous T-cell lymphoma)	100 mg *b.i.d.* x 3 days per week for 2 weeks followed by 1-week rest or 50 mg *b.i.d.* x 3 days per week for 2 weeks followed by 1-week rest	Not applicable	Ongoing (n=7)
CYC682-06	Ph II (acute myeloid leukemia)	200 mg *b.i.d.* x 7 days followed by 14-day rest or 300 mg *b.i.d.* x 7 days followed by 14 day-rest or 400 mg *b.i.d.* x 3 days/week x 2 weeks followed by 7 day-rest	Not applicable	Ongoing (n=12)

q.d. = once daily; *b.i.d.* = twice daily
*Encap formulation is now called Cyclacel BL formulation and is the only formulation used in all subsequent studies.

As of February 2008, 193 patients with advanced cancers have been enrolled in 6 clinical studies and 190 patients have received sapacitabine in one of 2 formulations, Sankyo or

Cyclacel BL formulation. One hundred and eight patients received the Sankyo formulation and 82 received the Cyclacel BL formulation. The recommended phase II dose (RD) has been established for three dosing schedules using the Sankyo formulation: a) 40 mg/m^2/day once daily for 5 consecutive days for 4 weeks followed by 2-week rest; b) 160 mg/m^2/day once daily for 3 days per week (Monday, Wednesday, Friday) for 4 weeks followed by 2-week rest; and c) 66 mg/m^2/day in 2 divided doses for 2 weeks followed by 1 week of rest. The RD has been established for three dosing schedules using the Cyclacel BL formulation: a) 50 mg *b.i.d.* x 14 days every 3 weeks (solid tumors) or 75 mg *b.i.d.* x 7 days every 3 weeks (solid tumors) or 325 mg *b.i.d.* x 7 days every 3 weeks (leukemias/myelodysplastic syndromes) or 425 mg *b.i.d.* x 3 days/week x 2 weeks every 3 weeks (leukemias/myelodypsplastic syndromes). The predominant dose-limiting toxicity (DLT) was myelosuppression in solid tumor patients which consisted of neutropenia, febrile neutropenia, neutropenic sepsis, and thrombocytopenia. Myelosuppression was generally reversible after interruption of drug dosing. To date, the DLTs reported in patients with advanced leukemias or MDS were gastrointestinal toxicities which included abdominal pain/small bowel obstruction, diarrhea and neutropenic enteritis. Common non-hematological toxicities were asthenia, nausea, fever, vomiting, diarrhea, constipation, anorexia, and dyspnea, which were generally mild to moderate.[3]

There have been three drug-related deaths. One solid tumor patient treated at 160 mg/m^2 once daily for 4 weeks followed by a 2-week rest, experienced grade 4 neutropenia and thrombocytopenia and subsequently died of apnea. Another solid tumor patient treated at 80 mg/m^2/day in two divided doses for 2 weeks followed by a 1-week rest, died of Candida sepsis in the setting of grade 4 febrile neutropenia and grade 4 thrombocytopenia. One acute myeloid leukemia (AML) patient treated at 750 mg/day in two divided doses for 7 days followed by 2-week rest died of complications of neutropenic colitis.

Pharmacokinetic analysis of sapacitabine and CNDAC was carried out in phase I studies using a validated assay. After oral administration of sapacitabine, CNDAC plasma concentration was higher than that of sapacitabine, although their half-lives are very similar (approximately 2 hours). In the small number of patients treated in the dose range of 13.0 to 67.0 mg/m^2/day for 5 days per week for 4 consecutive weeks, the maximum concentration (C_{max}) and area under the curve (AUC) values of sapacitabine did not increase in proportion with dose, but the C_{max} and AUC of CNDAC increased moderately with increasing doses of sapacitabine. At the maximum tolerated dose (MTD) or RD of 40 mg/m^2/day, the pharmacokinetic parameters of sapacitabine and CNDAC on Day 8 were similar to those on Day 1 and the CNDAC exposure appeared to correlate with the worst National Cancer Institute – Common Terminology Criteria (NCI-CTC) grade of neutropenia during the treatment cycle.

There appeared to be no gender difference in CNDAC exposure following sapacitabine administration. Metabolism appears to be the principle route of elimination, with renal excretion playing a negligible role.

The best response to sapacitabine treatment was stable disease by investigator assessment in

solid tumor patients. Twenty solid tumor patients had stable disease and remained on study for at least 4 months: non-small cell lung (n=5 , range 4-9 months); colorectal (n=4, range 4 - 6.5 months); gastrointestinal stroma tumor (n=2, 4 to > 50 months); renal cell (n=1, 17.5 months); bladder (n=2 , 5- 8 months); breast (n=1, 4 months), unknown primary (n=1, 6 months); small cell lung (n=1, 4 months), parotid (n=1, 5 months), and ovarian (n=2 , 4-6 months). The best response in patients with relapsed and refractory leukemias or MDS is complete remission (CR) or complete remission without platelet count recovery (CRp): AML (n=5); and MDS (n=1). [3, 4]

1.5. Rationale for a Phase II Study in Elderly Patients with AML or MDS

Nucleoside analogues play an important role in the treatment of leukemias and myelodysplastic syndromes (MDS). Ara-C and fludarabine, both nucleoside analogues, are the two most active drugs in these diseases. Despite the impressive ability of these agents to induce partial or complete responses, leukemias and MDS remain incurable in many patients, especially the elderly. This is because responses are usually not durable and the treatment carries significant toxicities. New effective drugs are required to improve the outcome of these diseases.

Sapacitabine, a rationally designed nucleoside analogue, has a unique mechanism of action and good oral bioavailability. In preclinical studies, it demonstrated significant activity against a wide range of malignancies. In the mouse P388 leukemia model, mice treated with sapacitabine had a survival advantage when compared with mice treated with 5'-DFUR.[3]

In the phase I trial of sapacitabine in advanced leukemias or myelodysplastic syndromes (CYC682-05-04), sapacitabine had a favourable safety profile and promising anti-leukemic activity in patients with relapsed and refractory AML and MDS when administered by two different dosing schedules. The MTD was reached at 375 mg on the 7-day schedule and 475 mg on the 3-day schedule. Among 42 patients with AML, the best responses were complete remissions (CR) or complete remissions without platelet recovery (CRp) in 5 patients (age 58, 59, 66, 82, 86) who have relapsed and/or refractory disease following prior therapies consisting of ara-C, anthracycline, clofarabine, mylotarg, fludarabine and/or bone marrow transplant. In addition, 13 patients had a significant decrease in bone marrow blasts including 5 with blast reduction to 5% or less. Among 3 patients with MDS, the best responses were complete remissions (CR) in 1 patient (age 79) and the other 2 patients (age 75, 73) had a decrease of bone marrow blasts to 5% or less. All 3 MDS patients had failed a prior therapy with azacitidine or decitabine.[4]

The rationale for conducting this study in elderly patients with AML or MDS is to assess the efficacy and safety of 3 dosing schedules in this patient population and to select a better dosing schedule for further clinical development.

1.6. Risks and Benefits to Elderly Patients with AML or MDS

Sapcitabine will be administered orally. The major toxicity is expected to be gastrointestinal

toxicities and myelosuppression which are generally reversible after interruption of drug dosing. Serious adverse events related to myelosuppression include febrile neutropenia, neutropenic sepsis, neutropenic colitis and thrombocytopenia. Common non-hematological toxicities include asthenia, nausea, fever, vomiting, diarrhea, anorexia, and dyspnea, which are generally mild to moderate. It is not known whether sapacitabine is an effective agent in the treatment of elderly patients with AML or MDS which is previously untreated or in first relapse. Alternatives to participating in this trial include receiving chemotherapy of other anti-leukemic agents, e.g., ara-C, anthracyclines, participating in clinical trial of a different investigational drug or receiving best supportive care for pain and other cancer-related symptoms.

1.7. Good Clinical Practice and Regulatory Requirements

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as described in the ICH tripartite harmonized guidelines, and applicable regulatory requirements.

2. STUDY OBJECTIVES

The primary objective of Part 1 of this study is to evaluate 1-year survival rate of 3 dosing schedules in elderly patients with previously untreated or first relapsed AML or previously treated MDS; the secondary objectives are to assess the number of patients who have achieved a CR, CRp, PR or CRi or hematological improvement and their corresponding durations, transfusion requirements, number of hospitalized days and safety.

The primary objective of Part 2 of this study is to evaluate the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and the rate of complete response (CR or CRp) in elderly patients with previously untreated AML and significant concomitant medical illnesses defined as having a HCTCI of 2 or higher; the secondary objectives are to assess response duration, transfusion requirements, number of hospitalized days, overall survival, and safety.

The primary objective of Part 3 of this study is to evaluate 1-year survival rate of 3 dosing schedules in elderly patients with previously untreated AML that evolved from MDS after receiving hypomethylating agents for the preceding MDS; the secondary objectives are to assess the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and their corresponding durations, transfusion requirements, number of hospitalized days and safety.

The primary objective of Part 4 of this study is to evaluate 1-year survival rate of 3 dosing schedules in older patients with MDS previously treated with hypomethylating agents; the secondary objectives are to assess the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and their corresponding durations, transfusion requirements, number of hospitalized days and safety.

3. STUDY DESIGN

3.1. Overall Study Design and Plan

Part 1: This is an open label, randomized, phase II study. Patients will be entered into two separate strata, AML or MDS, and randomized 1:1:1 to receive one of the following 3 dosing schedules within each stratum:

7-day low dose (Arm A): 200 mg *b.i.d.* x 7 consecutive days every 4 weeks

7-day high dose (Arm B): 300 mg *b.i.d.* x 7 consecutive days every 4 weeks

3-day high dose (Arm C): 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks

AML patients will be stratified by previously untreated vs. treated for AML within the AML stratum.

Part 2: This is an open-label, single arm, phase II study. Patients will receive sapacitabine at 300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks.

Part 3: This is an open label, randomized, phase II study. Patients will be randomized 1:1:1 to receive one of the following 3 dosing schedules and the randomization will be stratified by prior treatment with decitabine for MDS (Yes or No):

Arm D: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks

Arm E: 300 mg *q.d.* x 7 consecutive days every 4 weeks

Arm F: 300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks

Part 4: Eligible patients will be randomized to receive one of the following 3 dosing schedule and the randomization will be stratified by prior treatment with decitabine for MDS (Yes or No):

Arm G: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks

Arm H: 300 mg *q.d.* x 7 consecutive days every 4 weeks

Arm I: 100 mg *q.d.* x 5 consecutive days per week for 2 weeks every 4 weeks

Treatment will continue until: clinically significant progressive disease; lack of efficacy; unacceptable toxicity; patient withdrawal of consent; investigator's discretion that it is in the best interest of the patient to withdraw; intercurrent illness or changes in patient's condition that renders patient ineligible, or continuing treatment of sapacitabine unsafe, or regular

follow-up impossible; non-compliance with study medication or protocol-required evaluations and follow-up; or termination of the clinical trial by the sponsor.

Patients will be monitored regularly with physical exams and laboratory tests. Bone marrow aspirate and/or biopsy will be performed to assess response to sapacitabine. A post-treatment follow-up visit will be conducted within 4 weeks after the last dose of the study drug or prior to the initiation of new treatment, if possible. The post-treatment follow-up may be conducted by telephone if the patient is unable to return to the clinic.

For Part 1, 3 and 4 of the study, the primary efficacy endpoint will be 1-year survival; for Part 2 of the study, there will be two co- primary efficacy endpoints, the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and the rate of complete response (CR or CRp). Stratifications factors and assumptions for sample size and plans for statistical analysis are described in Section 11.

3.2. Rationale for the Study Design and Measures to Reduce Bias

The randomized design is used to ensure that the 3 dosing regimens are evaluated in a similar patient population.

3.3. Rationale for the Proposed Dosing Schedules

Preliminary pharmacokinetic analyses from two completed phase I studies indicate that sapacitabine and its active metabolite CNDAC have a relatively short half-life (approximately 2 hours) and that CNDAC exposure appears to correlate with the worst NCI-CTC grade of neutropenia experienced during treatment at the MTD. We hypothesize that the 7-day high dose regimen will lead to higher dose delivered per week (1400 mg/week) resulting in better antitumor activity than the 7-day low dose regimen (933 mg/week) but may cause more myelosuppression; the 3-day high dose regimen will have higher dose delivered per week (1600 mg/week) resulting in better anti-tumor activity than the 7-day high dose regimen but will have similar degree of myelosuppression and gastrointestinal toxicity because the consecutive days of dosing are shorter. Preliminary data from the 60 patients in the original cohort of the AML stratum showed that the dosing schedule of 400 mg *b.i.d.* x 3 days/week x 2 weeks every 3-4 weeks has the highest rate of CR/CRp, i.e., 25%, the longest durations of responses, and a 10% all-cause death rate within the first 30 days after randomization. However, all patients who achieved CRs were dose reduced for myelosuppression. We hypothesize that a 3-day dosing regimen of 300 mg *b.i.d.* x 3 days/week x 2 weeks every 4 weeks will be equally effective but with less myelosuppression and propose to test this dosing regimen in Part 2 of the study. Exploratory subgroup analyses from AML patients enrolled in Part 1 of the study suggest that the 7-day low dose schedule of 200 mg *b.i.d.* x 7 days every 3- 4 weeks (Arm A) may be more effective for AML preceded by MDS or MPD. Among 7 patients on Arm A who have survived at least 1 year, 4 patients have AML preceded by MDS or MPD. We hypothesize that a 7-day once daily (*q.d.*) dose regimen and a lower dose of the 3-day dose regimen may be equally effective but with less myelosuppression. We propose to evaluate 300 mg *q.d.* x 7 days and 300 mg *b.i.d.*

x 3 days/week x 2 weeks every 4 weeks in patients with newly diagnosed AML preceded by MDS after receiving hypomethylating agents for the preceding MDS (Part 3).

Interim data from MDS patients enrolled in Part 1 of the study showed that most of the responses occurred on the 7-day low dose and high dose regimens. We hypothesize that a 7-day once daily (*q.d.*) dose regimen may be equally effective but with less myelosuppression. In addition, we propose to evaluate a new dose regimen i.e.100 mg *q.d.* x 5 days/week x 2 weeks every 4 weeks. This 5-day dose regimen appears to be well tolerated in patients with lung cancer (study CYC682-8). We hypothesize that this increase in exposure may lead to further improvement in efficacy in patients with MDS that was previously treated with hypomethylating agents (Part 4).

3.4. Study Duration

Approximately 100 patients with AML and 60 patients with MDS will be enrolled in Part 1 of this study. Approximately 36 patients with AML will be enrolled in Part 2 of the study. Approximately 60 patients with AML preceded by MDS and 60 patients with MDS will be enrolled in Part 3 and Part 4 of this study, respectively. The patient accrual is projected to be 8 patients per month for approximately 41 months. The study may be closed approximately 6 months after the last patient was enrolled, thus the projected entire study duration is 47 months. After study closure, all patients who are deriving clinical benefit and continue to meet the eligibility criteria may be offered the option to continue treatment on an extension study.

3.5. Criteria for Study Discontinuation

This trial will be monitored by Cyclacel or its designees. The trial may be discontinued for safety concerns, slow accrual, or at the sponsor's discretion.

3.6. Maintenance of the Treatment Codes and Procedure for Breaking Codes

This is an open label study. There is no need to break the treatment codes.

3.7. Case Report Form as Source Data

The case report form (CRF) pages containing disease assessment by investigator, e.g., CR, CRp, PR, CRi and hematological improvement may serve as the source data for the secondary efficacy endpoints of Part 1, 3 and 4 and primary efficacy endpoints of Part 2 of the study.

3.8. Correlative Study

Analysis of the expression of key proteins that may be involved in the cellular biology and pharmacology of sapacitabine and its major metabolite CNDAC may be performed on bone marrow aspirate or biopsy samples obtained prior to and after the treatment with sapacitabine. The proteins of interest include nucleoside transporters, nucleoside kinases and

deaminases which may be involved in the entry of sapacitabine and CNDAC into cells and their subsequent activation and inactivation inside cells. The purpose of the correlative study is to explore whether there is any correlation between the expression levels of these proteins and clinical response to sapacitabine. The correlative study is optional for patients. Study details will be provided in the Operations Manual.

4. PATIENT SELECTION

Only patients with a diagnosis of AML based on the World Health Organization (WHO) classification [6,7], or with a diagnosis of MDS carrying an International Prognostic Scoring System (IPSS) scores of intermediate-2 or high-risk and who meet all inclusion and no exclusion criteria can be considered for enrollment in this study. Only investigators who are listed on the FDA form 1572 are authorized to obtain informed consent. No study-specific procedures can be performed until the potential patient has signed an informed consent form that has been approved by the Institutional Review Board (IRB) or Ethics Committee (EC). Procedures that are performed prior to patient signing an informed consent form can be used to satisfy protocol requirements if these procedures are performed as routine medical care for patient's underlying cancer and other illnesses.

4.1. Eligibility Criteria

Patients must fulfill all of the following criteria:

4.1.1. For Part 1 of the study, a histologically or pathologically confirmed diagnosis of AML based on WHO classification which is previously untreated by systemic therapy or is in first relapse after achieving a complete remission (CR or CRp) to initial induction, consolidation and/or maintenance therapy; a histologically or pathologically confirmed diagnosis of MDS based on French-American-British (FAB) classification with an IPSS score of intermediate -2 or high - risk which has been previously treated with hypomethylating agents. For Part 2 of the study, a histologically or pathologically confirmed diagnosis of AML based on WHO classification which is previously untreated by systemic therapy in the setting of significant concomitant medical illnesses defined by having a HCTCI of 2 and higher (See Appendix B). For Part 3 of the study, a histologically or pathologically confirmed diagnosis of AML preceded by MDS based on WHO classification after receiving hypomethylating agents for the preceding MDS but the newly diagnosed AML has not been treated with any systemic anti-leukemic therapy. For Part 4 of the study, a histologically or pathologically confirmed diagnosis of MDS based on FAB classification with an IPSS score of intermediate-2 or high- risk and 6 - < 20% blasts in bone marrow which has been previously treated with hypomethylating agents.

4.1.2. Age ≥ 70 years for AML or ≥ 60 years for MDS

4.1.3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (See Appendix C)

4.1.4. Adequate renal function

- Creatinine ≤ 1.5 x ULN

4.1.5. Adequate liver function

- Total bilirubin or direct bilirubin ≤ 1.5 x ULN
- Alanine aminotransferase (ALT or SGPT) ≤ 2.5 x institutional upper limit of normal (ULN) or ≤ 5 x ULN if the liver is involved by leukemia

4.1.6. Life expectancy reasonably adequate for evaluating the treatment effect

4.1.7. Patient must be able to swallow capsules.

4.1.8. Patients must be at least 2 weeks from prior systemic therapy for AML or MDS, radiation therapy, major surgery, or other investigational therapy, and have recovered from clinically significant toxicities of these prior treatments. Patients with ≥ 50, 000 WBC in peripheral blood may receive hydroxyurea to control the WBC <50,000 prior to starting sapacitabine if this is considered by the treating physician to be in the best interest of the patient.

4.1.9. All men of reproductive potential must agree to practice effective contraception for 4 weeks prior to study entry, during the entire study period and for one month after the study unless documentation of infertility exists.

4.1.10. Ability to understand and willingness to sign the informed consent form

4.2. Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

4.2.1. AML is of the sub-type of acute promyelocytic leukemia.

For Part 1 of the study, having received more than one induction systemic therapy for AML or having received a standard dose or high dose ara-C containing regimen for MDS; for Part 2 of the study, having received any systemic therapy for AML or having received hypomethylating agents or cytotoxic chemotherapy for the preceding MDS or myeloproliferative diseases (MPD); for Part 3 and 4 of the study, having received a standard dose or high dose ara-C containing regimen for the preceding MDS.

4.2.2. Patients with known central nervous system (CNS) involvement by leukemia should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

4.2.3. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, active cancer(s) other than AML or MDS, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Patients receiving intravenous antibiotics for infections that are under control may be included in this study. Active cancer other than AML or MDS refers to cancer that requires systemic chemotherapy or biological therapy within 6 months of the study entry. Patients who have received only hormonal therapy in the neoadjuvant or adjuvant setting in the past 6 months may participate in this study.

4.2.4. Pregnant or lactating women

4.2.5. Known to be HIV-positive

4.3. Removal of Patients from Therapy

Patients have the right to withdraw from the study at any time for any reason. The investigator has the right to withdraw patients from the study according to his/her discretion. When a patient discontinues treatment early, every effort will be made to conduct a post-treatment follow-up visit within 4 weeks after the last dose of study drug or prior to the initiation of new treatment. This post-treatment evaluation may be conducted over the phone if the patient is unable to return to the clinic. The reason(s) for withdrawal must be recorded.

Criteria for terminating participation in the study are listed below:

- Clinically significant progressive disease defined as > 50% increase in the percentage of blasts in bone marrow or peripheral blood over baseline to reach at least 20% blasts in bone marrow or peripheral blood by two assessments while on treatment with an adequate dose
- Lack of efficacy refers to treating physician's judgment that patients are unlikely to benefit from continuation of treatment despite not meeting the criterion of clinically significant progressive disease.
- Unacceptable toxicity
- Patient withdrawal of consent for treatment
- Investigator's discretion that it is in the best interest of the patient to withdraw
- Intercurrent illness: a condition, injury, or disease unrelated to cancer in the opinion of the investigator, that renders continuing sapacitabine treatment unsafe or regular follow-up impossible

- General or specific changes in the patient's condition that renders the patient ineligible for further treatment
- Noncompliance with study medication or protocol-required evaluations and follow-up visits
- Termination of the clinical trial by the sponsor

5. REGISTRATION AND RANDOMIZATION PROCEDURES

The patient registration and randomization procedures will be described in the Operations Manual.

6. TREATMENT PLAN

6.1. Treatment Administration

For Part 1 of the study, AML patients will be stratified by previously untreated vs. treated for AML. There are no stratification factors for MDS patients. All patients will be randomized 1:1:1 to receive one of the following dosing schedules:

7-day low dose (Arm A): 200 mg *b.i.d.* x 7 consecutive days (Day 1-7) every 4 weeks

7-day high dose (Arm B): 300 mg *b.i.d.* x 7 consecutive days (Day 1-7) every 4 weeks

3-day high dose (Arm C): 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks (Day 1-3, 8-10) every 4 weeks

For Part 2 of the study: AML patients will receive sapacitabine at 300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks

For Part 3 of the study: AML patients will be stratified by prior treatment with decitabine for the preceding MDS (Yes or No) and randomized 1:1:1 to receive one of the following 3 dosing schedules:

Arm D: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks

Arm E: 300 mg *q.d.* x 7 consecutive days every 4 weeks

Arm F: 300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks

For Part 4 of the study: MDS patients will be stratified by prior treatment with decitabine for MDS (Yes or No) and randomized 1:1:1 to receive one of the following 3 dosing schedules

Arm G: 200 mg *b.i.d.* x 7 consecutive days every 4 weeks

Arm H: 300 mg *q.d.* x 7 consecutive days every 4 weeks

Arm I: 100 mg *q.d.* x 5 consecutive days per week for 2 weeks every 4 weeks

Treatment will begin within 7 days of randomization or registration and be administered orally on an outpatient basis unless the patient is hospitalized for reasons other than drug-related toxicities. Patients who are assigned to *b.i.d.* dosing will receive two doses of sapacitabine per day, approximately 12 hours apart. Sapacitabine should be taken within one hour prior to a meal, if possible. Patients who are assigned to *q.d.* dosing will receive one dose of sapacitabine per day which should be taken within one hour prior to breakfast if possible. Patient compliance with study medication will be monitored by capsule count. There will be no make-up dosing for a dose that is missed due to forgetfulness or vomiting. One treatment cycle is 4 weeks. The timing of the subsequent cycles of treatment may vary depending on the disease status, and toxicities.

6.1.1. Intra-patient Dose Escalation

In Part 1 of the study, for patients who were assigned to the 7-day low dose arm (Arm A), have tolerated treatment well and have not achieved a CR, the dose may be increased up to 300 mg *b.i.d.* x 7 days every 4 weeks or up to 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks at the investigator's discretion. In Part 2 of the study, for patients who have tolerated treatment well and have not achieved a CR, the dose may be increased to up to 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks at the investigator's discretion. In Part 3 of the study, the dose may be increased up to 300 mg *b.i.d.* x 7 days every 4 weeks for patients who were randomized to 200 mg *b.i.d.* x 7 days every 4 weeks and up to 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks for those who were randomized to 300 mg *b.i.d.* x 3 days/week for 2 weeks every 4 weeks according to Table 4; there will be no dose escalation for patients who were randomized to 300 mg *q.d.* x 7 days every 4 weeks because safety experience at higher doses is limited. In Part 4 of the study, the dose may be increased up to 300 mg *b.i.d.* x 7 days every 4 weeks for patients who were randomized to 200 mg *b.i.d.* x 7 days every 4 weeks; there will be no dose escalation for patients who were randomized to 300 mg *q.d.* x 7 days every 4 weeks; dose escalation up to 150 mg *q.d.* x 5 days/week for 2 weeks may be allowed for patients who were randomized to 100 mg *q.d.* x 5 days/week for 2 weeks every 4 weeks after discussion with the study chair and medical monitor.

6.2. Dose Reduction Scheme and Treatment Delay

For treatment on Day 8 of Cycle 1 and on Day 1 and 8 of all subsequent cycles, dosing will not start until clinically significant and drug-related non-hematologic toxicities have resolved to ≤ grade 1 or baseline. After recovery, a dose reduction will be instituted for grade 3-4 drug-related non-hematologic toxicities for the next treatment cycle or next week of dosing according to Table 3:

Table 3 Treatment Delay and Dose Modification for ≥ grade 3 Drug-related Non-Hematologic Toxicities

Treatment Arm	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Part 1 of the study			
7-day low dose (Arm A)	200 mg *b.i.d.* x 7 consecutive days every 4 weeks	150 mg *b.i.d.* x 7 consecutive days every 4 weeks	100 mg *b.i.d.* x 7 consecutive days every 4 weeks
7-day high dose (Arm B)	300 mg *b.i.d.* x 7 consecutive days every 4 weeks	250 mg *b.i.d.* x 7 consecutive days every 4 weeks	200 mg *b.i.d.* x 7 consecutive days every 4 weeks
3-day high dose (Arm C)	400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks	350 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks	300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks
Part 2 of the study			
	300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks ever y 4 weeks	250 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks	200 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks
Part 3 of the study			
Arm D	200 mg *b.i.d.* x 7 consecutive days every 4 weeks	150 mg *b.i.d.* x 7 consecutive days every 4 weeks	100 mg *b.i.d.* x 7 consecutive days every 4 weeks
Arm E	300 mg *q.d.* x 7 consecutive days every 4 weeks	250 mg *q.d.* x 7 consecutive days every 4 weeks	200 mg *q.d.* x 7 consecutive days every 4 weeks
Arm F	300 mg *b.i.d.* x 3 consecutive days per week for 2 weeks ever y 4 weeks	250 mg *b.i.d.* x 3 consecutive days per week for 2 weeks ever y 4 weeks	200 mg *b.i.d.* x 3 consecutive days per week for 2 weeks ever y 4 weeks
Part 4 of the study			
Arm G	200 mg *b.i.d.* x 7 consecutive days every 4 weeks	150 mg *b.i.d.* x 7 consecutive days every 4 weeks	100 mg *b.i.d.* x 7 consecutive days every 4 weeks
Arm H	300 mg *q.d.* x 7 consecutive days every 4 weeks	250 mg *q.d.* x 7 consecutive days every 4 weeks	200 mg *q.d.* x 7 consecutive days every 4 weeks
Arm I	100 mg *q.d.* x 5 consecutive days per week for 2 weeks every 4 weeks	50 mg *q.d.* x 5 consecutive days per week for 2 weeks every 4 weeks	50 mg *q.d.* x 5 consecutive days every 4 weeks

Patients who had treatment delay > 2 weeks due to drug-related non-hematologic toxicities will also have dose reductions according to Table 3.

Dose reduction for drug-related toxicities may be undertaken temporarily or permanently for individual patients to ensure safety according to the assessment and judgment of the investigator in the following situations:

- Decrease dose by 50 mg *b.i.d.* (Arm A, B, C , D, F, G and Part 2) or 50 mg *q.d.*(Arm E, H, I) for grade 2 toxicity in a frail patient (See Appendix D)

- Decrease dose by 100 mg *b.i.d.* (Arm A, B, C, D, F, G and Part 2), or 100 mg *q.d.* (Arm E, H) or 50 mg *q.d.* (Arm I) for ≥ grade 3 toxicity in a frail patient or a patient who has experienced more than one ≥ grade 3 drug-related toxicity.

Decisions on treatment delay and dose modifications for drug-related hematologic toxicities should be guided by findings from bone marrow biopsy and/or aspirate as well as time to absolute neutrophil count (ANC) and platelet count recovery according to Table 4. Deviations from the guidelines are permitted to ensure safety and serve the best interest of the patient according to the assessment and judgment of the investigator. The reason for deviating from the guidelines should be documented in source documents.

Table 4 Guidelines on Treatment Delay and Dose Reduction for Hematologic Toxicities

Finding from bone marrow biopsy/aspirate	ANC ≥1000 and platelet count ≥100,000 by or on Day 28 of the cycle	ANC < 1000 or platelet count <100,000 on or after Day 28 of the cycle
Blasts are less than or equal to 5%	Administer study drug; Decrease dose by 50 mg *b.i.d** or 50 mg *q.d.*** for clinically significant and drug-related hematologic toxicity during the previous cycle	Hold study drug and repeat bone marrow when ANC and platelet count recover to baseline or better; if bone marrow blasts remains at 5% or less, continue to hold the study drug until ANC ≥1000 and platelets ≥100, 000 or until bone marrow blasts are increasing to >5%, whichever comes first; decrease by 100 mg *b,i.d** or 100 mg *q.d.*** for delay in ANC and platelet count recovery to the best level on study beyond Day 42
Blasts are >5% but ≤ 10%	Administer study drug; decrease dose by 50 mg *b.i.d.** or 50 mg *q.d.*** for clinically significant and drug-related hematologic toxicity during the previous cycle	For AML patients, hold study drug and repeat bone marrow in 1-2 weeks; if bone marrow blasts are decreasing, continue to hold the study drug until ANC ≥ 1000 and platelets ≥100, 000 or the recurrence of bone marrow blasts to >10%, whichever comes first; if bone marrow blasts are stable or increasing, administer the study drug; for MDS patients, hold study drug until ANC and platelet count have recovered to the best level on study or the recurrence of bone marrow blasts to >10%, whichever comes first. decrease sapacitabine dose by 50 mg *b.i.d** or 50 mg *q.d.*** for delay in ANC and platelet count recovery to the best level on study beyond Day 42.
Blasts have decreased 25% or more from baseline but are still >10 %	Administer study drug; decrease dose by 50 mg *b.i.d.** or 50 mg *q.d.*** for clinically significant and drug-related hematologic toxicity during the previous cycle	If ANC and platelet count have not recovered to baseline or better, hold study drug until ANC and platelet count recover to baseline or better or Day 42, whichever comes first; decrease dose by 50 mg *b.i.d.** 50 mg *q.d.*** for clinically significant and drug-related hematologic toxicity during the previous cycle or for delay in ANC and platelet count recovery to best level on study beyond Day 42 due to drug-related hematologic toxicity
Blasts have decreased less than 25% from baseline, have increased from baseline or have increased from the best response in bone marrow	Administer study drug****	Administer study drug****

* for patients enrolled on Arm A, B, C, D, F, G and Part 2.

** For patients enrolled on Arm E, H, I.

*** For patients in Part 1 of the study who were assigned to the 7-day low dose arm (Arm A) and have tolerated treatment well, consider intra-patient dose escalation up to 300 mg *b.i.d.* x 7 days every 4 weeks or up to 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks ; for patients assigned to the 7-day high dose (Arm B) and 3-day high dose (Arm C) and have had dose reductions for hematologic toxicities, consider dose escalation back up to the originally assigned dose. For patients in Part 2 of the study who have tolerated the treatment well, consider intra-patient dose escalation up to 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks. In Part 3 of the study, the dose may be increased up to 300 mg *b.i.d.* x 7 days every 4 weeks for patients who were randomized to 200 mg *b.i.d.* x 7 days every 4 weeks and up to 400 mg *b.i.d.* x 3 consecutive days per week for 2 weeks every 4 weeks for those who were randomized to 300 mg *b.i.d.* x 3 days/week for 2 weeks every 4 weeks; there will be no dose escalation for patients who were randomized to 300 mg *q.d.* x 7 days every 4 weeks. In Part 4 of the study, the dose may be increased up to 300 mg *b.i.d.* x 7 days every 4 weeks for patients who were randomized to 200 mg *b.i.d.* x 7 days every 4 weeks; there will be no dose escalation for patients who were randomized to 300 mg *q.d.* x 7 days every 4 weeks; dose escalation up to 150 mg *q.d.* x 5 days/week for 2 weeks may be allowed for patients who were randomized to 100 mg *q.d.* x 5 days/week for 2 weeks every 4 weeks after discussion with the study chair and medical monitor.

Dosing will be withheld in the presence of non-drug related grade 3 or grade 4 adverse events (AEs) if the investigator feels that it is unsafe to continue the administration of sapacitabine.

In general, a patient who requires more than two dose reductions, will be removed from the study unless, in the opinion of the investigator, the patient is experiencing a clinical benefit defined as achieving CR, CRi, or stable disease (SD) without unacceptable toxicities. In such instances, a decision regarding the continuation of treatment and further dose reductions will be made on an individual basis in consultation with the medical monitor and the justification will be recorded in the source documents.

6.3. Duration of Treatment

Patients may continue treatment at the discretion of the treating physician until they meet the criteria for terminating participation in the study (Section 4.3).

6.4. Post-Treatment Follow-up

All patients should be followed regularly until the resolution or stabilization of drug-related toxicity or the start of another anti-cancer treatment. Every effort will be made to conduct a post-treatment follow-up visit within 4 weeks after the last dose of the study drug or prior to the initiation of new treatment, whichever comes first. This post-treatment evaluation may be conducted over the telephone if the patient is unable to return to the clinic.

6.5. Concomitant Medications and Supportive Care

Patients may not receive any other anti-cancer therapies or investigational drugs while on this study. For this study, hydroxyurea which is used to lower peripheral WBC to <50,000 at the investigator's discretion are not considered anti-cancer therapy. All concomitant medications must be recorded. Supportive treatment may include anti-emetic, anti-diarrhea, anti-pyretic, anti-histamines, analgesics, antibiotics, and blood products.

At the discretion of the treating physician, patients may take allopurinol for prophylaxis against tumor lysis syndrome. Any other prophylactic treatment for drug-related symptoms is not planned for the first dose. Thereafter, prophylaxis may be allowed for ≥ grade 2 non-hematologic toxicity at the discretion of the Principal Investigator.

Prophylactic use of bone marrow growth factors is not allowed. The use of bone marrow growth factors may be allowed if its use is in compliance with the standard of care in clinical practice.

6.6. Treatment Compliance

Patient compliance with study drug will be monitored by capsule count.

7. STUDY CALENDAR

All procedures and evaluations may be performed within ± 3 calendar days of that specified in the protocol to accommodate patient convenience and scheduling. Patient consent must be obtained prior to any study-specific procedures.

Table 5 Study Flow Chart

Procedure	Pre-Study[c]	Cycle 1 (Day 1± 3 d)	Cycle 1 (Day 8 ± 3d)	Cycle 1 (Day 15 ±3d)	Cycle 2 and subsequent cycles (Day 1 ± 3d)	Post-treatment follow-up[i]
Sapacitabine administration		X[f]			X	
Informed consent	X					
Medical history	X					
Concomitant meds	X	X[g]	X	X	X	X
Capsule count					X	
Physical exam in clinic (including vital signs and performance status)	X	X[g]	X	X	X[g]	X
Height	X					
Weight	X				X	X
CBC[a]	X	X[g]	X	X	X	X
Chemistry panel[b]	X	X[g]	X		X	X
INR	X					
Transfusion requirements	X[d]		X	X	X	X
Number of hospitalized days	X[e]		X	X	X	X
Bone marrow aspirate and/or biopsy	X				X[h]	
Bone marrow cytogenetics	X[c]					
Pulmonary function test of FEV1 and DLco	X[c]					
ECG	X		X	X		X
Adverse events assessment			X	X	X	X
Chest x-ray (PA and Lateral)	X					

a: Differential of WBC will be done if WBC ≥ 300/μL
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, total protein, SGPT[ALT], SGOP (AST), sodium, uric acid
c: Within 2 weeks of the first dose of study drug except bone marrow cytogenetics which will be performed within 3 months (all patients) and pulmonary function test of forced expiratory volume in 1 second (FEV1) and lung diffusion capacity of carbon monoxide (DLco) which will be performed within 28 days prior to the first dose of the study drug as clinically indicated (Part 2 and 3 only); informed consent form may be obtained > 2 weeks prior to the first dose of drug but must be obtained prior to conducting any study-specific procedures
d: Transfusion requirements during the 8 weeks immediately prior to the first dose of study drug
e: Number of hospitalized days during the 8 weeks immediately prior to the first dose of study drug
f: The first dose of study drug must be administered within 7 days of randomization; sapacitabine may be dispensed at pre-study visit if the pre-study visit is within 7 days of the first dose of the study drug
g: These evaluations on Day 1 Cycle 1 may not need to be performed if the same evaluations performed during Pre-Study period are within 7 days of the first dose of the study drug; physical exam in clinic may be waived every 1-2 cycles at the investigator's discretion after cycle 6.
h: To be performed prior to the start of cycle 2 on patients who have >5% blasts in bone marrow, i.e., during Day –21-28 of Cycle 1 which may be delayed up to Day 35 for recovery of blood counts; as clinically indicated after subsequent cycles e.g., at the time when blood counts have recovered or worsened.
i: Within 28 days after the last dose of study drug if possible or prior to the initiation of new anticancer treatment, whichever comes first.

8. SAFETY ASSESSMENT

Safety parameters include early death rate and 30-day mortality rate as defined in section 11.2, adverse events, serious adverse events (SAEs), and overall survival.

8.1. Adverse Event Intensity and Relationship to Study Drug

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to treatment with the medicinal product. This includes the worsening of a pre-existing condition or the increase in frequency of a pre-existing condition. Treatment-emergent adverse events are defined as adverse events that occur after study drug administration begins through 28 days after the last dose of study drug or until the beginning of a new anticancer therapy, whichever comes first. This trial will record treatment-emergent adverse events. Adverse events that occur after the last dose of study drug, regardless of time frame, should also be reported if a casual relationship to the study drug is suspected. The NCI Common Terminology for Adverse Events (CTCAE) version 3.0 will be used to assess the severity of adverse events. Toxicities that cannot be graded using the CTCAE will be graded as grade 1 (asymptomatic), grade 2 (symptomatic but not interfering significantly with function), grade 3 (causing significant interference with function), or grade 4 (life-threatening). For this study, transfusion-dependent anemia and thrombocytopenia defined as requiring transfusion at least once per month will have a severity of grade 4.

An AE is considered serious if it meets any of the serious criteria listed in Section 8.2. To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following clarification is provided:

- The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

All AEs will be evaluated by the Investigator for potential relationship to the study drug in the following categories:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

All drug-related AEs and SAEs must be followed until resolution or until no further improvement is expected or until the initiation of a new anticancer treatment.

If a male patient's partner becomes pregnant while on study, the investigator will report the pregnancy to Theradex® within 24 hours after the first knowledge of the pregnancy via telephone or fax. The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus and newborn to Theradex® when it becomes available.

Safety Desk
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Princeton, New Jersey 08543
Tel: (609) 799-7580
Fax: (609) 799 -1567

8.2. Serious Adverse Event Reporting

A serious adverse event is defined as an untoward (unfavorable) medical occurrence that at any dose:

- Results in death
- Is life-threatening. The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Jeopardizes the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization could be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject, or require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

Any SAE or death that occurs after study drug administration through 28 days from the last dose of study drug or until the initiation of a new anticancer therapy, whichever comes first, must be reported to Theradex® immediately via telephone or FAX within 24 hours of the first

knowledge of the occurrence of the event. In addition, any SAE and death that occurs while a patient is not receiving the study drug but remains on study, must also be reported to Theradex as described above.

- For this study, myelosuppression and its associated complications due to underlying leukemia and/or anti-leukemia therapy are expected events during therapy. Hospitalizations for the treatment of the following events that are known to be associated with myelosuppression from leukemia and/or study drug are not required to be reported to Theradex® but still need to be captured as SAEs on the case report form [5]:
    - Fatigue, weakness and/or shortness of breath associated with anemia
    - Febrile neutropenia
    - Mucosal bleeding due to thrombocytopenia e.g., epistaxis, gastrointestinal bleeding
    - Bacteremia, sepsis, pneumonia, cellulitis, neutropenic colitis
- Death due to progression of AML and its associated complications are not required to be reported to Theradex® but still need to be captured as SAEs on the case report form [5].

Any SAE occurring at any other time after completion of the study must also be promptly reported to Theradex®, if a causal relationship to the study drug is suspected. If an SAE is initially reported via telephone, this must be followed-up with a written report via FAX within 24 hours of the telephone report. During both business and non-business hours, the telephone number listed below should be used to notify Theradex®.

Safety Desk
Theradex®
CN 5257
Princeton, New Jersey 08543
Tel: (609) 799-7580
Fax: (609) 799-1567

The investigator is required to complete the SAE report form provided by Cyclacel. Sufficient details must be provided to allow for a complete medical assessment of the SAE and independent determination of possible causality. The investigator is obliged to pursue and provide additional information as requested by the Cyclacel medical monitor or its designee. More details on SAE reporting and the SAE reporting form can be found in the Operations Manual.

It is the responsibility of the investigator to promptly notify the IRB or EC of SAEs and/or adverse drug reactions according to institutional guidelines and applicable local laws and regulations.

9. EFFICACY ASSESSMENT

The primary efficacy endpoint of Part 1 of this study is 1-year survival, i.e., the proportion of patients who are alive at 1-year measured from the date of the randomization. Secondary efficacy endpoints are the rate of CR, CRp, PR or CRi or hematological improvement and their corresponding durations, transfusion requirements and number of hospitalized days. The primary efficacy endpoints of Part 2 of this study are the rate of clinical benefit response (CR, CRp, PR, or major HI) and the rate of complete response (CR or CRp). Secondary efficacy endpoints are response durations, transfusion requirements, number of hospitalized days, and overall survival. The primary efficacy endpoint of Part 3 and 4 of this study is 1-year survival rate. Secondary efficacy endpoints are the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and their corresponding durations, transfusion requirements, number of hospitalized days and overall survival.

The tissue samples supporting the diagnosis of AML or MDS, and the responses to sapacitabine may be submitted for central review.

Table 6 Response Criteria

Response	Description
Complete Remission (CR) [8]	Normalization of peripheral neutrophils to ≥1000 /μL, platelet to ≥100,000/μL within 2 weeks of bone marrow biopsy/aspirate, and bone marrow to ≤5 % blasts; independent of transfusions*; and no extramedullary leukemia.
Complete remission with incomplete platelet count recovery (CRp) [8, 10]	Normalization of bone marrow to ≤5% blasts; peripheral neutrophils ≥1000 /μl, platelet <100,000 /μL within 2 weeks of bone marrow biopsy/aspirate; independent of transfusions*; and no extramedullary leukemia.
Complete remission with incomplete blood count recovery (CRi) [8]	Normalization of bone marrow to ≤5% blasts; peripheral neutrophils <1000 /μL, platelet <100,000/μL within 2 weeks of bone marrow biopsy/aspirate; independent of transfusions *; and no extramedullary leukemia.
Partial Remission (PR) [8]	Normalization of peripheral neutrophils to ≥1000 /μL, platelet to ≥100,000/μL within 2 weeks of bone marrow biopsy/aspirate, ≥50% decrease in bone marrow blasts over pretreatment but still >5%; independent of transfusions * .
Hematological improvement (HI) [9]	Major response: (1) For patients with pretreatment hemoglobin < 11 g/dL, >2g/dL increase in hemoglobin; for RBC transfusion - dependent patients, transfusion – independence* (2) For patients with a pretreatment platelet count <100,000/mm^3, an absolute increase of ≥30,000/mm^3; for platelet transfusion-dependent patients, stabilization of platelet counts and platelet transfusion independence*. (3) For patients with absolute neutrophil count (ANC) < 1,500/ mm^3 before therapy, ≥100% increase, or an absolute increase >500/mm^3, whichever is greater. Minor response: (1) For patients with pretreatment hemoglobin < 11 g/dL, 1-2 g/dl increase in hemoglobin; for RBC transfusion – dependent patients, 50% decrease in transfusion requirements. (2) Platelet response: for patients with a pretreatment platelet count <100,000/mm^3, ≥50% increase in platelet count with a net increase > 10,000/mm^3 but <30,000/mm^3. (3) For patients with absolute neutrophil count (ANC) < 1,500/ mm^3 before therapy, ≥100% increase, but absolute increase < 500/mm^3.
Stable disease (SD)**	Failure to achieve at least HI, but no evidence of clinically significant progression for > 16 weeks.

*independent of transfusions or transfusion –dependence refer to no packed red blood cell transfusion for 2 weeks and no platelet transfusion for 1 week [10].
** for Part 2, 3 and 4 of the study only

Transfusion requirements for each patient are defined as the number of weeks during which at least one transfusion for red blood cells (RBCs) or platelets is administered and the mean number of units of RBC and platelet transfusions administered per month.

Clinical benefit is defined as the achievement of CR, CRp, PR, major HI or SD. The duration of clinical benefit is measured from the earliest time when the patient achieved CR, CRp, PR or major HI to the first date when the major HI is lost; if the patient only achieved SD, the duration of clinical benefit is measured from the date of randomization or registration to the first date when clinically significant progression of disease is observed.

The duration of CR, CRp, PR or CRi or hematological improvement is measured from the time when response criteria are first met until the first date that recurrent or progressive disease is documented. To avoid premature discontinuation of patients who have had a temporary flare of the disease due to treatment interruptions, dose reductions, acute infection or other plausible explanations, a second assessment should be performed in these patients to confirm the recurrence or progression of disease.

10. INVESTIGATIONAL DRUG INFORMATION AND PROCUREMENT

10.1. Study Drug Identity

Chemical Name: 1-(2-C-cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N^4-palmitoylcytosine

Molecular Formula: $C_{26}H_{42}N_4O_5$ (MW 490.64)

Oral Formulation (Cyclacel BL formulation which was previously called Encap formulation): The drug is supplied as 25 mg, 50 mg and 75 mg strength liquid-filled capsules of a suspension of the crystalline Form B of the active pharmaceutical ingredient in miglyol 812N. Capsules are packaged in high-density polyethylene (HDPE) bottles, snap-on tamper evident low-density polyethylene (LDPE) lids closures.

Table 7 Encap Formulation Capsule (mg/capsule)

Ingredient	25 mg	50 mg	75 mg
Sapacitabine Form B	25 mg	50 mg	75 mg
Miglyol 812N Ph.Eur/GRAS	100 mg	200 mg	300 mg
White gelatin capsule with a gelatin band (comprising gelatin USP/Ph Eur and sterile water for irrigation)	Size 3	Size 2	Size 1
Printed white gelatin capsule (blue ink ring on the capsule body and a blue ink ring and a black ink band on the capsule cap) with a gelatin band (comprising gelatin USP/Ph Eur and sterile water for irrigation)	Not applicable	Size 2	Not applicable

Preparation: Gelatin capsules are filled with above components and sealed with a gelatin band under Good Manufacturing Practice (GMP) conditions.

Storage and Stability: The capsules should be stored at room temperature (15-25°C) in a closed container, protected from light in a secure, limited-access storage area. The 25, 50 and 75 mg capsules are stable for 5 years.

Route of administration: Oral

Source of Drug: Sapacitabine is an investigational drug supplied by Cyclacel under Investigational New Drug #53748.

10.2. Drug Procurement

FDA regulations require investigators to establish a record of the receipt, use, and disposition of all investigational agents. Investigators may delegate responsibility for drug ordering, storage, accountability, and preparation to their designees. Cyclacel's requirements for procurement, accountability, and disposition of study drug are provided below.

10.2.1. Drug Ordering

Sapacitabine should be requested by the Principal Investigator (or his/her authorized designees) at each participating institution. Sapacitabine may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in the clinical study. Cyclacel policy requires that sapacitabine be shipped directly to the institution where the patient is to be treated. Cyclacel does not permit the transfer of sapacitabine between institutions. The instructions for ordering study drug will be provided in the Operations Manual.

10.2.2. Drug Accountability

A capsule count of the drug will be maintained on the Drug Accountability Record (DAR) which has been approved for use by Cyclacel. All drug received, dispensed, and returned by the patient must be recorded on the DAR.

Patients must be instructed to return the dispensed capsule bottle on Day 1 of each cycle. Capsule count will occur at each visit to assess patient compliance with study drug.

10.2.3. Disposition of Unused Drug

All unused drug, including drug returned by patients, must be retained by study site staff until verified by Cyclacel's representative. After the drug accountability has been verified by Cyclacel's representative, unused drug will be destroyed at study site according to local Institutional guidelines and applicable laws and regulations.

11. BIOSTATISTICAL CONSIDERATIONS

11.1. Sample Size for Part 1 of the Study

This study is an open-label, randomized study of 3 dosing schedules of sapacitabine. The primary objective of this study is to evaluate 1-year survival rate of 3 dosing schedules in elderly patients with previously untreated or first relapsed AML or previously treated MDS; the secondary objectives are to assess the number of patients who have achieved a CR, CRp, PR or CRi or hematological improvement and their corresponding durations, transfusion requirements, number of hospitalized days and safety.

The primary efficacy endpoint is 1-year survival measured from the date of randomization. Statistically, the purpose of the trial is to reject the dosing schedules from further study if they were insufficiently active based on the rate of CR plus CRi for AML, and to accept them for further study if they were truly active. This will not apply to the MDS stratum because the CR rate of standard therapy by hypomethylating agents is only 6-9% and there is no effective therapy for those who have been previously treated by hypomethylating agents. For "screening" purpose, a Bayesian continuous futility monitoring rule is used for each dose schedule separately based on the rate of CR plus CRi for AML, and a "selection" design to choose the better dosing schedule based on 1-year survival rate if all 3 dosing schedules are found to have activity based on the rate of CR plus CRi. This randomized phase II trial is not expected to have sufficient power to compare the 3 dosing regimens on the basis of 1-year survival rate.

11.1.1. Screening Design

In the screening phase, a Bayesian continuous futility monitoring rule will be implemented based on the rate of CR plus CRi in each of the 3 arms of the AML stratum, respectively. An arm will be stopped if Prob (CR+CRi > 25% | data) < 0.05. The above stopping rule suggests that, given the data obtained from patients who have already been evaluated in an arm, if there is less than a 5% chance that the rate of CR+CRi is greater than 25% we will terminate the arm. This decision rule generates the following stopping boundaries, assuming a beta(1,1) prior distribution for the response (CR+CRi) rate in each arm. Stop an arm i if [# of pts with CR or CRi in arm i / # of pts evaluated in arm i] ≤ 0/10, 1/17, where i = 1, 2, or 3. The operating characteristics of this rule are shown in Table 8.

Table 8 Operating Characteristics of Futility Monitoring - Maximum 20 AML Patients

		Sample Size		
Rate of CR or CRi	Probability of stopping	P_{25}	P_{50}	P_{75}
0.05	0.822	10	10	17
0.10	0.54	10	17	20
0.15	0.313	17	20	20
0.20	0.165	20	20	20
0.25	0.082	20	20	20
0.30	0.039	20	20	20

After treating up to 10 evaluable AML patients defined as patients who have completed at least 1 cycle of treatment at each dosing schedule

- If no CR or CRi is observed, declare the treatment insufficiently active and no more AML patient will be treated with this dose regimen
- If at least one CR or CRi is observed, add AML patients to reach a total of 17 patients and
    - If less than two CR plus CRi are observed, declare the treatment insufficiently active
    - If at least two CR and CRi are observed, add AML patients to reach a maximum of 20 patients

For both AML and MDS patients, there is an early stopping rule for excessive toxicity. A dosing schedule will be declared to have excessive toxicity and no more patients will be treated with this dose regimen if among the first 10 patients treated with this dose regiment in either the AML or MDS stratum, there are > 2 patients experienced serious adverse events (excluding simple complications associated with myelosuppression such as neutropenic fever without shock or its complications from gram-negative bacteremia, anemia or mucosal bleeding, *e.g.*, epistaxis, due to thrombocytopenia easily controlled by transfusion) that are considered by investigator to be definitely, probably or possibly related to the study drug during the first two treatment cycles.

If a dosing schedule within the AML stratum has at least 4 CR and CRi, and the 30-day death rate is 20% or less, additional AML patients may be added to confirm the safety and tolerability of that dosing schedule. If a dosing schedule within the MDS stratum has at least 4 CR, CRp, PR, and major HI, and the 30-day death rate is 20% or less, additional MDS patients may be added to confirm the safety and tolerability of that dosing schedule.

11.1.2. Selection Design

Assuming that at least 2 dosing schedules show activity and that their toxicity profile is similar, a selection design will be used to choose the dosing schedule with the better observed 1-year survival rate. If the better dosing schedule has a true 1-year rate of 45% and the worse dosing schedule a true 1-year rate of 30%, the trial has better than 80% probability to choose the correct dosing schedule if 20 patients have been treated with each dosing schedule.

No formal hypothesis testing will be carried out for the 1-year survival rate. Instead, we will estimate the 1-year survival rate for each dosing schedule, along with the 95% confidence interval. Given a total of 20 patients in an arm and assuming a 1-year survival rate of 45%, the half-width of the 95% confidence interval will be 0.22. On the other hand, if assuming a 1-year survival rate of 30%, the half-width of the 95% confidence interval will be 0.20.

11.1.3. Stratification Factor

AML patients will be stratified by previously untreated vs. treated. The reason is that patients in first lapse are likely to have shorter survival and lower remission rate as compared to previously untreated patients.

11.2. Sample Size for Part 2 of the Study

The Part 2 of the study is an open-label, single arm phase II study in elderly patients with previously untreated AML and significant concomitant medical illnesses as measured by having HCTCI of 2 and higher. There are two co- primary efficacy endpoints, the rate of clinical benefit response (CR, CRp, PR, major HI or SD) and the rate of complete response (CR or CRp). Secondary endpoints are response duration, transfusion requirements, number of hospitalized days, overall survival, and safety. Statistically, the purpose of the trial is to reject sapacitabine from further study in elderly AML patients with HCTCI of 2 and higher if it were insufficiently active, and to accept it as active if it were truly active.

The trial is based on the following assumptions:

- The inactivity cut-off is chosen equal to 5% clinical benefit response; the activity cut-off is equal to 30% clinical response rate; hence, the hypotheses of interest are H_0: $r \leq 5\%$ against H_A: $r \geq 30\%$, where r is the response rate.

- The type I error rate (α, probability of accepting an insufficiently active treatment, a false positive outcome) is set to 5%.

- The type II error rate (β, probability of rejecting an active treatment, a false negative outcome) is set to 5%.

Under these assumptions, a two-stage design uses the following decision rule:

After treating up to 12 evaluable patients defined as those who have completed at least one treatment cycle,

- If no response is observed, declare the treatment insufficiently active and no more patient will be treated with this dose regimen

- If at least one response is observed, add patients to reach a maximum of 24 patients and

    - If three responses or less are observed, declare the treatment insufficiently active

    - If at least four responses are observed (an observed response rate of at least 17%), declare the treatment sufficiently active and add patients to reach a maximum of 36 patients.

The dose regimen will be considered active if the clinical benefit rate is at least 30% or the

rate of CR/CRp is at least 20%. Since the trial has two co-primary endpoints, the 97.5% confidence interval is calculated for each of the two endpoints. Assuming that the true response rate is equal to 30% clinical benefit rate and 20% CR/CRp, 36 patients are required for the lower bound the of the 97.5% confidence interval to exclude 5% for both endpoints.

11.3. Sample Size for Part 3 and 4

The primary objective of Part 3 and 4 of the study is to evaluate 1-year survival rate of 3 dosing schedules in elderly patients with previously untreated AML which evolved from MDS after receiving hypomethylating agents for the MDS or older patients with previously treated MDS; the secondary objectives are to assess the number of patients who have achieved a CR, CRp, PR, major HI or SD and their corresponding durations, transfusion requirements, number of hospitalized days and safety.

The primary efficacy endpoint is 1-year survival measured from the date of randomization. Statistically, the purpose of the trial is to reject the dosing schedules from further study if they were insufficiently active based on the rate of clinical benefit response and to accept them for further study if they were truly active. For "screening" purpose, a Bayesian continuous futility monitoring rule is used for each dose schedule separately based on the rate of clinical benefit response, and a "selection" design to choose the better dosing schedule based on 1-year survival rate if all 3 dosing schedules are found to have activity based on the rate of clinical benefit response. This randomized phase II trial is not expected to have sufficient power to compare the 3 dosing regimens on the basis of 1-year survival rate.

11.3.1. Screening Design

In the screening phase, a Bayesian continuous futility monitoring rule will be implemented based on the rate of clinical benefit response in each of the 3 arms, respectively. An arm will be stopped if Prob (clinical benefit response > 25% | data) < 0.05. The above stopping rule suggests that, given the data obtained from patients who have already been evaluated in an arm, if there is less than a 5% chance that the rate of clinical benefit is greater than 25% we will terminate the arm. This decision rule generates the following stopping boundaries, assuming a beta(1,1) prior distribution for the clinical benefit response rate in each arm. Stop an arm i if [# of pts with clinical benefit response in arm i / # of pts evaluated in arm i] $\leq$ 0/10, 1/17, where i = 1, 2, or 3. The operating characteristics of this rule are shown in Table 9.

Table 9 Operating Characteristics of Futility Monitoring - Maximum 20 AML Patients in Part 3 and Maximum 20 MDS Patients in Part 4

		Sample Size		
Rate of clinical benefit response	Probability of stopping	P_{25}	P_{50}	P_{75}
0.05	0.822	10	10	17
0.10	0.54	10	17	20
0.15	0.313	17	20	20
0.20	0.165	20	20	20
0.25	0.082	20	20	20
0.30	0.039	20	20	20

After treating up to 10 evaluable AML patients (Part 3) and 10 evaluable MDS patients (Part 4) defined as patients who have completed at least 1 cycle of treatment

- If no CR, CRp, PR, major HI or SD is observed in Part 3, declare the treatment insufficiently active and no more AML patient will be treated with this dose regimen; if no CR, CRp, PR, major HI or SD is observed in Part 4, declare the treatment insufficiently active and no more MDS patients will be treated with dose regimen;

- If at least one CR, CRp, PR, major HI or SD is observed in Part 3, add AML patients to reach a total of 17 patients and if at least one CR, CRp, PR, major HI or SD is observed in Part 4, add MDS patients to reach a total of 17 patients.

    - If less than two CR, CRp, PR, major HI or SD are observed in Part 3, declare the treatment insufficiently active for AML preceded by MDS previously treated with hypomethylating agents; if less than two CR, CRp, PR, major HI or SD are observed in Part 4, declare the treatment insufficiently active for MDS which were previously treated with hypomethylating agents.

    - If at least two CR, CRp, PR, major HI or SD are observed in Part 3, add AML patients to reach a maximum of 20 patients; if least two CR, CRp, PR, major HI or SD are observed in Part 4, add MDS patients to reach a maximum of 20 patients

There is an early stopping rule for excessive toxicity. A dosing schedule will be declared to have excessive toxicity and no more patients will be treated with this dose regimen if among the first 10 patients treated with this dose regiment, there are > 2 patients experienced serious adverse events (excluding simple complications associated with myelosuppression such as neutropenic fever without shock or its complications from gram-negative bacteremia, anemia or mucosal bleeding, *e.g.*, epistaxis, due to thrombocytopenia easily controlled by transfusion) that are considered by investigator to be definitely, probably or possibly related to the study drug during the first two treatment cycles.

If a dosing schedule has at least 4 CR, CRp, PR, major HI, or SD, and the 30-day death rate is 20% or less, additional AML or MDS patients may be added to confirm the safety and tolerability of that dosing schedule.

11.3.2. Selection Design

Assuming that at least 2 dosing schedules show activity and that their toxicity profile is similar, a selection design will be used to choose the dosing schedule with the better observed 1-year survival rate. If the better dosing schedule has a true 1-year rate of 45% and the worse dosing schedule a true 1-year rate of 30%, the trial has better than 80% probability to choose the correct dosing schedule if 20 patients have been treated with each dosing schedule.

No formal hypothesis testing will be carried out for the 1-year survival rate. Instead, we will estimate the 1-year survival rate for each dosing schedule, along with the 95% confidence interval. Given a total of 20 patients in an arm and assuming a 1-year survival rate of 45%, the half-width of the 95% confidence interval will be 0.22. On the other hand, if assuming a 1-year survival rate of 30%, the half-width of the 95% confidence interval will be 0.20.

11.3.3. Stratification Factor

AML and MDS patients will be stratified by prior treatment with decitabine (Yes or No). The reason is that patients who have been treated with decitabine may respond differently to sapacitabine than those who have only received azacitidine.[12]

11.4. Data Analysis

The intent-to-treat population for Part 1 of the study will include all patients who have received at least one dose of study drug on an assigned dosing schedule. The primary analysis population will consist of patients who underwent randomization. The primary and secondary efficacy endpoints will be analyzed separately within the AML or MDS stratum. Additional patients accrued to a dosing schedule that has produced at least 20% CR/CRi will be analyzed separately. The rate of 1-year survival and that of CR, CRp, PR CRi, or hematological improvement, will be reported with 95% confidence interval. The intent-to-treat population for Part 2 of the study will include all patients who have received at least one dose of the study drug. The rate of clinical benefit response (CR, CRp, PR, major HI or SD) and the rate of CR/CRp with be reported with 97.5% confidence interval. The intent-to-treat population for Part 3 and 4 of the study will include all patients who have received at least one dose of study drug on an assigned dosing schedule. The primary analysis population will consist of patients who underwent randomization. Additional patients accrued to a dosing schedule that has produced at least 20% clinical benefit response rate will be analyzed separately. Duration of CR, CRp, PR, CRi, HI, SD and overall survival will be estimated using the method of Kaplan and Meier. Patients who are discontinued from the study for reasons other than progression of disease will be censored at the time of the last response evaluation. The median number of transfusion-free weeks will be calculated for the 8 weeks

immediately prior to the first dose of study drug and while on study. For patients who required at least one transfusion of RBC or platelet within the 8 weeks immediately prior to the first dose of study drug, there will be a calculation of those who have achieved at least a 50% increase in the number of transfusion-free weeks on study over these at baseline, i.e., during the 8 weeks immediately prior to the receiving the first dose of the study drug.

The early death rate is defined as death due to any cause occurring within 14 days after the first dose of the study drug and will be reported with 95% confidence interval. In addition, 30-day mortality rate defined as death due to any cause occurring within 30 days after the first dose of the study drug will also be reported with 95% confidence interval. Treatment-emergent AEs will be summarized by system organ class and preferred term coded in accordance with the version of MedDRA that is most recent at the start of the study. Summaries of early withdrawal, deaths, SAEs and the number of hospitalized days measured from the first dose of the study drug to the date when the patient is discontinued from the study will be presented. The clinical significance of laboratory changes will be discussed. The safety analysis will be performed separately within the AML and MDS stratum as well as combining the two strata.

12. ETHICS

The Principal Investigator must ensure that the study will be carried out in accordance with the ethical principles in the Declaration of Helsinki (Appendix A). The Investigator agrees to conduct this study in accordance with the protocol, protocol amendments, the ICH guidelines of GCP and all applicable national, state, and local laws.

12.1. Institutional Review Board

Before the start of this study, the protocol and informed consent form must be reviewed and approved by the IRB or EC. The IRB or EC approval letter must be provided to Cyclacel before any study drug is shipped to the investigator.

The Investigator will ensure that no change will be made to the protocol without prior written approval from Cyclacel and the IRB/EC, except where necessary to eliminate an apparent immediate hazard to patients. All protocol amendments will be prepared by Cyclacel and must be approved by the IRB/EC before implementation. Administrative amendments that do not affect the conduct of the study or patient safety, and do not significantly reduce the scientific value of the protocol, do not require a formal review and approval from the IRB/EC but will be sent to the IRB/EC for informational purposes.

The Investigator must promptly notify the IRB/EC of all expedited safety reports that were sent to the applicable regulatory agency, regardless of the location of the reporting study site or study protocol according to institutional guidelines. In addition, the Investigator will follow local institutional guidelines on reporting AEs.

The Investigator will provide the IRB/EC with the current Investigator's Brochure and will be responsible for submitting periodic progress reports and a final report to the IRB/EC.

Copies of all study-related correspondence between the Investigator and the IRB/EC must be maintained in the appropriate section of the study file.

12.2. Informed Consent

The Investigator is responsible for ensuring that patients sign an appropriately approved informed consent, which meets the requirements of the code of Federal Regulations (Federal Register Vol. 46, No. 17, Jan. 27, 1981, part 50), the Declaration of Helsinki (Appendix A) and the IRB/EC of the study center before any study-related procedure is performed. Members of the treating team will review the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and alternative therapies including best supportive care. Patients must be informed that participation in the study is voluntary; that he/she may withdraw from the study at any time; and that withdrawal from the study will not affect his/her subsequent medical treatment or relationship with the treating physician. Financial costs that will or may be incurred as a result of participation in the study, as well as the efforts to maintain patient confidentiality will also be discussed. Patients must be allowed to ask questions and be provided with contact information for asking additional questions later on. The medical record will include documentation of the informed consent process. A copy of the signed informed consent must be provided to the patient, another copy kept with the study records, and the original kept with patient's medical record.

If the protocol is amended or if there is additional information available that may affect the patient's participation in the study, the informed consent form must also be amended. The amended informed consent form must be approved by Cyclacel as well as by the IRB/EC and be re-signed by applicable patients.

12.3. Protection of Privacy

The investigator agrees to uphold patient's right to privacy. Throughout this study, all data collected will be identified only by an identification number and initials. To verify compliance with the protocol, Cyclacel or its designee will need to review the patient's original medical records. The Investigator will ensure that Cyclacel or its designee can access the patient's medical record by obtaining permission in writing from the patient before the patient is enrolled in the study.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Audits may be conducted at selected study sites to review protocol adherence, study drug administration, eligibility criteria, efficacy assessment, and AEs. There will be a data management plan documenting data management procedures and validation of the database.

An audit will be performed prior to database lock and transfer of the database to the statistician for analysis. All data analyses and transformations will be performed using a validated statistical package. Data listings, tables, and figures will be examined for accuracy and completeness prior to being incorporated into the clinical study report.

14. DATA MANAGEMENT AND MONITORING

14.1. Study Monitoring

This study will be monitored by Cyclacel or its designee according to ICH guidelines of GCP. The protocol, CRFs, study drug supplies, and relevant procedures will be explained in detail prior to patient enrollment. The study site monitor will regularly visit the study sites to ensure that the study is conducted according to the protocol and GCP principles.

14.2. Access to Source Data

Regulatory agencies, the IRB or EC, and Cyclacel or its designee may request access to all source documents, CRFs, and other relevant documents for study monitoring, audit, or inspection. Direct access to these documents must be guaranteed and supported by the investigator and study site at all times.

14.3. Case Report Forms

Cyclacel will provide the study site with either paper or electronic CRFs for each patient. The investigator, or designated representative, must complete the CRFs expeditiously to capture all the relevant information. All data on the CRFs must be supported by source documents unless CRFs are the source data. An explanation must be given for all missing data. For paper CRFs, any incorrect entry should not be erased but should be struck with a single line, initialed, and dated by the person who made the correction using his or her initials. If the reason for the change is not obvious, a brief rationale should be provided. The investigator must review all CRFs, data queries and confirm that the data captured on CRFs is a complete and accurate record of a patient's data collected according to the protocol and GCP.

14.4. Record Maintenance

Records will be retained for at least 2 years after the last marketing approval or two years after discontinuation of the clinical development of the investigational drug. Cyclacel should be notified prior to the destruction of any files.

If the investigator relocates to another institution, the responsibility of keeping the study records must be transferred to another person at the current institution and Cyclacel must be notified in writing if such a change should occur. Cyclacel should also be notified if the files are transferred to an off-site facility.

15. PUBLICATION POLICY

In accordance with generally recognized principles of scientific collaboration, the number and order of co-authorship will be based on overall contribution to the design, conduct of the study, and compliance with study procedures. Because this is a multicenter study, publication or public disclosure of study results must be based on the entirety of the study. Any manuscripts, abstracts or public presentations of the results of this clinical trial must be provided to Cyclacel for review and comment prior to submission for publication or public presentation.

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17. APPENDICES

17.1. Appendix A. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude

the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

17.2. Appendix B. The Hematotopoietic Cell Transplantation Comorbidity Index Score (HCTCI)[11]

Comorbidity	Definition of Comorbidities	HCTCI Scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome or ventricular arrhythmias	1
Cardiac	Coronary artery disease (one or more vessel-coronary artery stenosis requiring medical treatment, stent or bypass graft), congestive heart failure, myocardial infarction, or ejection fraction ≤ 50%	1
Heart valve disease	Except mitral valve prolapse	3
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Peptic ulcer	Requiring treatment	2
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	1
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	Systemic lupus erythmatosis, rheumatoid arthritis, polymyositis, mixed connective tissue disease, or polymyalgia rhuematica	2
Moderate pulmonary	Moderate dysfunction defined as diffusion capacity of carbon monoxide and/or FEV1 66-80% or dyspnea on slight activity	2
Severe pulmonary	Severe dysfunction defined as diffusion capacity of carbon monoxide and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe renal	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Obesity	Obesity defined as a body mass index > 35 kg/m^2	1
Prior solid tumors	Prior solid tumor treated at any time point excluding nonmelanoma skin cancer	3

17.3. Appendix C. ECOG Performance Status

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.4. Appendix D. Definition of a Frail Patient

It is suggested that if a patient has three or more of the five factors below, the patient should be considered frail:

1. Unintentional weight loss of 10 pounds or more in a year
2. General feeling of exhaustion
3. Weakness as measured by grip strength
4. Slow walking speed
5. Low levels of physical activity

17.5. Appendix E. NCI Common Terminology Criteria (CTC version 3.0)