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Title: GLAD-AML - Glasdegib (Pf-04449913) With Two Standard Decitabine Regimens for Older Patients With Poor-risk Acute Myeloid Leukemia

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A RANDOMIZED, PARALLEL-ARM, PHASE 2 CLINICAL TRIAL OF THE COMBINATION OF GLASDEGIB (PF-04449913) WITH TWO STANDARD DECITABINE REGIMENS FOR PATIENTS WITH POOR-RISK ACUTE MYELOID LEUKEMIA WHO ARE UNFIT FOR OR REFUSE INTENSIVE CHEMOTHERAPY (GLAD-AML STUDY)

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1. ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
alloSCT	allogeneic hematopoietic stem cell transplant
ALT, SGPT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST, SGOT	aspartate aminotransferase
AUC	area under the curve
BID, b.i.d	twice daily
BSC	best supportive care
CNS	central nervous system
CBC	complete blood count
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5
CR	complete remission
CRc	cytogenetic complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRm	molecular complete remission
CR_{MRD}	complete remission with minimal residual disease
CRp	complete remission with incomplete platelet recovery
CRF	case report form
DAC	decitabine
DAC5	decitabine 20 mg/m^2 intravenous daily for five days on 28-day cycles
DAC10	decitabine 20 mg/m^2 intravenous daily for ten days on 28-day cycles
DLT	drug-limiting toxicity

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DL	dose level
DNMTi	deoxyribonucleic acid methyltransferase inhibitor
DNA	deoxyribonucleic acid
DoR	duration of response
EC	ethics committee
ECG, EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
G-CSF	granulocyte colony stimulating factor
GCP	good clinical practice
GLI	glioma
Hh	Hedgehog
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMA	hypomethylating agent(s)
IB	investigators brochure
IC	intensive chemotherapy
ID	identification
ICH	International Council for Harmonization
IHH	Indian hedgehog
IRB	institutional review board
IRT	Interactive Response Technology System
IVR	Interactive Voice Response

IWR	Interactive Web Response
IV	intravenous
IWG	International Working Group
LFS	leukemia-free survival
LFT	liver function test
MDS	myelodysplastic syndrome
MLF	morphologic leukemia-free [state]
MPN	myeloproliferative neoplasm
MRD	measurable residual disease
MTD	maximally tolerated dose
NCI	National Cancer Institute
OR	overall response
ORR	overall response rate
OS	overall survival
PE	physical exam
PI	package insert
PK	pharmacokinetics
PR	partial response
PrAML	poor-risk AML
PS	performance status
PT	prothrombin time
PTCH	patched
QTcF	QT interval with Fridericia's correction
RBC	Red blood cell
RFS	relapse-free survival
RP2D	recommended phase 2 dose
SAE	serious adverse event
SMO	smoothened
SOC	standard of care

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TTR	time to response
ULN	upper limit of normal
US	United States
VAF	variant allele frequency
WBC	white blood cell
WHO	World Health Organization

2. PROTOCOL SUMMARY

2.1. Introduction

The small molecule glasdegib (PF-04449913/PF-913) is an oral, selective SMO receptor antagonist which has recently been studied as a therapy in acute myeloid leukemia (AML); glasdegib, however, has not been extensively studied either as monotherapy or in combination with other chemotherapeutic agents for patients with cytogenetically or molecularly-defined poor-risk AML (PrAML).

This multi-center, randomized phase 2 study is designed to evaluate the complete remission (including complete remission with incomplete count recovery) rates of glasdegib in combination with either decitabine on a 5-day or 10-day schedule in patients with newly-diagnosed poor-risk AML who either refuse or are ineligible for intensive therapy.

2.2. Indication

Previously-untreated adult patients with cytogenetically or molecularly-defined PrAML who either decline or are not candidates for intensive chemotherapy

2.3. Background and rationale

2.3.1. Disease overview

Approximately 30% of newly-diagnosed AML is characterized as being poor-risk AML (PrAML) and is specifically-defined by specific myeloblast karyotypic aberrations including del(5q)/-5, del(7q)/-7, inv(3), t(3;3), t(6;9), -17, abn 17p, monosomal karyotype, complex karyotype (defined as three or more abnormalities) as well as those molecularly-defined by the presence of mutated TP53.[1, 2] Complete response (CR) rates to standard induction chemotherapy in PrAML are no higher than 55% in patients aged 55 years and only 32% in older patients.[3, 4] The presence of monosomal karyotype predicts CR as low as 18%.[5] Concordant with CR rates, survival also remains inferior in PrAML, with 4-year overall survival (OS) ranging from 4-10% and even as low as 1% based on the degree of poor-risk cytogenetic abnormality on the myeloblast karyotype.[3-6] TP53-mutated AML provides another informative example: only 41% of patients achieve CR and fewer than 10% remain alive three years following allogeneic stem cell transplantation (alloSCT) performed while in CR.[7, 8] PrAML patients have few if any curative therapeutic options.

Hedgehog (Hh) pathway proteins are a collection of small molecules which participate in intercellular signaling pathways responsible for embryogenesis and maintenance of adult stem cells. The primitive differentiation into definitive cell types is a result of cellular response to heterogeneous concentrations and gradients of Hh ligand which induces eventual expression of varying target genes responsible for such.[9] This cellular response is predicated upon Hh-induced activation of patched-1 and patched-2 (PTCH-1/2), the 12-pass transmembrane proteins which act as Hh ligand receptor.[9, 10] PTCH-1/2 acts upon smoothened (SMO), a 7-pass transmembrane Hh-related, constitutively-active signal transducer protein whose activation culminates in the downstream phosphorylation of the glioma (GLI) family zinc finger activating transcription factors GLI1 and GLI2 (oncogene homologues of the cubitus interruptus transcription factor), and the ultimate expression of target genes responsible for inciting cell cycling, anti-apoptotic mechanisms, and cellular differentiation.[9, 10] Conversely, the absence of Hh, its receptor or signaling transduction, Hh-related transcription factors are alternatively-cleaved, assume the role of transcriptional repressors, and halt differentiation that was not predestined.[9, 10] Indian Hh (IHH) is a tissue-specific Hh isoform which has been shown to have a crucial role in primitive hematopoiesis, the early stage at which embryogenesis commits cells to hematopoietic precursors and the development of

early hematopoietic tissue, which is also shown to express PTCH1/2, SMO and the GLI family transcription factors.[11, 12] Subsequent to its pivotal role in early tissue development, Hh additionally maintains an active role in adult multipotent hematopoietic stem cells (HSC) expansion, self-renewal in response to biological insults, and thus lifelong hematopoiesis.[11, 12]

AML pathology is likely founded in the presence **of leukemic stem cells (LSC),** which yield leukemic progenitor cells, downstream CD34+ leukemic effector cells, and the ultimate hematopoietic dysfunction with which AML manifests.[13] *Ex vivo* AML data has shown that CD34+ leukemic cells are characterized by high expression of IHH, GLI1, GLI2, and Hh-related downstream pro-survival gene expression, all indicative of Hh pathway activation.[13-16] Overexpression of downstream GLI2 mRNA has been shown to have a negative impact on overall survival.[17]

The Hh pathway has furthermore been implicated in the **leukemic cell chemoresistance**. **Direct SMO antagonists and anti-IHH monoclonal antibodies to cytarabine-resistant CD34+ human myeloid leukemic cell lines are shown to specifically inhibit the Hh pathway, induce Hh-specific apoptosis, and more strikingly, restore chemosensitivity**.[13] It is reasonable to posit that chemosensitivity to other standard AML therapies may be restored with leukemic cell exposure to Hh-pathway inhibitors.

2.3.2. Glasdegib

The small molecule glasdegib (PF-04449913/PF-913) is an oral, selective SMO receptor antagonist which has recently been studied as a therapy in AML. Initial *in vitro* and *ex vivo* studies of AML cell lines demonstrated that glasdegib reduced SMO-targeting gene transcripts, c-Myc expression, cell cycle progression and ultimately the fraction of $CD34^{+}CD38^{-}$ cells, which infers a reduced leukemia-initiation potential of AML LCS.[15]

A phase 1 study of glasdegib monotherapy in 47 patients with myeloid malignancies including 28 with AML established a maximum tolerated dose (MTD) of 400 mg daily with 60% of patients experiencing a treatment-related adverse event (three of which were grade 4), which included dysgeusia (28%), anorexia (19%), and alopecia (15%). A recommended phase 2 dose of 200 mg daily or lower was established; clinical activity was suggested in 49% of all patients.[18]

2.3.3. Decitabine in Patients with Poor-risk Acute Myeloid Leukemia

An initial phase II study of the DNA methyltransferase inhibitor (DNMTi) decitabine 20 mg/m^2 on a 5-day schedule in patients aged 60 years and older (median age 74) showed a 24% CR rate in the PrAML subset.[19] A subsequent phase II trial of decitabine 20 mg/m^2 given on a 10-day schedule in a comparable population induced a CR of 47%. Interestingly, half of these study patients had PrAML; a CR rate of nearly 50% was noted in this subset.[20] A recent study by Welch, et al claimed overall response rates (ORR, defined as CR/CRi plus morphologic remission) of 67% in PrAML using the 10-day schedule, with most strikingly a 100% ORR in TP53-mutated AML in addition to robust mutation clearance and survival rates that seemed to remit to those observed in intermediate-risk AML populations.[21] However, the largest randomized trial testing decitabine (the randomized DACO-16 trial) in older unfit adults showed a CR rate of 20%.[22]

2.3.4. Rationale for the Combination of Glasdegib with Decitabine in Poor-risk Acute Myeloid Leukemia

The use of targeted therapy in AML is made difficult by the heterogeneous nature of the disease with respect to the multitude of molecular and chromosomal abnormalities which initiate leukemogenesis. However, targeting and disrupting the Hh-pathway, the primary mechanism by which diseased and often

chemoresistant LSC maintain their self-renewal and leukemia-initiating potential offers the potential of more robust leukemic cell kill and clinical outcomes of standard AML therapies, which to date have yielded unacceptable results for the PrAML population.

Glasdegib has previously combined with decitabine in only very few AML patients. A recent, three-arm phase 1b study included an arm in which patients aged 65 years or older with newly-diagnosed AML (5 patients [71%]) or high-risk myelodysplastic syndrome and no prior DNMTi exposure received glasdegib 100 or 200 mg daily in combination with decitabine 20 mg/m^2 on a 5-day schedule; two patients (29%) were characterized by poor-risk cytogenetics.[23] Two patients (29%) were characterized by poor-risk cytogenetics and three patients (43%) were treated at the 200 mg daily dose. The MTD was not reached, no dose-limiting toxicities were observed, and the most common treatment-related effects (not surprisingly given the role of the Hh pathway in normal hematopoiesis) were hematologic toxicities: neutropenia (57%), thrombocytopenia (43%), anemia (43%).[23] Of the AML patient subset, 40% achieved CR/CRi with a median of 3 cycles administered, and median duration of response of 2.6 months.[23] Given the absence of a MTD, its well-tolerated nature and convincing efficacy signal, glasdegib 100 mg daily was selected as the randomized, phase 2 dose for use with other standard AML therapies including decitabine. Given the striking report of robust response to decitabine on the 10-day schedule in AML patients with TP53-mutated disease (an inherently large proportion of patients with PrAML), it stands to reason that glasdegib 100 mg daily in combination with decitabine on the 10-day schedule might induce more robust responses in comparison to that observed in combination with the decitabine on the 5-day schedule.

2.4. Study Objectives And Endpoints

2.4.1. Objectives

Primary objective

To determine the response rates, complete remission (CR) and complete remission with incomplete count recovery (CRi), of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML

Secondary objectives

To evaluate the toxicity and safety profiles of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML

To determine the event-free survival (EFS), relapse-free survival (RFS), overall survival (OS), duration of response, bone marrow mutational clearance, and remission clonality of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML

2.4.2. Endpoints

Primary endpoint

CR/CRi rate as defined by the 2017 European LeukemiaNet response criteria (**Appendix 1)**

Secondary endpoints

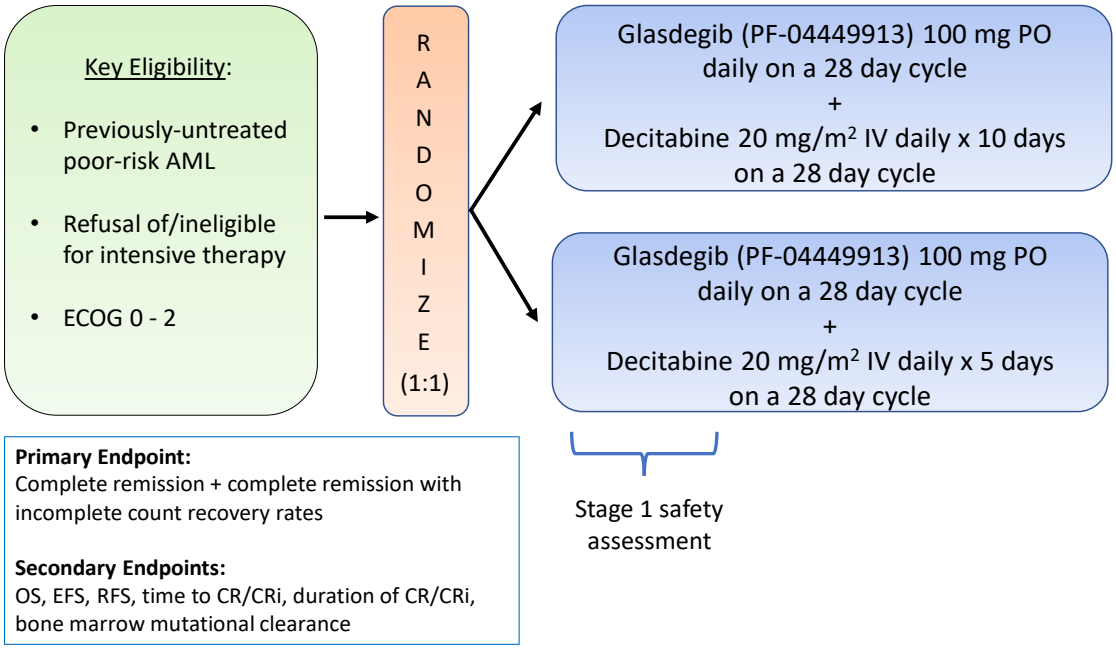
Adverse events (AE)
Serious Adverse Events (SAE)
CR
CRi
CRh

RBC transfusion independence (per the International Working Group [IWG] response criteria for MDS) for patients who are transfusion dependent
OS
EFS
RFS
Time to CR/CRi
Duration of CR/CRi
Bone marrow mutational clearance of frequently-mutated genes in AML (e.g. NPM1, CEBPA, DNMT3A, RUNX1, TET2, IDH1/2) via next-generation DNA sequencing
Remission clonality

2.5. Study Design

This multi-center, randomized phase 2 study is designed to evaluate the complete remission (including complete remission with incomplete count recovery) rates of glasdegib in combination with either decitabine on a 5-day or 10-day schedule in patients with newly-diagnosed poor-risk AML who either refuse or are ineligible for intensive therapy. Induction cycles are cycles 1-6 (or until CR or CRi is achieved, if earlier). Consolidation cycles are cycles 7 (or earlier if CR or CRi is achieved)-24. Patients who have achieved CR or CRi will remain on study beyond cycle 6 for up to 24 cycles.

Figure 1. Schematic of Study Design



2.6. Study Assessments

Patients will be followed for efficacy throughout the study by means of bone marrow aspirates. Following study entry, bone marrow biopsies will only be required if adequate bone marrow aspirates are not obtained. A CR/CRi needs to be confirmed at least 4 weeks after the bone marrow (BM) evaluation by assessing the stability of improved counts on peripheral blood (PB) according to the 2017 European

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LeukemiaNet response criteria (**Appendix 1**); an additional marrow confirmatory specimen is not required. Transfusional support (packed red blood cells and platelets) will also be recorded. Timely and complete disease assessments (BM evaluation and peripheral blood (PB) counts) at screening and during the study, whenever clinically indicated, are essential. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and may weaken the study conclusions. Safety assessments (laboratory, instrumental and clinical) will be performed regularly during the active treatment period. Please refer to the **Schedule of Activities** for a complete list of assessments to be performed on patients in the study.

2.7. Study Treatments

Treatment will be administered in 28-day cycles. All patients will receive glasdegib 100 mg oral daily and will be subsequently randomized 1:1 to receive glasdegib in combination with either decitabine 20 mg/m^2 IV on a 10-day schedule (DAC10) or decitabine 20 mg/m^2 IV on a 5-day schedule (DAC5).

Since responses to decitabine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles in patients with a response of stable disease (SD) or greater, or until progressive disease (PD), unacceptable toxicity, patient refusal, or death, whichever occurs first.

If glasdegib is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with decitabine may be continued if the patient has experienced at least a CRi to study therapy. In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from both study drugs and entered into the follow-up phase of the study. When study treatment with both drugs (decitabine and glasdegib) is permanently discontinued, patients will enter into the follow-up phase as detailed below.

2.8. Statistical Methods

The study will proceed as a pair of two-arm, randomized phase 2 study. Each arm will be compared to the historical record with its own early stopping rule for futility. Patients will be randomized to one of two arms (glasdegib/DAC10 or glasdegib/DAC5). For each arm separately, CR/CRi will be evaluated. Assuming a historical CR rate of 17% for decitabine 20 mg/m^2 on the standard of care five-day schedule (the null hypothesis, based on the largest, phase 3, multicenter, randomized study of decitabine in older patients with AML [DACO-16]), a minimum acceptable CR rate of 25% (given the addition of glasdegib and additional potential toxicity) and ultimately a predicted minimum CR rate of 47% (the alternative hypothesis) for patients accrued to either arm of the proposed randomized phase 2 study, a minimum of 23 evaluable patients per arm will be accrued to test for a statistically-significant difference with an 80% power and a 90% confidence interval (which is equivalent to a type 1 error rate, alpha one-sided of 0.05). Stage one of the Simon two-stage minimax decision rule will be assessed after 10 patients are treated in each arm. We will stop enrollment in either arm if 2 or fewer patients in that arm achieve CR. The probability of early termination is 0.53 in each arm, under the null hypothesis. The same null hypothesis will be applied to both treatment arms, separately, without correction for multiplicity. Randomization tables in blocks of four will be created before the trial begins.

If we achieve 3 or more responses among the first 10 patients in an arm, then we will move to stage 2 of enrollment to 23 patients per arm. If 8 or fewer responses are observed in an arm by the end of the second stage of the study then no future investigation of the drug combination is warranted. Accrual will be increased by 10% (a minimum total of 51 patients) to account for those patients that are anticipated to be unevaluable and maintain the integrity of the statistical design. The final analysis of CR/CRi will be performed when the full information of CR/CRi is reached. All eligible and treated patients will be included

into the analysis. For each arm separately, 80% and 95% confidence intervals of CR/CRi rates based on exact binomial distribution and will be compared to the historic CR/CRi (approximately 25%).

All toxicities will be graded according to NCI CTCAE v5.0. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawals and incidence of serious adverse events. Listing of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. The adverse events rate will be estimated accompanied by an exact 95% confidence interval.

Descriptive statistics will be used to summarize all patient data. When applicable, t-tests or Wilcoxon rank-sum tests will be used to make comparisons between patient subgroups of interest for continuous variables for parametric and non-parametric outcomes respectively. Categorical data will be summarized using frequencies and percentages. Chi-square tests or Fisher's exact tests will be used to make comparisons between patient subgroups of interest for categorical variables.

2.9. Schedule Of Activities

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Schedule of Activities for Study Participants

	Screening	Cycle 1 (28-day cycle)		Cycles 2-6 (28-day cycle)	Cycles 7-24 (28-day cycle)*	End of Treatment Visit[19]	Long Term Follow-up
Protocol activity	**(≤28 days from study entry)**	**Day 1 (+/- 3)**	**Day 15 (+/- 1)**	**Day 1 (+/- 3)**	**Day 1 (+/- 3)**	**Within 14 days of last dose (+/- 1)**	**Every 3 months[20] (+/- 7 days)**
Informed consent[1]	X						
Medical History[2]	X						
ECOG Performance Status[3]	X	X	X	X	X	X	
Disease classification[4]	X	X		X	X	X	
Physical Examination[5]	X	X	X	X	X	X	
Laboratory studies							
Hematology[6]	X	X	X	X	X	X	
Blood Chemistry[7]	X	X	X	X	X	X	
Urinalysis[8]	X						
Coagulation[9]	X						
Pregnancy Test/Contraception Reminders[10]	X	X		X	X	X	X
Triplicate 12-lead ECG	X	X		X	X	X	
Registration and Treatment							
Glasdegib[11]		Oral Once Daily Continuous Dosing					
Decitabine[12]		IV infusion Days 1-10 per local label or per the Investigational Product Manual					

Drug Compliance[13]				X	X	X	
Disease Assessments							
Bone Marrow Biopsy[14]	X			X[15]	X[,15]	X	
Bone Marrow Aspirate[14,15]	X			X[15]	X[15]	X	
Bone Marrow Immunophenotyping, Flow Cytometry and Cytogenetics[14,15]	X			X[15]	X[,15]	X	
Myeloid Gene Next Generation Sequencing[15]	X			X[15]	X[15]	X	
Other Clinical Assessments							
Adverse Event/Serious Adverse Event Monitoring[16]	X	X				X	X[20]
Survival Follow-up							X[20]
Review Prior/Concomitant Treatments[17]	X	X					
Recording of RBC and Platelet Transfusions[18]	X	X					

*Inclusive only of patients with response (CR/CRi) by cycle 6 of respective therapy; patients without response by cycle 6 will be taken off of study

Footnote for Schedule of Activities

1. **Informed Consent:** Must be obtained prior to undergoing any study procedure. Informed consent document may be signed up to 60 days prior to C1D1 as long ass all screening procedures take place within the 28 days immediately preceding C1D1.

2. **Medical History**: Includes cancer history as well as prior and concomitant illnesses.

3. **ECOG Performance Status**: See TBD Appendix

4. **Disease Classification**: AML by WHO 2016 classification (**Appendix 9**). Prognostic system using 2017 European Leukemia Net (ELN) criteria (**Appendix 1**). A disease classification does not need ot be repeated on C1D1 if the screening disease classification was done within 14 days prior to C1D1.

5. **Physical Examination**: Examination of major body systems (includes general appearance, head, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological), body weight, height, and vital signs (blood pressure and heart rate to be recorded in sitting position). Weight must be recorded at Screening, Day 1of each cycle, and End of Treatment. Height need not be recorded after the first measurement at screening. Date of last period should be assessed and documented.

6. **Hematology**: No need to repeat on C1D1 if screening assessment performed within 3 days prior to that date. The list of required laboratory tests is in **Appendix 6**.

7. **Blood Chemistry**: No need to repeat on C1D1if screening assessment performed within 3 days prior to that date. The list of required laboratory tests is in **Appendix 6**.

8. **Urinalysis**: Should be performed after Screening if clinically indicated. The list of required laboratory tests is in **Appendix 6**.

9. **Coagulation**: Should be performed after Screening if clinically indicated. The list of required laboratory tests is in **Appendix 6**.

10. **Pregnancy Tests/Contraception Reminders**: Pregnancy tests (serum/urine) for patients of child-bearing potential only must be performed on two occasions prior to starting study therapy (once at the start of screening and once prior to treatment), on C1D1 every cycle during the active treatment period and at the End of Treatment. Following a negative pregnancy result at screening, appropriate contraception for males and females (Refer to **Table 2**) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. It may also be repeated as per request of IRB/ECs (or if required by local regulations), if one menstrual cycle is missed or when potential pregnancy is otherwise suspected during the active treatment period or as clinically indicated.

11. **Glasdegib Dosing**: Treatment will be administered in 28-day cycles (cycle duration may be extended to allow for toxicity resolution). Glasdegib will be administered once daily, continuously, in the morning at approximately the same time each day.

12. **Decitabine Dosing:** Decitabine will be administered per local label. Treatment can be administered as an IV infusion on Days 1-10. Day 1 of each cycle is determined by the first day of decitabine. Visit time window added to accommodate varying decitabine dosing schedules to accommodate patient and treatment center availability. The start of subsequent cycles can be delayed to allow for toxicity resolution.

13. **Drug Compliance:** All glasdegib bottles including any unused tablets and patient dosing diaries will be returned to the clinic for compliance assessment and drug accountability.

14. **Bone Marrow Assessments for Disease Evaluation.**

- Type of Bone Marrow Sample: For all patients, a bone marrow aspirate sample is required at the timepoints of bone marrow sampling described below. Bone marrow biopsies are optional unless required for clinical staging in cases that the aspirate is not sufficient (e.g. dry tap). Samples taken prior to consent but within the 28-day window maybe used for disease evaluation and need not be repeated. Bone marrow samples required for other study assessments (e.g. MRD assessment) must be collected after consent is signed.

- Timepoints for Bone Marrow Sampling: Bone marrow assessment must be completed at screening (within 28 days prior to first dose), after completion of cycles 2, 4 and 6 and within 7 days prior to the start of cycles 3, 5 and 7, respectively. After cycle 6, bone marrow assessments will be required every six cycles until the completion of cycle 24/EOT, progression of disease or at any time as per investigators discretion if CR is suspected. Bone marrow assessment is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation or radiological/clinical assessment.

15. **Bone Marrow Genetics**: Genetics analysis (local), including molecular profiling, myeloid gene panel next generation sequencing and karyotyping will be conducted on all patients using any scheduled or unscheduled bone marrow samples collected during study participation. Genetics to be analyzed are specified in **Appendix 8**. Baseline genetics classification must be completed on a sample collected within 28 days prior to first dose.

16. **Adverse Event (AE)/Serious Adverse Event (SAE) Monitoring:** Adverse events should be documented and recorded at each visit using the NCI CTCAE version 5.0. . Patients must be followed for AEs for 30 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 30 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period begins from the time that the patient provides informed consent, through and including 30 calendar days after the last administration of the investigational product, even if another anticancer therapy has been started. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the project manager if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported,

17. **Concomitant Medications and Treatments**: All concomitant medications and treatments should be recorded in the eCRF.

18. **Red Blood Cells and Platelets Transfusion Recording:** Transfusion history up to 8 weeks prior to screening should be recorded. All red blood cell and platelet transfusions, including date of each transfusion and number of red blood cell and platelet units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded.

19. **End of Treatment**: Bone Marrow Samples collected at the following time point should be shipped according to the lab manual at the end of participation; screening, after cycle 2 and after cycle 6 (unless the patient is coming off study treatment for disease progression).

20. **Long Term Follow-up:** The first follow-up contact should occur at least 28 days, and no more than 35 days after the last dose of study drug to capture any potential adverse events and to confirm appropriate contraception usage (refer Table **2**). Follow-up may be made via telephone call, but must be performed every 3 months (+/- 7 days) for a total duration of 2 years. Patients continuing to experience toxicity following discontinuation of treatment will be followed by the Investigator at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

3. **SIGNATURE OF PRINCIPAL INVESTIGATOR**

The signatory agrees to the content of the final clinical study protocol as presented and in compliance with all applicable regulations including those outlined in Good Clinical Practice and the Code of Federal Regulations.

Name:

Affiliation:

Date: _____ Signature: _____

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

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4. INTRODUCTION

Glasdegib (PF-04449913/PF-913) is an oral, selective SMO receptor antagonist and thus inhibitor of the Hedgehog (Hh) pathway which has recently been studied as a monotherapy and in combination therapy in patients with acute myeloid leukemia (AML). Decitabine, a DNA methyltransferase inhibitor (DNMTi), has likewise been studied as monotherapy and in combination therapies for AML, and is reported to have promising activity in patients with molecularly or cytogenetically-defined poor-risk AML (PrAML).

This multi-center, randomized phase 2 study is designed to evaluate the efficacy (as defined by complete remission [including complete remission with incomplete count recovery] rates) of glasdegib in combination with either decitabine on a 5-day or 10-day schedule in patients with newly-diagnosed, PrAML who either refuse or are ineligible for intensive therapy.

4.1. Indication

Previously-untreated, older adult patients with cytogenetically or molecularly-defined PrAML who either decline or are not candidates for intensive chemotherapy (according to WHO 2016 classification)

4.2. Background and Rationale

4.2.1. Disease Overview

Acute myeloid leukemia (AML) comprises a variety of malignant diseases characterized by the clonal expansion of myeloid precursors. Of the estimated 21,380 new cases of AML in the United States during 2017, more than half will occur in patients aged 65 or older. Though older patients are traditionally burdened by both comorbidities precluding intensive induction therapy and a higher risk of treatment-related mortality, responses to induction therapy and the observed outcomes have been found to be critically and independently predicted by cytogenetically-determined and biologically-diverse subsets of risk. Poor-risk AML (PrAML) comprises approximately 30% of all newly-diagnosed AML and is defined by specific myeloblast karyotypic aberrations which include del(5q)/-5, del(7q)/-7, inv(3), t(3;3), t(6;9), -17, abn 17p, monosomal karyotype, complex karyotype (defined as three or more abnormalities) as well as those molecularly-defined by the presence of mutated TP53. These genotypes define the WHO-system category of AML with myelodysplasia-related changes (AML-MRC), regardless of whether the histology contains sufficient morphologic dysplasia to be included in that category in the absence of cytogenetic abnormalities.

Complete response (CR) rates to standard induction in PrAML remain inferior with no higher than 55% in patients aged 55 years or younger, but only 32% in older patients. The presence of monosomal karyotype predicts CR as low 18%. Concordant with CR rates, survival also remains inferior in PrAML, with a 4-year overall survival (OS) specifically ranging from 4-10% and even as low as 1% based on the degree of poor-risk cytogenetic burden on the myeloblast karyotype. TP53-mutated AML provides another informative example: only 41% of patients achieve CR and fewer than 10% remain alive three years following allogeneic stem cell transplantation (alloSCT) performed while in CR. In fact, event-free survival in TP53-mutated AML approximates one month. PrAML patients have few if any curative therapeutic options.

4.2.2. Hedgehog Signaling and Hematopoiesis

Hedgehog (Hh) proteins of a collection of small molecules which participate in intercellular signaling pathways responsible for embryogenesisand maintenance of adult stem cells.The primitive differentiation into definitive cell types is a result of cellular response to heterogeneous concentrations and gradients of Hh ligand which induces eventual expression of varying target genes responsible for such. This cellular

response is predicated upon Hh-induced activation of patched-1 and patched-2 (PTCH-1/2), the 12-pass transmembrane proteins which act as Hh ligand receptor. PTCH-1/2 acts upon smoothened (SMO), a 7-pass transmembrane Hh-related, constitutively-active signal transducer protein whose activation culminates in the downstream phosphorylation of the glioma (GLI) family zinc finger activating transcription factors GLI1 and GLI2 (oncogene homologues of the cubitus interruptus transcription factor), and the ultimate expression of target genes responsible for inciting cell cycling, anti-apoptotic mechanisms, and cellular differentiation. Conversely, the absence of Hh, its receptor or signaling transduction, Hh-related transcription factors are alternatively-cleaved, assume the role of transcriptional repressors, and halt differentiation that was not predestined. Indian Hh (IHH) is a tissue-specific Hh isoform which has been shown to have a crucial role in primitive hematopoiesis, the early stage at which embryogenesis commits cells to hematopoietic precursors and the development of early hematopoietic tissue, which is also shown to express PTCH1/2, SMO and the GLI family transcription factors. Subsequent to its pivotal role in early tissue development, Hh additionally maintains an active role in multipotent hematopoietic stem cells (HSC) expansion, self-renewal in response to biological insults, and thus lifelong hematopoiesis.

4.2.3. Acute Myeloid Leukemia and the Hedgehog Pathway

AML pathology is likely founded in the presence of **leukemic stem cells (LSC)**, which yield leukemic progenitor cells, downstream CD34+ leukemic effector cells, and the ultimate hematopoietic dysfunction with which AML manifests. *Ex vivo* AML data has shown that CD34+ leukemic cells are characterized by high expression of IHH, GLI1, GLI2, and Hh-related downstream pro-survival gene expression, all indicative of Hh pathway activation. Overexpression of downstream GLI2 mRNA has been shown to have a negative impact on overall survival.

The Hh pathway has furthermore been implicated in the **leukemic cell chemoresistance. Direct SMO antagonists and anti-IHH monoclonal antibodies to cytarabine-resistant CD34+ human myeloid leukemic cell lines are shown to specifically inhibit the Hh pathway, induce Hh-specific apoptosis, and more strikingly, restore chemosensitivity**. It is reasonable to posit that chemosensitivity to other standard AML therapies may be restored with leukemic cell exposure to Hh-pathway inhibitors.

4.2.4. Glasdegib (PF-04449913)

The small molecule glasdegib (PF-04449913/PF-913) is an oral, selective SMO receptor antagonist which has recently been studied as a therapy in AML. Initial *in vitro* and *ex vivo* studies of AML cell lines demonstrated that glasdegib reduced SMO-targeting gene transcripts, c-Myc expression, cell cycle progression and ultimately the fraction of $CD34^{+}CD38^{-}$ cells, which infers a reduced leukemia-initiation potential of AML LCS.

A phase 1 study of glasdegib monotherapy in 47 patients with myeloid malignancies including 28 with AML studied doses of glasdegib ranging from 5 to 600 mg daily.[18] Of evaluable patients, 60% experienced a treatment-related adverse event (three of which were grade 4), which included dysgeusia (28%), anorexia (19%), and alopecia (15%). Hematologic grade 3 events included lymphopenia (n=16), anemia (n=10), thrombocytopenia (n=8), and neutropenia (n=8); grade 4 hematologic adverse events included thrombocytopenia (n=33), neutropenia (n=26), leukopenia (n=15), lymphopenia (n=6), and anemia (n=4). Other grade 3 laboratory adverse events included elevations in aminotransferases or bilirubin, hypokalemia, hyponatremia, hyperglycemia, hypocalcemia and hypophosphatemia, but these events occurred in only 4 patients or less. Increases in corrected QT interval (QTc) to greater than 500 milliseconds (msec) occurred in 5 patients receiving the glasdegib 600 mg daily dose. A dose-dependent increase in QTc was noted with increasing doses of glasdegib, but no ECG changes were found to be clinically-significant or symptomatic. This phase 1b study established a maximum tolerated dose (MTD)

of 400 mg daily and a phase 2 dose of 200 mg daily or lower was recommended. Clinical activity was suggested in 49% of patients.[18]

Glasdegib is now FDA approved in combination with low-dose cytarabine for the treatment of newly-diagnosed AML in adult patients aged 75 years or greater or who have comorbidities that preclude the use of intensive induction therapy. Of note, glasdegib has not been studied in patients with severe renal or moderate-to-severe hepatic impairment.

4.2.5. Decitabine in Poor-risk Acute Myeloid Leukemia

An initial phase 2 study of the DNMTi decitabine 20 mg/m^2 on a 5-day schedule in patients aged 60 years and older (median age 74) reported a 25% CR/CRi in all patients with a 20% CR/CRi rate in the PrAML subset. All patients who achieved CR/CRi had a median relapse-free survival (RFS) of 16.3 months and a median OS of 14 months.[19] A subsequent phase II trial of decitabine 20 mg/m^2 given on a 10-day schedule in a comparable population induced a CR of 47%. Interestingly, half of these study patients had PrAML; a CR rate of nearly 50% was noted in this subset. A recent study by Welch, et al claimed overall response rates (ORR, defined as CR/CRi plus morphologic remission) of 67% in PrAML using the 10-day schedule, with most strikingly a 100% ORR in TP53-mutated AML in addition to robust mutation clearance and survival rates that seemed to remit to those observed in intermediate-risk AML populations. However, a recent retrospective review of TP53-mutated patients treated at MD Anderson included 13 patients treated with DAC10, 5 of whom achieved CR or CRp.[24] In addition, a small phase 2 study of DAC5 and DAC10 in AML patients (43% and 35% of whom with therapy-related or secondary AML and TP53-mutated disease, respectively) aged 60 years or older noted similar response rates and survival between the two dosing schedules including when stratified by TP53 status.[25] However, the largest randomized trial testing decitabine (the randomized DACO-16 trial) in older unfit adults showed a CR rate of 20%.[22]

4.2.6. Rationale for the Combination of Glasdegib with Decitabine in Poor-risk Acute Myeloid Leukemia

The use of targeted therapy in AML is made difficult by the heterogeneous nature of the disease with respect to the multitude of molecular and chromosomal abnormalities which initiate leukemogenesis. However, targeting and disrupting the Hh-pathway, the primary mechanism by which diseased and often chemoresistant LSC maintain their self-renewal and leukemia-initiating potential offers the potential of more robust leukemic cell kill and clinical outcomes of standard AML therapies, which to date have yielded unacceptable results for the PrAML population.

Glasdegib has been previously combined with decitabine in only very few AML patients. A recent, three-arm phase 1b study included an arm in which patients aged 65 years or older with newly-diagnosed AML (5 patients [71%]) or high-risk myelodysplastic syndrome and no prior DNMTi exposure received glasdegib 100 or 200 mg daily in combination with decitabine 20 mg/m^2 on a 5-day schedule; two patients (29%) were characterized by poor-risk cytogenetics. Two patients (29%) were characterized by poor-risk cytogenetics and three patients (43%) were treated at the 200 mg daily dose. The maximum tolerated dose (MTD) was not reached, no dose-limiting toxicities were observed, and the most common treatment-related effects (not surprisingly given the role of the Hh pathway in normal hematopoiesis) were hematologic toxicities: neutropenia (57%), thrombocytopenia (43%), anemia (43%). Of the AML patient subset, 40% achieved CR/CRi with a median of 3 cycles administered, and median duration of response of 2.6 months. Given the absence of a MTD, its well-tolerated nature and convincing efficacy signal, glasdegib 100 mg daily was selected as the randomized, phase 2 dose for use with other standard AML therapies including decitabine.

4.2.7. Glasdegib Clinical Toxicity Data in Patients with Myeloid Malignancies

4.2.7.1. Glasdegib as Monotherapy

A phase 1 dose escalation study of glasdegib monotherapy in 47 patients with myeloid malignancies including 28 (59.6%) with AML tested doses ranging from 5 mg to 600 mg oral daily. The median age of all patients was 69 years (range [R], 25-89 years) with the majority of patients being male (59.6%). Of 41 evaluable patients, only 2 patients experienced a dose-limiting toxicity with cycle 1. A maximum tolerated dose (MTD) of 400 mg daily was established with 60% of all patients experiencing a treatment-related adverse event (three of which were grade 4), which included dysgeusia (27.7%), anorexia (19.1%), and alopecia (14.9%). With regards to hematologic adverse events, grade 3 events included lymphopenia (n=16), anemia (n=10), thrombocytopenia (n=8), and neutropenia (n=8); other grade 3 laboratory adverse events included elevations in aminotransferases or bilirubin, hypokalemia, hyponatremia, hyperglycemia, hypocalcemia and hypophosphatemia, but these events occurred in only 4 patients or less. Grade 4 adverse events were most hematologic and included thrombocytopenia (n=33), neutropenia (n=26), leukopenia (n=15), lymphopenia (n=6), and anemia (n=4). Electrocardiogram (ECG) changes were also noted, specifically 3 patients (2 patients receiving glasdegib 600 mg daily and a single patient receiving glasdegib 400 mg daily) had an increased corrected QT interval (QTc) to greater than 500 milliseconds (msec) with 5 patients from the glasdegib 600 mg daily subset experiencing an increase in QTc greater than 60 msec from baseline; an increased incidence and severity of QTc change from baseline was noted in patients receiving higher doses of glasdegib, however, all ECG changes were asymptomatic and had no effect on other clinical parameters.[18]

A recommended phase 2 dose of 200 mg daily or lower was established given the observation of lower incidence of treatment-related adverse events observed at such doses. Although not a primary objective of the phase 1 study, clinical activity was suggested in 49% of all patients. Of the 28 patients with AML, one patient (3.6%) had morphologic CRi, 4 patients (14.3%) had partial remission with incomplete blood count recovery (PRi), and 4 patients (14.3%) had minor response (MR). The sum of these responses (CR + CRi + PR + PRi + SD + MR) yielded clinical benefit in 16 AML patients (57.1%). Treatment-resistant disease was reported in 7 patients (25%). The median duration of treatment of 64.5 days (R, 5- 261 days) for AML patients.[18] Based on the results of this phase 1 study, glasdegib appeared to be well tolerated with an efficacy signal noted in the AML subset of patients and advocated for further consideration of glasdegib in combination with other agents with known efficacy in hematologic disease including AML.

4.2.7.2. Glasdegib in Combination with Other Therapies

Given the favorable toxicity profile and preliminary efficacy signal noted in the first phase 1 study of glasdegib as monotherapy in hematologic malignancy, further studies evaluated glasdegib in combination with other therapies in similar populations. In a phase 2 study (NCT01546038) patients with previously-untreated AML or high-risk MDS and ineligible for intensive therapy were randomized 2:1 to receive either low-dose cytarabine (LDAC) 20 mg subcutaneously twice a day for 10 days on a 28-day cycle with oral glasdegib 100 mg daily versus glasdegib alone.[26] A total of 132 patients were enrolled (including 116 of such having a diagnosis of AML) and 88 were randomized to the LDAC plus glasdegib arm. Median treatment duration was 83 days in the combination arm. All-grade treatment-related adverse events were noted in 95.5% of patients in the combination arm with the most common being anemia (41.7%), febrile neutropenia (36.9%), nausea (35.7%), anorexia (31.0%), and fatigue (31.0%). Glasdegib-related adverse events included dysgeusia (23.8%), muscle spasms (20.2%) and alopecia (10.7%). Interestingly, grade 2-4 QTc prolongation was noted more frequently in the LDAC monotherapy arm. CR rates were higher in the combination arm in comparison to the LDAC monotherapy arm (n = 17, 15% vs. n = 1, 2.3%; p=0.0142). Based on intention to treat analysis, median OS was longer in the LDAC plus glasdegib arm in comparison to LDAC alone stratified by cytogenetic risk (8.3 months vs. 4.9 months; HR 0.511, 80% CI 0.386-0.675;

one-sided log rank p=0.0020). For the poor-risk cytogenetic group specifically, median OS for the LDAC plus glasdegib arm was 4.4 vs 2.3 months (HR 0.575, p=0.0422). When evaluating AML patients only, the median OS for the LDAC + glasdegib was 8.3 months was significantly-improved compared to 4.3 months for the LDAC monotherapy arm (HR 0.462, p=0.0004).[26]

A phase 1b/2 study evaluated the combination of glasdegib 100 mg or 200 mg daily not only with LDAC 20 mg administered subcutaneously twice daily on days 1 to 10 of each 28-day cycle (n=23), but also decitabine 20 mg/m^2 IV for the first 5 days of each 28-day cycle (n=7), or standard "7+3" induction chemotherapy (cytarabine/daunorubicin; n=22) in 52 patients with AML or higher-risk MDS.[23] The phase 1b portion of the study enrolled 23 patients onto the LDAC plus glasdegib arm with 17 (73.9%) of such receiving glasdegib 100 mg daily and the remaining patients receiving 200 mg daily. No dose-limiting toxicities were noted in this arm, but the most frequently noted treatment-related adverse events were nausea (35.3%), diarrhea (29.4%), neutropenia (29.4%), muscle spasms (23.5%), and dysgeusia (23.5%). Of the 7 patients randomized to the decitabine plus glasdegib arm, 4 received glasdegib 100 mg daily with 3 receiving glasdegib 200 mg daily. No dose-limiting toxicities were observed in this arm, and the most frequently observed treatment-related adverse events of any grade were nausea (75.0%), diarrhea (50.0%), thrombocytopenia (50.0%), and neutropenia (50.0%). Of the 22 patients receiving both 7+3 and glasdegib, 16 patients received glasdegib 100 mg daily and 6 received glasdegib 200 mg daily. The most common treatment-related adverse events were nausea (68.2%), diarrhea (50.0%), muscle spasms (45.5%), febrile neutropenia (36.4%), and dysgeusia (31.8%). Grade 3 pyrexia occurred in 2 patients in the 7+3 plus glasdegib arm.[23] The recommended phase 2 dose of glasdegib was established as 100 mg daily.[23]

In the phase 2 portion of the study, 2 patients (8.7%; 80% CI, 2.3%– 21.5%) in the LDAC plus glasdegib arm, 2 patients (28.6%; 80% CI, 7.9%–59.6%) in the decitabine plus glasdegib arm, and 12 patients (54.5%; 80% CI, 38.9%–69.5%) in the 7+3 plus glasdegib arm achieved CR/CRi. When evaluating only the AML patients in each arm, a clinically-beneficial response defined as CR/CRi, morphologic leukemia-free state, partial response (PR), or PR with incomplete blood count recovery (PRi) was noted in 10%, 60% and 60% of patients in the LDAC plus glasdegib, decitabine plus glasdegib and 7+3 plus glasdegib arms, respectively. AML patients in the decitabine plus glasdegib arm achieved were found to have a 40% CR/CRi rate. Median overall survival (OS) in the combined AML and MDS patient cohort was 4.4 months (80% CI: 2.5, 6.6) in the LDAC plus glasdegib arm, 11.5 months (80% CI: 4.5-17.4 months) in the decitabine plus glasdegib arm, and 34.7 months (80% CI: 14.5, not reached) in the 7+3 plus glasdegib arm.[23]

Another ongoing, multicenter, open-label, phase 2 study (NCT01546038) recently investigated the combination of glasdegib 100 mg daily with 7+3 (with daunorubicin 60 mg/m^2) in patients with previously-untreated AML or high-risk MDS.[27] Median age was 64 years (R, 27-75) and the majority of patients were males (60.0%) and Caucasian (84.5%). Of 69 evaluable patients, CR was reached in 46.4% (80% CI: 38.7-54.1%) including a 40% CR rate in patients aged 55 years or older (n=60; 80% CI: 31.9-48.1%). The most common treatment-related adverse events were nausea and diarrhea which each occurred in 50% or greater of patients. Consolidation therapy with 2-4 cycles of cytarabine 1 g/m^2 twice daily on days 1, 3, 5 of each cycle followed by maintenance glasdegib 100 mg daily for a maximum of 6 cycles was given to patients in CR. For 69 evaluable patients, the median OS was 14.9 months (80% CI 13.4-19.3 months). Of note, mutational status (as judged by the status of 12 myeloid related genes) had no effect on clinical response.[27] Given this favorable risk-benefit profile, a randomized phase 3 trial of glasdegib 100 mg daily in combination with 7+3 is ongoing.

4.2.8. Decitabine Clinical Toxicity Data

4.2.8.1. Decitabine Dosing Schedule

An initial phase 1 study of decitabine initially planned to treat patients with AML, acute lymphoblastic leukemia (ALL), MDS, or myeloproliferative neoplasm at 5, 10, 15, or 20 mg/m^2 IV daily on a 5-day schedule every for 2 weeks.[28] An additional two cohorts of 3 patients were treated with decitabine 15 mg/m^2 for either 15 or 20 days; a final cohort of 11 patients was ultimately treated at 15 mg/m^2 daily for 10 days as a means of confirming drug activity. Of the 48 total evaluable patients treated, 35 carried a diagnosis of AML (and a majority with relapsed/refractory disease; 67% with poor-risk cytogenetics). Cytopenias were noted in the vast majority of patients and the most commonly-observed treatment-related adverse event was febrile neutropenia (n=26, 56%). Grade 2 non-hematologic adverse events across all cohorts included bilirubin elevation (n=7, 14%), creatinine elevation (n=5, 10%), transaminase elevation (n=3, 6%), and nausea (n=2, 4%); the only grade 3-4 treatment-related adverse events were bilirubin elevation (n=4, 8%), transaminase elevation (n=4, 8%), and nausea (n=1, 2%).[28]

A phase 2 study of decitabine 20 mg/m^2 on a 5-day schedule in patients aged 60 years and older was the first to evaluate such a dosing schedule only in patients with AML.[19] The median age was 74 years (R, 61-87) with equal numbers of males and females. The majority (62%) of patients were older than 70 years. All patients on study experienced myelosuppression. A total of 26 patients (47.3%) experienced a decitabine-related serious adverse event. The most frequent grade 3-4 treatment-related adverse events were febrile neutropenia (29%), thrombocytopenia (22%), neutropenia (20%), anemia (18%), dyspnea (15%), bacteremia (13%), and pneumonia (n=6, 1%). Treatment-related adverse events caused dosing delays or reductions in 13 patients (24%) and 1 patient (2%), respectively. An adverse event led to discontinuation of treatment in 7 patients (13%) and 3 patients (6%) died as a result of an adverse events.[19]

A subsequent phase 2 trial investigated the use decitabine 20 mg/m^2, but given on a schedule extended to 10 days in 53 patients with previously-untreated AML (49% were defined as PrAML).[20] The median age was 74 years (R, 60–85) with 8 patients (15%) aged 80 years or older. The investigators also calculated the hematopoietic stem cell transplantation index to provide descriptive data on the risk of toxic death with treatment and noted that 26 patients (49%) had a comorbidity scores of 3 or greater. Febrile neutropenia was a common adverse event and occurred in 68% of patients. The most common grade 3-4 non-hematologic toxicities included infection (n=31), hypoxia (n=8), pain (n=7), febrile neutropenia (n=5), and hemorrhage/hematoma (n=5). One patients died within 30 days of starting therapy and 8 patients (15%) died during the first 2 cycles of therapy with cause of death felt to be related to documented infection, though 7 of these patients had active leukemia at time of death. Infectious complications after the achievement of CR was rare.[20] Another prospective study of 84 patients with AML or MDS treated with DAC10 reported a similar toxicity profile.[21] Untreated AML and relapsed AML comprised 47% and 31% of patients, respectively. The median age of all patients was 74 years (R, 29-88 years) and 59% were male. Similar to previous studies, the most common adverse events were related to myelosuppression, namely neutropenia and thrombocytopenia. During the first two cycles, grade 3-5 febrile neutropenia occurred in 56 patients and bleeding or transfusion reactions occurred in 8 patients. Death due to infection, acute kidney injury or cardiac arrest was noted in 6 patients, 1 patient and 1 patient, respectively.[21]

4.2.9. Rationale for the Glasdegib Dose Used in Combination with Decitabine

The MTD for glasdegib monotherapy in patients with a hematologic malignancy was previously-identified as 400 mg daily with a recommended phase 2 dose of 200 mg daily or lower. A dose of 100 mg daily is the FDA approved dose when used in combination with low-dose cytarabine and is suggested as the optimal starting dose of glasdegib when used in combination with other therapies (including DAC5) for patients with myeloid malignancies including AML. This conclusion is supported by the following data:

- In the phase 1b portion of the study conducted by Savona et al, treatment arms included the combination of glasdegib 100 mg or 200 mg daily with decitabine 20 mg/m^2 IV on a 5-day schedule and 28-day cycles (n=7), or glasdegib 100 mg or 200 mg daily with standard "7+3" induction chemotherapy (cytarabine/daunorubicin; n=22). Of the 7 patients randomized to the decitabine plus glasdegib arm, 4 received glasdegib 100 mg daily with 3 receiving glasdegib 200 mg daily. No dose-limiting toxicities were observed in this arm, and the most frequently observed treatment-related adverse events of any grade were nausea (75.0%), diarrhea (50.0%), thrombocytopenia (50.0%), and neutropenia (50.0%). In the absence of an estimated MTD for glasdegib plus DAC5 combination therapy, the recommended phase 2 dose of glasdegib was established as 100 mg daily.[23]

- Glasdegib 100 mg daily is found to have favorable and dose-proportional plasma pharmacokinetics congruent with expected plasma exposures (AUC and maximum plasma concentration). The median time to maximum concentration of glasdegib when administered at 100 mg daily in combination with DAC5 is found to range from 1.03 to 2.00 hour; in addition, exposures for glasdegib appear to be similar irrespective of co-administration with DAC5.[23]

- Glasdegib is markedly metabolized by CYP3A4 (99.8%). Co-administration with strong CYP3A4 inhibitors such as the -azole class of antifungals, which remain a mainstay of supportive care and often dedicated treatment of infectious complications of disease and therapy, influence the plasma exposures, AUC and peak plasma concentrations of glasdegib. Such advocates for the lower recommended phase 2 dose and optimal starting dose of glasdegib 100 mg daily.[29]

- In the phase 2 portion of the Savona et al study, 2 patients (28.6%; 80% CI, 7.9%–59.6%) in the decitabine plus glasdegib arm achieved CR/CRi. When evaluating only the AML patients, a clinically-beneficial response defined as CR/CRi, morphologic leukemia-free state, partial response (PR), or PR with incomplete blood count recovery (PRi) was noted in 60% of patients in the decitabine plus glasdegib arm. AML patients in the decitabine plus glasdegib arm achieved were found to have a 40% CR/CRi rate. Median overall survival (OS) in the combined AML and MDS patient cohort was 11.5 months (80% CI: 4.5-17.4 months) in the decitabine plus glasdegib arm and 34.7 months (80% CI: 14.5, not reached).[23]

These data provide strong rationale for the 100 mg daily dose of glasdegib being a safe and potentially clinically effective dose in combination with decitabine.

4.2.10. Assessment of the Drug-Drug Interaction (DDI) Potential between Glasdegib and Decitabine

Both *in vitro* and *ex vivo* data have demonstrated that glasdegib is primarily metabolized by CYP3A4.[30] The exact mode of metabolism and elimination of decitabine remains unknown in humans, but is postulated to occur via deamination by cytidine deaminase, which is extensively located in the liver, but is also present in the intestinal epithelium and granulocytes. Given the lack of related mechanisms of metabolism, the drug-drug interaction potential between glasdegib and decitabine is considered to be low.

4.2.11. Summary of Benefit-Risk Assessment

The available clinical data concerning glasdegib not only used as monotherapy but in combination with other chemotherapeutic agents including decitabine supports the conclusion of a predictable and safe toxicity profile, characterized by manageable, not unexpected and ultimately often-reversible mild to moderate toxicities. The primary toxicities observed to date are mostly related to anticipated myelosuppression with the major non-hematologic treatment-related toxicities being muscle spasms, dysgeusia, decreased appetite, and alopecia.

Prolongation of QTc intervals have been observed, though small and overwhelmingly not clinically significant or symptomatic. Dose modification recommendations for QTc changes can be found in **Table 5**. Given the established mechanism of glasdegib metabolism via CYP3A4, the concurrent use of moderate to strong CYP3A4 inhibitors (**Appendices 3 and 4**) is not recommended given the possibility of DDI and augmented effect of potential QTc prolongation. Concurrent administration of drugs known to increase the risk of Torsade de Pointes (**Appendix 5**) are similarly not recommended.

The data reported to date supports the use of Hh pathway antagonists such as glasdegib in hematologic malignancies and more recently increasing data supports its use in patients with AML. The combination of glasdegib with chemotherapeutic agents such as LDAC, decitabine and even standard 7+3 induction therapy for patients with AML has demonstrated attractive response rates as well as improvements in survival compared to historical controls. The efficacy of glasdegib in combination with low-dose cytarabine was evaluated in a multicenter, open-label, randomized study (Study BRIGHT AML 1003, NCT01546038) that included 115 patients age 55 years or older with newly-diagnosed AML who met at least one of the following criteria: a) age > 75 years, b) severe cardiac disease, c) baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, or d) baseline serum creatinine >1.3 mg/dL. Patients were randomized 2:1 to receive glasdegib at a 100 mg daily dose with low-dose cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle (N=77) or low-dose cytarabine alone (N=38) in 28-day cycles until disease progression or unacceptable toxicity. Patients were stratified by cytogenetic risk (good/intermediate or poor). Overall survival and CR were both improved with the addition of glasdegib to low-dose cytarabine compared to low-dose cytarabine alone.

Decitabine has recently been reported to induce robust responses and clinically meaningful survival improvement in PrAML patients with one study by Welch et al demonstrating a 100% response rate in TP53-mutated AML. In sum, given the increasingly-understood role of the Hh pathway as it related to leukemic stem cell survival and the impressive clinical improvements induced by decitabine in PrAML patients, the data support investigation into the efficacy of the combination of glasdegib with decitabine on both a standard of care 5-day schedule as well as the recently-promising 10-day schedule.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary objective

- To determine the response rates, complete remission (CR) and complete remission with incomplete count recovery (CRi) rates of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML

5.1.2. Secondary objectives

- To evaluate the toxicity and safety profiles of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML
- To determine the event-free survival (EFS), relapse-free survival (RFS), overall survival (OS), duration of response, bone marrow mutational clearance, and remission clonality of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML

5.1.3. Exploratory objectives

- To evaluate for specific cytogenetic and molecular markers which may predict efficacy of glasdegib/DAC5 and glasdegib/DAC10 in patients with newly-diagnosed PrAML
- To evaluate for any differences in the quantity and activity of Hh pathway-related effector proteins downstream to the effect of the SMO-antagonist glasdegib (GLI-1 and GLI-2) and if any such difference correlates with and predicts response to such

5.2. Endpoints

5.2.1. Primary endpoint

- CR/CRi rate as defined by the 2017 European LeukemiaNet (ELN) AML response criteria (**Appendix 1)**

5.2.2. Secondary endpoints

- AE
- SAE
- CR
- CRi
- CRh
- RBC transfusion independence (per the International Working Group [IWG] response criteria for MDS) for patients who are transfusion dependent
- OS
- EFS
- RFS
- Time to CR/CRi
- Duration of CR/CRi
- Bone marrow mutational clearance of frequently-mutated genes in AML (e.g. NPM1, CEBPA, DNMT3A, RUNX1, TET2, IDH1/2) via next-generation DNA sequencing
- Remission clonality

6. STUDY DESIGN

6.1. Study Overview

This multi-center, parallel-arm, randomized phase 2 study is designed to evaluate the complete remission (including complete remission with incomplete count recovery) rates of glasdegib 100 mg daily in combination with either decitabine 20 mg/m^2 IV daily on a 5-day or 10-day schedule every 28 days per local label in patients with newly-diagnosed poor-risk AML who either refuse or are ineligible for intensive therapy.

The assignment of lack of candidacy for intensive induction therapy will be determined based on each patient's comorbidity, performance status, baseline level of fitness, and any other clinical variable as deemed clinically-relevant by the Investigator. Patients will be randomized 1:1 to receive glasdegib 100 mg orally once daily and continuously either in combination with decitabine 20 mg/m^2 IV on a 10-day schedule (DAC10) or decitabine 20 mg/m^2 IV on a 5-day schedule (DAC5).

The primary objective of this randomized phase 2 study is to demonstrate that the CR/CRi rate of the combination of glasdegib treatment in each patient population (DAC5 and DAC10) outperforms the historical CR/CRi rate for DAC5 alone using decision criteria allowing early stopping for futility.

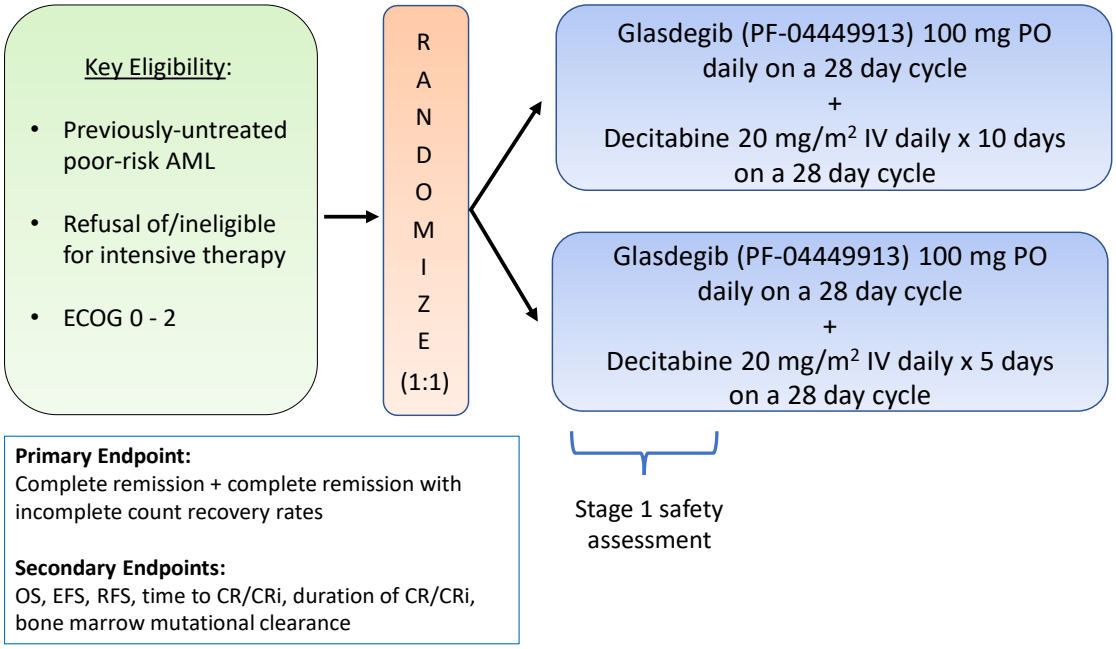
Using the historical CR rate of 17% for decitabine 20 mg/m^2 on the standard of care five-day schedule (based on the largest randomized study of decitabine in older patients with AML [DACO-16]), a minimum acceptable CR rate of 25% (given the addition of glasdegib and additional potential toxicity) and ultimately a predicted minimum CR rate of 47% (the alternative hypothesis) for patients accrued to either arm of the proposed randomized phase 2 study, a minimum of 23 patients per arm will be accrued to test for a statistically-significant difference with an 80% power and a 90% confidence interval (which is equivalent to a type 1 error rate, alpha one-sided of 0.05).

The separate, Simon two-stage minimax decision rule is to stop enrollment in either arm if 2 or fewer patients in that arm achieve CR of the first 10 patients required to be accrued during the stage 1 portion of the study. After the first 10 patients are enrolled and futility analysis of each arm allowed continued enrollment, the second stage of the study will be conducted.

Additionally, analysis of safety data will be performed to stop enrollment in an arm when there is at least 70% probability that the unacceptable toxicity rate in that arm is above 25%. The safety stopping criteria will be applied starting when at least 10 patients have completed 24 weeks (stage 1) or experienced a DLT, and applied continuously thereafter.

All AEs will be classified according to CTCAE version 5.0.

Figure 1. Schematic of Study Design



6.2. Study Treatments

Glasdegib will be administered at the starting dose of 100 mg orally once daily and continuously in combination with either DAC5 (decitabine 20 mg/m^2 IV on a 5-day schedule) or DAC10 (decitabine 20 mg/m^2 IV on a 10-day schedule) as per randomization. Treatment will be administered in 28-day cycles.

- All patients will be administered glasdegib 100mg orally once daily and continuously

- Decitabine will be administered per local label and will be administered by IV infusion at a dose of 20 mg/m^2/day for either 5 days or 10 days as determined by randomization. Each cycle will be every 28 days.

Induction cycles are cycles 1-6 (or until CR or CRi is achieved, if earlier). Consolidation cycles are cycles 7 (or earlier if CR or CRi is achieved)-24. Patients who have achieved CR or CRi will remain on study beyond cycle 6 for up to 24 cycles.

Since responses to decitabine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles in patients with a response of SD or greater, or until progressive disease PD, death, unacceptable toxicity, or patient refusal, whichever occurs first. If documentation of disease progression occurs beyond cycle 1, the patient should be withdrawn from study treatment. Treatment with the study drug combination should be continued beyond cycle 6, for cycles 7-24 of treatment, only for patients who achieve CR or CRi or until objective disease progression or relapse, unacceptable toxicity, patient refusal or death, whichever occurs first. Patients who do not achieve at least a CRi after 6 cycles should be taken off study treatment.

If glasdegib is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with decitabine may be continued if the patient has experienced at least a CRi to study therapy. In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase.

When study treatment with both drugs (glasdegib and decitabine) is permanently discontinued, patients will enter into the follow-up phase. Patients receiving at least one dose of study treatment will be followed up for survival for up to 2 years from the first visit of the last patient enrolled or until death, lost to follow-up, or consent withdrawal.

6.3. Study Assessments Summary

Patients will be followed for efficacy throughout the study by means of bone marrow aspirates. Following study entry, bone marrow biopsies will only be required if adequate bone marrow aspirates are not obtained. A CR or PR response needs to be confirmed at least 4 weeks following the BM evaluation by assessing the stability of improved counts on PB, an additional bone marrow confirmatory specimen is not required.

Blood counts will be monitored and transfusional support (red blood cells and platelets) will also be recorded. Timely and complete (bone marrow AND peripheral blood counts) disease assessments at screening and during the study essential. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and may weaken the conclusions of the study.

Safety assessments (laboratory, instrumental and clinical) will be performed regularly during the active treatment period.

7. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol

is suitable for a particular patient. These criteria must also be met prior to dosing on Cycle 1 Day 1. No exceptions will be granted.

Prior to obtaining signed consent from a patient, the site principal investigator or coordinator must email the project manager to inquire about study space availability. If a slot is available, the potential study participant will complete the consent process. The informed consent process must be completed before any study screening procedures may begin. The site principal investigator or other approved investigator must document that the patient has met all inclusion criteria and has none of the exclusion criteria. Following completion of eligibility testing, eligibility documents will be sent to the YCCI project manager.

7.1. Inclusion Criteria

Patient eligibility must be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study. Patients must meet all the following inclusion criteria to be eligible for enrollment into the study:

1. Patients must be ≥ 18 years of age

2. Patients must have a morphologically-confirmed diagnosis of AML according to WHO 2016 classification (**Appendix 9**) with poor-risk disease as defined by the cytogenetic or molecular abnormalities in **Appendix 8** (excluding FLT3-mutated AML).

3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2. See **Appendix 7**

4. Adequate Renal Function:

a. Calculated creatinine clearance (determined by MDRD) ≥50mL/min/1.73m^2, or serum creatinine <1.5x upper limit of normal (ULN);

5. Adequate Liver Function:

a. Total serum bilirubin ≤ 2.0 x ULN (unless the bilirubin is principally unconjugated and there is strong suspicion of sub-clinical hemolysis or the patient has documented Gilbert's disease);

b. Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤ 3.0 x ULN;

c. Alkaline phosphatase ≤ 3.0 x ULN.

6. Serum or urine pregnancy test (for female patients of childbearing potential) with a minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin (HCG) negative at screening.

7. Males and female patients both of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for 180 days after the last dose of decitabine and the last dose of glasdegib, whichever occurs later.

8. Female patients who are not of childbearing potential (i.e. meet at least 1 of the following criteria):

   a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

b. Have medically confirmed ovarian failure;

c. Have achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

7.2. Exclusion Criteria

Patients with any of the following may not be included in the study:

1. Patients who are candidates for and willing to receive intensive induction chemotherapy.
2.
3. Prior use of a hypomethylating agent.

4. Prior use of cytotoxic chemotherapy for any myeloid malignancy (prior immunosuppressive therapy is permitted provided that treatment is stopped within 8 weeks from study entry; hydroxyurea is allowed through the end of cycle 1 on study).

5. Previous hematopoietic stem cell transplant.

6. Prior treatment with a licensed or experimental smoothened inhibitor (SMOi) and/or hypomethylating agent (HMA).

7. Participation in a clinical study involving an investigational drug(s) (Phases 1-4) within 4 weeks prior to study entry or within 5 half-lives of the investigational agent, whichever is greater.

8. Major surgery or radiation within 12 weeks prior to study entry.

9. Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.

10. Treatment with hematopoietic growth factors including: erythropoietin, granulocyte colony stimulating factor (G-CSF), and granulocyte macrophage colony stimulating factor (GM-CSF), or thrombopoietin receptor agonists within 3 weeks prior to study entry.

11. Any ongoing medical condition requiring chronic use of moderate to high dose steroids (defined as ≥10 mg/day of prednisone or equipotent dose of another corticosteroid).

12. Any anti-cancer treatment within 2 weeks prior to study entry (including hydroxyurea as above).

13. Current use or anticipated requirement for drugs that are known moderate to strong CYP3A4 inducers (**Appendix 2**).

14. Presence of concurrent active malignancy requiring active systemic therapy

15. Patients with known active, uncontrolled bacterial, fungal or viral infection, including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness.

16. Known uncontrolled central nervous system (CNS) involvement.

17. Poorly-controlled active medical conditions that as per investigator judgement would interfere with the conduct of the study.

18. Active cardiac dysrhythmias of NCI CTCAE Grade ≥2 (e.g. atrial fibrillation) or QTcF interval >470 msec.

19. Pregnant or breastfeeding female patients.

7.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive decitabine, a compound that in preclinical studies in mice and rats has been shown to be teratogenic, fetotoxic, and embryotoxic, though no high-level studies of decitabine use in pregnant women exist or are published. Patients will also receive glasdegib, a compound which can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Glasdegib is embryotoxic, fetotoxic, and teratogenic in animals. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to pregnancy testing in females of reproductive potential prior to initiation of glasdegib treatment and use at least 1 highly effective form of contraception throughout the study and for at least 180 days after the last dose of investigational product. The investigator must advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with glasdegib and for at least 180 days after the last dose to avoid potential drug exposure.

The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected at least 1 appropriate method of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the **Table 1 Schedule of Activities**, the investigator or designee will inform the patient of the need to use at least 1 highly effective method of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner(s).

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e. perfect use) and include the methods described in **Table 2**.

Table 2. Methods of Birth Control

Highly effective low user dependency	Highly effective high user dependency

• Progestogen only contraceptive implant; • Intrauterine hormone releasing system (IUS); • Intrauterine device (IUD); • Bilateral tubal occlusion.	Combined hormonal contraception (estrogen and progestogen) • Oral; • Intravaginal; • Transdermal; •
Vasectomized partner: A vasectomized partner is a highly effective form of contraception provided they are the sole male partner of the women of child bearing potential and the absence of sperm has been confirmed. If not an additional highly effective method of contraception should be used.	Progestogen only hormonal contraception • Oral; • Injectable.

7.4. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by instructing patients to minimize exposure to light including high intensity ultraviolet b (UVb) sources such as tanning beds, tanning booths and sunlamps. Patients should be advised to apply sunscreen/sunblock daily.

8. STUDY TREATMENTS

8.1. Allocation to Treatment

Allocation of patients to treatment groups will proceed through the use of the OnCore System. The randomization and patient registration process is outlined in the eCRF guidelines.

8.2. Patient Compliance

For glasdegib, all patients will maintain patient dosing diaries throughout the study which will record the date of administration and all regular, missed, changed, or delayed doses.

Patients are required to return all bottles, unused study drug and the patient dosing diary, at each cycle and at End of Treatment visit for compliance assessment and drug accountability. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded.

8.3. Formulation and Packaging

8.3.1. Glasdegib

Glasdegib will be supplied by Pfizer Worldwide Research and Development as 25 mg and 100 mg tablets for oral administration. Supplies will be labeled according to local regulatory requirements.

Glasdegib will be packaged in high-density polyethylene (HDPE) bottles and should be handled with care. Each bottle will contain enough medication for a 28-day cycle of daily dosing, plus an additional amount to cover the time between site visits. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that patients clearly understand the directions for self-medication.

8.3.2. Decitabine

Decitabine will be prepared and administered according to local institutional practice. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

8.4. Administration

8.4.1. General Guidelines

Both study drugs are administered in 28-day cycles. Cycle duration maybe extended beyond 28 days to allow resolution of toxicities related to study treatments. All patients will receive glasdegib 100 mg oral daily. Patients will subsequently be randomized 1:1 to receive decitabine either 20 mg/m^2 IV on a 10-day schedule (DAC10) or 20 mg/m^2 IV on a 5-day schedule (DAC5).

Glasdegib will be self-administered by the patient at home. Glasdegib will be administered orally with approximately 8 ounces (240mL) of water and should be taken in the morning, at the same time each day. Tablets must not be crushed or cut; they must be swallowed whole, not manipulated or chewed prior to swallowing. Patients should be instructed to self-administer their medication in the morning at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient forgets to take their dose at the regularly scheduled time, and if less than 12 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible; two doses of glasdegib should not be taken within 12 hours. If more than 12 hours have passed since the scheduled dosing time, the dose should be skipped and the patient should continue on their normal dosing schedule. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume the next dose at the regular time. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of glasdegib. The patient will be reminded NOT to take their dose at home on clinic days but to bring their bottle(s) and patient dosing diary into clinic so that glasdegib may be administered there.

Patients requiring glasdegib dose reduction(s) will be administered multiples of 25mg tablets and should continue taking the glasdegib at the same time each morning at the dose prescribed by the Investigator (i.e. 75 mg daily and 50 mg daily in the form of three or two 25 mg tablets, respectively). Dose modifications are discussed in **Tables 4, 5&6.**

8.4.2. Treatment Duration

Since responses to decitabine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles in patients with a response of SD or greater, or until PD, death, unacceptable toxicity, or patient refusal whichever occurs first. If documentation of disease progression occurs beyond cycle 1, the patient should be taken off study treatment.

Treatment with the study drug combination should be continued beyond 6 cycles of treatment only for patients who achieve CR or CRi, until objective disease progression or relapse, death, unacceptable toxicity, or patient refusal whichever occurs first. Patients who do not achieve at least a CRi after 6 cycles should be taken off study treatment.

If glasdegib is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with decitabine may be continued if the patient has experienced at least a CRi to study therapy.

In cases of a significant toxicity that does not resolve with a dose interruption or a dose reduction as outlined below or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase of the study.

When study treatment with both drugs (glasdegib and decitabine) is permanently discontinued, patients will enter into the follow-up phase.

8.4.3. Dose Modifications

Every effort should be made to administer the study drug treatment according to the planned dose and schedule.

In the event of significant toxicity, dosing must be interrupted, delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients must be instructed to notify investigators at the first occurrence of any adverse symptom/s.

Dose modifications may occur in three ways:

- **Within a cycle**: Dosing interruption until adequate recovery followed by dose reduction (if required) of glasdegib during a given treatment cycle.

- **Between cycles:** The next treatment cycle may be delayed if toxicity from the preceding cycle persists.

- **In the next cycle**: Dose reduction may be required based on toxicities experienced in the previous cycle.

A cycle is determined by the decitabine administration schedule. A cycle is 28 days, but will be extended if there are dose delays or modifications for decitabine. Decitabine administration should not be interrupted if glasdegib dosing is interrupted for toxicity.

If start of glasdegib administration in the next cycle is delayed due to toxicities potentially attributable to glasdegib, decitabine administration should not be delayed, and the day when decitabine administration occurs will be counted as Day 1 of the next cycle for both study drugs.

8.4.3.1. Decitabine

Following the first cycle of decitabine, if any of the following non-hematologic toxicities are present, decitabine treatment should not be restarted until the toxicity is resolved:

- serum creatinine ≥2 mg/dL;
- ALT, SGPT ≥2 times ULN;
- total bilirubin ≥2 times ULN

- active or uncontrolled infection

Treatment should be permanently discontinued if any of the following hematologic toxicities occur in patients who do not have active disease in the absence of bone marrow hypocellularity, and the toxicity is possibly, probably or definitely related to study drug as determined by the investigator,

- Grade 4 neutropenia that does not resolve to ≤Grade 3 within 42 days of the start of each cycle
- Grade 4 thrombocytopenia that does not resolve to ≤Grade 3 within 42 days of the start of each cycle

8.4.3.2. Glasdegib

Glasdegib does not need to be delayed or dose reduced for hematologic toxicity deemed unrelated or unlikely related to study drug by the Investigator. However, as with decitabine, treatment should be permanently discontinued for the following hematologic toxicities in patients who do not have active disease in the absence of bone marrow hypocellularity and the toxicity is possibly, probably, or definitely related to study drug as determined by the investigator:

- Grade 4 neutropenia that does not resolve to ≤Grade 3 within 42 days of the start of each cycle
- Grade 4 thrombocytopenia that does not resolve to ≤Grade 3 within 42 days of the start of each cycle

Patients experiencing Grade 3 non-hematological toxicities potentially attributable to glasdegib should have their glasdegib treatment interrupted regardless of when it occurs in the cycle until the toxicity resolves or returns to baseline or remits to Grade 1 or less (as described in **Table 4**). If these parameters have not been met following >28 consecutive days of dose interruption, glasdegib should be permanently discontinued. Glasdegib should be permanently discontinued in patients experiencing a Grade 4 non-hematologic toxicity. If glasdegib treatment is permanently discontinued, patients may continue single agent treatment with decitabine, if the patient has experienced at least a CRi to study therapy.

Appropriate follow-up assessments should be implemented until adequate recovery (toxicity resolves or returns to baseline) occurs. Depending on when the adverse event resolved, treatment interruption may lead to the patient missing all subsequent planned doses of glasdegib within the cycle. If the AE leading to treatment interruption recovers within the same cycle, re-commencement of dosing in that cycle is allowed. The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined in **Table 5**, unless specifically agreed otherwise following discussion between the Investigator and the Sponsor. If a dose reduction for glasdegib is applied in the same cycle, the patient must return to the clinic to receive a new supply of drug. Glasdegib doses omitted for toxicity will not be replaced within that cycle (e.g. cycles will not be prolonged beyond the 28 days in order to make up for any missed glasdegib doses during that cycle).

Glasdegib may be interrupted or permanently discontinued for any reason as per Good Clinical Practice. In the event of glasdegib treatment interruption for reasons other than treatment-related toxicity (e.g. elective surgery) for a duration >28 days, the details of treatment resumption will be determined in consultation with the Sponsor PI.

Dose reduction of glasdegib by 1 or, if necessary, 2 dose levels (**Table 3**) will be allowed depending on the type and severity of toxicity encountered. All dose modifications/adjustments must be clearly documented in the patient's notes and electronic case report form (eCRF).

Once the glasdegib dose has been reduced, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed. Deviations from any of the dose modifications must be discussed and agreed with the Sponsor PI.

Table 3. Available Dose Levels

Glasdegib (mg daily)
100
75
50

Dose modifications for treatment-related non-hematologic toxicities (excluding QTc prolongation, muscle spasms, and myalgia) are outlined in **Table 4**.

Table 4. Dose Modifications for Non-Hematologic Toxicities Considered Possibly, Probably or Definitely Related to Study Therapy)

Toxicity (NCI CTCAE version 5.0)	Glasdegib
Grade 4 toxicity (any)	Permanently discontinue
Grade 3 toxicity (Nausea, vomiting, and/or diarrhea must persist for 7 days at Grade 3 (despite maximal appropriate medical therapy) or necessitate / prolong hospitalization or TPN or NGT feeding to require dose modification)	Hold glasdegib until toxicity has recovered to baseline or ≤ Grade 1. **First episode:** Decrease by 1 dose level **Second episode:** Permanently discontinue
Potential drug induced liver injury/Hy's Law (see below this table)	Investigate alternative causes of liver injury and interrupt glasdegib dosing until drug injury remits to grade 1 or less. If an alternative cause is found, restarting of glasdegib at the same dose may be considered. Discussion with the Sponsor PI is required.
Confirmed drug induced liver injury/Hy's Law (see below this table)	Permanently discontinue glasdegib.

Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value 2X ULN with no evidence of hemolysis and an alkaline phosphatase value 2X ULN or not available.

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3X ULN, or ≥8X ULN (whichever is smaller).

    Concurrent with

    - For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1X ULN or if the value reaches ≥ 3X ULN (whichever is smaller).

Patients should be closely monitored for potential cardiovascular symptoms. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AE monitoring at the times specified in the calendar of events or more often if clinically indicated. In case of QTc prolongation, concomitant conditions such as electrolyte imbalances, hypoxia, or use of medications affecting the QT interval should be ruled out and/or corrected. In case of clinically significant toxicities, glasdegib administration should be interrupted and the dose reduced as indicated in **Table 4**.

Concomitant administration of glasdegib with moderate to strong CYP3A4 inhibitors (**Appendices 3 and 4**) and drugs with known risk of Torsade de Pointes (TdP) (**Appendix 5**) is not recommended due to the potential for drug-drug interaction to prolong the QTc interval. All protocol specified QTcF prolongation-related exclusion criteria must be followed. Investigators must be aware of the QTcF-prolonging potential of all medications that patients on study are taking and should take appropriate action when clinically indicated. Given the potential for QTcF prolongation, the measurement and immediate correction of electrolyte abnormalities such as potassium and magnesium, and of other reversible causes of QTcF prolongation such as hypoxia, are especially important. In the event that the QTcF interval is prolonged beyond 480 msec (CTCAE v.5.0 ≥Grade 2), **Table 5** must be referenced and actioned. Additional ECG and cardiac consultation should be obtained if clinically indicated.

Table 5. Glasdegib Dose Modifications for mean QTcF (mQTcF) Prolongation

CTCAE v 5.0	Grade 1	Grade 2	Grade 3	Grade 4
Electrocardiogram QT corrected (QTc) interval prolonged*	450-480 msec	481-500 msec	≥501 msec at least two separate ECGs	QTc ≥ 501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or

				signs/symptoms of serious arrhythmia

*The severity of QTc prolongation assessment is to be done by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart by using the Fridericia correction method (mQTcF).

Category	Action	Grade 1	Grade 2	Grade 3	Grade 4
ECG monitoring	Monitor ECGs at least weekly for 2 weeks following resolution of mQTcF prolongation to ≤ 480 msec		X	X	X
Initial glasdegib action	Discontinue and do not re-challenge				X
	Interrupt treatment			X	
	Continue treatment at same dose	X	X		
General management	Assess electrolyte levels and supplement as clinically indicated		X	X	X
	Review and adjust concomitant medications with known QTc interval-prolonging effects		X	X	X
Resume glasdegib dosing	at a reduced dose of 50 mg once daily when QTc interval returns to within 30 ms of baseline or less than or equal to 480 ms.			X	
	Consider re-escalating the dose of glasdegib to 100 mg daily if an alternative etiology for the QTc prolongation can be identified.			X	
Discontinue glasdegib permanently	If **two** prior glasdegib dose interruptions related to QTcF prolongation have occurred			X	

Dose modifications for glasdegib in case of drug class related AEs are outlined in **Table 6**.

Table 6. Dose Modifications for Glasdegib in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	Grade 1	Grade 2	Grade 3

Glasdegib	Continue at same dose level. Administer oral rehydration solutions containing electrolytes.[a] Consider other appropriate interventions (e.g. anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferrin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine.	Continue at same dose level. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (e.g. anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferrin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine. If event persists for 7 days, hold dose until resolution to Grade ≤1. Upon resolution, restart at prior dose, or for prolonged muscle spasms, consider reducing dose by one dose level.	Hold dose. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (e.g. anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferrin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine. Upon resolution to Grade ≤1, restart study treatment at next lower dose level. If the event does not resolve within 3 weeks to Grade ≤1, glasdegib should be permanently discontinued.
Abbreviations: CK creatinine kinase; Vit vitamin; Na sodium; K potassium; Mg magnesium; Ca calcium; P phosphorous.			

a. Electrolyte replacement drinks should include Na, K, Mg, Ca and P. Consideration should be given to ensuring adequate hydration prior to bedtime, and whenever fluid intake is decreased for a prolonged duration.

b. Labs may be drawn as unscheduled assessments between protocol visits. In the event of alopecia or dysgeusia, investigator discretion should be applied with respect to dose interruption and/or dose reduction of glasdegib as preliminary analysis of available clinical data suggests that these events are not dose dependent.

8.5. Drug Storage

The investigator, or an approved representative, e.g. pharmacist will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable site and regulatory requirements.

Storage conditions stated in the SRSD (IB for glasdegib and PI for decitabine) will be superseded by the storage conditions stated in the labeling.

Glasdegib should be stored as described on the drug label. Note that the storage conditions in any study documentation will be superseded by the storage conditions stated on the product label. Patients should be instructed to keep their medication in its original container. Returned medication should be stored at the clinical site separately from medication that needs to be dispensed.

Decitabine will be stored according to the labeled storage conditions.

Investigators and site staff are reminded to check temperatures daily (i.e., manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the Project Manager.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Project Manager. Once a deviation is identified, the investigational product must be quarantined and not used until the Project Manager provides documentation of permission to use the investigational product.

8.6. Drug Accountability

The Investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. At each dispensing visit (Cycle 2 Day 1, Cycle 3 Day 1, etc. or when there is a dose reduction), all unused or partially used bottles must be returned by patients to the Investigator. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded. The Sponsor PI or designee will provide guidance on the destruction of unused investigational product (e.g. at the site). If destruction is authorized to take place at the study site, the local investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by drug manufacturer or designee and all destruction must be adequately documented.

8.7. Concomitant Treatment(s)

All concomitant medications and treatments must be recorded in the eCRF. Any prior treatment received within 28 days prior to study entry (including hematopoietic growth factor receptor agonists: erythropoietin, granulocyte colony stimulating factor (G-CSF), romiplostim, eltrombopag) will be recorded in the eCRF.

In addition, any transfusion (red blood cells or platelets) within 8 weeks prior to screening should be recorded in the eCRF.

All prior immunosuppressive therapy (e.g., cyclosporine) used to treat MDS, or all prior cytoreductive therapy (e.g. hydroxyurea) used to treat AML or other myeloid malignancy, will be recorded regardless of when they were received by the patient. Information collected will include dates of use, best treatment response and the reasons for stopping therapy.

Every concomitant treatment, blood products, growth factors, as well as interventions, required by the patients during the active study treatment (and up to 28 days following last study drug administration or until initiation of another anti-cancer treatment) and the reason for its administration must be recorded on the eCRF.

All concomitant medications the patient is currently receiving must be reviewed by the Sponsor prior to enrollment in the study.

8.7.1. Restricted or Prohibited Concomitant Medications

The following medications are not allowed during the active study treatment period:

- Investigational agents;

- CYP3A4 Inducers: A drug-drug interaction study in health patients with the strong CYP3A4 inducer, rifampin, resulted in a 70% decrease in plasma exposures (AUC_{inf}) and a 35% decrease in peak plasma concentration (C_{max}) of a single 100 mg oral dose of glasdegib. Therefore, co-administration of glasdegib and moderate to strong CYP3A4 inducers is not permitted. A comprehensive list of moderate to strong CYP3A4 inducers is provided in **Appendix 2**. However, if you are uncertain whether a concomitant medication is contraindicated, you should contact the Project Manger study team.

The following medications have use restrictions during the active study treatment period:

- CYP3A4 Inhibitors: In vitro studies with human liver microsomes and recombinant CYP enzymes indicated that glasdegib metabolism is primarily mediated by the drug-metabolizing enzyme CYP3A4. Clinically, there is likelihood that glasdegib plasma concentrations may be increased in the presence of co-administered inhibitors of the CYP3A4 enzyme. In a healthy volunteer study, ketoconazole, a potent CYP3A4 inhibitor, produced a 2.4-fold increase in plasma exposure and a 1.4-fold increase in peak plasma concentration of glasdegib. Therefore, a potential exists for drug-drug interactions with CYP3A4 inhibitors, and co-administration of glasdegib in combination with moderate to strong CYP3A4 inhibitors is not recommended. Selection of concomitant medication with no or minimal CYP3A4/5inhibition potential is recommended. Moderate to strong CYP3A4 inhibitors (**Appendices 3 and 4**) should be used with caution and only if considered medically necessary. If a moderate to strong CYP3A4 inhibitor is to be initiated in addition to glasdegib, the guidance provided below**.** and dose modifications for QT prolongation per **Table 5** must be followed.

- Drugs with a known risk of Torsade de pointes (TdP): Glasdegib has been shown to have the potential to prolong the QTc interval in pre-clinical studies and at doses >200 mg. While the glasdegib dose being evaluated in this study is 100 mg, the concomitant administration of glasdegib and drugs with a known risk of Torsade de pointes should be avoided whenever possible. A list of such drugs is provided in **Appendix 5**. Use of these drugs is not recommended unless there are no alternatives. If a drug listed in **Appendix 5** is to be initiated in addition to glasdegib, the guidance provided in the dose modifications for QT prolongation per **Table 5** must be followed.

- QT prolonging medications (without a risk of TdP) should be avoided whenever possible.

- Concomitant administration of multiple moderate to strong CYP3A4 inhibitors, TdP-associated drugs, and/or QT prolonging medications (without a risk of TdP) is not recommended and must be discussed with the Sponsor PIr.

8.7.2. Permitted Concomitant Medications

8.7.2.1. Best Supportive Therapy

Best Supportive Therapy (BST) administration is permitted according to Institutional guidelines for all patients on study. BST will be provided by the site and may vary depending on the patient's signs and symptoms, site current practice. It includes medications and supportive measures that may palliate disease-related symptoms, improve quality of life and treat bacterial, fungal or viral infections. BST may include:

- Blood transfusions;
- Platelet transfusions;
- Antibiotics;
- Anti-fungal agents;
- Anti-viral agents.

8.7.2.2. Hematopoietic Growth Factors

Hematopoietic growth factors (e.g. G-CSF, GM-CSF) may be used according to local practice and guidelines during active study treatment. They cannot be used for 3 weeks prior to study inclusion.

8.7.2.3. Anti-Emetic and Anti-Diarrheal Therapy

Patients should be pre-medicated with anti-emetics for nausea and vomiting before each dose of decitabine in all cycles according to local practice and guidelines. Primary prophylaxis of diarrhea is permitted at the Investigator's discretion. The choice of the prophylactic drug is up to the investigator assuming the drug is not contraindicated.

8.7.3. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and glasdegib required to minimize the risk of impaired wound healing

and bleeding has not been determined. Stopping glasdegib is recommended at least 7 days prior to surgery. Post-operatively, the decision to reinitiate glasdegib treatment is up to the local investigator with Sponsor PI approval and should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

9. STUDY PROCEDURES

9.1. Screening

Screening can be accomplished over one or multiple visits over a 4-week period (28 days), unless specifically noted otherwise. Protocol specific tests or procedures not considered standard of care can only be done after the patient has signed the Informed Consent document. The Informed Consent document may be signed up to 60 days prior to study entry.

See the **Schedule of Activities** for a complete list of assessments and procedures to be collected during the screening visit.

9.2. Study Period

See the **Schedule of Activities** for a detailed list of the assessments and procedures to be collected.

All assessments on Cycle 1 Day 1 should be collected and reviewed pre-dose, unless documented otherwise.

9.3. End of Treatment Visit

The End of Treatment Visit should be scheduled as soon as possible once a patient has been withdrawn from study drug. For a detailed list of assessments and procedures to be completed please refer to the **Schedule of Activities**.

9.4. Long Term Follow-up

The first follow up contact should occur at least 28 days, and no more than 35 days after the last dose of study drug to capture any potential adverse events and to confirm appropriate contraception usage. Follow-up may be made via telephone call, but must be performed every 3 months for a total duration of two years, unless a safety event has occurred at which point this event must be followed until resolution. For a detailed list of assessments and procedures to be completed please refer to the **Schedule of Activities**.

In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase of the study.

Patients who permanently discontinue both study drugs (decitabine and glasdegib) for any reason (except death, or withdrawal of patient consent) will enter into the follow-up phase.

Patients continuing to experience toxicity following discontinuation of treatment will continue to be followed minimally every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

Patients will be contacted every 3 months to confirm survival status, and to collect information on any new anti-cancer therapy initiated. Telephone calls are acceptable and patients will be followed up to the time of death or consent withdrawal.

Patients receiving at least one dose of study treatment will be followed for survival for up to 2 years from the first visit of the last patient enrolled or until death, lost to follow-up, or consent withdrawal.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the local investigator or Sponsor PI for safety or behavioral reasons or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for permanent discontinuation of study drug combination treatment may include:

- Objective disease progression or relapse;
- Global deterioration of health status;
- Unacceptable toxicity;
- Need for cycle start delay >28 days due to persistent drug combination related toxicity;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by the patient);
- Withdrawal of patient consent (cessation of follow-up);
- Pregnancy;
- Start of another anti-cancer treatment;
- Study terminated by Sponsor- PI or drug manufacturer;
- Death.

Reasons for withdrawal from study may include:

- Study terminated by Sponsor - PI or drug manufacturer;;
- Lost to follow-up;
- Withdrawal of patient consent for any further contact;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor- PI may retain and continue to use any data collected before such withdrawal of consent.

10. **ASSESSMENTS**

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that they have taken to ensure that normal processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner

10.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy -once at the start of screening and once at the C1D1, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the C1D1 visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of study drug combination and enter into the Follow-up phase. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethic Committees (ECs) or if required by local regulations.

10.2. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 5.0) timing, seriousness, and relatedness. Additional information regarding AE and Serious AE (SAE) reporting is provided below.

10.3. Laboratory Safety Assessments

Hematology, blood chemistry, coagulation and urinalysis assessments will be drawn at the time points described in the **Schedule of Activities** and will be analyzed by the site/Investigator at local laboratories. Laboratory certifications and normal ranges with units must be provided to the Project Manager.

If a complete blood count (CBC) with differential is obtained within 3 days of scheduled blood draw, the collection need not be repeated. For those patients achieving a CR or PR, a CBC should be done at least 4 weeks after the BM assessment in order to confirm response. Hematology tests may be repeated also as clinically indicated.

If blood chemistry or coagulations are obtained within 3 days of scheduled blood draw, the collection need not be repeated.

If a urinalysis was obtained within 3 days of the scheduled collection, it should not be repeated. For urinalysis, dipstick is acceptable. Microscopic analyses should be done if abnormal results (i.e. the presence of protein or blood).

See **Appendix 6** for list of required tests.

10.4. Transfusions

All red blood cell and platelet transfusions, including the date of each transfusion and number of red blood cell or platelet units transfused must be recorded while the patient is on treatment. Transfusion histories for the 8 weeks prior to screening must also be recorded in the CRF. Note that the number of units (not the number of bags) must be recorded.

10.5. Vital Signs and Physical Examination

Vital signs will include blood pressure and heart rate (to be recorded in sitting position). Patients will have a physical exam (PE) including an examination of major body systems (includes general appearance, head, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological), measurement by palpation of spleen and liver, weight, height and assessment of ECOG status. If PE obtained within 48 hours of previous assessments, the evaluation need not be repeated. Height need not be recorded after the first measurement at screening. Weight must be recorded at Screening, Day 1 of each cycle, and End of Treatment.

10.6. Triplicate (12-Lead) ECGs

See **Table 1** for the specific time points of ECG collection, and **Table 5** for dose modification related to management of QTcF prolongation.

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be performed for ECGs at every timepoint. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. The acceptable mean on treatment upper limit of QTc interval will be using the Fridericia (QTcF) correction method. At each time point 3 consecutive supine ECGs will be performed approximately 2 minutes (but no longer than 5 minutes) apart, to determine the mean QTcF interval.

If Grade 3 mean QTcF (mQTcF) prolongation occurs (mQTcF $\geq$ 501 msec), continuous ECG monitoring and cardiology specialist evaluation and guidance are required.

The acceptable mean on-treatment upper limit of QTcF interval is 480 msec. If any patient has a mean pre- or post-dose QTcF value >480 msec, please refer to **Table 5** of the protocol for detailed instructions on management of QTcF prolongation and handling dose delays and dose modifications for glasdegib. A 15-min window for each ECG collection is allowed around the nominal ECG time point.

10.7. Efficacy Assessments

10.7.1. Response Criteria

Disease response, will be evaluated using the 2017 European LeukemiaNet (ELN) Response Criteria (**Appendix 1**).

Genetics

For all patients, genetics analysis, including karyotyping, must be performed locally using any scheduled or unscheduled bone marrow samples collected during study participation as described in the Schedule of Activities. Genetics to be analyzed are specified in **Appendix 8**.

Baseline genetics classification must be completed on a sample collected within 28 days prior to first dose.

10.7.2. Bone Marrow Biopsies and Aspirates

Please see the **Schedule of Activities** for specific assessment timepoints for BM biopsy and aspirate collection. A CR or PR needs to be confirmed at least 4 weeks after the BM evaluation by assessing the stability of improved counts on PB according to the 2017 ELN response criteria (**Appendix 1**); the need for an additional marrow confirmatory specimen is not required. Minimal residual disease (MRD) assessment will be performed centrally on enrolled patients enrolled in this study using multi-parametric flow cytometry. In addition to epitopes traditionally used to define AML leukemic blasts such as CD34, additional antigens such as CD99 (potential myeloid leukemia stem cell marker) may be profiled to gain a broader standing of baseline patient immunophenotype and relationship to response, and potential changes in immunophenotype with study treatment. Full details regarding the collection, processing, storage and shipping of samples will be provided in the central laboratory manuals.

The importance of timely and complete disease assessments (including BM and PB assessments) at screening and during the study, whenever clinically indicated, cannot be understated. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and have the potential to weaken the conclusions of this study.

10.7.3. Banked Biospecimens

10.7.3.1. Purpose

Banked biospecimens will be collected from all patients for possible future biomarker studies and other exploratory research relating to the drug response, potential mechanisms underlying resistance and other aspects of AML biology. Such results may assist the future development of glasdegib as a single agent and/or in combination with other approved agents in AML. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (e.g. RNA, proteins, and metabolites).

Unless prohibited by local regulations or IRB/EC decision, all patients will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens collected as part of scheduled study activities will be used. Patients may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document that they will not be compensated in this event.

10.7.4. Collection, Processing and Storage

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K2EDTA] whole-blood

collection optimized for DNA analysis) will be collected on Cycle 1 Day 1 prior to first dose of study treatment to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study.

These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each patient's privacy and confidentiality. Banked biospecimens will be assigned the patient's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the patient's ID and the patient's direct personally identifying information (e.g. name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also post-marketing research. Patients may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

11. ADVERSE EVENT REPORTING

11.1. Definitions

11.1.1. Adverse Event (AE)

Broadly, an AE (also referred to as an adverse experience) is any expected or unexpected harmful and unintended occurrence or exacerbation in a clinical trial patient, whether or not related to the trial or the study drug.

An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, exacerbation of a concomitant disease, an accident, or any other deterioration in the patient's health. It can be an intercurrent disease temporally associated with the use of a drug, without and implication of causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Any medical condition that existed before the start of the study treatment and that remains unchanged or improves must not be recorded as an AE. If a medical condition worsens, it must be recorded as an AE. The diagnosis or syndrome rather than the individual signs or symptoms must be recorded on the AE pages of the case report form.

11.1.2. Serious Adverse Event (SAE)

An SAE is defined as an AE or suspected adverse reaction if it:

- results death (death due to disease progression is excluded);
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- causes a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- cases a congenital anomaly, birth defect, or abortion;
- is a new cancer;
- is associated with overdose;

- is another medically significant event.

Important *medically significant* event is any clinical event or laboratory finding considered by the investigator to be serious that does not meet the seriousness criteria defined above but based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following are not considered as serious adverse events:

- death due to disease progression;
- hospitalization for < 24 hours;
- hospitalization scheduled before the start of the trial and/or stipulated in the protocol (e.g. for biopsy or chemotherapy).

11.1.3. Expected Serious Adverse Event (SAE-E)

An expected SAE is an event already mentioned in the most recent version of the Investigator Brochure, or in the Summary of Product Characteristics (SmPC) for medicinal products that have already been granted marketing authorization (MA). This definition also applies to the study drug when it is administered for the same population but for an unlicensed indication.

11.1.4. Unexpected Serious Adverse Event (SAE-U)

Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

11.2. What to Do in Case of a Serious Adverse Event

The investigator must report any expected Serious Adverse Event (SAE-E) or unexpected Serious Adverse Event (SAE-U) that occurs during the treatment period starting at the time the consent is signed, or within 30 days after the last administration of the study drug, regardless of whether it is attributable to the study. Events must be reported to the Yale Project Manager and Sponsor PI within 24 hours of becoming aware of such events. Yale Project Manager and/or Sponsor PI will have up to 7 calendar days to report events to Pfizer either via a fax or email.

Sites are responsible for reporting to their IRB per local policy. All events will be forwarded by the Yale Project Manager who will submit to Pfizer and FDA as required following the method and timeline outlined below.

All SAEs should be entered into OnCore within 24 hours of the site becoming aware of the event.

Any delayed serious adverse event (occurring after the 30-day period) that may reasonably be considered related to the treatment(s) described in the protocol or to the study must be reported, and no time limit applies to such adverse events. For each event, the investigator shall complete the SAE reporting form.

SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

11.3. Protocol-Specified Serious Adverse Events

All cases of Grade >2 mQTcF prolongation regardless of causality and treatment arm must be reported as an SAE for up to 30 calendar days after the last dose of study drug administered. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database.

11.4. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value 2X ULN with no evidence of hemolysis and an alkaline phosphatase value 2X ULN or not available.

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT values $\geq$2 times the baseline values and $\geq$3X ULN, or $\geq$8X ULN (whichever is smaller).

    Concurrent with

    - For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1X ULN or if the value reaches $\geq$ 3X ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g. biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered

potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs.

Such potential Hy's law cases should be reported as SAEs. A potential Hy's law case becomes a confirmed case only after all results of reasonable investigations have excluded an alternative etiology.

11.5. Hospitalization

Admission also includes transfer within the hospital to an acute/intensive care unit (e.g. from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g. for workup of persistent pre-treatment laboratory abnormality);
- Social admission (e.g. patient has no place to sleep);
- Administrative admission (e.g. for yearly physical examination);
- Protocol-specified admission during a study (e.g. for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g. for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

11.6. Severity Assessment

AEs will be reported using concise medical terminology (verbatim) as well as the Common Terminology Criteria (CTC) term for Adverse Events (Version 5.0, Publish Date: November 27, 2017, https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm)) listed in the Cancer Therapy Evaluation Program.

The investigator may use the following definitions of Severity in accordance with CTCAE Version 5.0 to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
1	MILD adverse events
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

11.7. Causality Assessment

All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for AEs. Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after occurrence of the event, including diagnostic tests to assess the cause of the event. Clinically relevant data include, but are not limited to underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered. An adverse event is *associated with the use of the drug* when there is a reasonable possibility that the experience may have been caused by the drug. Attribution standards are described as follows:

- **unrelated:** the adverse event is **clearly not** related to the study drug(s); the event **has no temporal relationship to study drug(s)** administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease or a circumstance;

- **unlikely:** the adverse event is **doubtfully** related to the study drug(s); the event **with a temporal relationship to study drug(s)** administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations;

- **possible:** the adverse event **may be** related to the study drug(s); the event **follows a reasonable temporal sequence from the administration of the study drug(s)**, and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug, or the event could be the effect of a concomitant medication;

- **probable:** the adverse event **is likely** related to the study drug(s); the event **follows a reasonable temporal sequence from administration of the study drug(s),** and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication;

- **definitely:** the adverse event is **clearly** related to study drug(s); the event **follows a reasonable temporal sequence from administration of the study drug(s)**, and the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

11.8. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g. because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g. a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (e.g. because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the YCCI Project Manager must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) regardless of whether an SAE has occurred. This must be done irrespective of whether an AE has occurred and within 24hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).
The pregnancy of a study participant or their partner will be followed during long term follow up. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g. follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will request to follow the pregnancy.

11.9. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a Case Report Form e(CRF), however a copy of the completed SAE Report form is maintained in the investigator site file.

11.10. Withdrawal Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page. When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

11.11. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about AEs.

11.12. Reporting Requirements

11.12.1. Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded on the AE eCRF The information to be entered in the case report form will include:

- **time of onset** of any new AE or **worsening** of a previously observed AE; in most cases, only date of onset will be adequate; however, for days when the patient is evaluated in the clinic and receives study drug(s), the time (based on a 24-hour clock) of onset should also be recorded;

- specific type of reaction in standard medical terminology;

- time of resolution of the event (or confirmation ongoing); in most cases, the date of resolution only will be adequate; however, for events that initiate and resolve on days where the patient is in the clinic and receives study drug(s), the time (based on a 24-hour clock) of resolution should also be recorded;

- severity/grade of AE; it should be rated according to NCI-CTCAE version 5;
- an assessment should be made of the relationship of the AE to the study drug according to the definitions outlined above;
- description of action taken in treating the AE and/or change in study drug administration or dose.

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

11.12.2. Reporting of Serious Adverse Events, including Death

Serious adverse events (SAE) including death (except deaths due to disease progression) during this study or within 30 days following the last dose of the study drug(s), whether or not related to the administration of study drugs, must be reported to the Yale Project Manager and Sponsor PI (Dr. Amer Zeidan) by telephone or email **within 24 hours of knowledge of the event**.

The study site should send the SAE form to the Yale Project Manager and Sponsor PI as soon as possible so that the tracking procedure can begin immediately upon receipt of the information. Once the Yale Project Manager and Sponsor PI are informed of an SAE with preliminary information obtained, the study site will be instructed to update the SAE form with additional information, as per the following guidelines.

If all information is not known at the time of the incident, an initial report should still be made. In the event there is a question as to whether the event is serious, the information should be forwarded to the Yale Project Manager and Sponsor PI for review. Each Site PI is responsible for following up on completion of the SAE form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Yale Project Manager and Sponsor PI. In the case of fatality, autopsy reports will be furnished to the Yale Project Manager and Sponsor PI as soon as available. During the initial communication, the Yale Project Manager will require the following information about the patient and the reported SAE:

- patient identification including patient number, initials, and date of birth;
- date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose;
- date of last dose of study drugs (i.e., prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer, lot number, expiration date, and dose);
- medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);
- date of onset of the AE;
- date of resolution of the AE (or confirmation ongoing);
- severity of the AE;
- assessment of the attribution of the AE to the study drug;
- reason AE is considered serious
- whether the AE is expected
- action taken in treating the AE and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the patient was

discontinued from the study); all concomitant medications (including doses, routes, regimens, and indications);
- pertinent clinical laboratory testing data;
- medical history.

The Yale Project Manager and Sponsor PI will review each SAE report and evaluate the relationship of the adverse reaction to the study drug and to the underlying disease. Based on the Investigator's and Sponsor PI assessment of the adverse experience, a decision will be made concerning further actions. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor PI will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:
- modification of the protocol and alteration of existing research plans;
- discontinuation or suspension of the study;
- alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings;
- modification of previously identified expected adverse experiences to include adverse experiences newly identified as study medication-related.

11.12.3. Reporting to the IRB

Sites are responsible for reporting to their IRB per local policy.

11.12.4. Reporting to External Regulatory Bodies

The Yale Project Manager shall report all SAEs to the drug manufacturer and the FDA, as required.

SAE will be reported to Pfizer based on the following timeline, when required.

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;

- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs

Pfizer Inc at

1-800-438-1985

SAEs will be reported to the FDA based on the following timeline, when required.

There are two types of expedited safety reports to the FDA:
1. 7-Calendar-Day FDA Telephone or Fax Report: The sponsor-investigator will directly notify the FDA, within 7 calendar days after his initial receipt of the information, of any adverse event that is ALL of the following:

Death or immediately life-threatening
Unexpected
Associated with the use of study drug

Notification to the FDA will be made directly to the new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever was responsible for the review of the IND. [21CFR312.32(c)] A written report of the event is to follow within 15 calendar days.

2. 15-Calendar-Day FDA Written Report: The sponsor-investigator will directly notify the FDA within 15 calendar days of any adverse event that is ALL of the following:

Serious(due to non-fatal and non-life threatening criteria
Unexpected
Associated with the use of study drug

Note: Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

12. DATA ANALYSIS/STATISTICAL METHODS

12.1. Sample Size Determination

Using a historical CR rate of 17% for decitabine 20 mg/m^2 on the standard of care five-day schedule (based on the largest randomized study of decitabine in older patients with AML [DACO-16]), a minimum acceptable CR rate of 25% (given the addition of glasdegib and potential additional toxicity) and ultimately a predicted minimum CR rate of 47% (the alternative hypothesis) for patients accrued to either arm of the proposed randomized phase 2 study, a minimum of 23 evaluable patients per arm will be accrued to test for a statistically-significant difference with an 80% power and a 90% confidence interval (which is equivalent to a type 1 error rate, alpha one-sided of 0.05).

12.2. Futility Analysis

The separate, Simon two-stage minimax decision rule is to stop enrollment in either arm if 2 or fewer patients in that arm achieve CR of the 10 patients required to be accrued during the stage 1 portion of the study. The same null hypothesis will be applied to both treatment arms, separately, without correction for multiplicity. The probability of early termination is 0.53 in each arm, under the null hypothesis. After the first 10 patients are enrolled and futility analysis of each arm allowed continued enrollment, the second stage of the study will be conducted. If 8 of fewer responses are observed in an arm by the end of the second stage of the study then no further investigation of the drug combination is warranted in that arm. Accrual will be increased by 10% (a minimum total of 51 patients) to account for those patients that are anticipated to be unevaluable and maintain the integrity of the statistical design.

12.3. Analysis Populations

12.3.1. Full Analysis Set (FAS)

The FAS will include all enrolled patients who received at least one dose of any study treatment (glasdegib or decitabine). This will be the primary analysis population for evaluating efficacy endpoints and patient characteristics.

12.3.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of any study treatment (glasdegib). It will be the primary analysis population for evaluating treatment administration/compliance and safety endpoints.

12.4. Efficacy Analysis

Efficacy analyses will use the FAS. All CI for binary endpoint will use the exact method, unless otherwise stated.

12.4.1. Complete Response

The proportion of patients achieving CR/CRi is the primary endpoint. The final analyses will be performed after all patients have been followed for at least 24 weeks.

The proportion and two-sided 95% CI of patients achieving CR/CRi will be provided.

12.4.2. Response Rate

The proportion of patients achieving response (CR/CRi + PR) is a secondary endpoint. A confirmation of response (Peripheral Blood only) is required 4 weeks after the first assessment per ELN 2017. The final analyses will be conducted after all patients have been followed for 24 weeks (to allow for confirmation of response per ELN 2017). The proportion and two-sided 95% CI (using exact method) of patients achieving response (CR/CRi + PR) will be provided.

12.4.3. Overall Survival

Overall survival (OS) is defined as the time from date of first study treatment to date of death due to any cause. Patients last known to be alive will be censored at the date of last contact.

OS will be analyzed and displayed graphically for each arm separately using the Kaplan-Meier method. The median event time for each arm and corresponding two-sided 95% CI will be provided. The Kaplan-Meier estimate of survival probabilities at 12, 18, and 24 months and their two-sided 95% CI (using log-log transformation and back-transformation) will be provided for each arm separately.

First, OS will be analyzed when the primary endpoint of CR is analyzed in each respective arm. A follow-up analysis of updated OS will be conducted when the study concludes. OS is defined as the date of the first dose of any of the study medications to the date of death from any cause.

12.4.4. Duration of Response

Duration of Response (DoR) is only patients achieving a CR. DoR is defined as the duration from date of first achieving CR to the date of disease relapse after CR or death due to any cause. Patients last known to be alive who are free from disease progression or relapse after CR are censored at the date of the last assessment that verifies their disease status.

DoR will be analyzed and displayed graphically for each arm separately using the Kaplan-Meier method. The median DoR and corresponding two-sided 95% CI will be provided.

12.4.5. Time to Response

Time to response (TTR) is only defined for patients who have ever achieved response on study as the time from date of the first dose of study drug to date of the first documentation of response (CR+PR). TTR will be analyzed and displayed graphically for each arm separately using the Kaplan-Meier method. The median TTR and corresponding two-sided 95% CI will be provided.

12.4.6. Other Efficacy Measures

Additional efficacy measures of interest include CR with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh), morphologic leukemia-free state (MLFS), PR, SD, Cytogenetic CR (CRc), and molecular CR (CRm) per **Appendix 1**. The proportion of patients ever achieving each of the endpoints for the respective arm will be estimated with two-sided 95% CI respectively.

12.4.7. Analysis of Exploratory Endpoints

CR_{MRD}

CR_{MRD} negativity is assessed in CR and CRi patients only by central multiparameter flow cytometry (MFC) (**Appendix 1**). The proportion of patients who achieved CR_{MRD} negativity and its 95% CI will be provided.

12.5. Safety Analysis

Safety will be assessed primarily based on AEs. AEs will be tabulated by system organ class and preferred term (per Medical Dictionary for Regulatory Activities [MedDRA]), and will be further categorized by decitabine treatment arm (DAC5 and DAC10) and severity. The incidence for each AE will be provided as the total number of subjects that experienced the AE, as well as the percentage of the population that this represents. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawals and incidence of serious adverse events. Listing of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. The adverse events rate will be estimated accompanied by an exact 95% confidence interval.

12.5.1. Stopping Rules for Unacceptable Toxicity

Each of the treatment arms will have a separate stopping rule. Either arm may be discontinued for safety while the other continues to accrue. Specifically, either treatment arm will be discontinued when there is at least a 70% probability that the rate of any of the below pre-defined safety events of interest in that arm is above 25%

- Treatment-related deaths that occur during study treatment through 28 days following the last dose of any study treatment, or the beginning of another anti-cancer therapy, whichever occurs first.
- Drug-induced liver injury (Hy's Law cases), confirmed as detailed in Section 8.6.2, that occurs during study treatment through 28 days following the last dose of any study treatment, or the beginning of another anti-cancer therapy, whichever occurs first.
- Grade ≥3 non-hematologic treatment-related AEs except for;

  - Grade 3 electrolyte abnormalities or LFT abnormalities that resolve to baseline or ≤ Grade 1 within 7 days
  - Grade 3 nausea or vomiting that does not require/prolong hospitalization or require NGT feeding/TPN
- Grade 4 treatment-related neutropenia (ANC<500/mm3) lasting ≥42 days from the start of each cycle without evidence of active AML

The safety stopping criteria will be applied within each arm starting when at least 10 patients have completed one cycle or experienced an unacceptable toxicity, and continuously thereafter. Enrollment will continue unless the stopping boundary is crossed. Patients who have completed at least one cycle or have experienced a pre-defined unacceptable toxicity will be included in the safety decision making. The two arms will be analyzed independently.

Table 7: Safety Decision Criteria

Accrued Sample Size*	**Maximum number of unacceptable toxicities to continue treatment arm****
Up to -11	3
12-14	4
15-18	5
19-21	6
22-25 (full enrollment)	7
** Patients who have completed 24 weeks or who have experienced an unacceptable toxicity* *** A weak prior of Beta (0.5,0.5) was used in the calculation.*	

If the safety stopping rule is met, accrual to the affected arm will be temporarily suspended in order to conduct a review of safety data. If after review, a safety issue is identified and can be corrected, the protocol will be amended accordingly and enrollment will restart to that arm.

12.6. Monitoring

The Sponsor PI or an appointed designee must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On-site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, review regulatory and essential documents, review the investigational product, and verify that the facilities remain compliant.

In addition, remote monitoring of data may be performed periodically requiring the site to submit data for comparison to the OnCore database. The study will also be reviewed by the Yale University DSMC and may be reviewed by Yale's internal auditors. Yale University DSMC letters will be provided to external sites as evidence of continued oversight.

13. DATA HANDLING AND RECORD KEEPING

13.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient.
The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents.

13.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Yale, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g. retirement, relocation), Yale should be prospectively notified.

14. ETHICS

14.1. Ethical Principles

This study will be conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki; applicable Good Clinical Practice (GCP) Guidelines published by the International Conference on Harmonisation; and applicable US laws and regulations including those found in 21 CFR Parts 50, 54, 56, and 312.

14.2. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to the Project Manager.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients.

14.3. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor PI with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study

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APPENDICES

Appendix 1. 2017 ELN Response Criteria for Acute Myeloid Leukemia

Category	Definition	Comment
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9$/L (1000/μL); platelet count $\geq 100 \times 10^9$/L (100 000/μL)	MRD^+ or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia ($<1.0 \times 10^9$/L [1000/μL]) or thrombocytopenia ($<100 \times 10^9$/L [100 000/μL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Appendix 1. 2017 ELN Response Criteria for Acute Myeloid Leukemia (continued)

Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level ($>0.5 \times 10^9$/L [500/μL], and/or platelet count to $>50 \times 10^9$/L [50 000/μL] nontransfused); or • >50% increase in peripheral blasts (WBC × % blasts) to $>25 \times 10^9$/L (>25 000/μL) (in the absence of differentiation syndrome)†; or • New extramedullary disease	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

*The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

†Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Source: Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–447.

Appendix 2. CYP3A4/5 Inducers

Strong CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
Rifampin	Antibiotics
Rifabutin	Antibiotics
Avasimibe	Antilipedimics
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Phenobarbital	Anticonvulsants
Enzalutamide	Antiandrogens
St. John's Wort	Herbal Medications
Mitotane	Antineoplastics
Moderate CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
Semagacestat	Alzheimer's
Efavirenz	Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
Bosentan	Endothelin Receptor Antagonist
Genistein	Food Product
Thioridazine	Antipsychotics
Naficillin	Antibiotics
Talviraline	NNRTI
Lopinavir	Protease Inhibitor
Modafinil	Psychostimulant
Etravirine	NNRTI
Lersivirine	NNRTI

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: November 2018".

Appendix 3. Strong CYP3A4/5 Inhibitors

Inhibitor	Therapeutic Class
Ketoconazole	Antifungal
Itraconazole	Antifungal
Voriconazole	Antifungal
Posaconazole	Antifungal
Troleandomycin	Antibiotics
Clarithromycin	Antibiotics
Telithromycin	Antibiotics
Mibefradil	Calcium Channel Blocker
Conivaptan	Diuretics
Nefazodone	Antidepressants
Cobicistat	--
Indinavir/Ritonavir	Protease Inhibitors
Tipranavir/Ritonavir	Protease Inhibitors
Ritonavir	Protease Inhibitors
Indinavir	Protease Inhibitors
Nelfinavir	Protease Inhibitors
Saquinavir	Protease Inhibitors
Saquinavir/Ritonavir	Protease Inhibitors
Lopinavir/Ritonavir	Protease Inhibitors
Telaprevir	Antivirals
Boceprevir	Antivirals
Danoprevir/Ritonavir	Antivirals
Elvitegravir/Ritonavir	Antivirals
Idelalisib	Kinase Inhibitors
Grapefruit Juice DS	Food Products

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: November 2018".

Appendix 4. Moderate CYP3A4/5 Inhibitors

Inhibitor	Therapeutic Class
Fluconazole	Antifungals
Erythromycin	Antibiotics
Ciprofloxacin	Antibiotics
Diltiazem	Calcium Channel Blockers
Verapamil	Calcium Channel Blockers
Dronedarone	Antiarrhythmics
Aprepitant	Antiemetics
Casopitant	Antiemetics
Netupitant	Antiemetics
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressant
Faldaprevir	Antivirals
Crizotinib	Kinase Inhibitor
Nilotinib	Kinase Inhibitor
Atazanivir/Ritonavir	Protease Inhibitor
Darunavir	Protease Inhibitor
Darunavir/Ritonavir	Protease Inhibitor
Atazanavir	Protease Inhibitor
Amprenavir	Protease Inhibitor
Imatinib	Antineoplastic
Grapefruit Juice	Food Products

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: November 2018".

Appendix 5. List of Drugs with Known Risk of Torsade de Pointes

The following drugs are known to have the risk of Torsade de Pointes due to QTc prolongation and their current use in combination with glasdegib is not recommended. If any of these drugs are considered to be medically necessary, then they should be used with caution in combination with glasdegib.

Generic Name	Drug Class	Therapeutic Use	Route
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	Oral, injection
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	Oral
Arsenic trioxide	Anti-cancer	Leukemia	Injection
Astemizole (Off US mkt)	Antihistamine	Allergic rhinitis	Oral
Azithromycin	Antibiotic	Bacterial infection	Oral, injection
Bepridil (Off US mkt)	Anti-anginal	Heart pain	Oral
Chloroquine	Anti-malarial	Malarial infection	Oral
Chlorpromazine	Anti-psychotic/anti-emetic	Schizophrenia/nausea	Oral, injection, suppository
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication	Oral
Ciprofloxacin	Antibiotic	Bacterial Infection	Oral, injection
Cisapride (Off US mkt)	GI stimulant	Heartburn	Oral
Citalopram	Anti-depressant, SSRI	Depression	
Clarithromycin	Antibiotic	Bacterial infection	Oral
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	Oral
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	Oral
Domperidone (Not on US mkt)	Anti-nausea	Nausea	Oral, injection
Donepezil Erythromycin Antibiotic Bacterial infection; increase GI motility oral, injection	Cholinesterase inhibitor	Dementia	Oral
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	Oral
Droperidol	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea	Injection
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety disorders	Oral
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	Oral
Fluconazole	Anti-fungal	Fungal infection	Oral, injection
Gatifloxacin (Off US mkt)	Antibiotic	Bacterial infection	Oral, injection
Grepafloxacin (Off market worldwide)	Antibiotic	Bacterial infection	Oral
Halofantrine	Anti-malarial	Malaria infection	Oral
Haloperidol	Anti-psychotic	Schizophrenia, agitation	Oral, injection
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	Injection
Levofloxacin	Antibiotic	Bacterial infection	oral, injection

Levomethadyl (Off US mkt)	Opiate	Pain control, narcotic dependence	Oral
Mesoridazine (Off US mkt)	Anti-psychotic	Schizophrenia	Oral
Methadone	Opiate	Pain control, narcotic dependence	oral, injection
Moxifloxacin	Antibiotic	Bacterial infection	oral, injection
Ondansetron	Anti-emetic	Nausea, vomiting	oral, injection
Pentamidine	Antibiotic	Pneumocystis pneumonia	injection, inhaled
Pimozide	Anti-psychotic	Tourette's tics	oral
Probucol (Off US mkt)	Antilipemic	Hypercholesterolemia	oral
Procainamide (Oral off US mkt)	Anti-arrhythmic	Abnormal heart rhythm	injection
Propofol	Anesthetic	Anesthesia	injection
Quinidine	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Sevoflurane	Anesthetic, general	Anesthesia	inhaled
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin (Off US mkt)	Antibiotic	Bacterial infection	oral
Sulpiride (Not on US mkt.)	Anti-psychotic, atypical	Schizophrenia	oral
Terfenadine (Off US mkt)	Antihistamine	Allergic rhinitis	oral
Thioridazine	Anti-psychotic	Schizophrenia	oral
Vandetanib	Anti-cancer	Thyroid cancer	oral

US mkt = United States Market.

Source: Credible Meds.org (http://crediblemeds.org/healthcare-providers/drug-list/?rf=All). TdP risk category filtered on Drugs with known TdP risk. Assessed 12 November 2018.

Appendix 6. Laboratory Assessments

Hematology	Blood Chemistry	Urinalysis (microscopic analysis)	Coagulation Tests
Hemoglobin	ALT	If urine dipstick is positive for protein, perform urinalysis (U/A) with microscopic. If U/A with microscopic shows >2+ protein, collect 24-hour urine for protein.	aPTT
Platelets	AST	Urine dipstick for urine blood: If positive, collect a U/A with microscopic (unless hematuria can be explained by local bleeding such as menses).	INR
WBC	Alk Phos	Specific Gravity	
Neutrophils	Sodium	PH	
Lymphocytes	Potassium	Protein	
Monocytes	Magnesium	Glucose	
Eosinophils	Chloride	RBC	
Basophils	Calcium	WBC	
Bands	Bicarbonate	Ketones	
Blast Count	Total Bilirubin	Leukocyte Esterase	
	Direct Bilirubin	Casts	
	BUN or Urea	Crystals	
	Creatinine	Nitrate	
	Uric Acid		
	Glucose (non-fasting)		
	Albumin		
	Total Protein		
	Phosphorus		
	LDH		
	CPK		

Appendix 7. Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS

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

Source: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

By the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 8. 2017 ELN AML Risk Stratification by Genetics

Risk Category[b]	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high(c)] Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] (w/o adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d] Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[e] monosomal karyotype[f] Wild type *NPM1* and *FLT3*-ITD[high(c)] Mutated *RUNX1*[g] Mutated *ASXL1*[g] Mutated *TP53*[h]

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]

‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]

¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

#*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.[37,66-69]

Source: Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–447.

Appendix 9. 2016 World Health Organization Classification of Acute Myeloid Leukemia

AML and related neoplasms	AML and related neoplasms (cont'd)
AML with recurrent genetic abnormalities	Acute myelomonocytic leukemia
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Acute monoblastic/monocytic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Pure erythroid leukemia#
Acute promyelocytic leukemia with *PML-RARA**	Acute megakaryoblastic leukemia
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*†	Acute basophilic leukemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Acute panmyelosis with myelofibrosis
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	Myeloid sarcoma
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*‡	Myeloid proliferations related to Down syndrome
Provisional entity: AML with *BCR-ABL1*	Transient abnormal myelopoiesis
AML with mutated *NPM1*§	Myeloid leukemia associated with Down syndrome
AML with biallelic mutations of *CEBPA*§	Blastic plasmacytoid dendritic cell neoplasm
Provisional entity: AML with mutated *RUNX1*	**Acute leukemias of ambiguous lineage**
AML with myelodysplasia-related changes‖	Acute undifferentiated leukemia
Therapy-related myeloid neoplasms¶	MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1***
AML, NOS	MPAL with t(v;11q23.3); *KMT2A* rearranged
AML with minimal differentiation	MPAL, B/myeloid, NOS
AML without maturation	MPAL, T/myeloid, NOS
AML with maturation	

Sources:

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–447.

2. Arber DA, Orazi A, Robert, H, et.al. The 2016revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016; 127(20): 2391-2405.