Official Title: A Phase Ib/II Study Evaluating the Safety and Efficacy of Idasanutlin in Combination With Cytarabine and Daunorubicin in Patients Newly Diagnosed With Acute Myeloid Leukemia (AML) and the Safety and Efficacy of Idasanutlin in the Maintenance of First AML Complete Remission

NCT Number: NCT03850535

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PROTOCOL

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF IDASANUTLIN IN COMBINATION WITH CYTARABINE AND DAUNORUBICIN IN PATIENTS NEWLY DIAGNOSED WITH ACUTE MYELOID LEUKEMIA (AML) AND THE SAFETY AND EFFICACY OF IDASANUTLIN IN THE MAINTENANCE OF FIRST AML COMPLETE REMISSION**
PROTOCOL NUMBER:	GO40800
VERSION NUMBER:	1
EUDRACT NUMBER:	2018-002964-25
IND NUMBER:	117005
TEST PRODUCTS:	Idasanutlin (RO5503781), cytarabine, and daunorubicin
MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	31-Oct-2018 14:34:15

FINAL PROTOCOL APPROVAL

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PROTOCOL ACCEPTANCE FORM

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PROTOCOL NUMBER:	GO40800
VERSION NUMBER:	1
EUDRACT NUMBER:	2018-002964-25
IND NUMBER:	117005
TEST PRODUCTS:	Idasanutlin (RO5503781), cytarabine, and daunorubicin
MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF IDASANUTLIN IN COMBINATION WITH CYTARABINE AND DAUNORUBICIN IN PATIENTS NEWLY DIAGNOSED WITH ACUTE MYELOID LEUKEMIA (AML) AND THE SAFETY AND EFFICACY OF IDASANUTLIN IN THE MAINTENANCE OF FIRST AML COMPLETE REMISSION**
PROTOCOL NUMBER:	GO40800
VERSION NUMBER:	1
EUDRACT NUMBER:	2018-002964-25
IND NUMBER:	117005
TEST PRODUCTS:	Idasanutlin (RO5503781), cytarabine, and daunorubicin
PHASE:	Phase Ib/II
INDICATION:	Acute myeloid leukemia
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, efficacy, and pharmacokinetics of idasanutlin in the following groups:

- Idasanutlin in combination with cytarabine and daunorubicin (7+3 regimen) in induction, idasanutlin in combination with cytarabine in consolidation, and single-agent idasanutlin in maintenance in patients with newly diagnosed, previously untreated acute myeloid leukemia (AML)
- Idasanutlin as a single agent in maintenance for idasanutlin treatment–naive patients who received induction and chemotherapy consolidation for AML outside the study and had minimum residual disease (MRD)-positive complete remission (CR) after induction

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for idasanutlin when given in combination with cytarabine and daunorubicin during the dose-escalation phase on the basis of the following endpoint:
  - Incidence of dose-limiting toxicities (DLTs) during the first cycle of study treatment
- To evaluate the safety and tolerability of idasanutlin when given in combination with cytarabine and daunorubicin in induction, in combination with cytarabine in consolidation, and as a single agent in maintenance on the basis of the following endpoints:
  - Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
  - Change from baseline in targeted vital signs
  - Change from baseline in ECG parameters
  - Change from baseline in targeted clinical laboratory test results

- To compare the differences in patient-reported treatment-related symptoms
  - Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (nausea, vomiting, and diarrhea), as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)
  - Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE

The primary efficacy objective for this study is to evaluate the efficacy of idasanutlin when given in combination with cytarabine and daunorubicin as induction treatment, on the basis of the following endpoint:

- Proportion of patients with a CR at the end of induction treatment

The secondary objective for this study is to evaluate the efficacy of idasanutlin when given in combination with cytarabine and daunorubicin as induction treatment, in combination with cytarabine as consolidation treatment, and/or as a single agent during maintenance treatment, on the basis of the following endpoints, which will be analyzed in patients enrolled during specified phases:

<u>Dose-escalation or expansion phase</u>

- Proportion of patients with a CR, complete remission with incomplete blood count recovery (CRi), or complete remission with incomplete platelet count recovery (CRp) at the end of induction treatment
- Proportion of patients with a CR or complete remission with partial hematologic recovery (CRh) at the end of induction treatment
- Proportion of patients with a negative MRD status at the end of induction treatment
- EFS, defined as the time from initiation of study treatment to treatment failure (failure to achieve CR, CRi, CRp, or CRh), hematologic relapse, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study treatment to death from any cause
- RFS in patients who achieve remission (CR, CRi, CRp, or CRh), defined as the time from remission to the date of hematologic relapse or death from any cause, whichever occurs first

<u>Post-consolidation phase</u>

- Proportion of patients converting from MRD-positive to MRD-negative status at any time
- EFS, defined as the time from initiation of induction treatment (prior to study entry) to hematologic relapse or death from any cause, whichever occurs first
- OS, defined as the time from remission (prior to study entry) to death from any cause
- RFS in patients who achieved remission (CR, CRi, CRp, or CRh), defined as the time from remission (prior to study entry) to the date of hematologic relapse or death from any cause, whichever occurs first

<u>All phases</u>

- Change from baseline in patient-reported disease-related symptoms and health-related quality of life at specified timepoints, as assessed through use of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30 (EORTC QLQ-C30) (selected scales), and European Organisation for Research and Treatment of Cancer (EORTC) Item Library (selected symptoms)

The exploratory efficacy objectives for this study are as follows:

- Primary and secondary endpoints (defined above) in the subset of patients with wild-type p53
- MRD response over time (i.e., during induction, consolidation, and maintenance)

- Time to MRD-negative status, defined as time from initiation of treatment to confirmation of negative MRD status

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the PK profiles of idasanutlin (and its metabolites, if appropriate), cytarabine, and daunorubicin on the basis of the following endpoint:
  - Plasma concentration of idasanutlin (and metabolites, if appropriate), cytarabine, and daunorubicin at specified timepoints
- To assess potential PK interactions among idasanutlin, cytarabine, and daunorubicin on the basis of the following endpoint:
  - Plasma concentration of idasanutlin (and metabolites, if appropriate), cytarabine, and daunorubicin at specified timepoints

The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of idasanutlin, cytarabine, and daunorubicin on the basis of the following endpoints:

- Relationship between plasma concentration or PK parameters for each drug (idasanutlin, cytarabine, and daunorubicin) and efficacy endpoints
- Relationship between plasma concentration or PK parameters for each drug (idasanutlin, cytarabine, and daunorubicin) and safety endpoints

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), can contribute to improvement of diagnostic assays, or can increase the knowledge and understanding of disease biology, drug safety, or study treatment mechanism of action, on the basis of the following endpoint:

- Relationship between biomarkers in blood or bone marrow and efficacy, safety, PK, or other biomarker endpoints

The health status utility objective for this study is to evaluate health status utility scores of patients treated with idasanutlin on the basis of the following endpoint:

- Change from baseline in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and visual analogue scale scores at specified timepoints

Study Design

Description of Study

This Phase Ib/II, open-label, multicenter, non-randomized study will evaluate the safety, efficacy, and pharmacokinetics of idasanutlin when given in combination with cytarabine and daunorubicin in induction, in combination with cytarabine in consolidation, and as a single agent in maintenance.

The study will include an initial dose-escalation phase designed to determine the RP2D for idasanutlin when given in combination with cytarabine and daunorubicin in induction. The dose-escalation phase includes patients with newly diagnosed, previously untreated AML who have favorable or intermediate risk to maximize accumulated safety data on consolidation by minimizing the number of patients moving to allogenic hematopoietic stem cell transplant (allo-HSCT) instead of systemic consolidation. A post-consolidation phase, run in parallel to the dose-escalation phase, includes idasanutlin treatment–naive patients who received induction and chemotherapy consolidation for AML outside the study and had MRD-positive remission after induction. Patients enrolled in the post-consolidation phase will be treated with idasanutlin at a set dose of 150 mg. An expansion phase, to be conducted after completion of the dose-escalation phase, includes two distinct cohorts of patients with newly diagnosed, previously untreated AML: patients with favorable or intermediate risk and patients with high risk. High risk is defined as patients with adverse risk or secondary AML (i.e., AML evolving

from antecedent hematologic disorder [AHD]). Patients enrolled in the expansion phase will be treated with induction therapy consisting of idasanutlin at the RP2D in combination with cytarabine and daunorubicin. After completion of induction therapy, patients enrolled in the dose-escalation phase or expansion phase will receive idasanutlin in combination with cytarabine in consolidation, followed by single-agent idasanutlin in maintenance.

Number of Patients

Approximately 80 patients (9–15 patients in the dose-escalation phase, 30 patients in the post-consolidation phase, and 40 patients in the expansion phase) are expected to be enrolled in this study at approximately 20 investigational sites worldwide. Given the nature of the dose escalation, the number of patients enrolled may vary.

Target Population

Inclusion Criteria

For all study cohorts, patients must meet the following inclusion criteria for enrollment in the study:

- Signed Informed Consent Form
- Age ≥18 years old
- Eastern Cooperative Oncology Group performance status ≤2
- Adequate hepatic function, as assessed by the following:

  Serum total bilirubin ≤1.5× institutional upper limit of normal (ULN), unless resulting from hemolysis, Gilbert syndrome, or liver infiltration with leukemia (up to 3× ULN)

  AST or ALT ≤ 3× institutional ULN (or ≤5× upper limit of institutional laboratory reference range if liver infiltration with leukemia)
- Adequate renal function assessed by serum creatinine within reference laboratory ranges or creatinine clearance (by Cockcroft-Gault formula) ≥50 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 6 months after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (> 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the final dose of study drug. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of study drug to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Ability to understand and willingness to sign a written informed consent form and comply with all study requirements including completion of patient-reported questionnaires

Inclusion Criteria for Patients in the Dose-Escalation and Expansion Phases

Patients in the dose-escalation and expansion cohorts must meet the following inclusion criterion for enrollment in the study:

- Documented/confirmed newly diagnosed AML not previously treated according to WHO

Inclusion Criteria for Patients in the Post-Consolidation Phase:

Patients in the post-consolidation cohort must meet the following inclusion criterion for enrollment in the study:

- Documented/confirmed AML according to WHO in remission after induction, within 21 days of end of last chemotherapy consolidation cycle and were MRD positive at end of induction as per local laboratory assessment (validated quantitative AML specific MRD assessment with a >0.1% threshold)

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry in any part of the study:

- Clinical evidence of CNS leukemia
- Any Grade ≥2 non-hematological toxicities prior to starting therapy (except fatigue, anorexia, and alopecia).
- Current treatment with any other investigational or commercial agents or therapies administered with the intention to treat their malignancy with the exception of hydroxyurea (HU) or 6-mercaptopurine (6-MP).

  HU and 6-MP must be discontinued at least 24 hours before initiation of study treatment.
- Treatment-related AML
- Acute promyelocytic leukemia
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

  Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer

  Any previously treated malignancy that has been in remission without treatment for ≥2 years prior to enrollment
- Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, impair the ability of the investigator to evaluate the patient, or impair the patient's ability to complete the study such as the following:

  Unstable angina, symptomatic or otherwise uncontrolled arrhythmia (does not include stable, lone atrial fibrillation), uncontrolled hypertension, symptomatic congestive heart failure (New York Heart Association Class III and IV cardiac), myocardial infarction ≤6 months prior to first study treatment, and cerebrovascular accidents ≤6 months before study treatment start

  Unstable seizure disorders
- Echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan showing ejection fraction ≤40%

- Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study treatment, such as hereditary coagulation disorders, insulin-dependent diabetes mellitus not optimally controlled with medical management (e.g., presence of ketoacidosis), or active GI conditions affecting absorption
- Infection considered by the investigator to be clinically uncontrolled or of unacceptable risk to the patient upon the induction of neutropenia, that is, patients who are or should be on antimicrobial agents for the treatment of active infection such as the following:

  Fungal infection with visceral involvement, other than mucosal candidiasis, with less than 2 weeks of appropriate systemic antifungal therapy

  Bacterial infection with positive cultures in the 7 days prior to dosing

  Patients who have received less than 5 days of appropriate therapeutic antibiotic therapy for an identified infection

  Neutropenic fever that is considered infection related within 72 hours prior to dosing

  History of symptomatic *C. difficile* infection that required treatment within 1 month prior to dosing.

  - Upon clinical response to *C. difficile* treatment, the stool consistency and frequency must have returned to normal.
- Febrile patients within 72 hours of study treatment initiation
- Patients with a history of active or chronic infectious hepatitis unless serology demonstrates clearance of infection
- Patients unable to interrupt treatment with moderate to strong CYP2C8 inducers and inhibitors (including gemfibrozil, which is also an inhibitor of UGT1A3), CYP2C8 or OATP1B1/3 substrates, or strong CYP3A4 inducers during the treatment phase.

  These agents must be discontinued 7−14 days prior to the start of study.
- Patients unable to temporarily interrupt treatment with oral or parenteral anticoagulants/anti-platelet agents (e.g., warfarin, chronic daily treatment with aspirin [>325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban, or subcutaneous [SC] anticoagulant prophylaxis) during the treatment phase. These agents must be discontinued 7 days (or 5 half-lives) prior to the start of study medication
- Patients who have a history of clinically significant liver cirrhosis (e.g., Child–Pugh class B and C)
- Patients with extramedullary AML with no evidence of systemic involvement
- Pregnant or breastfeeding patients
- Known history of HIV-positive status

  For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local legislation.
- Patients who might refuse to receive blood products and/or have a hypersensitivity to blood products
- Prior treatment with an MDM2 antagonist
- Patients with clinically relevant QTc prolongation (QT interval corrected using Fridericia's formula >480 ms), a family history of long QT syndrome

Exclusion Criteria for Patients in the Phase Ib Dose-Escalation Phase Only

Patients who meet any of the following exclusion criterion will be excluded from enrollment in the dose-escalation cohort in any part of the study:

- Adverse risk patients as per Europe LeukemiaNet 2017

Exclusion Criteria for Patients in Phase Ib Post-Consolidation Phase Only

Patients who meet any of the following exclusion criterion will be excluded from enrollment in the dose-escalation cohort in any part of the study:

- Any Grade ≥2 hematologic adverse events prior to starting therapy

- Previous HSCT

Exclusion Criteria for Patients in the Dose-Escalation Phase and Patients in the Favorable/Intermediate-Risk Cohort of the Expansion Phase Only

Patients who meet any of the following exclusion criterion will be excluded from the dose-escalation phase and the favorable/intermediate-risk cohort of the expansion phase:

- Secondary AML defined as AML evolving from AHD

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. Patients will be followed up to 2 years after last patient is enrolled or all patients have died, whichever occurs first.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Idasanutlin: Patients will self-administer idasanutlin tablets by mouth each day in the morning according to the schedule of activities.

On days when idasanutlin is given in combination with chemotherapy, idasanutlin should be administered first. During consolidation when idasanutlin is given in combination with cytarabine, idasanutlin should be administered first.

Cytarabine: Cytarabine will be administered in the first cycle of induction at a dose of 200 mg/m^2 daily by IV for 7 days, immediately after the corresponding dose of idasanutlin. Dose and regimen can be lowered per investigator choice in the second induction cycle

Cytarabine will be administered in consolidation at a dose of 1.5 g/m^2 once a day (QD) for 5 days as an IV infusion over a minimum of 3 hours, immediately after corresponding dose of idasanutlin.

The dose of cytarabine should be calculated based on a body weight measurement within 2 days of the first day of each cycle.

Daunorubicin: Daunorubicin will be administered in induction at a dose of 60 mg/m^2 QD for 3 days as IV infusion, immediately after the corresponding dose of idasanutlin. Dose and regimen can be lowered per investigator choice in the second induction cycle.

The dose of daunorubicin should be calculated based on a body weight measurement within 2 days of the first day of each cycle.

Statistical Methods

Primary Analysis

The primary efficacy analysis will be the estimation of the proportion of patients with a CR at the end of induction treatment.

Determination of Sample Size

Dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a modified continuous reassessment method (mCRM) algorithm. It is anticipated that enrollment of up to five cohorts of 3–6 patients each, for a total of 9–15 evaluable patients, will be required to establish the RP2D during the dose-escalation phase. Assuming 5 not-evaluable patients; the expected maximum sample size will be approximately 20 patients.

Approximately 40 patients (20 favorable/intermediate–risk patients and 20 high-risk patients in two separate cohorts) will be enrolled during the expansion phase. A sample size of 20 patients in the high-risk cohort is deemed sufficient to provide adequate precision for the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting probability of response of $<$50% with an observed CR proportion of $>$70%. Depending on the proportions of patients with adverse risk or secondary AML enrolled, a CR proportion up to 50%–55% is expected for high-risk patients under current 7+3 standard of care.

Interim Analyses

Optional interim safety and/or efficacy data review may be carried out by an internal monitoring committee (IMC) that includes Sponsor members at the discretion of the Medical Monitor. The decision to conduct such an analysis and the corresponding timing will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. In particular, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim efficacy analyses for early stopping (futility) by using observed proportion of patients achieving complete response (e.g., predictive probability that this trial will have a positive outcome if carried out to completion based on historical control data available at the time of analysis).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6-MP	6-mercaptopurine
7+3	7 days of cytarabine and 3 days of daunorubicin
AHD	antecedent hematologic disorder
allo-HSCT	allogenic hematopoietic stem cell transplant
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
AUC	area under the concentration–time curve
$AUC_{0-\tau}$	area under the concentration–time curve during one dosing interval
AUC_{0-24h}	area under the concentration–time curve during a 24 hour dosing interval
BID	twice a day
BSA	body surface area
CL	total clearance of drug
CL/F	apparent clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration observed
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CRh	complete remission with partial hematologic recovery
CRp	complete remission with incomplete platelet count recovery
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLS	clinical tumor lysis syndrome
C_{trough}	steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration)
CYP	cytochrome P450
DDI	drug–drug interaction
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EFS	event-free survival
ELN	European LeukemiaNet

Abbreviation	Definition
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
GI	gastrointestinal
HIPPA	Health Insurance Portability and Accountability Act
HMRA	hematologic malignancy response assessment
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
HU	hydroxyurea
ICH	International Council on Harmonisation
IDCC	independent Data Coordinating Center
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LFS	leukemia-free survival
LPLV	last patient, last visit
mCRM	modified continual reassessment method
MDM2	murine double minute 2
MIC-1	macrophage inhibitory cytokine-1
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
OATP	organic anion-transporting polypeptide
OS	overall survival
PK	pharmacokinetic
PO	orally
PR	partial remission
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
QD	once a day

Abbreviation	Definition
QTcF	QT interval corrected using Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	relapse-free survival
RP2D	recommended Phase II dose
R/R	relapsed or refractory
TLS	tumor lysis syndrome
ULN	upper limit of normal
VAS	visual analogue scale

1. BACKGROUND

1.1 BACKGROUND ON FRONT-LINE ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is an aggressive malignancy arising from hematopoietic progenitor cells in the bone marrow and is characterized by accumulation of blasts that fail to mature and differentiate. It is the most common form of acute leukemia in adults, with a median age of 67 years at diagnosis (Howlader et al. 2014).

The yearly incidence of AML in European adults is 5–8 cases per 100,000 individuals, with a steep increase in the population aged over 70 years, where the incidence reaches 15–25 cases per 100,000 individuals per annum (Fey and Buske 2013). Approximately 20,000 patients were diagnosed with AML with greater than 10,000 AML patient deaths in the United States during 2015 (Siegel et al. 2015).

Specific genetic markers have been shown to correlate with prognosis (Döhner et al. 2017) and therefore are the basis of risk classification in AML, which drives the treatment strategy (see Appendix 7). Development of targeted therapies in the past 2 years led to recent approvals (FLT3 inhibitors, IDH inhibitors) (Döhner et al. 2017) but only for a subset of patients, and for the majority of patients the treatments have not changed in decades. Patients fit for intensive chemotherapy receive up to 2 cycles of induction followed by a consolidation phase with cytarabine-based regimen or hematopoietic stem cell transplant (HSCT); unfit patients receive a low-intensity regimen given in consecutive cycles. A major field of research has included a maintenance phase, but no conclusive data have yet shown clinical benefit.

Intensive treatment of de novo AML in adults using standard cytarabine- and anthracycline–based chemotherapy induction regimens achieves complete remission (CR) proportions ranging from 50% to 80% (Estey 2001; Appelbaum et al. 2006). Nonetheless, 60%–70% of patients under the age of 60 years who achieve a CR will relapse, and only less than 20% of elderly patients are long-term survivors (Burnett et al. 2011). Secondary AML (s-AML) includes patients with a history of an antecedent hematologic disorder (AHD), such as myelodysplastic syndrome or myeloproliferative neoplasms, whose disease has progressed to AML. s-AML accounts for 10%–20% of AML and is associated with poor outcomes (Granfeldt Østgård et al. 2015; Hulegardh et al 2015; Zeichner and Arellano 2015). Survival after relapse in patients with AML is poor, especially in elderly patients.

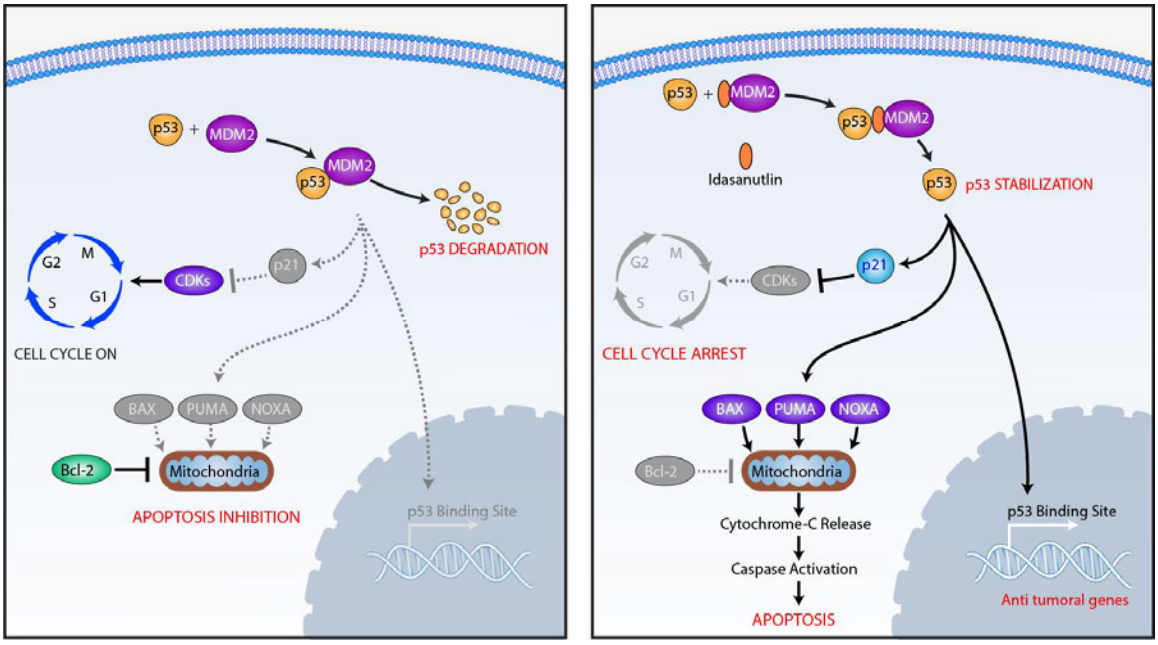
Although some patients with AML benefit from chemotherapy-based regimens, these therapies are rarely curative. There continues to be an unmet need for novel treatments that can significantly extend overall survival (OS). The use of therapies that specifically target signaling pathways known to be dysregulated or aberrant in AML may improve outcomes in AML.

1.2 BACKGROUND ON IDASANUTLIN

Idasanutlin is a potent, selective, and orally bioavailable small molecule inhibitor of MDM2. In cell-free assays, idasanutlin has been shown to bind to the MDM2 protein with high affinity and to inhibit MDM2–p53 binding. Exposure of tumor cells, including lymphoma cells, to the compound leads to a dose-dependent accumulation of p53 protein and activation of its transcriptional targets and the p53 pathway. As a result, cancer cells undergo a cell-cycle block during G1 and G2 phases followed by apoptosis in vitro and in vivo (see Figure 1) (Ding et al. 2013).

See the Idasanutlin Investigator's Brochure for additional details on nonclinical and clinical studies.

Figure 1 Regulation of p53 Stability and Activity by MDM2



BAX=BCL-2–associated X protein; BCL-2=B-cell lymphoma 2 protein; CDK=cyclin-dependent kinase; Cyto C=cytochrome C; G1=Growth 1/Gap 1 phase; G2=Growth 2/Gap 2 phase; M=mitosis; MDM2=murine double minute 2; NOXA=phorbol-12-myristate-13-acetate–induced protein 1; p21=cyclin-dependent kinase inhibitor 1A (CDKN1A, CIP1); PUMA=p53 upregulated modulator of apoptosis; S=synthesis phase.

1.2.1 Clinical Studies with Idasanutlin

Idasanutlin was investigated in patients with solid tumors (Phase I Studies NP27872, NP28902, and NP29910) and in patients with AML (Phase I Study NP28679). It is currently being developed in patients with relapsed or refractory (R/R) AML in a Phase III study (WO29519), exploring the combination of cytarabine and idasanutlin in fit patients. In parallel, the Phase Ib/II study GH29914 is exploring the combination of idasanutlin and venetoclax in a chemotherapy-free regimen in unfit patients with R/R AML. Exploration of idasanutlin in combination with obinutuzumab and rituximab, with or without venetoclax, in patients with non-Hodgkin lymphoma (NHL) (Phase Ib/II

Studies BH29812 and BH39147) are ongoing as well as the bioequivalence study NP39051 in patients with solid tumors and a Phase I/II, single-agent study in patients with polycythemia vera. See the Idasanutlin Investigator's Brochure for additional details on clinical studies.

1.2.2 Idasanutlin in AML

All patients in the Phase I/Ib study NP28679 (n = 122) have experienced at least one adverse event. The most common adverse events across the study groups were from the gastrointestinal (GI) disorders system organ class; in particular, patients experienced diarrhea and nausea, and to a lesser extent, vomiting. These events were also the most common adverse events considered by investigators to be related to study treatment. Serious adverse events occurred in 71 of 122 patients during the study; the most common were infectious and hematologic events. Infectious adverse events were more common for patients with AML compared with patients with solid tumors (Studies NP27872 and NP28902). The most frequent serious adverse events that were considered by investigators to be related to study treatment (febrile neutropenia and sepsis) occurred in 25 of the 71 patients.

Although the maximum tolerated dose (MTD) was not reached in a formal manner for the 56 patients with AML during dose escalation, the clinical experience for patients treated at 800 mg twice a day (BID) was evaluated by investigators as not tolerable for those patients, primarily due to GI adverse events (mainly diarrhea) and bone marrow failure (a dose-limiting toxicity [DLT]), and the 600 mg BID dose was therefore selected as the recommended Phase II dose (RP2D).

In a Phase Ib/II study (GH29914) in elderly unfit patients with R/R AML, 34 patients had received combination therapy with venetoclax (daily dosing) and idasanutlin (Days 1–5) as of cutoff date of 6 April 2018. As of this date, the most frequent adverse events in the venetoclax plus idasanutlin arm were GI toxicities (diarrhea, nausea, and vomiting) and hematologic toxicities (neutropenia and thrombocytopenia). The most frequent Grade ≥3 adverse events in the venetoclax plus idasanutlin arm were febrile neutropenia, neutropenia, thrombocytopenia, and anemia.

The Phase III study WO29519 in patients with R/R AML fit for intensive chemotherapy is designed to compare 300 mg idasanutlin (adjusted for formulation differences) BID plus 1 g/m^2 cytarabine with placebo plus 1 g/m^2 cytarabine. This study is currently ongoing.

For further details on clinical studies, please refer to the Idasanutlin Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Patients newly diagnosed with AML and treated with standard induction chemotherapy (such as cytarabine on Days 1–7 plus daunorubicin on Days 1–3 [7+3 regimen]) will achieve a CR rate of 50%–80%, depending on their risk classification. Nevertheless, a

vast majority of patients will relapse within months and OS in patients with AML remains poor (Döhner et al. 2017). Improvement of the CR rate at end of induction and sustainability of the response through consolidation to achieve deeper and more durable remissions remains a high unmet need. Furthermore, the role of maintenance treatment to prevent relapse remains to be assessed. This study will combine idasanutlin with cytarabine and daunorubicin in induction and idasanutlin with cytarabine in consolidation followed by single-agent idasanutlin as maintenance. One additional cohort will investigate the benefit of single-agent idasanutlin as maintenance therapy in idasanutlin treatment–naive patients who were minimal residual disease (MRD) positive at end of induction. Those patients are known to have a higher rate of relapse (Jongen-Lavrencic et al. 2018).

Cytarabine and daunorubicin are both myelosuppressive and, as such, have an overlapping toxicity profile with idasanutlin. In the AML population, this combination appears nevertheless desirable because the additive effect might lead to increased clearance of blasts and deeper responses for the combination treatment.

Comorbidities and characteristics such as older age, frailty, and presence of prolonged cytopenias prior to study initiation are common among patients with AML. The induction and consolidation treatment proposed in this study is anticipated to lead to cytopenias, rendering patients susceptible to infections. To reduce the risk to patients enrolled, this study will rely on stringent enrollment criteria for performance status, diligent clinical observation, and management (for detailed information on toxicity management guidelines, please refer to Appendix 5), and pharmacovigilance. Doses for 7+3 chemotherapy in induction and cytarabine in consolidation have been chosen in accordance to standard clinical practices and aim to minimize combination toxicities.

A maintenance phase will be investigated in this study in both idasanutlin predosed patients and idasanutlin treatment–naive patients with the goal to decrease relapse rate following consolidation hence improving OS in all comers (regardless of cytogenetic risk). Idasanutlin will be given as single agent every month for a year.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of idasanutlin in the following groups:

- Idasanutlin in combination with cytarabine and daunorubicin (7+3 regimen) in induction, idasanutlin in combination with cytarabine in consolidation, and single-agent idasanutlin in maintenance in patients with newly diagnosed, previously untreated AML
- Idasanutlin as a single agent in maintenance for idasanutlin treatment–naive patients who received induction and chemotherapy consolidation for AML outside the study and had MRD-positive remission after induction

This study is composed of a dose-escalation phase, an expansion phase, and a post-consolidation phase (see Figure 2).

Specific objectives and corresponding endpoints for the study are outlined below.

In this study, "study treatment" refers to the protocol-mandated treatments under study (i.e., idasanutlin, cytarabine, and daunorubicin).

2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To determine the RP2D for idasanutlin when given in combination with cytarabine and daunorubicin during the dose-escalation phase on the basis of the following endpoint:
  - Incidence of DLTs during the first cycle of study treatment
- To evaluate the safety and tolerability of idasanutlin when given in combination with cytarabine and daunorubicin in induction, in combination with cytarabine in consolidation, and as a single agent in maintenance on the basis of the following endpoints:
  - Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
  - Change from baseline in targeted vital signs
  - Change from baseline in ECG parameters
  - Change from baseline in targeted clinical laboratory test results
- To compare the differences in patient-reported treatment-related symptoms
  - Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (nausea, vomiting, and diarrhea), as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)
  - Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE

2.2 EFFICACY OBJECTIVES

Response is determined by the investigator according to European LeukemiaNet (ELN) and additional response criteria for AML (see Appendix 19).

Efficacy will be evaluated in patients enrolled in the expansion phase and the post-consolidation phase but will also be assessed for patients enrolled in the dose-escalation phase. Data from patients who were treated at the RP2D during the dose-escalation phase will be pooled with data from the corresponding cohort of the expansion phase (favorable/intermediate–risk patients; see Section 3.1.1).

2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of idasanutlin when given in combination with cytarabine and daunorubicin as induction treatment, on the basis of the following endpoint:

- Proportion of patients with a CR at the end of induction treatment

2.2.2 Secondary Efficacy Objectives

The secondary objective for this study is to evaluate the efficacy of idasanutlin when given in combination with cytarabine and daunorubicin as induction treatment, in combination with cytarabine as consolidation treatment, and/or as a single agent during maintenance treatment, on the basis of the following endpoints, which will be analyzed in patients enrolled during specified phases:

Dose-escalation or expansion phase

- Proportion of patients with a CR, complete remission with incomplete blood count recovery (CRi), or complete remission with incomplete platelet count recovery (CRp) at the end of induction treatment
- Proportion of patients with a CR or complete remission with partial hematologic recovery (CRh) at the end of induction treatment
- Proportion of patients with a negative MRD status at the end of induction treatment
- EFS, defined as the time from initiation of study treatment to treatment failure (failure to achieve CR, CRi, CRp, or CRh), hematologic relapse, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study treatment to death from any cause
- RFS in patients who achieve remission (CR, CRi, CRp, or CRh), defined as the time from remission to the date of hematologic relapse or death from any cause, whichever occurs first

Post-consolidation phase

- Proportion of patients converting from MRD-positive to MRD-negative status at any time
- EFS, defined as the time from initiation of induction treatment (prior to study entry) to hematologic relapse or death from any cause, whichever occurs first
- OS, defined as the time from remission (prior to study entry) to death from any cause
- RFS in patients who achieved remission (CR, CRi, CRp, or CRh), defined as the time from remission (prior to study entry) to the date of hematologic relapse or death from any cause, whichever occurs first

All phases

- Change from baseline in patient-reported disease-related symptoms and health-related quality of life at specified timepoints, as assessed through use of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30 (EORTC QLQ-C30) (selected scales), and European Organisation for Research and Treatment of Cancer (EORTC) Item Library (selected symptoms)

2.2.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are as follows:

- Primary and secondary endpoints (defined above) in the subset of patients with wild-type p53
- MRD response over time (i.e., during induction, consolidation, and maintenance)
- Time to MRD-negative status, defined as time from initiation of treatment to confirmation of negative MRD status

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the PK profiles of idasanutlin (and its metabolites, if appropriate), cytarabine, and daunorubicin on the basis of the following endpoint:
  - Plasma concentration of idasanutlin (and metabolites, if appropriate), cytarabine, and daunorubicin at specified timepoints
- To assess potential PK interactions among idasanutlin, cytarabine, and daunorubicin on the basis of the following endpoint:
  - Plasma concentration of idasanutlin (and metabolites, if appropriate), cytarabine, and daunorubicin at specified timepoints

The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of idasanutlin, cytarabine, and daunorubicin on the basis of the following endpoints:

- Relationship between plasma concentration or PK parameters for each drug (idasanutlin, cytarabine, and daunorubicin) and efficacy endpoints
- Relationship between plasma concentration or PK parameters for each drug (idasanutlin, cytarabine, and daunorubicin) and safety endpoints

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), can contribute to improvement of diagnostic assays, or can increase the knowledge and understanding of disease biology, drug safety, or study treatment mechanism of action, on the basis of the following endpoint:

- Relationship between biomarkers in blood or bone marrow (listed in Section 4.5.8) and efficacy, safety, PK, or other biomarker endpoints

2.5 HEALTH STATUS UTILITY OBJECTIVE

The health status utility objective for this study is to evaluate health status utility scores of patients treated with idasanutlin on the basis of the following endpoint:

- Change from baseline in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and visual analogue scale (VAS) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

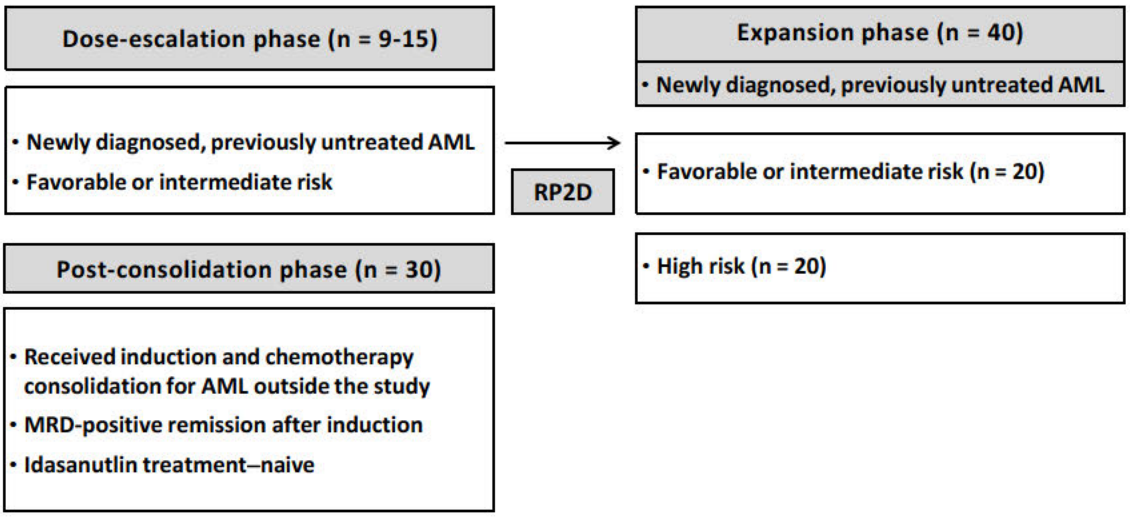
3.1.1 Overview of Study

This Phase Ib/II, open-label, multicenter, non-randomized study will evaluate the safety, efficacy, and pharmacokinetics of idasanutlin when given in combination with cytarabine and daunorubicin in induction, in combination with cytarabine in consolidation, and as a single agent in maintenance.

The study will include an initial dose-escalation phase designed to determine the RP2D for idasanutlin when given in combination with cytarabine and daunorubicin in induction. The dose-escalation phase includes patients with newly diagnosed, previously untreated AML who have favorable or intermediate risk (see Appendix 8) to maximize accumulated safety data on consolidation by minimizing the number of patients moving to allogenic hematopoietic stem cell transplant (allo-HSCT) instead of systemic consolidation. A post-consolidation phase, run in parallel to the dose-escalation phase, includes idasanutlin treatment–naive patients who received induction and chemotherapy consolidation for AML outside the study and had MRD-positive remission after induction. Patients enrolled in the post-consolidation phase will be treated with idasanutlin at a set dose of 150 mg (see Figure 2). An expansion phase, to be conducted after completion of the dose-escalation phase, includes two distinct cohorts of patients with newly diagnosed, previously untreated AML: patients with favorable or intermediate risk and patients with high risk (see Figure 2). High risk is defined as patients with adverse risk or secondary AML (i.e., AML evolving from AHD). Patients enrolled in the expansion phase will be treated with induction therapy consisting of idasanutlin at the RP2D in combination with cytarabine and daunorubicin. After completion of induction therapy,

patients enrolled in the dose-escalation phase or expansion phase will receive idasanutlin in combination with cytarabine in consolidation, followed by single-agent idasanutlin in maintenance.

Figure 2 Study Schema



AHD = antecedent hematologic disorder; AML = acute myeloid leukemia; MRD = minimal residual disease; RP2D = recommended Phase II dose.
Note: High risk is defined as patients with adverse risk or secondary AML (i.e., AML evolving from AHD).

Approximately 80 patients (9–15 patients in the dose-escalation phase, 30 patients in the post-consolidation phase, and 40 patients in the expansion phase) are expected to be enrolled in this study at approximately 20 investigational sites worldwide. Given the nature of the dose escalation, the number of patients enrolled may vary (see Section 3.1.2).

All patients will be closely monitored for adverse events throughout the study and for at least 28 days after the last dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the NCI CTCAE v5.0.

To characterize the PK properties of idasanutlin, cytarabine, and daunorubicin when given in combination, blood samples will be taken at various timepoints before and during study treatment administration (see Appendix 2).

Response will be determined according to ELN and additional response criteria for AML (see Appendix 19). Refer to Section 4.5.6 for details on tumor assessments.

The schedules of activities is provided in Appendix 1; the schedule for PK and biosample assessments is presented in Appendix 2.

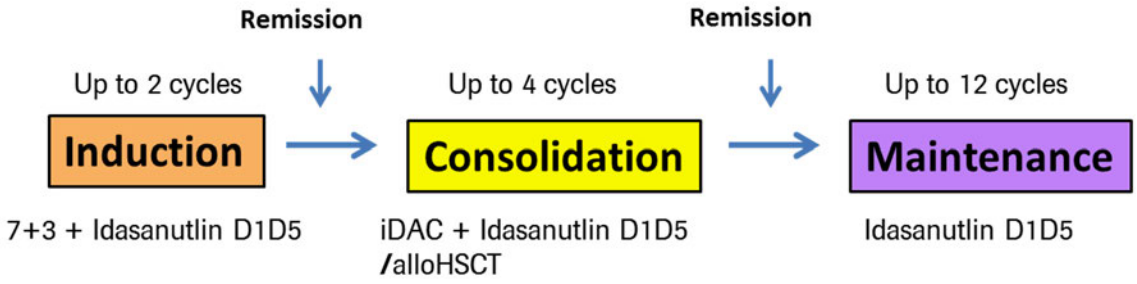
The Sponsor may decide to delay or suspend enrollment within a given treatment cohort or a cohort may be expanded to include more patients based on safety and efficacy. New experimental arms may be added during the study by amending the protocol.

3.1.2 Dose-Escalation Phase

All patients in the dose-escalation phase will undergo the treatment sequence of induction, consolidation, and maintenance (see Figure 3). The purpose of the dose-escalation phase is to identify the RP2D for idasanutlin when combined with fixed doses of cytarabine and daunorubicin in induction. The dose-escalation phase will also allow identifying the idasanutlin dose to be used in consolidation based on all available safety data. The consolidation dose will match the induction dose unless prevented by unacceptable toxicities. As a result, there could be two different idasanutlin doses in induction and consolidation.

The RP2D will be based on the MTD of idasanutlin when combined with fixed doses of 200 mg/m^2/day on Days 1–7 of cytarabine and 60 mg/m^2/day of daunorubicin on Days 1–3 but will also take into account all safety data during treatment.

Figure 3 Induction, Consolidation, and Maintenance Phases



7+3=7 days of cytarabine plus 3 days of daunorubicin; allo-HSCT=allogenic hematopoietic stem cell transplant; iDAC=intermediate dose cytarabine.

A minimum of 9 patients and a maximum of approximately 15 evaluable patients will be enrolled during the dose-escalation phase. Cohorts of 3–6 patients each will be treated at escalating doses of idasanutlin (starting at 200 mg) in accordance with the treatment regimens and dose-escalation rules described in Section 3.1.2.2.

A Bayesian modified continual reassessment method (mCRM) (see Section 3.1.2.3) is planned to guide the dose-escalation phase to determine the MTD that achieves the efficacious exposure observed. The principle underlying this trial design is the assessment of the dose–toxicity relationship in a safe and efficient manner, allowing for enrollment of patients at subsequent dose levels and/or defining the MTD with robust data.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as the first induction cycle. Adverse events meeting the criteria for DLT, as defined in Section 3.1.2.1, will be reported to the Sponsor within 24 hours (see Section 5.3.1).

Patients experiencing a DLT during the DLT window (first induction cycle) may continue treatment after consultation with the Medical Monitor based on safety, tolerability, and clinical benefit.

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD assessments and will be replaced by an additional patient at that same dose level. Patients who miss more than one dose of idasanutlin, cytarabine, or daunorubicin during the DLT assessment window for reasons other than a DLT will also be considered non-evaluable and will be replaced.

Additional cohorts may be added following the Sponsor's decision to explore idasanutlin's therapeutic advantage (e.g., change of regimen). The decision for opening such cohorts will be based on available safety and tolerability data.

3.1.2.1 Definition of DLT

In this study, a DLT is defined as at least one of the following events occurring during the first induction cycle of treatment and assessed by the investigator as clearly not attributable to the patient's underlying disease or concurrent medications:

- Any Grade 5 adverse event unless unequivocally due to the underlying malignancy or extraneous causes
- Any clinically significant, non-hematologic adverse event Grade ≥3 unless clearly unrelated to the treatment (except GI toxicity, fatigue, anorexia, and alopecia)
- GI toxicity: nausea, vomiting and/or diarrhea if Grade ≥3 severity despite adequate supportive care measures (>72 hours of treatment, requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization) which is attributable to study treatment
- Grade 3 AST or ALT toxicity lasting for >7 days, or Grade 4 lasting for any duration of time not attributable to disease progression
- Prolonged myelosuppression: hypocellular (≤5% cellularity) bone marrow without evidence of leukemia, lasting >28 days from first observation (i.e., the first post-treatment bone marrow examination showing ≤5% cellularity or aplasia [Kantarjian et al. 2007])

Other toxicities that are considered clinically relevant and related to study treatment as determined by the investigator and the Medical Monitor may also be considered DLTs.

3.1.2.2 Treatment Regimens and Dose-Escalation Rules

During this first dose-escalation phase, patients will be enrolled as described below.

Three patients will initially be enrolled in each dose cohort, and up to an additional 3 patients can be enrolled in a cohort at the Sponsor's discretion. A minimum of 3 patients enrolled in a cohort must complete at least the first induction cycle (i.e., the DLT assessment window) before enrollment commences in the next cohort(s). Intra-patient dose escalation is not permitted with the exception of the maintenance dose, which can be increased to 200 mg on the basis of safety, tolerability and clinical benefit and after consultation with the Medical Monitor (see Table 1).

Enrollment will begin in Cohort 1 in which patients will be treated at idasanutlin starting doses of 200 mg once a day (QD) on Days 1–5 in the induction cycle(s) given in combination with cytarabine 200 mg/m^2 on Days 1–7 and daunorubicin 60 mg/m^2 on Days 1–3 (see Table 1 for details on treatment regimens).

If safety and tolerability in the first cycle allow (the DLT assessment window), the next cohort will be enrolled. Patients in this cohort will receive an escalated dose of idasanutlin (see Table 2).

During the dose-escalation phase, study treatment will be administered as outlined in Table 1. Patients who achieve remission (CR, CRi, CRp, or CRh) after up to 2 induction cycles will receive chemotherapy consolidation treatment up to 4 cycles or allo-HSCT consolidation at the investigator's discretion. Patients who achieved a confirmed remission at the end of chemotherapy consolidation or allo-HSCT or who underwent allo-HSCT in MLFS after induction (see definition of MLFS in Appendix 19) will receive maintenance treatment for 12 cycles (see Table 1). In cases where the patient receives allo-HSCT consolidation, maintenance should start within 90 days of the transplant and a full pre-transplant hematologic response assessment must be provided if the transplant is performed more than 4 weeks after end of induction. Patients receiving chemotherapy consolidation should start maintenance right after completion of the consolidation. On the basis of safety, tolerability, and clinical benefit and after consultation with the Medical Monitor, patients may be allowed to continue maintenance at the same dose beyond 12 cycles. All patients will be followed for disease progression and survival. The dose for idasanutlin in consolidation will be determined by the Sponsor upon review of all available safety, PK, pharmacodynamic, and efficacy data. The dose for consolidation will not exceed the dose the patient received during induction.

After the last patient in each cohort has completed the DLT assessment window (first induction cycle), the Sponsor will evaluate the next dose recommended according to the mCRM (see Section 3.1.2.3) and determine doses for the subsequent cohort(s), taking into account relevant demographic, adverse event, laboratory, dose administration, and PK (if available) data. At each dose-escalation step, the dose may be escalated or de-escalated, or an additional cohort at the same dose level may be enrolled.

On the basis of review of real-time safety data from this study and all available data from other studies in the program, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

Although the DLT assessment window is defined as the first induction cycle, cumulative toxicities occurring beyond the first cycle may be considered when determining the MTD for idasanutlin. At the end of the dose-escalation phase, the idasanutlin RP2D in combination with cytarabine and daunorubicin will be decided.

Table 1 Treatment during the Dose-Escalation Phase

Cycles		Drug Regimens
Induction Up to 2 cycles [a]		• Cytarabine 200 mg/m^2 IV on Days 1–7 • Daunorubicin 60 mg/m^2 IV on Days 1–3 • **Idasanutlin TBD QD (starting dose 200 mg) orally on Days 1–5**
Chemotherapy consolidation or allo-HSCT (per investigator discretion):		
	Chemotherapy Up to 4 cycles	• Cytarabine 1.5 g/m^2 IV on Days 1–5 administered over 3 hours • **Idasanutlin TBD [b] QD orally on Days 1–5**
	Allo-HSCT	• As per local guidelines
Maintenance Cycles 1–12 [c]		• **Idasanutlin 150 mg QD orally on Days 1–5 [d]**

allo-HSCT = allogenic hematopoietic stem cell transplant; QD=once a day; TBD=to be determined.

[a] Cytarabine/daunorubicin doses/regimen can be lowered in the second cycle as per site guidelines.

[b] Dose in consolidation will be determined by the Sponsor after determination of all available data. It will not exceed induction dose.

[c] On the basis of safety, tolerability, and clinical benefit and after consultation with the Medical Monitor, intra-patient escalation may be allowed to 200 mg.

[d] On the basis of safety, tolerability, and clinical benefit and after consultation with the Medical Monitor, patient may be allowed to continue maintenance at the same dose within past the 12 cycles

3.1.2.3 Use of mCRM for Dose and MTD Determination

The dose escalation will employ a mCRM with overdose control design in order to define the MTD and/or the recommended dose for subsequent cohorts.

The design is based on the primary safety variable, that is, the occurrence of a DLT. The MTD is defined as the dose that maximizes the probability of a DLT being in the targeted toxicity interval of 25%–35%, subject to the probability of the DLT being in the

excessive toxicity interval of 35%–100% being <35%. Simulations of the designs under various scenarios of true toxicity are presented in Appendix 18.

Patients within a phase will be enrolled in cohorts of at least 3 patients each, which, if required, can be expanded with additional patients. Each patient will be observed over 1 cycle of treatment for DLT assessment. After the last patient in each cohort has completed the first cycle of the observation period, the next dose recommended by the mCRM design will be evaluated and that analysis will support the dose decision for the subsequent cohort. At each dose-escalation step, the dose can be escalated, the dose can be de-escalated, or an additional cohort at the same dose level can be enrolled. The idasanutlin starting dose will be 200 mg QD on Days 1–5, and maximum allowable increments for the highest dose already tested will not exceed 150 mg, with a minimum increment of 50 mg. In addition, the dose of idasanutlin will not be escalated above 800 mg QD. The selection of the next dose will be subject to clinical judgment and mandated safety constraints that limit the size of the dose increments. Clinical judgment will always override mCRM recommendations in the dose-selection process.

Dose escalation will stop when the maximum allowed sample size, approximatively 15 evaluable patients, has been reached or if there is enough confidence in the prediction of the MTD (e.g., at least 6 patients have been recruited at the MTD dose and there is a >40% probability of having a DLT rate of 25%–35%).

The dose–toxicity relationship is described by a two-parameter logistic regression model:

$$logit\left(p(d_i^*)\right) = \alpha_1 + \beta_1 log(d_i^*)$$

In this model, α_1 and β_1 are model parameters and $p(d_i^*)$ is the probability of experiencing a DLT at a dose d_i^*, where $d_i^* = \frac{d_i}{d^R}$ being the normalized dose using the reference dose d^R=300 mg.

In order to define the prior distributions (priors) for the parameters of the model, the Sponsor's clinical team completed Bayesian prior elicitation to reach a consensus on the following questions, based on expert knowledge and previous idasanutlin data (e.g., Studies NP27872 and BH29812):

- What is the (low) probability that the DLT rate for the lowest-tested dose (200 mg) is above a threshold of 30%?
- What is the (low) probability that the DLT rate for the highest potentially tested dose (800 mg) is below a threshold of 30%?

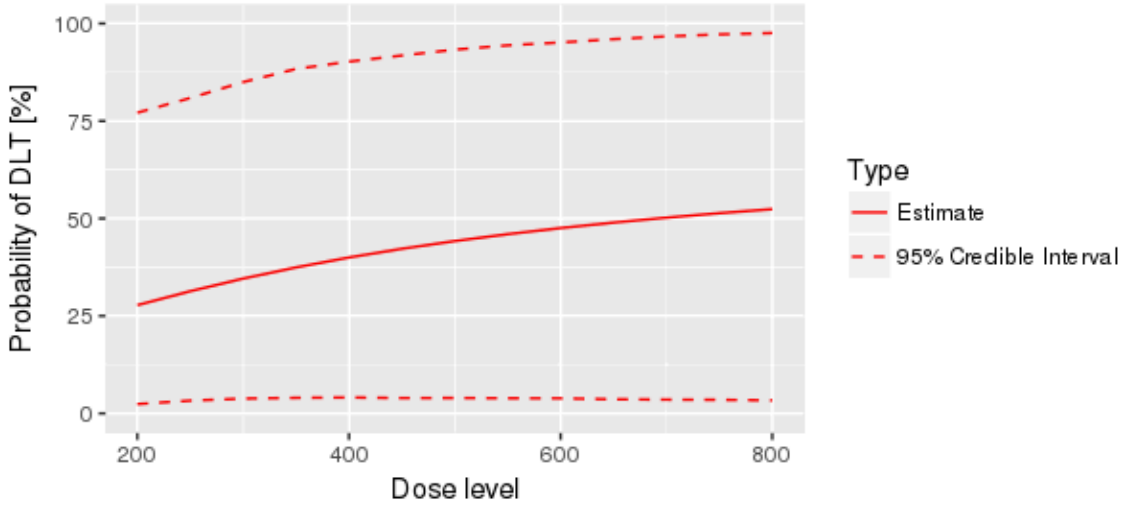
These probabilities reflecting the prior knowledge of dose toxicity were chosen by the team to be 40% and 25%, respectively, for the first and second questions. Of note, a lower or a higher probability would reflect respectively more or less prior knowledge that is borrowed by the model.

As a consequence of this choice, the following prior was defined:

$$\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix} \sim N\left[\begin{pmatrix}-0.797\\ 0.995\end{pmatrix}, \begin{pmatrix}1.699 & 0.280\\ 0.280 & 1.076\end{pmatrix}\right]$$

A visual representation of the prior is shown in Figure 4.

Figure 4 Selected Prior Distribution with 95% Credible Interval



DLT = dose-limiting toxicity.

Consider the various hypothetical trial realizations. If 3 patients are given the starting dose of 200 mg and none develop a DLT, then the next mCRM dose recommendation is 350 mg. Afterward the mCRM recommendations are 450 and 600 mg if the next cohorts of 3 patients also have no DLT observed each time.

If DLTs are observed, the next recommended dose is (almost) equal to or lower than the current dose. Specifically, if the first cohort is at 200 mg QD with 3 patients when one DLT is observed, then the dose recommended for the second cohort is again 200 mg QD. If the first DLTs are observed in the second cohort of 3 patients at 300 mg QD and none in the first cohort of 200 mg QD, the dose for the third cohort is recommended as 300 mg QD. When two or three DLTs are observed in a cohort, a dose de-escalation is always recommended by the model (even if no DLTs were observed in previous cohorts).

A summary of dose recommendations among same principle is provided in Table 2. Of note, these recommendations are subject to the constraint that the dose increase in the subsequent cohort cannot exceed a 50% increment of the previous cohort dose.

Table 2 Hypothetical Trial Realizations (Cohort Size=3)

Dose (mg) at Which the First DLTs Were Observed (mg)	Number of DLTs	Recommended Next Dose (mg)
200	0	350
200	1	200
200	2	≤200
200	3	≤200
350	0	450
350	1	300
350	2	200
350	3	≤200
450	0	600
450	1	450
450	2	300
450	3	200

DLT = dose-limiting toxicity.

The operating characteristics of the proposed mCRM were also carefully evaluated through the use of simulations across different scenarios, and the results are reported in Appendix 18. The general conclusion is that the current design provides, with an assumed sample size of approximatively 15 evaluable patients, overall good performances in selecting the correct MTD, while at the same time limiting the potential amount of overdose across all scenarios.

3.1.3 Post-Consolidation Phase and Expansion Phase

The post-consolidation cohort of 30 patients is designed to further assess the safety and efficacy of idasanutlin given as a single agent to idasanutlin treatment–naive patients in a maintenance setting. Patients will start maintenance right after consolidation completion.

The expansion phase is designed to further assess the safety and efficacy of idasanutlin in combination with cytarabine and daunorubicin at its RP2D in induction and in combination with cytarabine in consolidation followed by a single-agent maintenance.

The expansion phase (approximately 40 patients) is composed of two cohorts: 20 patients with favorable or intermediate risk and 20 patients with high risk (see Table 3).

All expansion patients will be enrolled and treated as described in Table 4, and patients in the post-consolidation cohort will receive maintenance treatment as described in Table 5.

In the expansion cohorts, patients who achieve remission after up to 2 induction cycles will receive chemotherapy consolidation treatment up to 4 cycles with 1.5 mg/m^2 cytarabine or allo-HSCT (as per site guidelines). Patients who achieved a confirmed remission at the end of chemotherapy consolidation or allo-HSCT or who underwent allo-HSCT in MLFS after induction will receive maintenance treatment for 12 cycles (see Table 4).

Patients receiving chemotherapy consolidation in the expansion should start maintenance right after consolidation completion. Patients receiving allo-HSCT consolidation should start within 90 days of the transplant and a full pre-transplant hematologic response assessment must be provided if the transplant is performed more than 4 weeks after end of induction.

On the basis of safety, tolerability, and clinical benefit and after consultation with the Medical Monitor, patients may be allowed to continue maintenance past 12 cycles.

Table 3 Post-Consolidation and Expansion Cohorts

Cohorts	Population
Post-consolidation	Idasanutlin treatment–naive patients in remission who received chemotherapy consolidation but were MRD positive after induction as locally assessed
Expansion: favorable or intermediate risk	Favorable and intermediate risk patients (ELN 2017; see Appendix 8)
Expansion: high risk	Adverse-risk patients (ELN 2017; see Appendix 8) and secondary AML defined as AML evolving from AHD

AHD=antecedent hematologic disorder; AML=acute myeloid leukemia; ELN=European Leukemia Net; MRD=minimum residual disease.

Table 4 Treatment for Expansion Phase (Favorable/Intermediate-Risk and High-Risk Cohorts)

Cycles		Dosing Regimens
Induction Cycles 1–2 [a]		• Cytarabine 200 mg/m^2 IV on Days 1–7 • Daunorubicin 60 mg/m^2 IV on Days 1–3 • **Idasanutlin RP2D QD orally on Days 1–5**
Chemotherapy consolidation or allo-HSCT (per investigator discretion):		
	Chemotherapy Cycles 1–4	• Cytarabine 1.5 g/m^2 IV on Days 1–5 over 3 hr • **Idasanutlin TBD [b] QD orally on Days 1–5**
	Allo-HSCT	As per local guidelines
Maintenance Cycles 1–12 [c]		• **Idasanutlin 150 mg QD orally on Days 1–5 [d]**

HSCT=hematopoietic stem cell transplant; QD=once a day; RP2D = recommended Phase II dose; TBD=to be determined.

[a] Cytarabine/daunorubicin doses/regimen can be lowered in the second cycle as per site guidelines.

[b] Dose in consolidation will be determined by the Sponsor after review of all available data. It will not exceed induction dose.

[c] Based on safety, tolerability, and clinical benefit, and after consultation with the Medical Monitor, patients may be allowed to continue maintenance at the same dose past 12 cycles.

[d] Based on safety, tolerability, and clinical benefit, and after consultation with the Medical Monitor, intra-patient escalation may be allowed to 200 mg.

Table 5 Treatment for Post-Consolidation Phase

Cycle	Dosing Regimen
Maintenance Cycles 1–12 [a]	• Idasanutlin 150 mg QD orally on Days 1–5 [b]

QD=once a day.

[a] Based on safety, tolerability, and clinical benefit and after consultation with the Medical Monitor, patients may be allowed to continue maintenance at the same dose past 12 cycles.

[b] Based on safety, tolerability, and clinical benefit and after consultation with the Medical Monitor, intra-patient escalation may be allowed to 200 mg.

3.1.4 Post-Treatment Follow-Up and Survival Follow-Up

Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments (see Appendix 1) during the post-treatment follow-up period, which will continue until morphologic relapse or up to 2 years, whichever occurs first. Patients who experience morphologic relapse or were followed for 2 years in the post-treatment phase will be evaluated for survival status and

initiation of new anti-leukemia treatment until the end of the study. Details are provided in the schedules of activities (see Appendix 1).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. Patients will be followed up to 2 years after last patient is enrolled or all patients have died, whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Idasanutlin Dose and Schedule

Idasanutlin dosing for this study is based on experience in both single-agent testing (Studies NP27872 and NP28902) in solid tumors and from the combination with 1 g/m^2 cytarabine in Study NP28679 in patients with both R/R and elderly front-line AML. The lowest dose where responses were seen in AML was 200 mg adjusted for formulation differences in combination with cytarabine 1 g/m^2, and as this dose has been proven safe and allowed for escalation (see the Idasanutlin Investigator's Brochure), it has been chosen as the starting dose for idasanutlin. A lower dose of 150 mg has been chosen in maintenance to minimize side effects as patients in remission would not require aggressive treatment. This dose is below the MTD in solid tumor (see the Idasanutlin Investigator's Brochure) where patients have functional bone marrow and is used in polycythemia vera studies over multiple cycles (see the Idasanutlin Investigator's Brochure).

The QD×5-day schedule was proven safe and efficacious in the Phase I AML study NP28679 and is investigated in the ongoing registrational R/R AML study (WO29519). Therefore, it was chosen also for the front-line regimen.

3.3.2 Rationale for Study Population

The dose-escalation phase includes patients with favorable or intermediate risk to maximize accumulated safety data on consolidation by minimizing the number of patients moving to HSCT instead of systemic consolidation.

The expansion phase of the study is separated into two cohorts, patients with favorable or intermediate and patients with high risk, on the basis of their significantly different relapse rates to allow a proper assessment of the benefit within all cytogenetic categories based on a defined sample size.

The post-consolidation cohort will enroll patients in remisssion who received chemotherapy consolidation for whom no transplant is foreseen, but only those who have been identified as MRD positive at the end of induction, and who have not been previously treated with idasanutlin. MRD-positive patients are known to have a higher

risk of relapse and are in greater medical need than patients with MRD-negative status (Jongen-Lavrencic et al. 2018). This cohort will assess the safety and benefit of maintenance regardless of previous treatment in idasanutlin naive patients. Additional cohorts might be opened to test maintenance in a post-HSCT setting or to explore combinations with other drugs, after amendment of the protocol.

3.3.3 Rationale for Population PK/Pharmacodynamic Analysis

Minimal blood sampling is required for conducting population pharmacokinetics analyses to characterize the pharmacokinetics of idasanutlin, cytarabine, and daunorubicin in plasma in the patient population. The population and individual PK parameters will be estimated and the influence of covariates (such as ages, sex, body weight, ethnicity, and disease status, including organ impairments) on these parameters will be investigated in order to determine any subpopulations with higher- or lower-than-expected exposure.

With these PK exposure data, the exposure–response relationship of idasanutlin in combination with cytarabine and daunorubicin on efficacy measures, such as clinical response and OS, as well as the relationship between the exposure of idasanutlin in combination with cytarabine and daunorubicin and the occurrence of serious adverse events—such as GI disorders, pancytopenia, neutropenia, or thrombocytopenia (i.e., acute versus delayed)—if relevant, will be explored. The impact of potential influential covariates will be investigated. Covariates that indicate whether subpopulations may be at increased risk will be investigated.

3.3.4 Rationale for Biomarker Assessments

MDM2 is overexpressed in approximately 50% of AML (Fenaux et al. 1992; Hu et al. 1992; Wattel et al. 1994). This is believed to result in decreased levels of the tumor suppressor p53. Idasanutlin inhibits the interaction of MDM2 with p53, leading to accumulation and activation of p53 and thus inhibition of cancer cell growth and induction of apoptosis.

P53 function can also be lost through mutations. However, mutations occur along the entire sequence of the gene and may not always be detrimental to p53 activity. The p53 mutations status, as well as that of other mutations associated with AML biology and amenable to therapy is therefore important.

Activated p53 induces or inhibits the expression of multiple genes, some of which are secreted (e.g., *Mic-1*) and may be useful as pharmacodynamic indicators of clinical activity of idasanutlin. Additional biomarkers related to the mechanism of action of idasanutlin (p53 and MDM2 activity) and disease biology may be evaluated as appropriate.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing

adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.4.1 AML-Associated Mutations, *MDM2* Protein Expression, *MIC-1* Secretion and Gene Expression

The mutation status of *TP53* as well as mutations of other genes with clinical relevance or prognostic value including *FLT-3, IDH1* and *IDH2* will be assessed by a sequencing panel. MDM2 expression in AML cells in pretreatment blood specimens in patients with AML will be assessed by multi-color flow cytometry. *Mic-1* secretion will be analyzed by ELISA. Various gene expression signatures have been explored for their predictive value for MDM2 inhibitors. In this study, gene expression profiling is planned to clinically validate and explore additional signatures.

3.3.4.2 MRD Assessment

MRD responses are associated with improved outcomes, whereas patients who have MRD after induction and consolidation have a poor prognostic outcome (Jongen-Lavrencic et al. 2018).

MRD will be assessed as a secondary endpoint. Patients achieving remission will undergo additional serial MRD assessments at subsequent scheduled hematologic malignancy assessments (Appendix 1).

These MRD assessments will serve as an exploratory monitoring tool to investigate the depth of response and afford early detection of impending relapse (before cytomorphologic relapse occurs) after idasanutlin therapy.

In patients achieving remission, MRD monitoring from bone marrow aspirates will be prioritized over analysis of other exploratory markers.

MRD assessments can be made with the use of several technologies (e.g., by flow cytometry for abnormal cell phenotypes or leukemia-associated immune phenotype, by next-generation sequencing (NGS) of leukemia-associated mutations, or by polymerase chain reaction [PCR] technologies to detect AML-specific translocations or mutations). Recent reports suggest MRD in AML can also be assessed in cell-free DNA in plasma (Assi et al. 2018) and blood will be collected for this purpose.

MRD in this study will be primarily analyzed by flow cytometry. Other methods may be employed for orthogonal validation and exploration of the correlation of MRD detected in cell-free DNA with that in bone marrow aspirates.

3.3.5 Rationale for Patient-Reported Outcomes

Symptom presentation in AML is variable with patients frequently presenting with fatigue and loss of appetite at the time of diagnosis. Fatigue is the most common and severe

symptom reported by patients, as well as the most persistent over time (Møller et al. 2012), and is associated with decrements in health-related quality of life (HRQoL) and functioning (Schumacher et al. 2002; Messerer et al. 2008).

In addition to disease-related symptoms, cancer treatments, particularly combination therapies, can produce significant treatment-related symptoms and impacts. Patients with AML in particular experience substantial HRQoL burden during treatment, experiencing the greatest decrements shortly after starting induction and rebounding thereafter (Redaelli et al. 2004; Korol et al. 2017). Research has shown that clinicians may underreport the incidence and severity of symptoms patients experience during treatment (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch et al. 2009; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012). Collecting information about these symptoms directly from patients can provide a better understanding of treatment characteristics and their effects. In order to measure baseline symptoms and characterize symptomatic treatment toxicities from the patient perspective, patients will be asked to report on their experience of relevant treatment-related symptoms selected from the validated PRO-CTCAE item bank. On the basis of preliminary safety data, nausea, vomiting, and diarrhea symptoms were identified as being salient to patients' experience of treatment with idasanutlin.

In this study, important disease- and treatment-related symptoms, as well as functioning will be assessed with the FACIT-Fatigue, EORTC QLQ-C30, and EORTC Item Library (selected symptoms), and PRO-CTCAE. The EQ-5D-5L will be administered for the purpose of producing health utility scores for economic modeling.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with AML who meet the eligibility criteria presented below.

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for All Study Phases

For all study cohorts, patients must meet the following inclusion criteria for enrollment in the study:

- Signed Informed Consent Form
- Age ≥18 years old at the time of signing the Informed Consent Form
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Adequate hepatic function, as assessed by the following:

  Serum total bilirubin ≤1.5× institutional upper limit of normal (ULN), unless resulting from hemolysis, Gilbert syndrome, or liver infiltration with leukemia (up to 3× ULN)

  AST or ALT ≤ 3× institutional ULN (or ≤5× upper limit of institutional laboratory reference range if liver infiltration with leukemia)

- Adequate renal function assessed by serum creatinine within reference laboratory ranges or creatinine clearance (by Cockcroft-Gault formula) ≥50 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 6 months after the final dose of idasanutlin, cytarabine, or daunorubicin. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the final dose of idasanutlin, cytarabine, or daunorubicin. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of idasanutlin, cytarabine, or daunorubicin to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Ability to understand and willingness to sign a written informed consent form and comply with all study requirements including completion of patient-reported questionnaires

4.1.1.2 Inclusion Criteria for Patients in the Dose-Escalation and Expansion Phases

Patients in the dose-escalation and expansion cohorts must meet the following inclusion criterion for enrollment in the study:

- Documented/confirmed newly diagnosed AML not previously treated according to WHO (Arber et al. 2016)

4.1.1.3 Inclusion Criteria for Patients in the Post-Consolidation Phase

Patients in the post-consolidation cohort must meet the following inclusion criterion for enrollment in the study:

- Documented/confirmed AML according to WHO (Arber et al. 2016) in remission after induction, within 21 days of end of last chemotherapy consolidation cycle, and were MRD positive at the end of induction as per local laboratory assessment (validated quantitative AML-specific MRD assessment with a >0.1% threshold)

4.1.2 Exclusion Criteria

4.1.2.1 Exclusion Criteria for All Study Phases

Patients who meet any of the following criteria will be excluded from study entry in any part of the study:

- Clinical evidence of CNS leukemia
- Any Grade ≥2 non-hematologic toxicities prior to starting therapy (except fatigue, anorexia, and alopecia).
- Current treatment with any other investigational or commercial agents or therapies administered with the intention to treat their malignancy with the exception of hydroxyurea (HU) or 6-mercaptopurine (6-MP).

  HU and 6-MP must be discontinued at least 24 hours before initiation of study treatment.
- Treatment-related AML
- Acute promyelocytic leukemia
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

  Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer

  Any previously treated malignancy that has been in remission without treatment for ≥2 years prior to enrollment
- Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, impair the ability of the investigator to evaluate the patient, or impair the patient's ability to complete the study such as the following:

  Unstable angina, symptomatic or otherwise uncontrolled arrhythmia (does not include stable, lone atrial fibrillation), uncontrolled hypertension, symptomatic

congestive heart failure (New York Heart Association Class III and IV cardiac disease), myocardial infarction ≤6 months prior to first study treatment, and cerebrovascular accidents ≤6 months before study treatment start

Unstable seizure disorders

- Echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan showing ejection fraction ≤40%
- Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study treatment, such as hereditary coagulation disorders, insulin-dependent diabetes mellitus not optimally controlled with medical management (e.g., presence of ketoacidosis), or active GI conditions affecting absorption
- Infection considered by the investigator to be clinically uncontrolled or of unacceptable risk to the patient upon the induction of neutropenia, that is, patients who are or should be on antimicrobial agents for the treatment of active infection such as the following:

  Fungal infection with visceral involvement, other than mucosal candidiasis, with less than 2 weeks of appropriate systemic antifungal therapy

  Bacterial infection with positive cultures in the 7 days prior to dosing

  Patients who have received less than 5 days of appropriate therapeutic antibiotic therapy for an identified infection

  Neutropenic fever that is considered infection related within 72 hours prior to dosing

  History of symptomatic *C. difficile* infection that required treatment within 1 month prior to dosing.

  - Upon clinical response to *C. difficile* treatment, the stool consistency and frequency must have returned to normal.

- Febrile patients within 72 hours of study treatment initiation (exception of AML-related fever)
- Patients with a history of active or chronic infectious hepatitis unless serology demonstrates clearance of infection
- Patients who are unable to interrupt treatment with moderate to strong CYP2C8 inducers and inhibitors (including gemfibrozil, which is also an inhibitor of UGT1A3), CYP2C8 or OATP1B1/3 substrates, or strong CYP3A4 inducers as defined in Appendix 17 during the treatment phase

  These agents must be discontinued 7−14 days prior to the start of study medication per Section 4.4.2.

- Patients who are unable to temporarily interrupt treatment with oral or parenteral anticoagulants/anti-platelet agents (e.g., warfarin, chronic daily treatment with aspirin [>325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban, or subcutaneous [SC] anticoagulant prophylaxis) during the treatment phase

These agents must be discontinued 7 days (or 5 half-lives) prior to the start of study medication per Section 4.4.2

- Patients who have a history of clinically significant liver cirrhosis (e.g., Child–Pugh class B and C)
- Patients with extramedullary AML with no evidence of systemic involvement
- Pregnant or breastfeeding patients
- Known history of HIV-positive status

  For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local legislation.
- Patients who might refuse to receive blood products and/or have a hypersensitivity to blood products
- Prior treatment with an MDM2 antagonist
- Patients with clinically relevant QTc prolongation (QT interval corrected through use of Fridericia's formula [QTcF] >480 ms), a family history of long QT syndrome

4.1.2.2 Exclusion Criteria for Patients in the Phase Ib Dose-Escalation Phase Only

Patients who meet the following exclusion criterion will be excluded from enrollment in the dose-escalation cohort in any part of the study:

- Adverse risk patients as per ELN 2017 criteria (see Appendix 8)

4.1.2.3 Exclusion Criteria for Patients in Phase Ib Post-Consolidation Phase Only

Patients who meet any of the following exclusion criteria will be excluded from enrollment in the dose-escalation cohort in any part of the study:

- Any ongoing Grade ≥2 hematologic adverse events prior to starting therapy
- Previous HSCT

4.1.2.4 Exclusion Criteria for Patients in the Dose-Escalation Phase and Patients in the Favorable/Intermediate–Risk Cohort of the Expansion Phase Only

Patients who meet any of the following exclusion criterion will be excluded from the dose-escalation phase and the favorable/intermediate–risk cohort of the expansion phase:

- Secondary AML, defined as AML evolving from AHD

4.2 METHOD OF TREATMENT ASSIGNMENT

This Phase Ib/II, open-label, multicenter, non-randomized study evaluates the safety, efficacy, and pharmacokinetics of idasanutlin when given in combination with cytarabine and daunorubicin in induction, in combination with cytarabine in consolidation, and as a single agent in maintenance. During the dose-escalation phase, patients will be assigned to dosing groups through use of an interactive voice or web-based response

system (IxRS). During the expansion phase, all patients will be assigned to receive the RP2D via IxRS. If eligible, patients will receive consolidation and maintenance treatment (see Section 3.1.1 for details).

Enrollment tracking will be performed through the use of the IxRS. Prior to initiation of screening, study site personnel should confirm through the appropriate communication channel that the planned dose-escalation, expansion or post-consolidation cohort is open for enrollment. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves a patient for enrollment, a patient number will be assigned and the patient will be enrolled via the IxRS. The Sponsor will communicate to the sites impending closure of screening for a particular disease cohort.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are idasanutlin, cytarabine, and daunorubicin.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Idasanutlin

Idasanutlin will be supplied by the Sponsor as film-coated tablets. Four different dose strengths of 50 mg (Ro 550-3781/F17), 200 mg (Ro 550-3781/F16), 300 mg (Ro 550-3781/F13) were developed and optimized for use in clinical studies. For information on the formulation and handling of idasanutlin, see the Idasanutlin Investigator's Brochure.

4.3.1.2 Cytarabine

Cytarabine will be supplied locally. For information on the formulation, packaging, and handling of cytarabine, see the local prescribing information for cytarabine as used in standard practice.

4.3.1.3 Daunorubicin

Daunorubicin will be supplied locally. For information on the formulation, packaging, and handling of daunorubicin, see the local prescribing information for daunorubicin as used in standard practice.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Idasanutlin

Patients will self-administer idasanutlin tablets by mouth (PO) each day in the morning according to the schedule of activities (see Appendix 1).

On days when idasanutlin is given in combination with chemotherapy, idasanutlin should be administered first. During consolidation when idasanutlin is given in combination with cytarabine, idasanutlin should be administered first. If vomiting occurs within 15 minutes of taking idasanutlin and all expelled tablets are still intact, another dose may be given, and the second dose noted in the drug log. Otherwise, no replacement dose is to be given. In cases in which a QD dose of idasanutlin is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose. Otherwise, the dose should not be taken. On days when patients are scheduled to have blood samples collected for PK assessments, the time of each dose of idasanutlin will be recorded to the nearest minute. Guidelines for dosage modification and treatment interruption or discontinuation for safety reasons are provided in Section 5.1.3.

Idasanutlin must be stored according to labeled storage conditions.

4.3.2.2 Cytarabine

Cytarabine will be administered in the first cycle of induction at a dose of 200 mg/m^2 QD by IV for 7 days, immediately after the corresponding dose of idasanutlin. Dose and regimen can be lowered per investigator choice in the second induction cycle

Cytarabine will be administered in consolidation at a dose of 1.5 g/m^2 QD for 5 days as IV infusion over a minimum of 3 hours, immediately after corresponding dose of idasanutlin.

The dose of cytarabine should be calculated based on a body weight measurement within 2 days of the first day of each cycle. To calculate body surface area (BSA) for the cytarabine dose, refer to Appendix 9.

4.3.2.3 Daunorubicin

Daunorubicin will be administered in induction at a dose of 60 mg/m^2 QD for 3 days as IV infusion, immediately after the corresponding dose of idasanutlin. Dose and regimen can be lowered per investigator choice in the second induction cycle.

The dose of daunorubicin should be calculated based on a body weight measurement within 2 days of the first day of each cycle. To calculate BSA for the daunorubicin dose, refer to Appendix 9.

4.3.2.4 Premedication

Patient must receive premedication as outlined in Table 6. Further details are provided in Appendix 5.

Table 6 Premedication

Timepoints	Premedication	Administration
Induction and consolidation All cycles	Anti-emetic medicines (second-generation anti-emetic medicines, such as palonosetron, ondansetron, or granisetron)	Mandatory prior to each idasanutlin dosing Dosing as per individual drug prescribing information
	Anti-diarrheal medicines (unless medically contraindicated) [a]	Mandatory prior to each idasanutlin dosing. Dosing as per individual drug prescribing information
	Anti-fungal agents	Strongly recommended prior Day 1 of Cycle 1 Dosing as per individual drug prescribing information (until neutrophil count recovery Grade ≤2)
	Antimicrobial medicines	Strongly recommended prior Day 1 of Cycle 1 Dosing as per individual drug prescribing information (until neutrophil count recovery Grade ≤2)
Maintenance All cycles	Prophylaxis may be utilized on the basis of investigator discretion and patient tolerability. Supportive therapies, including prophylaxis for diarrhea and nausea, are encouraged in the maintenance phase of the study	

[a] Contraindication should be recorded in the medical history or as a separate adverse event.

4.3.3 Investigational Medicinal Product Accountability

Idasanutlin, cytarabine, and daunorubicin are considered IMPs in this trial. Idasanutlin that is required for completion of this study will be provided by the Sponsor. Cytarabine and daunorubicin will be obtained from local sources.

The study site will acknowledge receipt of idasanutlin, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The IMP should only be returned to the Sponsor if

the site is unable to destroy IMP per their standard operating procedure. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Idasanutlin

Currently, the Sponsor does not have any plans to provide the Roche IMP idasanutlin or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing idasanutlin in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) or blood product (e.g., RBCs and platelets) used by a patient from 28 days prior to screening up to the study drug completion/discontinuation visit. All such therapies should be reported to the investigator and recorded on the Concomitant Medications eCRF. The investigator should instruct the patient to notify the investigator (or designee) about any new medications (including over-the-counter drugs and herbal/alternative medications) he/she takes after the start of study medication. Patients must be instructed not to take any additional medications (including over-the-counter products and herbal/alternative medications) during the study without prior consultation with the investigator (or designee).

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy

4.4.2 Prohibited Therapy

Use of the following therapies (excluding protocol-specified treatments) is prohibited during the study:

- Any anti-cancer therapy, approved or investigational, other than intrathecal CNS prophylaxis (except during HSCT consolidation)
- Hormonal therapy other than contraceptives, stable hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors

MDM2 antagonists were shown in vitro to affect all types of hematopoietic progenitors, including megakaryocytic differentiation. They inhibit both early and late stages of megakaryopoiesis, including ploidization and proplatelet formation (Mahfoudhi et al. 2016). As a consequence, the effect on early progenitors might induce long-lasting thrombocytopenia in vivo.

Therefore, because of the potential severity and duration of thrombocytopenia induced by study treatment, patients in clinical need of chronic treatment with oral or parenteral anticoagulant/antiplatelet agents (e.g., warfarin, chronic daily treatment with aspirin [> 325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban, and systemic low-molecular weight heparin), or subcutaneous anticoagulant prophylaxis) are excluded from this study. For patients considered eligible for the study because they are able to tolerate interruption of anticoagulant or antiplatelet treatment, these agents must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study treatment (except used as flushes for indwelling catheters). After the study treatment completion or discontinuation visit, treatment with anticoagulant/antiplatelet agents may be re-initiated for patients with transfusion-independent adequate platelet levels as clinically indicated. An exception can be made for patients with stable blood parameters in need of prophylaxis or after consultation with the Medical Monitor if use is clinically needed. The maintenance of anti-thrombotic treatment should be continuously reassessed. Sustained use over time must be clinically warranted.

Oral or parenteral use of the following drugs will be prohibited during the treatment phase in order to prevent undesirable drug–drug interactions (DDIs).

- Strong/moderate inducers or inhibitors of CYP2C8, including gemfibrozil, which is also an inhibitor of UGT1A3 (see Appendix 17, Table 1)
- CYP2C8 (see substrates or OATP1B1/3 substrates (see Appendix 17, Table 3)
- Strong inducers of CYP3A4 (see Appendix 17, Table 2)

Substrates and inhibitors (Appendix 17, Table 1 and Table 3) must be discontinued 7 days prior to start of study treatment.

Inducers (Appendix 17, Table 1 and Table 2) must be discontinued 14 days prior to start of study treatment.

Drugs listed in Appendix 17 (Table 1, Table 2, and Table 3) may be re-initiated per protocol after the study drug completion or discontinuation visit.

Exception might be made upon discussion with the Medical Monitor based on the medical needs (such as anti-rejection drugs) and patient benefit. In such cases, decision will be clarified in a note to file and filed accordingly.

The above medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the

Internet references provided below when determining whether a certain medication should be inhibited by the above rationale. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.5 STUDY ASSESSMENTS

The schedule of activities performed during the study is detailed in Appendix 1.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Those patients who fail screening because of long waiting times for results or study technical reasons (such as, "cohort on hold") can be rescreened once at a later date if deemed eligible before the screen failure. The decision to rescreen individual patients will be made jointly by the Medical Monitor and the investigator and any other person the investigator or Medical Monitor considers necessary to assist with this decision. Any such decision and the reasons for it will be clearly documented. Any out-of-window assessments need to be repeated and undergo a complete review by the Medical Monitor. Patients deemed ineligible based on screening results for the following exclusion criterion will be allowed to be re-screened once:

- Infection considered by the investigator to be clinically uncontrolled or of unacceptable risk to the patient upon the induction of neutropenia, that is, patients who are or should be on antimicrobial agents for the treatment of active infection

Screening and pretreatment assessments will be performed within 14 days prior to Cycle 1, Day 1 unless otherwise specified. However, results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within the protocol-defined window (prior to randomization/Cycle 1, Day 1) may be used rather than repeating required tests. If a bone marrow aspirate cannot be obtained or is not evaluable, a bone marrow biopsy must be performed for AML diagnostic purposes. If biopsy is performed at screening, a bone marrow sample should be provided for biomarker analysis.

Cytogenetic and molecular risk according to ELN standardized reporting system (see Appendix 7 and Appendix 8) must be available from initial diagnosis prior to enrolment of the patient to allow risk category identification. At a minimum cytogenetic information allowing stratification into the two risk categories (favorable/intermediate versus adverse) needs to be available. Additional information on molecular markers is desirable and should be entered into the eCRF.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

For patients enrolled in the post-consolidation cohort, all details with regards to their previous AML history and treatment will be collected including but not limited to dates, medications, regimens, and responses

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), targeted (limited, symptom-directed) physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline.

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In cases that physical examinations reveal visible manifestations of leukemia or of toxicities (skin involvement, rashes, etc.), additional assessments and measures (such as pictures and measurements) could be undertaken upon additional patient consent.

4.5.4 Performance Status

Performance status will be measured using the ECOG performance status at baseline and will be assessed at regular intervals throughout the study. Further details can be found in Appendix 1 and Appendix 3.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, BSA, and body temperature (°C). Weight will be recorded at screening and as indicated in Appendix 1. Height will be recorded only at screening.

4.5.6 Tumor and Response Evaluations

Hematologic malignancy response will be assessed according to ELN and additional response criteria for AML (see Appendix 19).

Hematologic malignancy response assessments (HMRAs) require sampling of blood and bone marrow on the same day as indicated (a window of 4 days is acceptable between the blood and bone marrow sampling). Bone marrow aspirates are required, but if bone marrow biopsies are performed, the biopsy results should be provided along with the aspirate. Depending on the timepoint in the schedule of activities, the HMRA is established on the basis of blood counts only, or includes the assessment of bone marrow. Patients will be considered to be in their best response state until definitive evidence of relapse is available from blood counts, bone marrow aspirate, or bone marrow biopsy.

In the event that a bone marrow aspirate or biopsy is equivocal (i.e., a recovering marrow), the bone marrow assessment and complete blood count should be repeated >7 days later.

In case disease progression/relapse is determined solely by symptomatic deterioration or by a hematology assessment, a bone marrow aspirate should be performed at that time to complete HMRA. If a patient progresses or relapses outside of the scheduled visit, an unscheduled HMRA must be provided.

If a bone marrow aspirate is performed at any unscheduled timepoint during the study, an unscheduled HMRA must be provided.

Please note that at the time of bone marrow sampling for HMRA, the bone marrow sample collected (aspirate) should also allow for further analyses (e.g., MRD by flow cytometry, MRD by NGS) and the amount taken should be taken into consideration.

During the treatment period, HMRAs are to be performed and reviewed before the start of a new treatment cycle. In the event that a patient has a dosing delay >7 days in consolidation or induction, weekly blood counts must be performed for HMRA to

document evidence of non-progression. Treatment failure and relapse will lead to discontinuation of the study medication and patients will enter follow-up (see Appendix 1).

During the follow-up of patients who remain in remission after treatment, blood will be required every month and a bone marrow aspirate will be required every 6 months to allow for HMRA until relapse. Refer to Appendix 1 for further details.

4.5.7 Laboratory Assessments

Normal ranges for the study laboratory parameters must be submitted to the Sponsor before the study starts.

Samples for the following laboratory tests will be sent to the study site's laboratory for analysis.

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, blasts, promyelocytes, myelocytes, metamyelocytes)

  A manual differential (including WBC) may be needed if an automated differential does not provide blasts. Each differential should add up to 100% (or as close as possible).

- Biochemistry: procalcitonin, glucose, urea or BUN, serum creatinine, creatinine clearance (at screening only determined by Cockcroft-Gault Formula), AST, ALT, LDH, ALP, total bilirubin (and direct bilirubin where total bilirubin > ULN), total protein, albumin, calcium, phosphorus, magnesium, sodium, potassium, bicarbonate, chloride, and uric acid)

- Urinalysis using standard dipstick assessment (pH, protein, glucose, blood, ketones, and leukocytes)

  This must be supplemented with laboratory quantification of any potentially relevant abnormalities as deemed necessary by the investigator.

- *C. difficile* infection at screening

- Viral serology

  Hepatitis B testing includes hepatitis B surface antigen and total hepatitis B core antibody.

  Hepatitis C testing includes hepatitis C virus antibody.

- Coagulation: INR, aPTT (or PTT), and PT

- Serum pregnancy test in females of child bearing potential and postmenopausal females with less than 1 year of amenorrhea

- Bone marrow aspirate pathology report

Total cells counted, absolute mature neutrophils, mature eosinophils, mature basophils, monocytes, lymphocytes, blasts, promyelocytes, myelocytes, metamyelocytes, plasma cells, pronormoblasts, normoblasts, and nucleated erythrocytes

Quantitative and validated AML-specific MRD assessment at end of induction in the post-consolidation cohort

- Bone marrow biopsy (leukemia histology, cellularity, percent cellularity, percent blasts)

4.5.8 Mandatory Samples for Pharmacokinetic, Pharmacodynamic Biomarker, and Exploratory Biomarker Analyses

All samples listed below will be collected according to the schedule of activities outlined in Appendix 2. Unscheduled PK samples matched to ECG recordings may be required in case any prolongation of the QTc interval or other adverse cardiac findings is identified (see Section 4.5.9 for details). For PK analysis, it is of utmost importance to record dosing and blood sampling times accurately.

For sampling procedures, storage conditions, and shipment instructions see the laboratory manual(s).

4.5.8.1 MRD Assessments for Patients in the Post-Consolidation Phase

Patients in the post-consolidation phase with an MRD-positive remission after induction will be enrolled after local MRD assessment with a validated quantitative AML specific method. In order to monitor MRD during maintenance, assessments will be performed at 3 monthly intervals (see Appendix 1).

4.5.8.2 Pharmacokinetic Analyses

PK blood samples will be collected in all patients according to the sample schedule outlined in Appendix 2.

All PK samples will be collected from the arm (limb) that is not being used during the administration of IV drugs (i.e., from the alternate arm). If IV drugs are administered via a central line, PK samples may be collected via the same access after completely flushing the line.

In case a patient experiences an adverse event without plausible clinical explanation, the investigator may perform an additional blood draw for unscheduled PK analysis. Care should be taken to accurately record timing of blood sampling on the unscheduled PK sampling page of the eCRF.

All PK blood samples may be destroyed when the analysis is complete and the Bioanalytical Report finalized. Residual PK samples may be used for additional validation experiments as appropriate.

4.5.8.3 Pharmacodynamic and Exploratory Biomarkers

Bone marrow and blood samples will be collected from patients for pharmacodynamic and exploratory biomarkers. These samples will be tested for protein, nucleic acid, or other tumor cell–derived biomarkers relating to the proposed mechanism of action of idasanutlin, disease-associated markers, or improvement of diagnostic assays. Analysis to include, but are not limited to:

- Sequencing of cancer-related genes including TP53
- Measurement of transcript gene expression
- Protein expression in tumor cells by flow cytometry
- MRD in bone marrow

  MRD will be monitored along clinical response assessments during induction, consolidation and maintenance. MRD will be assessed primarily by flow cytometry. Subsequent confirmation may use NGS panel following AML-specific mutations.

This research involves extraction of DNA, or RNA, analysis of mutations and genomic profiling through use of NGS for a comprehensive panel of genes. Research will not be aimed at distinguishing germline mutations from somatic mutations.

The specimens will also be used for research purposes to identify biomarkers useful for predicting and monitoring response to idasanutlin treatment, identifying biomarkers useful for predicting and monitoring safety, assessing pharmacodynamic effects of idasanutlin treatment, evaluating potential combination partners, and investigating mechanism of therapy resistance. Additional markers may be measured in case a strong scientific rationale for these analyses develops. On the basis continuous analysis of biomarker data any analysis, timepoint, or sample type not considered to be critical for safety may be stopped at any time if the data do not support a strong scientific justification to continue. Some samples that are collected may not be analyzed. Furthermore, some analysis may depend on patient's molecular status or response to treatment.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (Research Biosample Repository; see Section 4.5.11), biologic samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8.4 Clinical Genotyping

DNA will be analyzed from whole blood for polymorphisms which may predict potential DDI and altered metabolism (such as *CYP* genes) of idasanutlin.

If the sample is missed on Day 1, it can be collected at any other scheduled visit. This specimen will be destroyed after analysis. Data arising from clinical genotyping samples will be subject to the confidentiality standards described in Section 8.4.

4.5.8.5 Bone Marrow

Bone marrow (i.e., aspirate and, if sampled, bone marrow biopsy for the analysis of biomarkers) will be collected at screening. Bone marrow aspirate will be collected each time that bone marrow is required for HMRAs (see Appendix 1). If an unscheduled bone marrow aspirate is being collected to assess disease state, then additional bone marrow aspirate should be collected for flow and biomarker analyses. Procedures are described in detail in the laboratory manual(s).

- Bone marrow for MRD flow cytometry (heparin): Analysis will include determination of abnormal cell phenotypes by flow cytometry. After screening, the bone marrow for MRD flow cytometry is the priority sample.
- Bone marrow sample for DNA (in ethylenediaminetetraacetic acid [EDTA]): This is the priority bone marrow sample at screening. Mutation profiling, including TP53 and gene mutations, rearrangements, and fusions are commonly seen in patients with AML. The EDTA bone marrow will potentially be used for MRD monitoring by sequencing
- Bone marrow (PAXgene®): Analysis will include, but will not be limited to, gene expression analysis.

For patients who proceed to transplant, pre-transplant bone marrow samples for MRD and biomarkers should be obtained, when possible.

If sites do their own MRD assessments locally or collect mutational data, please provide this information in the eCRF.

If a patient consents to optional exploratory research, the remainder of the bone marrow sample(s) will be stored in the RBR (see Section 4.5.11) until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9 Electrocardiograms

Resting 12-lead ECG recordings will be obtained in triplicate at specified timepoints, as outlined in the schedule of activities (see Appendix 1) and may be obtained at unscheduled timepoints as clinically indicated. ECGs for each patient should be obtained using the same machine wherever possible. All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and under no conditions while the patient is receiving premedication or an IV infusion of study drug. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of a patient's permanent study file at the site. The following should be recorded on the appropriate eCRF: ECG abnormality (including waveform); heart rate; PQ, PR, RR, and QRS intervals; and QT interval and corrected QTcF interval based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular post-dose timepoint the mean QTcF is >500 ms and/or 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, and severe bradycardia) and provide this information on the eCRF. In the event a patient presents with an episode of Grade ≥2 supraventricular arrhythmia (e.g., atrial fibrillation, atrial flutter, sinus tachycardia), an unscheduled ECG should be reported. Standard-of-care treatment may be instituted at the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled idasanutlin PK sample should be obtained.

4.5.10 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be collected to document the treatment benefit and more fully characterize the safety profile of idasanutlin. PRO data will be obtained through the use of the following instruments: FACIT-Fatigue, EORTC QLQ-C30 (selected scales), EORTC Item library (selected items), PRO-CTCAE (selected symptoms), and EQ-5D-5L.

The questionnaires, translated into the local language as appropriate, should be completed in their entirety at specified time points during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires need to be self-administered before the patient receives any information on disease status and prior to the administration of study treatment. Completion of PRO questionnaires should occur prior to the performance of non-PRO assessments whenever possible. Laboratory blood collections are permitted prior to completing the PRO assessments.

Study site staff will ensure that PRO questionnaires are provided to the patients for completion per the schedule of activities (see Appendix 1), and before drug administration, site staff will confirm completion or alternatively document any reasons questionnaires were not completed. Paper versions of the questionnaires will be administered to patients and entered into the study database by site personnel.

4.5.10.1 FACIT-Fatigue

The FACIT-Fatigue (Version 4) is a validated, reliable, self-report measure for use in a variety of conditions (Yellen et al. 1997; Cella et al. 2005; Lai et al. 2011). It consists of 13 items that assess fatigue using a 7-day recall period. Items are scored on a 0 ("not at all") to 4 ("very much so") response scale (see Appendix 12). Relevant items are reverse scored, and all items are summed to create total scores where higher scores are indicative of better functioning (i.e., less fatigue).

4.5.10.2 EORTC QLQ-C30

The EORTC QLQ-C30 (Version 3) is a validated, reliable, self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week (see Appendix 13). Scale scores can be obtained for the multi-item scales. The first 28 items are scored on a 4-point scale that ranges from "not at all" to "very much," and the last two items are scored on a 7-point scale that ranges from "very poor" to "excellent." Higher scores indicate higher response levels (i.e., higher HRQoL, higher symptom severity). For this study only the physical function (5 items), role function (2 items), and global health status/quality of life (2 items) will be administered to patients.

4.5.10.3 EORTC Item Library

The EORTC Item Library is a database of items used in fully and partially validated EORTC quality-of-life questionnaires (see Appendix 14). Three items from the library will be used to assess disease-related symptoms relevant to patients with AML. Selected symptoms include headaches, dizziness, and bruising. All items are scored on a 4-point scale that ranges from "not at all" to "very much," with higher scores indicative of higher symptom severity.

4.5.10.4 PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize presence, frequency, severity, and interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated on either a 5-point Likert-type scale (frequency, severity, and interference) or dichotomously (presence/absence). Included treatment toxicity terms can be subjective, with or without observable components (e.g., vomiting and nausea, respectively) or primarily observable with subjective components (e.g., rash). The standard PRO-CTCAE recall period is "the past 7 days."

A subset of three symptoms (nausea, vomiting, diarrhea) deemed most applicable to treatment with idasanutlin was selected for this study based on known adverse events. The five items assessing these symptoms will be used to characterize the patient experience of symptomatic adverse events (see Appendix 15).

4.5.10.5 EQ-5D-5L

The EQ-5D-5L is a validated, self-report, health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status. It will be used in this study for informing pharmacoeconomic evaluations (see Appendix 16).

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to study drugs, study disease or other types of cancer, or drug safety:

- Remaining tumor tissue samples (except for remaining blocks, which will be returned to the sites), bone marrow aspirate and blood samples, and any derivatives thereof (e.g. DNA, RNA)
- Blood for serum
- Blood for plasma

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES) or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies.

The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Pregnancy
- Treatment failure
- Unacceptable toxicity

The primary reason for study medication discontinuation should be documented on the appropriate eCRF. Patients discontinuing study medication will be followed as per the schedule of activities (Appendix 1).

After the study drug completion/discontinuation visit, adverse events should be followed as outlined in Section 5.3.1.

Patients who discontinue study treatment will not be replaced, except as outlined below:

- During the dose-escalation phase, patients who discontinue study treatment prior to completing the DLT assessment window for reasons other than a DLT will be replaced by an additional patient at that same dose level.
- Patients who discontinue before having received at least one dose of each scheduled study drugs in induction (idasanutlin, cytarabine, daunorubicin) will be replaced.
- Patients who discontinue before having received at least one dose of idasanutlin in the post-consolidation cohort will be replaced.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determination that it is in the best interest of the patient
- Patient non-compliance (e.g., consistent failure to show up for scheduled visits)

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

If a patient withdraws consent, this request must be documented in the source documents and signed by the investigator. Study personnel may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with study treatment components in completed and ongoing studies. The anticipated important safety risks of IMPs in this study (i.e., idasanutlin, cytarabine, and daunorubicin) are outlined below. Please refer to the Idasanutlin Investigator's Brochure and the local labels for cytarabine and daunorubicin for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk of toxicities (see Section 4.1.2). In addition, patients will undergo adequate safety monitoring during the study, as described in this section. Guidelines for managing adverse events, including criteria for dosage modification and treatment delays or discontinuation, are provided in Section 5.1.3.

5.1.1 Safety Risks of Idasanutlin, Cytarabine, and Daunorubicin in Leukemia

Patient well-being and safety will be protected by applying stringent exclusion criteria specified in Section 4.1.2, by applying the toxicity management guidelines detailed in Appendix 5, and through pharmacovigilance/safety monitoring of all adverse events and laboratory assessments and will be graded according to the NCI CTCAE v5.0 criteria. All treatment-emergent adverse events, whether treatment related or not, will be monitored to resolution or stabilization as feasible. All serious adverse events and any adverse event of special interest will be reported in an expedited fashion (see Sections 5.2.2 and Section 5.2.3). The safety reviews will include summary tables of patient disposition, all adverse events, serious adverse events, deaths, adverse events leading to study discontinuations, adverse events of special interest, and treatment exposure.

Information related to the risks associated with idasanutlin treatment is based on the Idasanutlin Investigator's Brochure. Many of the toxicities experienced by patients were manageable with appropriate prophylaxis and supportive therapy and/or were reversible with discontinuation of the drug. Refer to the current Idasanutlin Investigator's Brochure for details on the safety data from previous studies and for additional information on idasanutlin warnings and precautions.

5.1.1.1 Gastrointestinal Toxicity

The adverse GI events in the Phase I idasanutlin studies include primarily diarrhea, nausea, vomiting, abdominal pain, constipation, and anorexia. Diarrhea was the most common adverse event observed in $>$90% of patients in the AML study NP28679 (mostly Grades 1 and 2 in severity). Nausea and vomiting were also reported in this study but to a lesser extent and all events were generally Grades 1 and 2. Supportive therapies, including prophylaxis for diarrhea and nausea, are encouraged in this study. In addition to institutional guidelines, specific instructions for the management of GI side effects are provided in Section 5.1.3.1 and Appendix 5.

5.1.1.2 Cytopenias

Cytopenias including myelosuppression are an anticipated consequence of the leukemia treatment proposed. Bone marrow toxicity may manifest as cytopenias (i.e., pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, and anemia). The NP27872 study evaluating idasanutlin in patients with solid tumors has shown possible exposure-dependent neutropenia and thrombocytopenia. Most of them were reversible and clinically manageable. In patients with leukemia, who are neutropenic and thrombocytopenic as part of their disease process at baseline, elimination of leukemic blasts is essential for normal marrow recovery. Idasanutlin was associated with myelosuppression in the AML study NP28679, but normal marrow recovery was observed in responding patients. In patients with leukemia, drug-induced myelosuppression is expected during idasanutlin treatment. In this study, blood counts will be monitored closely throughout study treatment (see Appendix 1).

5.1.1.3 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially life-threatening metabolic disorder that occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. This complication is common in patients with acute leukemia but had been very rare with idasanutlin. Please refer to the Idasanutlin Investigator's Brochure.

5.1.1.4 Infections

Infections of various etiologies have been reported in patients with AML in Study NP28679, and patients with AML generally have a higher susceptibility to infection. Infectious diarrhea, and in particular *C. difficile* infection, was reported in approximately 10% of patients with AML administered idasanutlin in Study NP28679, including 1 fatal

case of *C. difficile* infection. In addition to institutional guidelines, specific instructions for the management of *C. difficile* infection are provided in Appendix 5.

5.1.1.5 Electrolyte Disorders

Hypokalemia, hypophosphatemia, and hypomagnesemia were commonly observed in patients treated with idasanutlin. In addition to institutional guidelines, electrolytes should be monitored during treatment, and electrolyte disorders should be treated according to institutional guidelines.

5.1.1.6 Other Adverse Events

Other adverse events commonly reported with idasanutlin include fatigue, asthenia, pyrexia, peripheral edema, headache, dyspnea, dizziness, and chills. These adverse events have been of mild severity and controllable with symptomatic treatment and/or nutritional support.

All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, ECGs as clinically indicated, vital signs, and laboratory measurements (hematology, chemistry, and urinalysis).

5.1.2 Risk of Overlapping Toxicities

Overlapping toxicities from the combined administration of cytarabine, daunorubicin and idasanutlin are anticipated during study treatment phase. These toxicities include myelosuppression (thrombocytopenia, neutropenia, and febrile neutropenia), infectious complications, and GI disorders (diarrhea, nausea and vomiting; see Table 7).

Table 7 Overlapping Toxicities Grade ≥3: Idasanutlin, Cytarabine, and Daunorubicin

	Adverse Events	7+3 [a]	Idasanutlin [b]
Hematologic toxicities	Thrombocytopenia	98%	24.5%
	Neutropenia/febrile neutropenia	91%/35%	12.4%/26%
	Anemia	76%	18.2%
Infections	Infections (SOC)	49%–73.7% (<60 yr) 86% (>60 yr)	30.2%
GI toxicities	Diarrhea	10.8%	13%
	Nausea/vomiting		4%/1.3%

7+3=7 days of cytarabine plus 3 days of daunorubicin; AML=acute myeloid leukemia; GI=gastrointestinal; R/R=relapsed or refractory; SOC=system organ class.

[a] Fernandez et al. 2009; Löwenberg et al. 2009; Lee 2011.

[b] Idasanutlin Investigator's Brochure, Version 10. Cumulative incidences across all solid tumor and R/R AML studies (except GH29914).

5.1.3 Management of Patients Who Experience Specific Adverse Events

Patients should be assessed clinically before each study treatment administration.

Guidelines for management of toxicities (see Appendix 5) are based on laboratory values obtained within 3 days prior to Day 1 of each scheduled drug administration. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to idasanutlin. The dose of idasanutlin may be reduced as outlined in Table 8.

Table 8 Idasanutlin Dose-Reduction Steps

	Dose Reduction in Milligrams		
Initial Dose	Step 1	Step 2	Step 3
150 mg	Minus 50 mg	No further reduction [a]	No further reduction [a]
200 mg	Minus 50 mg	Minus 50 mg	No further reduction [a]
250 mg	Minus 100 mg	Minus 50 mg	No further reduction [a]
300 mg	Minus 100 mg	Minus 50 mg	Minus 50 mg
350 mg	Minus 100 mg	Minus 100 mg	Minus 50 mg
400 mg	Minus 100 mg	Minus 100 mg	Minus 50 mg

[a] When no further idasanutlin dose reduction is possible, the patient will be discontinued from the study drug.

Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications. Guidelines for management of toxicities during treatment are provided in Sections 5.1.3.1 and 5.1.3.2. Exceptions to those guidelines may be allowed by the Sponsor after careful review of the case and discussion with the Medical Monitor.

5.1.3.1 Toxicities during Induction and Consolidation Treatment

Hematologic Toxicities

Table 9 provides guidelines for management of hematologic toxicities that occur during induction and consolidation treatments. Hematologic toxicity is defined as neutropenia, febrile neutropenia, anemia, or thrombocytopenia. If toxicity is thought to be caused mainly by AML, the investigator may decide not to reduce idasanutlin dose.

Table 9 Guidelines for Management of Idasanutlin-Related Hematologic Toxicities in Induction and Consolidation Treatment

Event	Action to Be Taken
Grade 3 or 4 hematologic toxicity	For patients who have had one or no prior dose reductions: • Withhold study treatment. • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles (consolidation only) as required. • If improvement to Grade ≤ 2 or baseline within ≤ 21 days after the scheduled date for the next cycle, resume idasanutlin at current dose (consolidation only). • If improvement to Grade ≤ 2 or baseline 21–28 days after the scheduled date for the next cycle, resume idasanutlin at a reduced dose according to guidelines for current and subsequent cycles (consolidation only). • No more than two dose reductions of idasanutlin are allowed per study phases (induction, consolidation) • If study treatment is withheld for >28 days, permanently discontinue study treatment. • Permanently discontinue study treatment if any of the following events occur: • Grade 3 or 4 thrombocytopenia of any duration if associated with Grade ≥3 bleeding • Recurrent Grade 3 or 4 neutropenia if associated with fever of > 38°C for > 5 days or a documented infection despite use of G-CSF and after one idasanutlin dose reduction • Recurrent Grade 4 neutropenia or thrombocytopenia lasting more than 7 days despite use of G-CSF (for neutropenia) and after one idasanutlin dose reduction For patients who present with recurrent Grade 3 thrombocytopenia/neutropenia in consecutive cycles: • If despite the use of G-CSF, for subsequent cycles, reduce idasanutlin to the next dose level. For patients who have had two dose reductions in the same study phase (induction, consolidation) or for patients who reach the lowest dose level and no further dose reduction is applicable. • Permanently discontinue study treatment

G-CSF = granulocyte colony-stimulating factor.

5.1.3.1.1 Non-Hematologic Toxicities

Guidelines for management of non-hematologic toxicities that occur during induction and consolidation treatment are presented in Table 10 and Table 11.

Table 10 Guidelines for Management of Idasanutlin-Related Gastrointestinal Toxicities in Induction and Consolidation

Event	Action to Be Taken
Diarrhea	Permanently discontinue study treatment for Grade 4 events. Grade 3 diarrhea: • If Grade 3 diarrhea occurs between Days 1 and 5 of the treatment cycle, withhold idasanutlin only if diarrhea does not improve to Grade ≤2 within 72 hours with appropriate treatment. After the study treatment is withheld, if diarrhea improves to Grade ≤2, resume idasanutlin at a reduced dose according to guidelines in Sections 5.1.3 for current and subsequent cycles.
Vomiting	Grade 4 vomiting: • Permanently discontinue study treatment. Grade 1, 2, or 3 vomiting: • If vomiting occurs within 15 minutes of taking idasanutlin, and all expelled tablets are still intact, another dose may be given and the second dose noted in the drug log. Otherwise, no replacement dose is to be given (see Section 4.3.2).

Table 11 Guidelines for Management of Idasanutlin-Related Non-Hematologic Toxicities in Induction and Consolidation

Event	Action to Be Taken
• General guidance for treatment delays, discontinuation, and resumption	• If study treatment is withheld for >21 days because of a toxicity that is attributable to study treatment, permanently discontinue study treatment. • Permanently discontinue study treatment for Grade 4 events. • Dosing may be resumed after resolution to Grade ≤ 2 or baseline status. Resumption of dosing without complete resolution of toxicity may be considered in special circumstances after having obtained Medical Monitor agreement.
IRRs and anaphylaxis	• Guidelines for the management of IRRs are provided in Appendix 5. In case of Grade 4 IRRs or anaphylaxis, study treatment should be permanently discontinued.
Clinical and laboratory TLS	Grade 4 events: • Permanently discontinue study treatment in the case of Grade 4 events. Grade ≤ 3 events: • Withhold study treatment • Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. • If symptoms (laboratory and clinical) have resolved completely, resume idasanutlin at current dose
AST, ALT, or bilirubin increase	Grade 4 events: • Permanently discontinue study treatment. Grade 2 or 3 events (or ≥10 × ULN for patients with liver involvement): • Withhold study treatment. • If improvement to Grade ≤ 1 (or ≤5×ULN [Grade 2]) for patients with liver involvement), resume idasanutlin at full dose for current and subsequent cycles per guidelines. No more than two dose reductions are allowed per study phase (induction, consolidation, maintenance). Patients who have had two prior dose reductions of idasanutlin should be permanently discontinued. • Permanently discontinue study treatment for life-threatening liver toxicity (including Hy's Law cases).

IRR=infusion-related reaction; TLS=tumor lysis syndrome; ULN=upper limit normal.

Table 11 Guidelines for Management of Idasanutlin-Related Non-Hematologic Toxicities in Induction and Consolidation (cont.)

Event	Action to Be Taken
Other non-hematologic toxicities (i.e., not described above), excluding alopecia	Grade 4 events • Permanently discontinue study treatment. Grade 3 events • Withhold study treatment. • If improvement to Grade ≤2 or baseline, resume idasanutlin at reduced dose for subsequent cycles. No more than three dose reductions of idasanutlin per study phase (induction, consolidation) are allowed. For patients who have had two dose reductions in the same study phase (induction, consolidation) or for patients who reach the lowest dose level and no further dose reduction is applicable. • Permanently discontinue study treatment.

IRR=infusion-related reaction; TLS=tumor lysis syndrome; ULN=upper limit normal.

5.1.3.2 Toxicities during Maintenance Treatment

Guidelines for management of toxicities that occur during maintenance treatment are presented in Table 12.

Table 12 Guidelines for Management of Toxicities That Occur during Maintenance

Event	Action to Be Taken
Hematologic toxicity: Grade 3 or 4	• Withhold study treatment. • If improvement to Grade ≤ 2 within 14 days, resume treatment at full dose. • If improvement to Grade ≤ 2 after >14 days, resume study drug at next lower dose for subsequent cycles per guideline in Section 5.1.3. Patients who are not eligible for further dose reductions should be permanently discontinued. • Patients missing two consecutive cycles should be permanently discontinued.
Non-hematologic toxicity: Grade ≥ 3	• Withhold study treatment. • If improvement to Grade ≤ 2 within 14 days, resume treatment at full dose. • If improvement to Grade ≤ 2 after >14 days, resume study drug at next lower dose for subsequent cycles per guideline in Section 5.1.3. Patients who are not eligible for further dose reductions should be permanently discontinued. • Patients missing two consecutive cycles should be permanently discontinued.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- TLS (clinical TLS per Howard criteria, see Appendix 4)
- Bleeding if associated with Grade ≥3 thrombocytopenia
- Grade ≥3 febrile neutropenia
- Grade ≥2 diarrhea
- Grade ≥2 *C. difficile* infection

Note that patients with hematologic adverse events of special interest should be monitored with weekly blood counts until resolution. The final outcome must be reported in the eCRF. Hematologic adverse events of special interest (bleeding and febrile neutropenia) are not reportable for patients in whom myelosuppression arises as a result of confirmed relapsed disease.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 28 days after the final dose of study treatment.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.1.1 Adverse Events Associated with Allo-HSCT

Because of the multiple safety issues associated with the procedure, adverse events clearly related to allo-HSCT and associated procedures (e.g., conditioning, DILs, etc.) should not be reported. Reporting in the maintenance following consolidation will resume following the first dose of study drug as per standard reporting rules.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 13 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 13 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of acute myeloid leukemia should be recorded on the dedicated eCRF page. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.2.2)

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Acute Myeloid Leukemia

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on criteria using 2017 ELN recommendations (see Section 4.5.6). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Hospitalization data will be collected. Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be

documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2 except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and sites are not expected to review the PRO data for adverse events. The PRO-CTCAE will be used to document patient-reported treatment-related symptoms. No attempt will be made to reconcile the findings from reports of treatment-related symptoms by clinicians (NCI CTCAE) and patients (PRO-CTCAE).

5.3.5.12 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to any of the study treatments:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in see Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- DLTs (defined in Section 3.1.2.1; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3; see Section 5.4.2 for details on reporting requirements)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], Ph.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.:

Roche Medical Responsible: [redacted], M.D. (Secondary)

Telephone No.: [redacted]

Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur 28 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the final dose of any study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than

24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of any study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For idasanutlin, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with idasanutlin, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported. Patients with ongoing hematologic adverse events should be monitored with weekly blood counts until resolution. The final outcome must be reported in the eCRF. Hematologic adverse events are not reportable for patients for whom myelosuppression arises as a result of confirmed relapsed disease.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Idasanutlin Investigator's Brochure
- Local prescribing information for cytarabine
- Local prescribing information for daunorubicin

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a mCRM algorithm, as outlined in Section 3.1. It is anticipated that enrollment of up to five cohorts of 3–6 patients each, for a total of 9–15 evaluable patients, will be required to establish the RP2D during the dose-escalation phase (see Appendix 18 for modeling details and simulation results). Assuming 5 not-evaluable patients (see Section 3.1.2 for the definition of evaluable patients), the expected maximum sample size will be approximately 20 patients.

Approximately 40 patients (20 favorable/intermediate–risk patients and 20 high-risk patients in two separate cohorts) will be enrolled during the expansion phase. A sample size of 20 patients in the high-risk cohort is deemed sufficient to provide adequate precision for the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting probability of response of $<$50% with an observed CR proportion of $>$70%. Depending on the proportions of patients with adverse risk or secondary AML enrolled, a CR proportion up to 50%–55% is expected for high-risk patients under current 7+3 standard of care (see Table 14). This assumption is based on the literature related to adverse-risk patients (per ELN 2017 recommendations; Fernandez et al. 2009; Löwenberg et al. 2009; Burnett et al. 2015; Luskin et al. 2016) and secondary AML efficacy data as well as real world data obtained from the clinic (Østgårdt et al. 2014).

Table 14 Potential 90% CI for the True Probability of Achieving Complete Response at the End of Induction for N=20 in High-Risk Patients

Observed Proportion of Patients Achieving Complete Response at End of Induction/Consolidation	2-Sided 90% Clopper-Pearson CI for True Population Proportion (%)
60	(39, 78)
65	(44, 82)
70 [a]	(49, 86)
75	(54, 90)
80	(60, 93)

[a] 14 patients with complete response out of 20 patients in total (75%).

A sample size of 20 favorable/intermediate–risk patients (including patients in the dose-escalation phase already on RP2D) is deemed sufficient for the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting probability of CR <65% if the observed proportion is >85%. Of note, a CR proportion of 65%-80% (Fernandez et al. 2009; Löwenberg et al. 2009; Burnett et al. 2015; Luskin et al. 2016) is expected for favorable/intermediate–risk patients under current 7+3 standard of care (see Table 15).

Table 15 Potential 90% CI for the True Probability of Achieving Complete Response at End of Induction/Consolidation for N=20 in Favorable/Intermediate–Risk Patients

Observed Proportion of Patients Achieving Complete Response at End of Induction/Consolidation	Two-Sided 90% Clopper-Pearson CI for True Population Proportion (%)
70	(49, 86)
75	(54, 90)
80	(60, 93)
85 [a]	(66, 96)
90	(72, 98)

[a] 17 patients with complete response out of 20 patients in total (85%).

In addition, the post-consolidation cohort will enroll 30 idasanutlin-naive patients in remission and MRD-positive at the end of induction.

6.2 SUMMARIES OF PATIENTS CHARACTERISTICS

Major protocol violations and discontinuations from the study will be listed.

Demographics as well as the incidence of treatment discontinuation for reasons other than disease progression will be tabulated. Data related to administration of study treatment components will be listed, and any dose modifications will be flagged. The

number of doses, treatment cycles, and the average dose received for each cohort will be summarized using descriptive statistics (mean, standard deviation, median, and range). Number of patients who enroll, discontinue, or complete the study will be summarized.

6.3 EFFICACY ANALYSES

Efficacy analyses will be performed including all patients who received at least one dose of any study drug given in combination or as a single agent.

Data from patients enrolled during the dose-escalation phase will be analyzed separately, by dose. Data from patients who were treated at the RP2D during the dose-escalation phase will be pooled with the corresponding cohort of the expansion phase (favorable/intermediate cohort). Data from the favorable/intermediate cohort, high-risk cohort (expansion phase), and post-consolidation cohort will be analyzed separately, without direct comparison among cohorts. Response definitions used in the section below are provided in Appendix 19.

6.3.1 Primary Efficacy Endpoint

The primary efficacy analysis will be the estimation of the proportion of patients with a CR at the end of induction treatment.

Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

6.3.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed in patients enrolled during specified phases through use of the same methods described for the primary efficacy endpoint:

Dose-escalation or expansion phase

- Proportion of patients with a CR, CRi, or CRp at the end of induction treatment
- Proportion of patients with a CR or CRh at the end of induction treatment
- Proportion of patients with a negative MRD status at the end of induction treatment

Post-consolidation phase

- Proportion of patients converting from MRD-positive to MRD-negative status at any time during treatment

The following secondary efficacy endpoints will be analyzed in patients enrolled during the dose-escalation and expansion phases:

- EFS, defined as the time from initiation of study treatment (for post-consolidation patients, date of initiation of induction treatment prior to this study) to treatment

failure (failure to achieve CR, CRi, CRp, or CRh), hematologic relapse, or death from any cause, whichever occurs first

Patients with no EFS event at the time of analysis will be censored at the date of last response assessment. Patients with no EFS event and no postbaseline response assessment will be censored at Day 1.

- OS, defined as the time from initiation of study treatment to death from any cause

  Patients who have not died at the time of analysis will be censored at the date the patient was last known to be alive.

- RFS in patients who achieve remission (CR, CRi, CRp, or CRh), defined as the time from remission to the date of hematologic relapse or death from any cause, whichever occurs first

  Patients with no RFS event at the time of analysis will be censored at the date of last response assessment.

The following secondary efficacy endpoints will be analyzed in patients enrolled during the post-consolidation phase:

- EFS, defined as the time from initiation of induction treatment (prior to study entry) to hematologic relapse or death from any cause, whichever occurs first

  Patients with no EFS event at the time of analysis will be censored at the date of last response assessment. Patients with no EFS event and no postbaseline response assessment will be censored at Day 1.

- OS, defined as the time from remission (prior to study entry) to death from any cause

  Patients who have not died at the time of analysis will be censored at the date the patient was last known to be alive.

- RFS in patients who achieved remission (CR, CRi, CRp, or CRh), defined as the time from remission (prior to study entry) to the date of hematologic relapse or death from any cause, whichever occurs first

  Patients with no RFS event at the time of analysis will be censored at the date of last response assessment.

The following secondary efficacy endpoint will be analyzed in patients enrolled during all phases:

- Change from baseline in patient-reported disease-related symptoms and health-related quality of life at specified timepoints, as assessed through use of the FACIT-Fatigue, EORTC QLQ-C30 (selected scales), and EORTC Item Library (selected symptoms)

EFS, OS, and RFS will be analyzed descriptively using the Kaplan–Meier method (Kaplan and Meier 1958).

Where medians are reached, the corresponding estimated median will be provided, along with the 95% CI by means of the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). In addition, when available at the time of the analysis, landmark estimates of the proportion of patients who are event free at 6 months, 9 months, 1 year, and 2 years will be provided, along with 95% asymptotic CIs using Greenwood's formula for standard errors.

Descriptive summary statistics and change from baseline will be calculated at each assessment timepoint for the FACIT-Fatigue, EORTC QLQ-C30 scales, and EORTC Item Library symptoms. Further details of the PRO analyses will be provided in the Statistical Analysis Plan.

6.3.3 Exploratory Efficacy Endpoints

All endpoints listed as primary and secondary will also be analyzed separately within the subset of patients with wild-type p53.

The following exploratory efficacy endpoints will also be assessed:

- MRD response over time (i.e., during induction, consolidation, and maintenance)
- Time to MRD-negative status, defined as time from initiation of treatment to confirmation of negative MRD status

  Patients with continuing MRD positive status at the time of analysis will be censored at the date of last MRD assessment. Patients with no post baseline MRD assessment will be censored at Day 1.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of any study drug, given in combination or as a single agent.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

Safety will be determined using incidence rates for adverse events including mortality, adverse event severity, seriousness, adverse events leading to discontinuation, abnormalities of clinical laboratory tests, and vital signs. Incidence of clinically significant ECG abnormalities will be reported in patient listings and change from baseline summarized. ECG QT and QTcF intervals will be summarized using descriptive statistics.

Exposure to study medication will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics.

The number and proportion of patients reporting each symptom (nausea, vomiting, and diarrhea) on the PRO-CTCAE and the change from baseline by category ("frequency," "severity," "interference") will be reported at each assessment timepoint. A summary of

the maximum post-baseline score and change from baseline will also be provided. Graphical representation of PRO-CTCAE items over time may be provided. PRO-CTCAE analyses will be presented separately from the safety analyses.

6.5 PK ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g., area under the concentration–time curve [AUC], time to maximum concentration, maximum concentration [C_{max}], and terminal half-life).

Individual and mean plasma of each study drugs concentration versus time data will be tabulated and plotted by dose level. The plasma pharmacokinetics of each study drugs will be summarized by estimating total exposure (AUC), C_{max}, total clearance, volume of distribution at steady-state, and terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-patient variability and drug accumulation will be evaluated.

Additional PK analyses will be conducted as appropriate.

6.6 BIOMARKER ANALYSES

Biomarker results will be analyzed for association with patient clinical characteristics, prognostic and predictive value, as well as outcome, prevalence, and correlation with other biomarkers.

Data may be analyzed in the context of this study and in aggregate with data from other studies.

6.7 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.8 INTERIM ANALYSES

Optional interim safety and/or efficacy data review may be carried out by an internal monitoring committee (IMC) that includes Sponsor members at the discretion of the Medical Monitor. The decision to conduct such an analysis and the corresponding timing will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. In particular, given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim efficacy analyses for early stopping (futility) by using observed proportion of patients achieving complete response (e.g., predictive probability that this trial will have a positive outcome if carried out to completion based on historical control data available at the time of analysis).

Further details regarding the rules and guidelines of the data review will be provided in an IMC charter if applicable.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for

Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in

each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health 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 (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

An EDC system will be used for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.7; otherwise, local laboratories will be used. Data from this study will be shared with an expert scientific committee that will provide scientific input for the benefit–risk assessment.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1: Induction

Assessment/Procedure	Screening [a] Days −14 to −1	Induction (28-Day Cycle) up to 2 Cycles									
		D1	D2	D3	D4	D5	D7	D8	D15	D22	D28
Informed consent(s) [b]	x										
Serum pregnancy test [c]	x										
Demographics, medical history, determination of cytogenetic and molecular risk, physical examination, height, chest X-ray (or chest CT) [d]	x										
Vital signs [e], weight, ECOG performance status	x	x						x	x	x	x [f]
Triplicate 12-Lead ECG [g]	x	x	x	x		x					
MUGA or ECHO	x										
Coagulation (INR, aPTT [or PTT], and PT)	x										
Targeted physical examination [h]		x						x	x	x	x [f]
Urinalysis	x	x									
Hepatitis B and C testing [i]	x										
C. difficile toxin and toxin-producing *C. difficile* in stool	x										
Chemistry [j]	x	x	x			x		x	x	x	x [f]
Hematology [j]	x	x	x			x		x	x	x	x [f]
FACIT-Fatigue, EORTC Item Library, PRO-CTCAE [k]		x									

Table 1: Induction (cont.)

Assessment/Procedure	Screening [a] Days −14 to −1	Induction (28-Day Cycle) up to 2 Cycles									
		D1	D2	D3	D4	D5	D7	D8	D15	D22	D28
EORTC QLQ-C30, EQ-5D-5L [k]		x [l]									
HMRA											x [f]
Bone marrow sampling for HMRA [m]	x										x [f]
Bone marrow sampling [n] (MRD/Flow, EDTA, PAXgene®)	x										x [f]
Whole blood sampling (flow, EDTA, clinical)	x	x									x [f, o]
Whole blood sampling PAXgene		x									
RBR sampling/blood serum and plasma (optional)	x										
PK sampling and MIC-1		Refer to Appendix 2									
Concomitant medications	x	To be recorded continually; see Section 4.4									
Adverse events		To be assessed continually; see Section 5.3.1									
Daunorubicin treatment (60 mg/m^2 IV) [p]		x	x	x							
Idasanutlin treatment (PO QD) [p]		x	x	x	x	x					
Cytarabine treatment (200 mg/m^2 IV) [p]		x	x	x	x	x	x				

AML=acute myeloid leukemia; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EDTA=ethylenediaminetetraacetic acid; EOI=end of induction; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality-of-Life Questionnaire–Core 30; EQ-5D-5L=EuroQol 5-Dimension, 5-Level; FACIT=Functional Assessment of Chronic Illness Therapy; HMRA=hematologic malignancy response assessment; MRD=minimal residual disease;

Table 1: Induction (cont.)

MUGA=multiple-gated acquisition (scan); PK=pharmacokinetic; PO=orally; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD=once a day; RBR=Research Biosample Repository; TB=tuberculosis.

[a] The screening period starts with the signing of the Informed Consent Form, including the optional Informed Consent Form if appropriate. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.

[b] Informed consent must be documented before any study-specific screening procedure is performed.

[c] Must be performed within 7 days of the planned D1

[d] If a chest CT is performed up to 28 days prior to study drug administration, a chest X-ray is not required. Patients with a medical history of fungal and TB infections should have a chest CT performed within 28 days prior to study drug administration.

[e] Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate. Body surface area will also be measured at screening.

[f] Should Day 28 not be the last day of the cycle the following will be assessed every 7 days following D28 until end of cycle: biochemistry, hematology, vital signs, ECOG performance status. Bone marrow, HMRA and whole blood sampling should be repeated on the last day of the cycle with D56 as the limit and if not performed within the previous 2 weeks.

[g] All ECGs should be performed within 2 hours prior to idasanutlin administration and 6 hours after idasanutlin administration.

[h] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.

[j] All hematology and biochemistry assessments may be performed up to 3 days prior to the scheduled timepoint. Results must be reviewed by the investigator (or designee) prior to study drug administration.

[k] PRO questionnaires need to be self-administered before the patient receives any information on disease status and prior to the administration of study treatment. Completion of PROs should occur prior to the performance of non-PRO assessments whenever possible. PRO assessments include the FACIT-Fatigue, EORTC QLQ-C30, EORTC Item Library symptoms, PRO-CTCAE, and EQ-5D-5L.

[l] Only first cycle of induction.

[m] At screening, bone marrow examination will require biopsy if an aspirate is not evaluable to confirm the AML diagnosis. For HMRAs during study, bone marrow aspirates are required, but bone marrow biopsies may be performed at the discretion of the investigator.

Table 1: Induction (cont.)

[n] Bone marrow MRD/Flow, EDTA, and PAXgene to be collected at same time as bone marrow for response assessment. If unscheduled bone marrow aspirate is being collected for hematologic response assessment, then bone marrow MRD/flow, EDTA, and PAXgene samples should also be collected. If any MRD assessments are done locally, please record this information in the eCRF. At screening, the priorities for bone marrow samples are EDTA > MRDFlow > PAXgene. At subsequent timepoints the priorities are MRD/Flow > EDTA > PAXgene.

[o] EDTA only.

[p] Refer to Section 4.3.2 for instructions on study treatment administration.

Table 2: Chemotherapy Consolidation

Assessment/Procedure	Consolidation (28-Day Cycle) up to 4 Cycles								
	D1	D2	D3	D4	D5	D8	D15	D22	D28
Vital Signs [a], weight, ECOG performance status	x					x	x	x	x [b]
Single 12-Lead ECG [c]	x	x	x		x				
Targeted physical examination [d]	x					x	x	x	x [b]
Urinalysis	x								
Biochemistry [e]	x	x			x	x	x	x	x [b]
Hematology [e]	x	x			x	x	x	x	x [b]
FACIT-Fatigue, EORTC Item Library, PRO-CTCAE, EORTC QLQ-C30, EQ-5D-5L [f]	x								
HMRA									x [b]
Bone marrow sampling for HMRA [g]									x [b]
Bone marrow sampling for MRD/Flow, EDTA, PAXgene® [h]									x [b]
Whole blood sampling for EDTA and clinical	x								x [b, i]
RBR sampling, blood serum and plasma (optional)	x								
PK sampling	Refer to Appendix 2								
Concomitant medications	To be recorded continually; see Section 4.4								
Adverse events	To be assessed continually; see Section 5.3.1								
Cytarabine (1.5 g/m^2 IV) [j]	x	x	x	x	x				
Idasanutlin (PO QD) [j]	x	x	x	x	x				

Table 2: Chemotherapy Consolidation (cont.)

CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EDTA=ethylenediaminetetraacetic acid; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality-of-Life Questionnaire–Core 30; EQ-5D-5L=EuroQol 5-Dimension, 5-Level; FACIT=Functional Assessment of Chronic Illness Therapy; HMRA=hematologic malignancy response assessment; MRD=minimal residual disease; PK=pharmacokinetic; PO=orally; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD=once a day; QLQ-30=Quality-of-Life Questionnaire Core 30; RBR=Research Biosample Repository.

[a] Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate. Body surface area will also be measured at screening.

[b] Should D28 not be the last day of the cycle the following will be assessed every 7 days following D28 until end of treatment: biochemistry, hematology, vital signs, ECOG performance status. HMRA and whole blood sampling should be repeated last day of the cycle with D49 as limit if not done within the previous 2 weeks. Bone marrow sampling should not be repeated if already done within the last 56 days

[c] All ECGs should be performed within 2 hours prior to idasanutlin administration and 6 hours after idasanutlin administration.

[d] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF

[e] All hematology and biochemistry assessments may be performed up to 3 days prior to the scheduled timepoint. Results must be reviewed by the investigator (or designee) PRIOR to study drug administration.

[f] PRO questionnaires need to be self-administered before the patient receives any information on disease status and prior to the administration of study treatment. Completion of PROs should occur prior to the performance of non-PRO assessments whenever possible. PRO assessments include the FACIT-Fatigue, EORTC QLQ-C30, EORTC Item Library symptoms, PRO-CTCAE, and EQ-5D-5L.

[g] For HMRAs during study, bone marrow aspirates are required, but bone marrow biopsies may be performed at the discretion of the investigator

[h] Bone Marrow MRD/Flow, EDTA, and PAXgene to be collected at same time as bone marrow for response assessment. If unscheduled bone marrow aspirate is being collected for hematologic response assessment, then bone marrow MRD/Flow, EDTA, and PAXgene samples should also be collected. If any MRD assessments are done locally, please record this information in the eCRF. The priorities are MRD/Flow > EDTA > PAXgene.

[i] EDTA only.

[j] Refer to Section 4.3.2 for instructions on study treatment administration.

Table 3: Maintenance in the Dose-Escalation Cohort and Expansion

Assessment/Procedure	Maintenance (28-Day Cycle; ± 2 days) All Cycles						
	D1	D2	D3	D4	D5	D15	D28 (Q3M)
Vital signs [a], weight, ECOG performance status	x						
Single 12-Lead ECG [b]	x						
Targeted physical examination [c]	x						
Urinalysis	x						
FACIT-Fatigue, EORTC Item Library, EQ-5D-5L [d]	x [e]						
PRO-CTCAE, EORTC QLQ-C30 [d]	x						
Biochemistry [f]	x					x [g]	
Hematology [f]	x					x [g]	
HMRA	x						x
Bone marrow sampling for HMRA [h]	x [i]						x
RBR sampling Blood serum, plasma (optional)	x						
Bone marrow sampling for MRD/Flow, EDTA, PAXgene® [j]	x [i]						x
Whole blood sampling for EDTA and clinical	x						x [k]
PK sampling	Refer to Appendix 2						
Concomitant medications	To be recorded continually; see Section 4.4						
Adverse events	To be assessed continually; see Section 5.3.1						
Idasanutlin (PO QD) [l]	x	x	x	x	x		

Table 3: Maintenance in the Escalation Cohort and Expansion (cont.)

CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EDTA=ethylenediaminetetraacetic acid; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality-of-Life Questionnaire–Core 30; EQ-5D-5L=EuroQol 5-Dimension, 5-Level; FACIT=Functional Assessment of Chronic Illness Therapy; HMRA=hematologic malignancy response assessment; MRD=minimal residual disease; PK=pharmacokinetic; PO=orally; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; Q3M=once every 3 months; QD=once a day; RBR=Research Biosample Repository.

[a] Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Body surface area will also be measured at screening.

[b] All ECGs should be performed within 2 hours prior to idasanutlin administration and 6 hours after idasanutlin administration.

[c] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[d] PRO questionnaires need to be self-administered before the patient receives any information on disease status and prior to the administration of study treatment. Completion of PROs should occur prior to the performance of non-PRO assessments whenever possible. PRO assessments include the FACIT-Fatigue, EORTC QLQ-C30, EORTC Item Library symptoms, PRO-CTCAE, and EQ-5D-5L.

[e] Every 3 months starting at Cycle 1.

[f] All hematology and biochemistry assessments may be performed up to 3 days prior to the scheduled timepoint. Results must be reviewed by the investigator (or designee) PRIOR to study drug administration.

[g] Only the first 3 cycles of maintenance.

[h] For HMRAs during study, bone marrow aspirates are required, but bone marrow biopsies may be performed at the discretion of the investigator

[i] Only required at maintenance Month 1 to confirm response in patients having received a transplant, bone marrow examination will require biopsy if an aspirate is not evaluable.

[j] Bone marrow MRD/Flow, EDTA, and PAXgene to be collected at same time as bone marrow for response assessment. If unscheduled bone marrow aspirate is being collected for hematologic response assessment, then bone marrow MRD/Flow, EDTA, and Paxgene samples should also be collected. If any MRD assessments are done locally, please record this information in the eCRF. The priorities are MRD/Flow > EDTA > PAXgene.

[k] EDTA only.

[l] Refer to Section 4.3.2 for instructions on study treatment administration.

Table 4: Maintenance in Post-Consolidation Cohort

Assessment/Procedure	Screening [a]	Maintenance (28-Day Cycle; ± 2 days) All Cycles						
	Days −14 to −1	D1	D2	D3	D4	D5	D15	D28 (Q3M)
Informed consent(s) [b]	x							
Demographics, medical history, determination of cytogenetic and molecular risk, physical examination, height, chest X-ray (or chest CT) [c]	x							
MUGA or ECHO	x							
Urinalysis	x							
Hepatitis B and C testing [d]	x							
C. difficile toxin and toxin-producing *C. difficile* in stool	x							
Serum pregnancy test [e]	x							
Coagulation (INR, aPTT [or PTT], and PT)	x							
Vital signs [f], weight, ECOG performance status	x	x						
Single 12-Lead ECG [g]	x	x						
Targeted physical examination [h]		x						
Urinalysis	x	x						
FACIT-Fatigue, EORTC Item Library, EQ-5D-5L [i]		x [j]						
PRO-CTCAE, EORTC QLQ-C30 [i]		x						
Biochemistry [k]	x	x					x [l]	

Table 4: Maintenance in Post-Consolidation Cohort (cont.)

Assessment/Procedure	Screening [a]	Maintenance (28-Day Cycle; ± 2 day) All Cycles						
	Days −14 to −1	D1	D2	D3	D4	D5	D15	D28 (Q3M)
Hematology [k]	x	x					x [l]	
HMRA								x
Bone marrow sampling for HMRA [m]	x							x
Bone marrow sampling for MRD/Flow, EDTA, PAXgene® [n]	x							x
Whole blood sampling for flow, for EDTA and clinical	x	x						x [o]
RBR sampling, blood serum and plasma (optional)	x							
PK sampling		Refer to Appendix 2						
Concomitant medications	x	To be recorded continually; see Section 4.4						
Adverse events		To be assessed continually; see Section 5.3.1						
Idasanutlin treatment (PO QD) [p]		x	x	x	x	x		

AML=acute myeloid leukemia; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=day; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EDTA=ethylenediaminetetraacetic acid; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality-of-Life Questionnaire–Core 30; EQ-5D-5L=EuroQol 5-Dimension, 5-Level; FACIT=Functional Assessment of Chronic Illness Therapy; HMRA=hematologic malignancy response assessment; MRD=minimal residual disease; MUGA= multiple-gated acquisition (scan); PK=pharmacokinetic; PO=orally; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; Q3M=every 3 months; QD=once a day; RBR=Research Biosample Repository; TB=tuberculosis.

[a] The screening period starts with the signing of the Informed Consent Form, including the optional Informed Consent Form if appropriate. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.

Table 4: Maintenance in Post-Consolidation Cohort (cont.)

[b] Informed consent must be documented before any study-specific screening procedure is performed.
[c] If a chest CT is performed up to 28 days prior to study drug administration, a chest X-ray is not required. Patients with a medical history of fungal and TB infections should have a chest CT performed within 28 days prior to study drug administration. All data related to previous AML treatment such as but not limited to study drugs, regimens, doses, and dates will be collected.
[d] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.
[e] Must be performed within 7 days of the planned D1.
[f] Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Body surface area will also be measured at screening.
[g] All ECGs should be performed within 2 hours prior to idasanutlin administration and 6 hours after idasanutlin administration.
[h] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
[i] PRO questionnaires need to be self-administered before the patient receives any information on disease status and prior to the administration of study treatment. Completion of PROs should occur prior to the performance of non-PRO assessments whenever possible. PRO assessments include the FACIT-Fatigue, EORTC QLQ-C30, EORTC Item Library symptoms, PRO-CTCAE, and EQ-5D-5L.
[j] Every 3 months starting at Cycle 1.
[k] All hematology and biochemistry assessments may be performed up to 3 days prior to the scheduled timepoint. Results must be reviewed by the investigator (or designee) PRIOR to study drug administration.
[l] Only the first 3 cycles of maintenance.
[m] At screening, bone marrow examination will require biopsy if an aspirate is not evaluable. For HMRAs during the study, bone marrow aspirates are required, but bone marrow biopsies may be performed at the discretion of the investigator.
[n] Bone marrow MRD/Flow, EDTA, and PAXgene to be collected at same time as bone marrow for response assessment. If unscheduled bone marrow aspirate is being collected for hematologic response assessment, then bone marrow MRD/Flow, EDTA, and PAXgene samples should also be collected. If any MRD assessments are done locally, please record this information in the eCRF. At screening, the priorities for bone marrow samples are EDTA > MRD Flow > PAXgene. At subsequent timepoints the priorities are MRD/FLOW > EDTA > PAXgene.
[o] EDTA only.
[p] Refer to Section 4.3.2 for instructions on study treatment administration.

Table 5: Post-Treatment Phase

Assessment/Procedure	Study Drug Discontinuation/Early Termination Visit 28 Days after Last Dose of Study Drug	Post-Tx Follow-Up Period		Survival Follow-Up Period (Q3M) [b]
		Q1M up to 2 Years [a]	Q6M up to 2 Years [a]	
Serum pregnancy test	x			
Triplicate 12-lead ECG	x			
Biochemistry	x	x		
Hematology	x	x		
Urinalysis	x			
HMRA	x		x	
Bone marrow sampling for HMRA [c]	x		x	
Bone marrow sampling (MRD/Flow, EDTA, PAXgene®) [d]	x		x	
Whole blood sampling (EDTA, clinical)	x	x		
FACIT-Fatigue, EORTC Item Library, PRO-CTCAE, EORTC QLQ-C30, EQ-5D-5L [e]	x			
Concomitant medications	x			
Adverse events	x	x		
New leukemia treatment		x		x
Survival follow-up				x

Table 5: Post-Treatment Phase (cont.)

CTCAE=Common Terminology Criteria for Adverse Events; eCRF=electronic Case Report Form; EDTA=ethylenediaminetetraacetic acid; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality-of-Life Questionnaire–Core 30; EQ-5D-5L=EuroQol 5-Dimension, 5-Level; FACIT=Functional Assessment of Chronic Illness Therapy; HMRA=hematologic malignancy response assessment; MRD=minimal residual disease; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; Q1M=once a month; Q3M=once every 3 months; Q6M=once every 6 months; Tx=treatment.

[a] Patients who discontinue treatment for any reasons other than morphological relapse (see Section 4.5.6) will undergo assessments during the post-treatment follow-up period, which will continue until morphological relapse (see Section 4.5.6) or 2 years, whichever occurs first. The first post-treatment follow-up visit is 1 month after the end of drug discontinuation visit.

[b] Patients who experience morphological relapse (see Section 4.5.6) or ended their 2 years post-treatment follow-up will be evaluated for survival status and new anti-leukemia treatment every 3 months during the survival follow-up period, which will continue until the end of the study.

[c] For HMRAs during the study, bone marrow aspirates are required, but bone marrow biopsies may be performed at the discretion of the investigator.

[d] Bone marrow MRD/Flow, EDTA, and PAXgene to be collected at same time as bone marrow for response assessment. If unscheduled bone marrow aspirate is being collected for hematologic response assessment, then bone marrow MRD/Flow, EDTA, and PAXgene samples should also be collected. If any MRD assessments are done locally, please record this information in the eCRF. The priorities are MRD/FLOW > EDTA > PAXgene.

[e] PRO questionnaires need to be self-administered before the patient receives any information on disease status. Completion of PROs should occur prior to the performance of non-PRO assessments whenever possible. PRO assessments include the FACIT-Fatigue, EORTC QLQ-C30, EORTC Item Library symptoms, PRO-CTCAE, and EQ-5D-5L.

Appendix 2
Schedule of Pharmacokinetic and PD Biomarker Samples

Table 1 All Cohorts

Study Visit		Plasma Idasanutlin PK Sample	Serum MIC-1 Sample	Plasma Cytarabine PK Sample	Plasma Daunorubicin PK Sample
Induc-tion Cycle 1	Day 1	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)
		30 (±10) min after end of daunorubicin infusion	30 (±10) min after end of daunorubicin infusion	30 (±10) min after end of daunorubicin infusion	30 (±10) min after end of daunorubicin infusion
		3 hr (±20 min) post-idasanutlin administration	3 hr (±20 min) post-idasanutlin administration	3 hr (±20 min) post-idasanutlin administration	3 hr (±20 min) post-idasanutlin administration
		6 hr (±20 min) post-idasanutlin administration	6 hr (±20 min) post-idasanutlin administration	6 hr (±20 min) post-idasanutlin administration	6 hr (±20 min) post-idasanutlin administration
		9 (±1) hr post-idasanutlin administration	9 (±1) hr post-idasanutlin administration	9 (±1) hr post-idasanutlin administration	9 (±1) hr post-idasanutlin administration
	Day 3	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)
			1.5 hr (±10 min) post-idasanutlin administration		1.5 hr (±10 min) post-idasanutlin administration
			3 hr (±10 min) post-idasanutlin administration		3 hr (±10 min) post-idasanutlin administration
			6 hr (±20 min) post-idasanutlin administration		6 hr (±20 min) post-idasanutlin administration
			9 hr (±1 h) post-idasanutlin administration		9 hr (±1 h) post-idasanutlin administration

PK=pharmacokinetic.

Table 1 All Cohorts (cont.)

Study Visit		Plasma Idasanutlin PK Sample	Serum MIC-1 Sample	Plasma Cytarabine PK Sample	Plasma Daunorubicin PK Sample
Induc-tion Cycle 1 (cont.)	Day 5	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)	Pre-idasanutlin administration (any time prior to dose on that day)
		30 (±10) min after end of daunorubicin infusion	30 (±10) min after end of daunorubicin infusion		
		3 hr (±20 min) post-idasanutlin administration	3 hr (±20 min) post-idasanutlin administration		
		6 hr (±20 min) post-idasanutlin administration	6 hr (±20 min) post-idasanutlin administration		
		9 (±1) hr post-idasanutlin administration	9 (±1) hr post-idasanutlin administration		
Consol-idation Cycle 1	Day 1	Pre-idasanutlin administration (any time prior to dose on that day)		Pre-idasanutlin administration (any time prior to dose on that day)	
		3 hr (end of cytarabine infusion)		3 hr (end of cytarabine infusion)	
		6 hr (±20 min) post-idasanutlin administration		6 hr (±20 min) post-idasanutlin administration	

PK=pharmacokinetic.

Table 1 All Cohorts (cont.)

Study Visit		Plasma Idasanutlin PK Sample	Serum MIC-1 Sample	Plasma Cytarabine PK Sample	Plasma Daunorubicin PK Sample
Consolidation Cycle 1 (cont.)	Day 5	Pre-idasanutlin administration (any time prior to dose on that day)		Pre-idasanutlin administration (any time prior to dose on that day)	
		1.5 hr (±10 min) post-idasanutlin administration		1.5 hr (±10 min) post-idasanutlin administration	
		3 hr (±10 min) post-idasanutlin administration		3 hr (±10 min) post-idasanutlin administration	
		6 hr (±20 min) post-idasanutlin administration		6 hr (±20 min) post-idasanutlin administration	
		9 (±1) hr post-idasanutlin administration		9 (±1) hr post-idasanutlin administration	
Maintenance Cycle 1 (expansion and post-consolidation)	Day 1	Pre-idasanutlin administration (any time prior to dose on that day)			
		6 hr (±20 min) post-idasanutlin administration			

PK=pharmacokinetic.

Table 1 All Cohorts (cont.)

Study Visit		Plasma Idasanutlin PK Sample	Serum MIC-1 Sample	Plasma Cytarabine PK Sample	Plasma Daunorubicin PK Sample
Maintenance Cycle 1 (expansion and post-consolidation) (cont.)	Day 5	Pre-idasanutlin administration (any time prior to dose on that day)			
		1.5 hr (±10 min) post-idasanutlin administration			
		3 hr (±10 min) post-idasanutlin administration			
		6 hr (±20 min) post-idasanutlin administration			
		9 (±1) hr post-idasanutlin administration			

PK=pharmacokinetic.

Appendix 3
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
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, for example, light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about $>$50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair $>$50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 4
Howard Definition and Classification of Tumor Lysis Syndrome (Howard et al. 2011)

Definitions of Laboratory and Clinical Tumor Lysis Syndrome [a]		
Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 μmol/L) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/L) in adults or >6.5 mg/dL (2.1 mmol/L) in children	
Hyperkalemia	Potassium >6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/L) or ionized calcium <1.12 (0.3 mmol/L) [b]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury [c]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 μmol/L) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hours

[a] In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

[b] The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter $+ 0.8 \times (4 -$ albumin in grams per deciliter).

[c] Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL (26.5 μmol/L) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin et al. (2007).

REFERENCES

Howard SC, Jones P, Pui CH. The Tumor Lysis Syndrome. N Engl J Med. 2011 May 12;364(19):1844–54.

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Appendix 5
Toxicity Management Guidelines

DIARRHEA MANAGEMENT GUIDELINES AND RECOMMENDATIONS

Diarrhea has been the most frequently reported adverse event in patients with acute myeloid leukemia (AML) administered with idasanutlin (Study NP28679).

Prior to first study medication administration

Patients should be carefully screened for active GI conditions (e.g., graft-versus-host disease, G≥2) and uncontrolled irritable bowel disease (i.e., Crohn's disease, ulcerative colitis, diverticulosis-associated colitis, and Behçet disease) prior to enrollment. Patients with active GI conditions as noted in the exclusion criteria are not permitted to start treatment.

Establish the individual patient's normal bowel function. Discuss how function could change in the future with treatment. Discuss dietary management/rehydration.

Prophylactic antidiarrheal therapy is to be instituted for all patients administered study medications in induction and consolidation as follows (unless medically contra-indicated):

Loading dose of loperamide 4 mg orally 30 minutes before first administration of idasanutlin

Instruct patients on warning signs (e.g., bloody stools, associated fever, and dizziness).

- **Event management**

  Should diarrhea occur: administer loperamide 2 mg orally every 4 hours or after every unformed stool to a maximum dose of 16 mg/24 hr.

  Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, and antacids), *C. difficile* infection (CDI), malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber

  Dietary measures: Discontinue all lactose-containing products, alcohol and high-osmolar supplements; instruct patients to eat frequent small meals (e.g., bananas, rice, apples, and toast).

  Loperamide treatment should be continued until patient is diarrhea-free for ≥24 hours or until Day 10 of the specific cycle, whichever occurs first.

  Record the number of stools and report complications (e.g., fever or dizziness upon standing).

  Encourage adequate hydration.

  Monitor electrolytes daily (i.e., potassium, magnesium, calcium, and sodium).

  Administer IV fluids as clinically indicated and aim at all times for electrolyte correction.

Table 1 Diarrhea Management According to CTCAE Grade

Diarrhea Grade	Recommended Actions
Grade 1/2	a) See all supportive recommendations indicated above (i.e., loperamide, symptomatic management, dietary counselling, rehydration, and electrolyte correction).
	b) No change in study medication dose will be implemented for Grade ≤ 2 diarrhea; patients should receive maximal supportive care as described above.
	c) If diarrhea persists after 48 – 72 hours despite administration of the maximum recommended daily loperamide dose (16 mg/24 hr), second-line agents may be considered.
Grade 3	d) Consider second-line agents (i.e., diphenoxylate, atropine, octreotide, budesonide, or tincture of opium) if the patient is receiving loperamide at the maximum recommended daily dose (16 mg/24 hr).
	e) If no improvement is observed within 24 hours, test for CDI.
	f) If, despite adequate supportive care, Grade 3 diarrhea persists >48 hours without responding to loperamide at the maximum recommended daily dose (16 mg/24 hr), the idasanutlin dose should be reduced as per Table 11.
	g) If clinical characteristics have NOT improved to Grade ≤ 1 or baseline by 28 days despite the patient receiving maximal supportive care, idasanutlin must be permanently discontinued.
	h) If the diarrhea recurs at Grade 3 despite supportive care and idasanutlin dose reduction, idasanutlin must be permanently discontinued.
Grade 4	i) If, despite prophylaxis and adequate supportive care, Grade 4 diarrhea is diagnosed, idasanutlin must be permanently discontinued.
	j) Consider second-line agents (i.e., diphenoxylate, atropine, octreotide, budesonide, or tincture of opium) if the patient is currently receiving loperamide at the maximum recommended daily dose (16 mg/24 hr).
	k) If no improvement is observed within 24 hours, test for CDI.

CDI = *Clostridium difficile* infection; CTCAE = Common Terminology Criteria for Adverse Events.

***CLOSTRIDIUM DIFFICILE* INFECTION**

Due to the high incidence of diarrhea, CDI may occur undetected. Once diagnosed, monitoring CDI is also challenging, as treatment-induced diarrhea may be persistent. The risk factors for CDI are common in this patient population (treatment with systemic

antibiotics, decreased leukocyte count, decreased albumin, and increased temperature, and increased ATLAS score).

- **Prior to first administration of study medication**

  Patients should be carefully screened for active/uncontrolled infections prior to enrollment. Patients receiving antimicrobial agents with therapeutic intent to eradicate *C. difficile* are not permitted to begin study medication, as noted in the exclusion criteria

  Testing the stool from asymptomatic patients, at screening, or during an ongoing episode of diarrhea to verify cure is not clinically useful.

- **Diarrhea management**

  If loperamide at the maximum recommended daily dose (16 mg/24 hours) does not improve the severity of diarrhea within 24 hours, test for C. difficile toxin and toxin-producing C. difficile in stool.

  Consider clinically appropriate empirical therapy before microbiological evidence is found such as the following:

  Metronidazole: if the initial episode is mild CDI, administer 500 mg orally, three times daily for 10–14 days.

  Vancomycin: if recurrent disease is suspected or moderate to severe CDI is present, administer 125 mg orally four times daily for 10–14 days.

  Once CDI is confirmed (colonoscopic or histopathological findings demonstrating pseudomembranous colitis may NOT suffice to confirm CDI), perform the following:

  Discontinue unnecessary antimicrobial therapy.

  Maintain adequate replacement of fluid and electrolytes.

  Avoid any anti-motility medications/dietary supplements.

  Use of proton pump inhibitors should be reviewed, as it has been shown to increase CDI susceptibility (Garey et al. 2008; Janarthanan et al. 2012).

  Loperamide should not be used as a primary therapy.

  Vancomycin is preferred antibiotic of choice (125 mg orally four times daily for 10–14 days or 500 mg four times daily for 10 days).

  Fidaxomicin (200 mg twice daily for 10 days) can be administered as an alternative if CDI is severe or in case of recurrence.

  Simple measures such as thorough hand washing with soap and water (alcohol-based hand cleanser is not effective against spores) and avoidance of rectal thermometers is recommended for patients and healthcare providers.

EMESIS GUIDELINES

Nausea and vomiting have been reported in $>30\%$ of AML patients who are administered idasanutlin in combination with cytarabine.

All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Treatment to mitigate emesis must be given prophylactically in induction and consolidation. Emesis should be managed symptomatically throughout the study conduct.

- Second-generation anti-emetics such as palonosetron, ondansetron or granisetron should be given prior each Idasanutlin dosing as per individual drug prescribing information in induction and consolidation
- Re-dosing of study medication after emesis:

If vomiting occurs within 15 minutes of administering study medication and all expelled tablets are still intact, another dose may be administered, and the second dose must be recorded in the drug log. Otherwise, no replacement dose is to be administered.

ANTIMICROBIAL GUIDELINES

Patients with leukemia are at increased risk for infections; therefore, the following guidelines must be followed and instituted for prophylactic anti-microbial therapy. Any additional prophylactic antimicrobial therapy per institutional/local guidelines is allowed for patients unless prohibited otherwise.

- **Prior to first administration of study medication in induction and consolidation**

Patients should be carefully screened for evidence of active/uncontrolled infections prior to enrollment. Patients with acute/active infection or receiving antimicrobial agents with therapeutic intent (as noted in the exclusion criteria) are not permitted to begin treatment.

Prophylaxis is strongly recommended in this study.

- **Recommended antifungal prophylaxis:**

  Oral posaconazole administered at 200 mg PO three times daily from Day 1 until neutrophil recovery (sustained neutrophil count >0.5 g/L or until therapeutic antifungal therapy started) or according to local/institutional guidelines

  Substitution of PO formulation with IV formulation (e.g., in patients who do not tolerate the PO formulation) is not recommended.

- **Recommended antibacterial prophylaxis**

  Levofloxacin administered at 500 mg once daily from Day 1 until neutrophil recovery or until IV antibiotic treatment is administered (whichever occurs first) or according to local/institutional guidelines

Prophylaxis for *Pneumocystis carinii* will be administered according to local/institutional guidelines (trimethoprim [and combinations] is allowed if used with prophylactic purposes.

Patients in this study will be closely monitored for infection, and prompt therapy will be instituted as necessary.

CYTOPENIA MANAGEMENT GUIDELINES

Idasanutlin was associated with myelosuppression in patients with AML in Study NP28679, but normal bone marrow recovery was observed in patients showing a clinical response. In the current study, blood counts will be monitored closely throughout study treatment.

- **Recommended transfusion thresholds**

  Prophylactic platelet transfusion is recommended when platelet counts is $< 10 \times 10^9$/L, and therapeutic transfusions are recommended when clinically indicated (any platelet value in the presence of hemorrhagic symptoms).

  In patients with human leukocyte antigen (HLA) sensitization, HLA-compatible platelet transfusions should be administered.

  Filtrated packed red blood cells will be administered to maintain the hematocrit $>$ 30% or the hemoglobin > 8 g/dL, or for any hemoglobin level if related symptomatology is present (e.g., profuse asthenia).

  In patients who have previously received allogenic or autologous bone marrow transplantation, filtered and irradiated hemoderivatives are recommended.

  Plasma transfusion is recommended in patients with disseminated intravascular coagulation or severe hemorrhage with abnormal coagulation parameters.

  Please refer to existing guidelines for optimal management of febrile neutropenia (Montesinos et al. 2008; de Naurois et al. 2010; Flowers et al. 2013).

TUMOR LYSIS SYNDROME MANAGEMENT GUIDELINES

Five cases with laboratory evidence of tumor lysis syndrome (TLS) have been reported in AML patients who were treated in Study NP28679 as a treatment-related adverse event. Of these, a single case with clinical features was reported. The patient was treated for TLS and recovered.

Per the exclusion criterion, WBC counts should be $\leq 50{,}000/mm^3$. Hydroxyurea (HU) or leukapheresis is allowed to meet this criterion. HU must be discontinued at least 24 hours prior to initiating study medication.

- **Prior to first administration of study medication**

  Assess the risk for TLS based on a clinical assessment and comorbidities (e.g., presence of renal dysfunction or cardiac failure) prior to initiating study medication.

  Risk factors for TLS risk are not unique to idasanutlin and are multifactorial (i.e., WBC count $\geq 25{,}000/mm^3$, serum uric acid > 7.5 mg/dL, and LDH $> 4 \times$ ULN).

Use of scores or algorithms can help in the assessment (Montensinos et al. 2008).

Prior to initiating study medication, correct preexisting hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia.

Prophylactic IV hydration and administration of uric acid reducing agents is permitted according to patient's TLS risk factors and the investigator's clinical judgment (further guidance can be found in [Jones et al. 2015]).

- **TLS management during study treatment**

  Monitor clinical chemistries (sodium, potassium, chloride, calcium, carbonate, BUN, uric acid, serum creatinine, LDH, and phosphorus) and hydration status.

  Withhold study medication if any of the following are observed:

  Potassium ≥7.0 mmol/L and/or symptoms of hyperkalemia (e.g., muscle cramps, arrhythmias, paresthesia, and nausea)

  Serum uric acid (SUA) ≥10 mg/dL (595 µmol/L) or SUA ≥ 8.0 mg/dL (476 µmol/L) with a 25% increase and a creatinine increase ≥0.3 mg/dL from baseline

  Nephrology assessment warrants initiating dialysis

  Appropriate hydration is strongly recommended for all patients C1D1 – C1D5, especially patients considered at risk.

  Correct relevant clinical chemistry abnormalities promptly.

  Maintain a low threshold for recourse with IV fluids and consideration of uric acid reducing agents.

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Jones GJ, Will A, Jackson GH, et al. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. British Journal of Haematology 2015;169:661–71.

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Appendix 6
Calculation of Creatinine Clearance Using the Modified Cockcroft-Gault Formula

$$eCCR = (140 - Age) \times IBM\ a\ (kg) \times [0.85\ if\ female])/(72 \times serum\ creatinine\ [mg/dL])$$

Or, if serum creatinine is in micromoles per liter (μmol/L):

$$eCCR = (140 - Age) \times IBM^{a}\ (kg) \times [1.23\ if\ male,\ 1.04\ if\ female])/(serum\ creatinine\ [\mu mol/L])$$

eCCR = estimated creatinine clearance; IBM = ideal body weight.

[a] IBM (kg) = ([height in cm − 154] × 0.9)] + (50 if male, 45.5 if female).

Appendix 7
Classification of Acute Myeloid Leukemia (World Health Organization, 2016 revision)

WHO myeloid neoplasm and acute leukemia classification
Myeloid neoplasms with germ line predisposition[a]
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
APL with PML-RARA
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
AML with t(6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of CEBPA
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes [b]
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)

Myeloid leukemia associated with Down syndrome
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1
MPAL with t(v;11q23.3); KMT2A rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS

[a] This includes Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction (AML with germ line CEBPA mutation, Myeloid neoplasms with germ line DDX41 mutation*), Myeloid neoplasms with germ line predisposition and preexisting platelet disorders (Myeloid neoplasms with germ line RUNX1 mutation*, Myeloid neoplasms with germ line ANKRD26 mutation*, Myeloid neoplasms with germ line ETV6 mutation*), and Myeloid neoplasms with germ line predisposition and other organ dysfunction (Myeloid neoplasms with germ line GATA2 mutation, Myeloid neoplasms associated with BM failure syndromes, Myeloid neoplasms associated with telomere biology disorders, JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders, Myeloid neoplasms associated with Down syndrome*) * Lymphoid neoplasms also reported.

[b] Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities: −7/del(7q), del(5q)/t(5q), i(17q)/t(17p), −13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13)
Balanced abnormalities: t(11;16)(q23.3;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2), t(3;5)(q25.3;q35.1)

REFERENCE

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Appendix 8
European LeukemiaNet Standardization Reporting System

2017 ELN Risk Stratification by Genetics

Risk category*	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}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	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,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Notes: 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.

‡ 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).

¶ 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.

REFERENCE

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;129:424–47.

Appendix 9
Mosteller and Dubois Calculation for Body Surface Area (BSA)

Mosteller Formula

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times weight\ (kg)}{3600}}$$

Or

$$BSA\ (m^2) = ([Height(cm) \times Weight(kg)]/3600)^{½}$$

DUBOIS FORMULA

$$BSA\ (m^2) = (W^{0.425} \times H^{0.725}) = 0.007184$$

Weight in kilograms

Height in centimeters

Appendix 10
New York Heart Association Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, for example, shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than ordinary activity, for example, walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

NYHA = New York Heart Association.

Appendix 11
Fridericia's Formula for Corrected QT interval

$$QTcF = QT/RR^{0.33}$$

Appendix 12
FACIT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 13
EORTC QLQ-C30 (Selected Scales)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): __ __ __ __ __ __

Today's date (Day, Month, Year): 31 __ __ __ __ __ __

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

Appendix 14
EORTC Item Library Symptoms

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

Please fill in your initials: αααα
Your birthdate (Day, Month, Year): βδβδβχχδ
Today's date (Day, Month, Year): 31 βδβδβχχδ

		Not at All	A Little	Quite a Bit	Very Much
1.	Have you had headaches?	1	2	3	4
2.	Have you been dizzy?	1	2	3	4
3.	Did you bruise?	1	2	3	4

Appendix 15
Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 26 May 2018

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

Appendix 16
EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

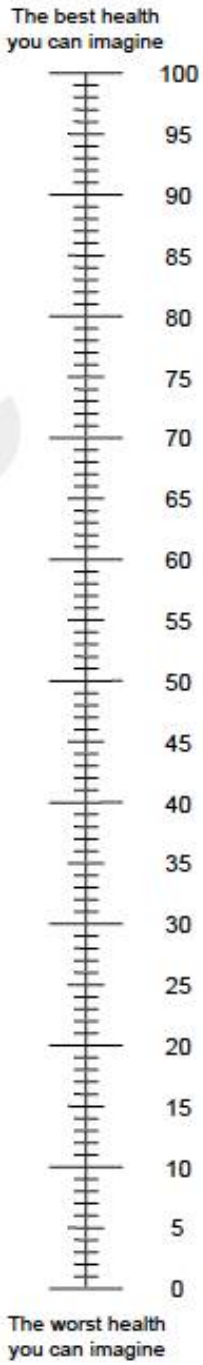
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 17
PROHIBITED MEDICATIONS

Table 1 Prohibited CYP2C8 Substrates, Inhibitors, and Inducers

Substrates	Inhibitors	Inducer
Amodiaquine	Gemfibrozil [a]	Rifampicin
Cerivastatin	Monteleukast	
Ibuprofen	Pioglitazone	
Paclitaxel	Quercetin	
Repaglinide	Rosiglitazone	
Rosiglitazone	Trimethoprim [b]	
Torasemide		

[a] Gemfibrozil is also a strong inhibitor of UGT1A3.

[b] Trimethoprim may be allowed if *Pneumocystis* pneumonia prophylaxis is required per local/institutional guidelines and no therapeutic alternative (pentamidine) is considered clinically suitable. Trimethoprim use and rationale should be documented in the patient notes.

Table 2 Prohibited CYP3A4 Inducers

Inducers (Strong)
Carbamazepine
Cyproterone
Efavirenz
Etravirine
Modafinil
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin
Rifampicin
St. John's wort

Table 3 Prohibited OATP1B1/3 Substrates

OATP1B1/3 Substrates [a]
Atorvastatin
Atrasentan
Bosentan
Ezetimibe
Fluvastatin
Glyburide
Irinotecan
Olmesartan
Pitavastatin
Pravastatin
Repaglinide
Rifampin
Rosuvastatin
Simvastatin Acid
Telmisartan
Valsartan

OATP1B1/3 = organic anion-transporting polypeptide 1B1/3.

[a] OATP1B1/3 substrates with a half-life shorter than 1 day are allowed except during idasanutlin treatment and for 72 hours after the last dose of idasanutlin.

Appendix 18
Modified Continual Reassessment Method Simulations

Dose Escalation

This appendix provides details of the design that will guide the dose-escalation stage of this study and of its operating characteristics through simulations. All analyses were performed using the R statistical software R version 3.4.4 (2018-03-15) (Team 2017) (see Section 3.1.2.3 for additional information).

Rationale for Model-Based Design

The modified continuous reassessment method (mCRM) design uses a statistical model that actively seeks a dose level close to the maximum tolerated dose (MTD) by using toxicity data from all enrolled evaluable patients to compute a precise dose-toxicity curve. It locates the MTD efficiently and minimizes the number of patients treated at possibly pharmacological inactive dose levels. Such model-based designs have been successfully applied in many Phase I dose-escalation studies (S. P et al. 2004; C, JJ, and LL 2009; B, M, and T 2008). The simulations in this appendix investigate the operating characteristics of the design as implemented for this study.

In this design the MTD is defined as the dose maximizing the posterior probability that the DLT rate, $\pi(MTD) \in [0.2, 0.35]$ while keeping the probability of overdose $P\{p(MTD) > 0.35\} < 0.35$.

Statistical Model

A two-parameter logistic model will be used to fit the dose-toxicity relationship. The probability of DLT at dose d_j, $p(d_j)$ is defined as (1)

$$p(d_j) = \frac{exp(\alpha + \beta x_j)}{1 + exp(\alpha + \beta x_j)} \qquad (1)$$

where

$$x_j = ln\left(\frac{d_j}{d^*}\right)$$

and d^* is the reference dose (in this case $d^* = 300$ mg).

The model (1) thus can be rewritten as (2):

$$ln\left(\frac{p(d_j)}{1-p(d_j)}\right) = \alpha + \beta x_j \qquad (2)$$

where α and β are the parameters to be estimated and assumed to follow a bivariate normal distribution.

Model Prior

A minimally informative bivariate normal prior for the parameters of the DLT-dose response curve (α, β) is constructed in order to have a weak impact to the final MTD determination (B, M, and T 2008).

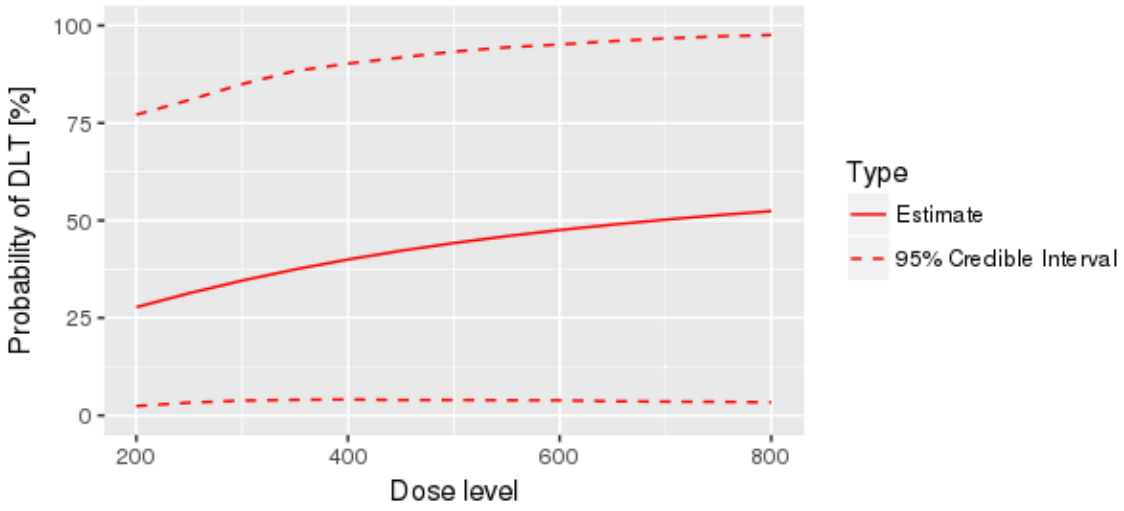
The parameters of the minimally informative prior are listed below (3):

$$\mu = (\alpha, \beta) = (-0.797, 0.995)$$
$$\Sigma = \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha\beta} \\ \sigma_{\alpha\beta} & \sigma_\beta^2 \end{pmatrix} = \begin{pmatrix} 1.699 & 0.280 \\ 0.280 & 1.076 \end{pmatrix} \qquad (3)$$

where μ and Σ are the parameters of the bivariate normal distribution.

The prior distribution used to determine the dose-escalation decision for this study is shown in Figure 1.

Figure 1 Minimally Informative Prior



Maximum Dose Increments

The maximum dose Increments relative to the previous dose level is 150 mg. Only increments that are multiples of 50 mg (e.g. 50 mg, 100 mg or 150 mg) are allowed.

Stopping Rules

The algorithm will recommend ending the dose escalation if any of the following criteria applies:

- Maximum number of patients: the maximum sample size of 15 DLT-evaluable patients has reached **OR**
- Enough information on MTD: at least a minimum of 6 patients evaluated *and* at least 6 patients have been accrued near the MTD dose (where near means differing from the MTD by at most 5%) *and* the posterior probability that the MTD dose lies within the target toxicity interval is above 50% **OR**
- Maximum dose is safe: at least 6 subjects have been observed at the maximum dose or near (differing from the maximum dose by at most 0.05%) *and* it is at least 50% likely that the probability of a DLT for the maximum dose is below 0.2.

Dose Grid

The dose grid that has been used in this design starts from 200 mg and ends at 800 mg, with an increment of 50 mg.

Model Performance Evaluation

To illustrate how the design will perform, different escalation scenarios are explored and results are tabulated in Table 1. Each row represents four different situations: which dose would the model recommend, after seeing no DLTs in previous cohorts and when 0, 1, 2, or 3 DLTs are observed in the current cohort. The evaluation is based on cohort size=3, "<200" indicates that the model would stop escalating and the trial would be halted.

Table 1 Hypothetical Trial Realizations (Cohort Size=3)

Dose (mg) at which the First DLTs Were Observed (mg)	Number of DLTs	Recommended Next Dose (mg)
200	0	350
200	1	200
200	2	<200
200	3	<200
350	0	450
350	1	300
350	2	200
350	3	<200
450	0	600
450	1	450
450	2	300
450	3	200

As can be seen from the Table above, in general in presence of no DLTs the model will suggest to escalate close to what the max increment allow, while in presence of one DLT the increment is in general zero. Then, with 2 or 3 DLTs the model always recommends to de-escalate or STOP. Therefore, the results show that the design will adequately adapt the dose in the presence of observed DLTs.

Simulation Study

A simulation study is conducted to evaluate the operating characteristics for the chosen design parameters (priors, reference dose, stopping rule) under various dose-toxicity scenarios. The different scenarios have been selected in order to cover a wide range of dose-toxicity possibilities and to be able to quantify the risk and benefit, should these scenarios actually occur.

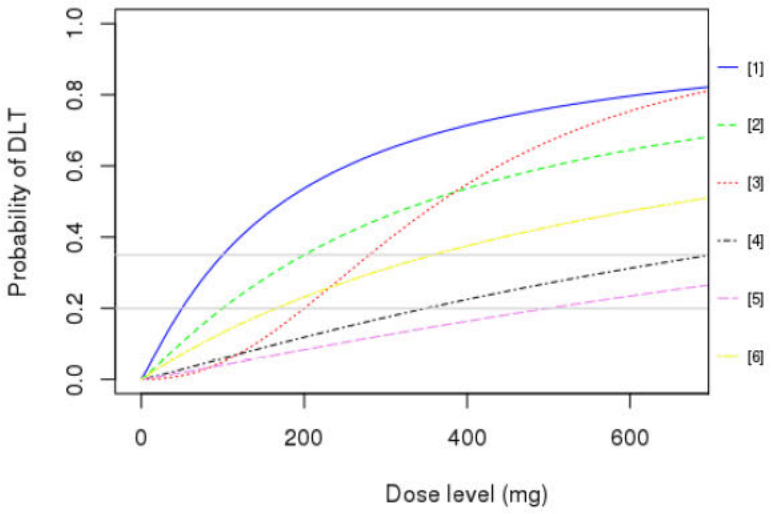
Dose–Toxicity Scenarios

The different scenarios have been selected in order to cover a wide range of dose-toxicity possibilities and to be able to quantify the risk and benefit, should these scenarios actually occur.

As shown in Figure 2, we explore 6 scenarios. The first 5 represent decreasing levels of toxicity, while the last one considers the toxicity depicted in the prior as true toxicity. Scenario 3 has a steeper dose-toxicity curve meaning that the acceptable dose interval is very narrow. Some scenarios are relatively extreme, but still they will be informative on

how the model would eventually perform, despite the likelihood of the scenario remains extremely low.

Figure 2 True Dose-Toxicity Scenarios



Notes: [Scenario number]: dose range corresponding to target toxicity. Scenario [6] considers the toxicity depicted in the prior as the true toxicity. True target dose ranges corresponding to these scenarios are shown in Table 2 below.

Simulation Results

For each of the scenarios, 1000 trials were simulated.

The design is evaluated using the following criteria: the MTD chosen, the number of subjects treated at doses higher than the MTD and the total number of subjects treated. For each criterion, we report in Table 2 the median (and 10th 90th percentiles) from the 1000 simulations.

Table 2 Summary of Simulations Results

Scenario	Target Dose Interval	Total Number of Patients	Number of Patients Treated Above Target Toxicity	Proportion of DLTs in the Trials	Dose Selected as MTD
1	50 - 100	3 (3, 9)	3 (3, 9)	66.7% (33.3%, 100%)	0 (0, 0)
2	100 - 200	6 (3, 15)	6 (3, 15)	41.7% (26.7%, 66.7%)	0 (0, 250)
3	200 - 280	15 (3, 15)	3 (0, 12)	33.3% (20%, 66.7%)	200 (0, 300)
4	350 - 700	15 (3, 15)	0 (0, 0)	20% (6.7%, 33.3%)	350 (0, 650)
5	500 - 1000	15 (6, 15)	0 (0, 0)	13.3% (6.7%, 33.3%)	450 (0, 750)
6	166 - 359	15 (3, 15)	0 (0, 6)	33.3% (20%, 66.7%)	200 (0, 400)

From these simulations, it can be seen that the design is able to provide a reliable estimate of the MTD: usually, the median of the doses selected as MTD is within or slightly below the target toxicity dose range (at the lower end of the range), which means that the design is relatively conservative.

For dose-toxicity curves corresponding too most toxic scenarios (e.g. scenarios 1, 2) the median selected dose is 0, indicating that no MTD within the tested dose range can be found most of the time. In these cases, the required number of treated patients is far less than 15 evaluable patients, meaning that the design tends to recommend stopping dose escalation, avoiding therefore unnecessary exposure to toxic doses

In addition, we see that the number of patients treated over the dose toxicity interval is quite limited, with the exception of the first two scenarios where all doses were too toxic (all patients being treated at or above the target toxicity).

The good performances of the algorithm are also confirmed by the median proportion of DLTs observed in the simulations, which is always $\leq 1/3$ (except for toxic scenarios 1 and 2).

Finally, in terms of sample sizes, the median number of patients required to give a MTD recommendation is usually 15 patients across all scenarios. In case of too high toxicity, the required number is, as outlined above, lower.

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Le Tourneau C, Lee JJ, and Siu LL. Dose escalation methods in Phase I cancer clinical trials. J Natl Cancer Inst 2009;101:708–20.

Schöffski P, Riggert S, Fumoleau P, et al. Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. Ann Oncol 2004;15:1816–24.

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Appendix 19
Response Criteria for Acute Myeloid Leukemia

Patients will be assessed according to European LeukemiaNet (ELN) response categories (adapted from Döhner et al. 2017) and two additional response categories: complete remission with incomplete platelet count recovery (CRp) and complete remission with partial hematologic recovery (CRh) (see Table 1).

At least 500 nucleated cells on spiculated marrow smears should be counted to qualify for complete remission (CR), complete remission with incomplete blood count recovery (CRi), CRp, or CRh. For other response categories, no minimal cell count is required.

Table 1 Response Criteria for Acute Myeloid Leukemia

Response	Definition
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); and platelet count $\geq 100 \times 10^9$/L (100,000/μL)
CRi	All CR criteria except for residual neutropenia (ANC $< 1.0 \times 10^9$/L [1000/μL]) or residual thrombocytopenia (platelet count $< 100 \times 10^9$/L [100,000/μL])
CRp	All CR criteria except for residual thrombocytopenia (platelet count $< 100 \times 10^9$/L [100,000/μL])
CRh	All CR criteria except ANC $> 0.5 \times 10^9$/L (500/μL) but $< 1.0 \times 10^9$/L (1000/μL) and platelet count $> 50 \times 10^9$/L (50,000/μL) but $< 100 \times 10^9$/L (100,000/μL)
MLFS	Bone marrow blasts $<5\%$; absence of blasts with Auer rods; absence of extramedullary disease; and residual neutropenia (ANC $<0.5 \times 10^9$/L [500/μL]) and residual thrombocytopenia (platelet count $<50 \times 10^9$/L [50,000/μL])
PR	All hematologic criteria for CR; bone marrow blast percentage of 5%-25%; and $\geq 50\%$ decrease from baseline in percentage of bone marrow blasts
SD	Absence of CR, CRi, CRp, CRh, MLFS, and PR; and no clinical or cytologic progressive disease by investigator assessment
PD	Evidence of an increase in bone marrow blast percentage and/or increase in absolute blast counts in the blood, defined as at least one of the following: • $>50\%$ increase from baseline in bone marrow blasts (a minimum increase of 15 percentage points is required in cases with $<30\%$ bone marrow blasts at baseline) • $>50\%$ increase in peripheral blasts (WBC count $\times$ % blasts) to $> 25 \times 10^9$/L (25,000/μL) (in the absence of differentiation syndrome) • New extramedullary disease
Hematologic relapse	Following CR, CRi, CRp, or CRh, development of extramedullary disease or reappearance of either of the following that is not attributable to another cause (e.g., bone marrow regeneration after consolidation therapy): peripheral blasts or $\geq 5\%$ bone marrow blasts
Death in aplasia	Death occurring ≥ 7 days following completion of induction treatment while cytopenic, with an aplastic or hypoplastic bone marrow obtained within 7 days of death and no evidence of persistent leukemia
Death from indeterminate cause	Death occurring before completion of induction treatment or <7 days following its completion; or death occurring ≥ 7 days following completion of induction treatment therapy with no peripheral blasts, but no bone marrow examination available

BM = bone marrow; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet count recovery; MLFS = morphologic leukemia-free state; PD = progressive disease; PR = partial remission; SD = stable disease.