Official Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase III Study of Idasanutlin, an MDM2 Antagonist, With Cytarabine Versus Cytarabine Plus Placebo in Patients With Relapsed or Refractory Acute Myeloid Leukemia (AML)

NCT Number: NCT02545283

Document Date: Protocol Version 6: 12-July-2019

PROTOCOL

TITLE:	**A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE III STUDY OF IDASANUTLIN, AN MDM2 ANTAGONIST, WITH CYTARABINE VERSUS CYTARABINE PLUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (AML)**
PROTOCOL NUMBER:	WO29519
VERSION NUMBER:	6
EUDRACT NUMBER:	2014-003065-15
TEST PRODUCT:	Idasanutlin (RO5503781)
MEDICAL MONITOR:	[redacted], *Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 10 August 2015
DATES AMENDED:	Version 2: 27 August 2015 Version 3 (VHP): 19 November 2015 Version 4: 2 June 2016 Version 5: 20 December 2018 Version 6: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
12-Jul-2019 09:42:53	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol WO29519 has been amended to include the addition of an interim overall survival (OS) analysis. Changes to the protocol, along with a rationale for each change, are summarized below:

- Table 1 has been removed and the reader has been referred instead to the Idasanutlin Investigator's Brochure, which contains the most recent information on completed and ongoing studies with idasanutlin (Section 1.2.1).
- The secondary and exploratory endpoints have been updated to also assess the efficacy of treatment in *FLT3*, *IDH1*, and *IDH2*-mutated AML subpopulations, since these have become clinically actionable with targeted treatment (Sections 2.2, 2.3, 3.3.5, 3.4.3, 6.4.2, and 6.4.3).
- An interim efficacy analysis has been added to allow early testing of OS in the event of relevant efficacy, which could influence faster access to study drug for patients (Sections 3.1 and 6.11).
- The total length of study has been revised to 5.5 years (Sections 3.2 and 6.4.1.1).
- The majority of the patients (~85%) are expected to be *TP53* wild type (WT); therefore, the overall results for this trial are expected to be driven by the outcome in the *TP53* WT population. To assess the efficacy of idasanutlin treatment, the assessment of secondary efficacy endpoints has been modified to limit testing within the *TP53* WT population only (Sections 2.2 and 3.3.2), with analysis of intent-to-treat population (all-patient population) as exploratory. In addition, the efficacy analysis section has been revised to reflect the updated study design (Section 6.4). The list of secondary and exploratory efficacy endpoints, as well as the list of outcome measures, have been modified (Sections 3.4, 6.4.2, and 6.4.3).
- To align with Section 4.4.2.2 of the protocol, a clarification has been added to the exclusion criterion that medications known to prolong the QT interval must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study medication until 5 days after the final administration of study medication (Section 4.1.2).
- A correction was made in the exclusion criteria from "irritable bowel disease" to "inflammatory bowel disease" (Section 4.1.2).
- Clarification has been made that written informed consent is necessary again for re-screening and must be obtained before any re-screening related tests and evaluations (Section 4.5.1 and Appendix 1).
- The hematologic malignancy response assessment criteria have been updated to align with 2017 European LeukemiaNet recommendations for diagnosis and management of AML in adults (Section 4.5.8).
- The pharmacodynamic and biomarker section has been updated to include *TP53* mutation status determination and to provide reference to the technical information of the assay used, [redacted] (Section 4.5.10.2).

- Clarification has been added that reporting of the adverse event of special interest thrombocytopenia (Grade≥3 if associated with hemorrhage or bleeding) requires two separate adverse event of special interest forms to be completed (one for each of hemorrhage and thrombocytopenia) to facilitate complete safety analysis of patients experiencing thrombocytopenia Grade ≥ 3 concurrently with hemorrhage or bleeding (Section 5.2.3).
- Additional sensitivity analyses have been added in order to develop comprehensive interpretation of the data (Section 6.5).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.6).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- Clarification has been added that the adherence to protocol-mandated prophylaxis for diarrhea, emesis, and fungal and bacterial infections is applicable to all treatment cycles (Appendix 14).
- Emesis guidelines have been modified to clarify that 5-HT3-receptor antagonists with long half–life, such as palonosetron, may be taken on Day 1 only of the respective cycle (Appendix 14).
- The Medical Monitor names and associated contact information have been updated throughout the document.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE III STUDY OF IDASANUTLIN, AN MDM2 ANTAGONIST, WITH CYTARABINE VERSUS CYTARABINE PLUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (AML)**
PROTOCOL NUMBER:	WO29519
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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 return the signed original of this form as instructed by your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE III STUDY OF IDASANUTLIN, AN MDM2 ANTAGONIST, WITH CYTARABINE VERSUS CYTARABINE PLUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (AML)**
PROTOCOL NUMBER:	WO29519
VERSION NUMBER:	6
EUDRACT NUMBER:	2014-003065-15
TEST PRODUCT:	Idasanutlin (RO5503781)
PHASE:	Phase III
INDICATION:	Relapsed/Refractory Acute Myeloid Leukemia
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Objective

The primary objective for this study is as follows:

Within the *TP53* wild type (WT) population

- To compare overall survival (OS) in patients with relapsed or refractory acute myeloid leukemia (AML) who have been randomized to idasanutlin in combination with cytarabine versus those who have been randomized to cytarabine and placebo

Secondary Objective

The secondary objectives for this study are as follows:

Within the *TP53* WT population

- To compare the proportions of complete remission (CR) between treatment arms
- To compare event-free survival (EFS) between treatment arms
- *To compare ORR (defined as CR), complete remission with incomplete platelet count recovery [CRp], and complete remission with incomplete blood count recovery [CRi]) between treatment arms*
- *To compare duration of remission following CR (DOR) between treatment arms*
- To compare the proportions of allogeneic hematopoietic stem cell transplant (HSCT) following *CR* between treatment arms
- *To assess OS and CR in clinically actionable mutation-defined AML subpopulations, including FLT3, IDH1, and IDH2*
- *To assess the safety of idasanutlin plus cytarabine as compared with cytarabine and placebo*
- *To compare the differences in disease and treatment-related symptoms and health-related quality of life between treatment arms*

Within the all-patient population

- To assess the safety of idasanutlin plus cytarabine as compared with cytarabine and placebo
- To characterize the pharmacokinetics of both idasanutlin and cytarabine
- To compare the differences in disease and treatment related symptoms and health-related quality of life between treatment arms

Exploratory Objective

The exploratory objectives for this study are as follows:

Within the all-patient population

- *To evaluate primary and secondary efficacy endpoints, including OS, CR, proportion of HSCT, EFS, and DOR in the all-patient population and OS and CR in the clinically actionable mutation-defined AML subpopulations (including FLT3, IDH1, and IDH2)*

Within the all-patient and TP53 WT populations

- *To evaluate efficacy endpoints, including proportion of HSCT, CR, ORR, and DOR on the basis of response assessed over complete treatment period*
- *To evaluate LFS (leukemia-free survival, or duration of OR)*
- To explore minimal/*measurable* residual disease (MRD) in the bone marrow after treatment with idasanutlin plus cytarabine compared with cytarabine and placebo
- To evaluate candidate response biomarkers (gene *expression signatures*) and murine double minute 2 (MDM2) protein expression in blast cells
- *To assess prognostic and predictive effect of disease-associated mutations*

Study Design

Description of Study

This is a Phase III multicenter, double-blind, randomized, placebo-controlled study of idasanutlin in combination with cytarabine compared with cytarabine and placebo.

A total of 440 patients with AML who have relapsed following, or are refractory to cytarabine–containing standard induction chemotherapy after at least one and no more than two prior cytarabine–containing induction chemotherapy regimen(s) are planned to be enrolled. Relapsed patients are defined as patients with first or second relapse; first relapsed patients who are young and had a good response to initial therapy (i.e. age <60 years with first CR achieved [CR1] duration >1 year) are excluded. Refractory patients are defined as patients with persistent leukemia after one or two induction cycles, or patients with CR1 duration of <90 days. Patients may have received prior HSCT in remission. Note that patients with prior allogenic HSCT within 90 days prior to randomization will not be eligible for this study. The *TP53* WT population will consist of patients with WT *TP53*, established centrally.

Re-screening is allowed under the conditions listed in the protocol.

Patients will be randomly assigned to each treatment arm. The arms will be stratified according to the following factors:

- Age (<60 years versus ≥ 60 years)
- Cytogenetic and molecular risk according to *the 2010* European LeukemiaNet (ELN) standardized reporting system at initial diagnosis (favorable/intermediate versus adverse). Cytogenetic information allowing stratification in those two groups must be available.
- Response to initial anti-leukemic therapy (refractory versus CR ≥ 90 days but ≤ 1 year; versus CR >1 year)
- Prior HSCT versus no prior HSCT

Patients will receive induction treatment with idasanutlin/placebo 300 mg twice daily (BID) and cytarabine 1 g/m^2 for 5 days followed by 23 days of rest (Cycle 1). For patients who achieve clinical response after induction and for whom HSCT for consolidation is not an option, it is

strongly recommended to continue study medication with a maximum of two additional cycles of consolidation (Cycles 2 and 3) unless clinically contraindicated

Responding patients, including those who proceed to HSCT, will be followed for EFS and *DOR*. All patients irrespective of response to treatment will be followed for OS until the end of the study.

An interim analysis for futility based on CR, EFS, and safety is planned after 120 *TP53* WT patients are enrolled, have received at least one cycle, and confirmatory response assessment is available, to allow early stopping of the study in the event of inadequate CR, EFS, or safety concerns. The *futility* interim analysis will be performed by an independent Data Monitoring Committee (iDMC). Enrollment of patients will continue while *this* interim analysis takes place. If the Sponsor decides to stop the study based on iDMC recommendation following the *futility* interim analysis, enrollment will be discontinued.

An efficacy interim analysis on OS is planned to be conducted by iDMC to allow early testing of OS in the event of relevant efficacy. The efficacy interim analysis will be conducted when 80% of the OS events have occurred (i.e., approximately 220 events). At this time, it is anticipated that all patients will have been enrolled.

Accompanying this interim efficacy analysis, a non-binding additional futility assessment will be performed based on a hazard ratio on overall survival ≥1.

In the case of not reaching significance for OS at interim analysis, a primary analysis of OS will be performed (i.e., when 275 events have occurred).

Number of Patients

Overall, 440 patients with relapsed or refractory AML are expected to be enrolled in this study, over approximately *41* months.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age ≥ 18 years
- Documented/confirmed first or second refractory or relapsed AML using World Health Organization classification, except acute promyelocytic leukemia. Please note that first relapsed AML patients with CR1 duration of > 1 year AND age < 60 years are excluded.
- No more than 2 prior induction regimens (excl. prior HSCT) in their first line treatment, and one must have included cytarabine with an anthracycline (or anthracenedione).
- Eastern Cooperative Oncology Group performance status of 0–2
- Adequate hepatic function assessed by the following:

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

  AST/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
- WBC count at randomization of ≤ 50,000/mm^3

  Note: When treatment is not started immediately upon randomization, the WBC count at the start of induction therapy (Cycle 1) must remain at ≤ 50,000/mm^3. The use of hydroxyurea (HU) or leukapheresis to meet eligibility is allowed. HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for up to 6 months after the last dose of study drug

  A woman is considered to be of childbearing potential if she has not reached a postmenopausal state (≥ 12 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, and established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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. Barrier methods must always be supplemented with the use of a spermicide.

- For men unless permanently sterile by bilateral orchidectomy: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for up to 6 months after the last dose of study drug. Men must refrain from donating sperm during this same period.

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

Exclusion Criteria

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

- First relapsed patients aged <60 years with a CR1 duration of >1 year
- Patients with prior documented antecedent hematological disorder including the following: myelodysplastic syndrome, myeloproliferative disease (i.e., chronic myelomonocytic leukemia, polycythemia vera, primary myelofibrosis, and essential thrombocythemia), and aplastic anemia
- AML secondary to any prior chemotherapy unrelated to leukemia
- Patients who are either refractory to or have relapsed within 90 days of receiving a regimen containing a cumulative dose of ≥ 18 g/m^2 cytarabine
- Patients who have received allogeneic HSCT within 90 days prior to randomization. HSCT should have been performed in remission and not used for salvage (patients who have received autologous HSCT as consolidation in CR1 are eligible).
- Patients who have received immunosuppressive therapy for graft-versus-host disease or for engraftment syndrome after autologous stem cell transplantation within 2 weeks prior to randomization
- Prior treatment with an MDM2 antagonist
- Patients with clinically relevant QTc prolongation (QT interval corrected using Fridericia's formula [QTcF] >480 ms), a family history of long QT syndrome, or who are currently receiving treatment with medications that are known to prolong the QT interval

  Medications that are known to prolong the QT interval must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study medication until 5 days after the final administration of study medication.

- Patients receiving any other investigational or commercial agents or therapies administered with the intention to treat their malignancy within 30 days (or 5 half-lives) from first receipt of study drug

  Note: The exception is HU or leukapheresis in patients who need to continue this therapy to maintain a WBC count $\leq$ 50,000/mm^3. HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication.
- Patients with acute toxicities from any prior anti-leukemia therapy which have not resolved to Grade $\leq$ 2 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03
- Patients with a history of other malignancy within 5 years prior to screening, except for malignancy that has been in remission without treatment for at least 2 years prior to randomization
- Patients unable to temporarily 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 medication.
- 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) during the treatment phase. These agents must be discontinued 7 days (or 5 half-lives) prior to the start of study medication.

  Note: Treatment with or switch to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is allowed, according to local practice. However, platelet levels need to be closely monitored in these patients (see protocol).
- Patients with a history of systemic hypersensitivity reactions $\geq$ Grade 2 attributed to cytarabine or components of the formulated product
- Patients who have 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 III, IV), myocardial infarction $\leq$ 6 months prior to first study medication, and cerebrovascular accidents $\leq$ 6 months before study medication start

  Unstable seizure disorders

  Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study medication, such as hereditary coagulation disorders or insulin-dependent diabetes mellitus not optimally controlled with medical management (e.g., presence of ketoacidosis) or active gastrointestinal (GI) conditions (e.g., Grade $\geq$2 graft−versus-host disease) and uncontrolled $inflammatory$ bowel disease (i.e., Crohn's disease, ulcerative colitis, diverticulosis-associated colitis, and Behçet's disease).
- 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 $<$ 2 weeks of appropriate systemic antifungal therapy

  Active bacterial infection and/or bacterial infection with positive cultures in the 7 days prior to dosing

  Patients who have received $<$ 5 days of appropriate therapeutic antibiotic therapy for an identified infection

History of symptomatic *Clostridium 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.

In all cases, the patient should be afebrile (exception of AML-related fever) and hemodynamically stable for at least 72 hours at the time of study medication initiation.

- Patients with a history of active or chronic infectious hepatitis unless serology demonstrates clearance of infection

  Patients with occult or prior hepatitis B virus (HBV) infection (defined as negative hepatitis B surface antigen and positive total hepatitis B core antibody) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody after vaccination or prior but cured hepatitis B are eligible. Patients positive for hepatitis C virus antibody are eligible provided polymerase chain reaction (PCR) is negative for HCV RNA.
- Patients who have a history of clinically significant liver cirrhosis (e.g. Child-Pugh class B and C).
- Patients with electrolyte abnormalities such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade >1 per NCI CTCAE v4.03. Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility.
- Patients with extramedullary AML with no evidence of systemic involvement
- Patients with active CNS leukemia
- Pregnant or breastfeeding patients
- HIV-positive patients
- Patients who might refuse to receive blood products and/or have a hypersensitivity to blood products

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur 2 years after the last patient is enrolled or after 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 5.5 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Idasanutlin/placebo will be administered at 300 mg BID orally, without regard to meals. Water can be given ad libitum.

In case the patient proceeds to consolidation therapy, only 50% of idasanutlin should be given (300 mg once daily [QD] in the morning).

Cytarabine will be administered at a dose of 1 g/m^2 QD as a 1–3 hour intravenous infusion. In case the patient proceeds to consolidation therapy the dose may need to be reduced to 50% (0.5 g/m^2 QD).

Statistical Methods

Efficacy Analysis

Patients will be analyzed according to the treatment arm to which they were randomized. *The TP53 WT population is the efficacy population and refers to all randomized TP53 WT patients as identified by a central laboratory test.*

Description of efficacy analysis in this section is valid for both interim and primary analysis.

Primary Efficacy Endpoint

The primary efficacy endpoint, OS, is defined as the time from randomization to death due to any cause. OS for patients who have not died at the time of the analysis will be censored at the date last known alive.

The primary OS analysis of the study will assess the null hypothesis of equality of OS functions in the idasanutlin in combination with cytarabine (MDM2-chemo) arm versus the cytarabine given with a placebo (chemo) arm in the *TP53* WT population as follows:

H0: $OS_{MDM2\text{-}chemo} = OS_{chemo}$ versus H1: $OS_{MDM2\text{-}chemo} \neq OS_{chemo}$

A formal treatment comparison will be made using a two-sided stratified log-rank test at a significance level *defined using the O´Brien-Fleming alpha-spending function with overall Type I error rate at 0.05 corresponding to available information.* Stratification factors that will be used are the same as for randomization, i.e. age (<60 versus ≥ 60 years), cytogenic and molecular risk (favorable/intermediate versus adverse), prior response to initial anti-leukemic therapy (refractory versus CR ≥ 3 months but ≤ 1 year versus CR > 1 year) and prior HSCT versus no prior HSCT.

Survival curves in each treatment arm will be estimated using Kaplan−Meier estimates. The Kaplan–Meier estimates will provide a visual description of the survival curves and the difference across treatment arms. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% CI. To further describe and quantify OS, estimated median OS per arm and 1-year and 2-year survival probabilities, all including 95% CI, will be given. The effect of prognostic factors on OS will be assessed in an exploratory analysis using Cox multivariate regression.

Secondary Efficacy Endpoint

The following secondary endpoints will be tested for the TP53 WT population, as described in the Statistical Analysis Plan:

- *CR proportion*
- EFS
- ORR (CR, CRp, and CRi)
- *DOR (duration of remission following CR)*
- Proportion of HSCT *following CR*
- *CR proportion and OS in clinically actionable mutation-defined subpopulation (FLT3, IDH1, and IDH2)*

Patients with no response assessments (for any reason) will be considered non-CR.

Difference in proportions of CR will be assessed between the two treatment arms using Cochran–Mantel–Haenszel test stratified by randomization stratification factors. In addition, proportions and 95% CI will be reported for each treatment arm. The effect of prognostic factors on CR will be assessed in an exploratory analysis using logistic regression.

EFS is defined for all patients and measured from the date of randomization. It is measured until treatment failure, relapse from CR, or death from any cause, whichever occurs first. For patients with none of these events before *time of analysis,* EFS is censored at the date of the patient's last response assessment.

DOR is defined for patients achieving complete remission and is the time from clinical remission until relapse or death from any cause, whichever occurs first. For patients with none of these events before time of analysis, DOR is censored at the date of the patient's last response assessment.

EFS and *DOR* will in general be analyzed using the same statistical methods as those described for OS. If only very few patients qualify for *DOR* analysis, only descriptive statistics will be given.

ORR (CR, CRp, and CRi) and proportion of HSCT will be compared between the two treatment arms using the same statistical methods as those described for CR.

Sensitivity Analyses

The following sensitivity analyses for OS will be performed in the *TP53* WT population:

- An unstratified log-rank test.
- To assess the relevance of HSCT against other long-term effects, OS will be alternatively defined with censoring at date of HSCT and analyzed using the same methods as for the primary endpoint.
- *Discontinuation of assessments or patient lost to follow up considered as an event*

Safety Analyses

All safety analyses will be based on *both the TP53 WT population (defined here as TP53 WT patients who have received any study medication at least once) and* the complete safety analysis population (defined as all patients who have received any study medication at least once), and patients will be analyzed according to the treatment received (patients receiving idasanutlin at least once will be analyzed in the idasanutlin arm). Safety analyses will include, but not be limited to, incidence rates for adverse events including mortality, adverse event severity, seriousness, and adverse events leading to discontinuation. In addition, abnormalities of clinical laboratory tests and vital signs assessed during the study treatment period and post-treatment follow-up will be assessed. Exposure to study medication will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics.

This trial is designed to allow for early termination or a modification of the protocol for safety concerns or lack of efficacy, based on the advice of an iDMC. The iDMC will be incorporated into the study to review safety data on a regular basis, including adverse events of special interest. Both the Sponsor and the iDMC can request ad hoc iDMC meetings if potential safety concerns arise. Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm as a result of safety reasons. The iDMC will also perform a safety review at the preplanned interim analyses for futility and efficacy.

Pharmacodynamic and Biomarker Analyses

The following pharmacodynamic parameters will be presented by listings and descriptive summary statistics.

- Blood samples analyzed for macrophage inhibitory cytokine-1
- Analysis of *TP53, FLT3, IDH1, and IDH2* mutation status
- *MDM2 protein expression level in AML blasts*
- *A 4-gene signature (including MDM2 gene expression)*
- *MRD*

Pharmacokinetic Analyses

Key pharmacokinetic (PK) parameter values (apparent clearance and apparent volume of distribution) of idasanutlin and cytarabine (total clearance and volume of distribution) will be estimated using a population pharmacokinetics (popPK) approach. The influence of covariates such as gender, race/ethnicity, weight, hematological parameters at baseline, renal/hepatic impairment, and degree of underlying disease will be investigated. Other PK parameters such as maximum concentration observed (C_{max}), steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration) (C_{trough}), area under the concentration–time curve during one dosing interval, area under the concentration-time curve during a 24-hour dosing interval (AUC_{0-24h}), and half-life will be derived from the individual post hoc predictions. Details of the population analysis will be described in the Modeling and Simulation Analysis Plan. Results of this analysis will be reported separately.

If appropriate, an exploratory PK/pharmacodynamic analysis may be performed post hoc. The primary focus will be exploration of the relationship between measures of exposure to idasanutlin in combination with cytarabine (C_{max}, C_{trough}, and AUC_{0-24h}) and ECG, drug-related adverse effects as well as clinical efficacy parameters.

Determination of Sample Size

A mechanistic simulation model *was* used to determine the sample size in this event-driven study, based on the following global assumptions:

- Final analysis for OS in patients with *TP53* WT disease based on two-sided log-rank test at 0.05 level of significance
- 85% power to detect an OS hazard ratio for idasanutlin + cytarabine versus cytarabine + placebo of 0.67 in patients with *TP53* WT disease, corresponding to an improvement in median OS from 6 to 9 months (50%)
- Proportion of long term survivors of 8.0% in the cytarabine + placebo arm and 16.1% in the idasanutlin + cytarabine arm

To compute the necessary number of events, we *simulated* OS times based on the following assumptions:

- All simulated OS times for patients not considered long-term survivors are exponentially distributed.
- Probability of being a complete responder in the cytarabine + placebo arm is 0.16
- Probability of being a complete responder in the idasanutlin + cytarabine arm is 0.323, implying an odds ratio for CR comparing the idasanutlin + cytarabine versus the cytarabine + placebo arm of 2.5
- Probability for a complete responder to be a long-term survivor is 0.5 in either arm
- An annual dropout rate of 5% (every effort will be made to contact patients for survival information in case of study withdrawal or loss to follow-up)

To have the targeted 85% power, 275 events *in patients with TP53 WT disease* are required. The minimum detectable hazard ratio in a 2:1 randomized trial corresponding to 275 events and a significance level of 0.05 amounts to 0.78, corresponding to a minimal detectable median improvement from 6 to 7.7 months assuming exponentiality.

All patients*, regardless of TP53 mutation status,* will be randomized to this *study. Assuming 85% of patients will have TP53 WT disease and 15% will have TP53 mutant disease, approximately* 440 patients will be enrolled over approximately 29 months, corresponding to an estimated number of 374 patients *with TP53 WT disease.*

In Version 6 of the protocol, an interim analysis for efficacy on OS of TP53 WT patients was added. The sample size assumptions above remain unchanged other than the recruitment time (now estimated at 41 months). The interim analysis will occur at an information fraction of 80%, providing a maximum power of 83% for the final OS analysis.

Interim *Analyses*

Futility

A non-binding interim analysis for safety and futility will be performed by an iDMC after 120 patients with *TP53* WT have been enrolled and assessed for response. For the purposes of the *futility* interim analysis, CR is defined as confirmed CR. Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of study results. The iDMC may recommend stopping the study for futility if:

- the observed odds ratio for CR in the cytarabine and idasanutlin arm versus the cytarabine and placebo arm in the population of patients WT for TP53, is <2.0,
- or the observed odds ratio for CR in the cytarabine and idasanutlin arm versus the cytarabine and placebo arm in the population of patients WT for TP53, is <2.5 and the hazard ratio for EFS >1.

To compute stopping probabilities for the *futility* interim analysis, the following additional assumptions are made within *TP53* WT patients and the simulation model is extended accordingly:

- Median OS for non-responders in cytarabine arm is 5.1 months
- Median OS for responders, but short-term survivors in cytarabine arm is 7.5 months
- EFS follows an exponential distribution

- Median EFS times for non-responders and CR short-term responders is assumed to be shorter by a factor 2.5 compared to OS in these same subpopulations
- The correlation between uncensored EFS and OS times is 0.5
- Hazard ratio for a comparison of idasanutlin + cytarabine versus cytarabine + placebo in both non-responders and short-term responders is 0.8

Using these assumptions, we expect 63 EFS events at the *futility* interim analysis under the alternative hypothesis. The probability of early stopping due to futility is 89.9% if the null hypothesis of equal OS survival functions is true and 31.9% if the alternative assumption of an increase in median OS from 6 to 9 months is true.

The analysis in both the *TP53* WT population and in the overall population will be provided to the iDMC.

The iDMC may recommend stopping the study for safety at the *futility* interim analysis if any of the following criteria are met (note: early death is defined as any death within the first 30 days after randomization):

- The proportion of GI toxicity (nausea, vomiting, diarrhea) events in the experimental arm (idasanutlin + cytarabine): Grade 3 > 40% or Grade 4 > 15%
- The proportion of early deaths in the experimental arm (idasanutlin + cytarabine) is ≥ 10 percentage points greater than in the control arm (cytarabine + placebo)
- > 20% of early deaths overall in the treatment arm

More details on the interim analysis are provided in the iDMC charter.

Efficacy

An interim analysis for efficacy on OS is planned to be conducted by iDMC. The efficacy interim analysis will be conducted when 80% of the OS events have occurred (i.e., approximately 220 events). At this time, it is anticipated that all patients will have been enrolled.

For the interim efficacy analysis of OS, the significance level will be determined using the O'Brien-Fleming alpha-spending function with overall type I error rate at 0.05 level. At the time of the interim efficacy analysis, it is expected that 80% of the OS events will have occurred, corresponding to an alpha spending of 0.025 for the interim and 0.043 for the final OS analysis leading to a power of 83% for the final analysis.

The iDMC will test OS for efficacy and check if there is a significant difference (alpha level 0.025 or as assessed based on actual number of OS events) in OS in favor of the experimental arm.

Accompanying this interim efficacy analysis, a non-binding additional futility assessment will be performed and the iDMC may recommend stopping the study for futility if the hazard ratio on overall survival is greater than or equal to one.

Further details of the interim analyses will be described in the iDMC Charter and Statistical Analysis Plan.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AHD	antecedent hematological disorder
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 daily
BSA	body surface area
bWBC	baseline white blood cell count
CI	*confidence interval*
CL	total clearance of drug
CL/F	apparent clearance
C_{max}	maximum concentration observed
CR	complete remission
CR1	first CR achieved
CRi	complete remission with incomplete blood count recovery
CRp	complete remission with incomplete platelet count recovery
CSR	clinical study report
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
DOR	*duration of remission following CR*
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
ELN	European LeukemiaNet
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5 Dimension 5-Level

FDA	U.S. Food and Drug Administration
GI	gastrointestinal
HBV	hepatitis B virus
HCT-CI	hematopoietic cell transplantation-specific comorbidity index
HI	hematologic improvement
HiDAC	high-dose cytarabine
HMRA	hematologic malignancy response assessment
HSCT	hematopoietic stem cell transplant
HU	hydroxyurea
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDAC	intermediate-dose cytarabine
IDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LAIP	leukemia-associated immunophenotype
LFS	leukemia-free survival *or duration of OR (CR, CRp, CRi)*
LMWH	low molecular weight heparin
LPLV	last patient, last visit
LTLS	laboratory TLS
MBP	microprecipitated bulk powder
MDM2	murine double minute 2
MIC-1	macrophage inhibitory cytokine-1
MRD	minimal*/measurable* residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
OATP	organic anion-transporting polypeptide
ORR	overall remission rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PK	pharmacokinetic
PO	orally

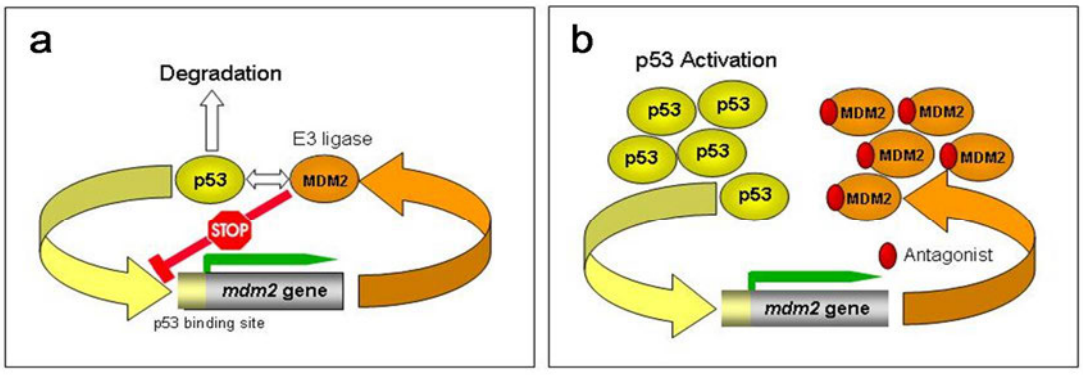
popPK	population pharmacokinetics
PR	partial remission
PRO	patient-reported outcome
QD	once daily
qRT-PCR	quantitative real-time polymerase chain reaction
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RCR	Roche Clinical Repository
RT-PCR	reverse transcription polymerase chain reaction
SC	subcutaneous
SD	stable disease
SDP	spray-dried bulk powder
$t_{1/2}$	half-life: time for drug in the body to be reduced by one-half
TLS	tumor lysis syndrome
UFH	unfractionated heparin
ULN	upper limit of normal
V_d	volume of distribution
V_d/F	apparent volume of distribution
WT	wild type

1. BACKGROUND

The tumor suppressor p53 is a powerful growth suppressive and pro-apoptotic protein that plays a central role in protection from tumor development and is frequently inactivated in human cancer. It is a transcription factor that is activated following cellular stress and regulates multiple downstream genes implicated in cell cycle control, apoptosis, DNA repair, and senescence (Kussie et al. 1996). Some cancer cells have mutant p53, which lacks these activities and as a result permits the proliferation of cells that carry damaged DNA. Tumor cells with wild type (WT) p53 can inactivate p53 in alternative ways (in order to proliferate) including overexpression of murine double minute 2 (MDM2).

In non-stressed normal cells, the level of p53 is controlled tightly by MDM2. As illustrated in Figure 1, MDM2 regulates p53 through a negative feedback loop. When nuclear p53 level is elevated, it activates the transcription of the *MDM2* gene. In turn, MDM2 binds to p53, which blocks its transactivation domain and targets p53 for ubiquitin-dependent degradation in the proteasome. Both p53 and MDM2 have short half-lives and their nuclear concentrations are kept very low as a result of the functioning of the regulatory circuit. However, this feedback loop is deregulated in cancer cells that overexpress MDM2. Stress-induced p53 activation mechanisms in these tumors are believed to be inadequate to overcome the negative control of MDM2, leading to inefficient growth arrest and/or apoptosis. Therefore, blocking the p53-MDM2 interaction is expected to overcome the oncogenic consequences of MDM2 overproduction and to restore p53 function. Blocking the p53-MDM2 interaction is also expected to increase p53 function in tumors that do not overexpress MDM2, leading to anticancer activity.

Figure 1 Regulation of p53 Stability and Activity by MDM2



MDM2 = murine double minute 2.

[a] An autoregulatory feedback loop between p53 and its negative regulator MDM2.

[b] MDM2 antagonist blocks the p53-MDM2 binding, thereby releasing p53 from negative control and activating the p53 pathway.

Genetic and biochemical studies mapped p53–MDM2 binding sites to the N-terminal domain of MDM2 and the N–terminal part of the transactivation domain of p53. The crystal structure of a p53–derived peptide bound to the p53 binding domain of MDM2 reveals the existence of a relatively deep cavity on the surface of the MDM2 molecule (Vassilev et al. 2004). More importantly, only three amino acid residues from the p53 peptide (i.e., Phe19, Trp23, and Leu26) appear to play a critical role in the binding between the two proteins, by projecting residues deep into the hydrophobic cavity of the p53 pocket (Kussie et al.1996). These structural features of the p53–MDM2 complex suggest an increased likelihood of the identification of small molecules that might interfere successfully with the protein–protein binding by mimicking the key amino acid contacts between the two proteins.

A class of small-molecule compounds has been identified as potent and selective inhibitors of the p53-MDM2 interaction (Tovar et al. 2006). These molecules, termed nutlins, interact specifically with the p53-binding pocket of MDM2, and therefore, free p53 from negative control. Treatment of cancer cells expressing WT p53 with nutlins stabilizes p53 and activates the p53 pathway leading to activation of p53 target genes, cell cycle arrest, and apoptosis (Tovar et al. 2006; Vassilev 2007).

1.1 BACKGROUND ON ACUTE MYELOID LEUKEMIA

The yearly incidence of acute myeloid leukemia (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 15–25/100,000 per annum (Fey 2013). Approximately 20,000 patients will be diagnosed with AML with greater than 10,000 AML patient deaths in the United States during 2015 (American Cancer Society 2015). By intensive initial treatment of AML, using cytarabine and anthracycline–based chemotherapy induction regimens, complete remission (CR) proportions ranging from 50% to 80% can be achieved. Nonetheless, the majority of responding patients under the age of 60 relapse (60%–70%), and results are poorer in older patients, with fewer than 20% of elderly patients being long-term survivors (Burnett et al. 2011).

Prognostic factors for AML include age, WBC count, percentage of CD34-positive blasts, cytogenetic and molecular risk factors, and secondary or therapy-related AML. Improvements have been made in prognostic subclassification of patients—including those with normal cytogenetics—by testing for molecular abnormalities (i.e., FLT3, NPM1, CEBPalpha, MLL, WT-1, and EVI1) to allow early identification of patients at high risk of relapse who should be treated with more intensive therapies (i.e., hematopoietic stem cell transplant (HSCT), or for whom experimental therapies are warranted. Patients who do not respond to standard therapy or who relapse within a year of initial treatment have median survival measured in months (Breems et al. 2005*; Wattad et al. 2017*). No standard regimen exists for the treatment of patients with relapsed or refractory AML, particularly in patients with a remission duration of less than 1 year in response to their initial induction regimen. These patients are candidates

for novel therapeutic interventions with the goal of disease remission, making potentially curative transplant options available for appropriate patients (Forman 2005). This will be the population studied in this clinical trial.

1.2 BACKGROUND ON IDASANUTLIN

Roche has clinical experience with MDM2 antagonists. An initial compound brought to the clinic (RO5045337) was tested in Phase I and Ib trials in both hematologic and solid tumor indications. This compound demonstrated proof of mechanism in MDM2–amplified liposarcomas (Ray-Coquard et al. 2012), as well as clinical responses in hematologic malignancies, including CRs in patients with AML treated with monotherapy, as well as CRs in combination with cytarabine (Andreeff et al. 2012; Yee et al. 2013). Development of this compound was halted because of less than optimal potency and pharmacologic properties in favor of the current compound (idasanutlin).

Idasanutlin is a second generation MDM2 antagonist containing a different chemical backbone. As with RO5045337, idasanutlin is a small molecule with high affinity that binds selectively to the p53 site on the surface of the MDM2 molecule in vitro and can effectively displace p53 from MDM2, which leads to stabilization and accumulation of the p53 protein, and activation of the p53 pathway. However, idasanutlin has substantially improved pharmacologic properties, for example, it has lower variability of exposure than RO5045337 because it does not have significant pH-dependent solubility; fasted- and fed-state simulated intestinal fluid solubility is similar. Idasanutlin exhibits improved in vitro and in vivo potency against tumor cell lines and xenografts, an improved cytochrome P450 (CYP) inhibition profile, and shows a several fold lower efficacious dose in AML clinical studies.

For clinical development, idasanutlin was initially formulated as microprecipitated bulk powder (MBP) tablets. While Phase I/Ib studies were ongoing, an alternative idasanutlin formulation termed the spray-dried bulk powder (SDP) formulation was developed which improved the stability of the drug with regard to decreased formation of a genotoxic impurity over the shelf life. This formulation was extensively tested in the AML patient population. Details on the use of both formulations in idasanutlin clinical trials are provided in Section 3.3.1.

1.2.1 Clinical Experience with Idasanutlin

To date, idasanutlin has been studied in several Phase I/Ib and Phase Ib/II programs; safety and efficacy results *from relevant studies* are outlined below. For more information, please refer to the idasanutlin Investigator's Brochure (IB).

1.2.1.1 NP28679 in AML

Study NP28679 in patients with AML is completed. The study enrolled 122 patients; however, 1 patient initially diagnosed with AML was subsequently diagnosed with chronic myelomonocytic leukemia. This was a dose escalation study for idasanutlin

monotherapy (Part 1) and idasanutlin in combination with cytarabine 1 g/m^2 (Part 2) with two extensions for Part 1 and Part 2, both parts using the MBP formulation of idasanutlin. Part 4 of this study investigated the pharmacokinetics and safety of 300 mg twice daily (BID) and 400 mg BID of the optimized idasanutlin SDP formulation in combination with 1 g/m^2 cytarabine. In comparison with the MBP formulation, the SDP formulation was shown to be approximately two-fold more bioavailable in patients treated with idasanutlin (Study NP28902). Therefore, doses of 300 mg BID and 400 mg BID of the SDP formulation were chosen to be investigated for a target exposure range of idasanutlin similar to that reported in the dose escalation and extensions for the MBP formulation. The 300 mg BID dose was chosen for the current Phase III study as available data demonstrated a trend towards higher efficacy and a better safety profile compared with the 400 mg BID dose.

Safety

In Study NP28679, consistent with other ongoing studies of idasanutlin, gastrointestinal (GI) adverse events—including nausea, vomiting, and diarrhea—were the most common adverse events across all study groups ($>$90%). Other frequently reported adverse events were infection-related. The most common serious adverse events were febrile neutropenia, sepsis, neutropenic sepsis, and pneumonia. The most common Grade $\geq$ 3 adverse events were febrile neutropenia, hypokalemia, thrombocytopenia, diarrhea, and anemia.

The maximum tolerated dose (MTD), as defined in Study NP28679, was not reached. Dose escalation was halted after the 800 mg MBP BID monotherapy cohort consistently experienced GI adverse events, and, thus, this dose was considered a tolerability threshold. The dose of idasanutlin recommended for further development was determined to be 600 mg MBP BID for both monotherapy and combination therapy with cytarabine for subsequent extensions of the study.

The overall adverse event profile in patients treated with idasanutlin alone was similar to that of patients treated with idasanutlin in combination with cytarabine; however, the number of adverse events was higher for the combination treatment. The adverse event profile of the SDP formulation of idasanutlin is similar to that of the MBP formulation. The incidence and severity of gastrointestinal toxicity and associated electrolyte abnormalities was higher in the 400 mg SDP cohorts than in the 300 mg SDP cohorts.

Additional information on clinical safety is found in the idasanutlin IB.

Efficacy

In Study NP28679, all 121 patients with AML in the per-protocol population were evaluated for hematological response. One patient was found to have chronic myelomonocytic leukemia and not AML, and was therefore not included in the efficacy analysis.

In total, 46 patients received monotherapy with the MBP formulation during the dose escalation and extension parts of the study, and 43 patients received the MBP formulation in combination with cytarabine.

An additional 32 patients were enrolled in the bridging arm and received 300 or 400 mg BID per day of the SDP formulation of idasanutlin in combination with cytarabine.

The proportion of evaluable patients with CR/CRp who were treated with either MBP or SDP in combination with cytarabine was 28% (21 of 75 patients), and the proportion of evaluable patients with clinical response (defined as CR+ complete remission with incomplete platelet count recovery [CRp]+ complete remission with incomplete blood count recovery [CRi]) was 29% (22 of 75 patients). Patients with clinical response were followed until relapse or until 1 year from the start of therapy; the median duration of clinical response was 8.35 months (range: 1.1−11.7 months).

For patients receiving the SDP formulation in combination with cytarabine, the proportion of patients with CR/CRp was 31% (10 of 32 patients), and the proportion of patients with clinical response was 34% (11 of 32 patients). The median duration of clinical response in patients receiving 300 mg BID or 400 mg BID was 10.4 months (range: 1.1−11.4 months) and 10.2 months (range: 2.3−10.4 months), respectively.

1.2.1.2 NP27872 in Solid Tumors

A Phase I study of idasanutlin monotherapy (Study NP27872) in solid tumors has also been conducted. In Study NP27872, patients with solid tumors received escalating doses of idasanutlin. The dose limiting toxicities on a 5-day dosing schedule were primarily thrombocytopenia and neutropenia. At the MTD (500 mg MBP once daily [QD] $\times$ 5 days), patients demonstrated evidence of MDM2 antagonist mechanism of action in tumor biopsies including, p53 activation, increased p21 and MDM2 expression by immunohistochemistry, and increased MDM2 gene expression by reverse transcription polymerase chain reaction (RT-PCR). There was also evidence of apoptosis by terminal deoxynucleotidyl transferase dUTP nick end labeling. Dose escalation was limited by myelosuppression. No responses by Response Evaluation Criteria in Solid Tumors were seen; however, prolonged stable disease (SD; median 72.5 days, minimum 8 days, and maximum 696 days) and long treatment duration (21%, $>$ 2 cycles) were seen in some patients.

Two additional dosing schedules had been evaluated in solid tumor patients: daily $\times$ 3 days and weekly $\times$ 3. While there was evidence of p53 activation, the daily $\times$ 3 days dose regimen did not achieve steady-state exposure, displayed shorter duration for SD (median 57 and 103 days for daily $\times$ 3-day and daily $\times$ 5-day schedules, respectively), and did not alleviate thrombocytopenia.

1.2.2 Clinical Pharmacology Summary

1.2.2.1 Clinical Pharmacokinetics

Evaluable pharmacokinetic (PK) data for patients treated with the idasanutlin MBP or SDP formulation are available from Studies NP27872, NP28902, NP28679, and NP29910. Overall, clinical PK data are summarized as follows:

- Half-life ($t_{1/2}$) was approximately 1 day.
- There was apparent dose-proportionality for the daily schedule in patients with solid tumors (Study NP27872).
- There was no apparent difference in idasanutlin PK exposure between patients with solid tumors (Study NP27872) and patients with AML (Study NP28679) in the dose range of 400 to 1600 mg daily dosing for 5 days.
- Inter-patient variability was approximately 50% and intra-patient variability was approximately 26%.
- In comparison with the MBP formulation, the SDP formulation is approximately two-fold more bioavailable in patients with AML treated with idasanutlin in combination with cytarabine.
- There was no major effect of high-fat or low-fat food on PK exposure.
- Metabolite M4 (RO6802287) was the only major metabolite in human plasma samples (at steady-state on Day 5).
- At steady-state, the drug level in the bone marrow was approximately 70% of plasma.
- Idasanutlin is not excreted through urine.
- There was no major impact of a strong CYP3A4 inhibitor, posaconazole, or concomitant cytarabine on idasanutlin pharmacokinetics.

1.2.2.2 Clinical Pharmacodynamics

Macrophage inhibitory cytokine-1 (MIC-1) is a secreted protein that is induced by activated p53 in response to MDM2 antagonists and can be detected in the serum. MIC-1 levels were used to assess pharmacodynamic effects of idasanutlin in the Phase I studies. An analysis of patients given 100–3200 mg/day of idasanutlin showed that MIC-1 induction was demonstrated at the lowest tested dose of 100 mg/day, with a corresponding exposure level of 500 ng/mL of idasanutlin. No upper limit has been observed for MIC-1 induction *(plateau not reached)*.

There is an apparent PK/pharmacodynamic relationship for the daily dosing regimen in regards to Cycle 1 platelet nadir and maximum grade of ANC and platelet.

No correlation was observed between drug concentration and QT interval corrected using Fridericia's formula (QTcF) or its change from baseline.

1.2.2.3 Metabolic Drug-Drug Interactions

Idasanutlin is a CYP2C8 inhibitor that may affect concomitant CYP2C8 substrates, and its M4 metabolite is an organic anion-transporting polypeptide (OATP)-1B1/3 transporter inhibitor that may affect concomitant OATP1B1/3 substrates. These are the basis for the prohibited therapy list for the present study. However, idasanutlin is not expected to interact with substrates of deaminases such as cytarabine (no interaction observed with cytarabine from Study NP28679).

Only one inactive metabolite RO6802287 (Hydroxy pyrrolidine metabolite M4) (approximately 25% of parent exposure) was identified in plasma samples. This metabolite is generated by CYP3A4 and CYP2C8 metabolic pathways. A strong CYP3A4 inhibitor, posaconazole, had no impact on idasanutlin maximum concentration observed (C_{max}) values but increased area under the concentration-time curve (AUC) values by 32%, which suggests a minimal (no clinically significant) drug-drug interaction (DDI) potential with a single use of a strong/moderate CYP3A4 or CYP2C8 inhibitor. However, a concomitant second strong/moderate inhibitor of the other CYP pathway (e.g., from CYP2C8 to CYP3A4) may increase idasanutlin exposure to a clinically significant level.

UGT1A3 is also a major clearing enzyme; its strong inhibitor gemfibrozil is also a CYP2C8 inhibitor that will be excluded from the current study.

As idasanutlin is a substrate for both CYP3A4 and CYP2C8, the known inducers of CYP3A4 and CYP2C8 will also be prohibited from the current study to prevent loss of exposure for idasanutlin.

Guidance on the use of these drugs within the study is provided in Section 4.4.2.1.

See the idasanutlin IB for additional details on nonclinical and clinical studies.

1.3 BACKGROUND ON CYTARABINE

The anti-metabolite cytarabine enters the cell and is phosphorylated to the active triphosphorylated state known as Ara-CTP. Cytarabine exerts its cytotoxic effect in two ways: by DNA polymerase inhibition and by incorporation into the DNA strand causing chain termination, which blocks DNA synthesis. After intravenous (IV) administration, the pharmacokinetics are most commonly described with a two-compartment model. The initial distribution phase is rapid ($t_{½}$ of about 10 minutes) followed by a slower elimination $t_{½}$ (about 2.5 hours). Baseline white blood cell count (bWBC) influenced the pharmacokinetic for cytarabine; its clearance was significantly decreased by increased bWBC. However, 10-fold changes in bWBC were needed for these relationships to have potential clinical relevance (cytarabine package insert; Section 4.3.1.2).

The main toxic effect of cytarabine injection is bone marrow suppression with leukopenia, thrombocytopenia, and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction. For further details of efficacy and toxicity of cytarabine in relapsed/refractory AML patients, refer to Section 3.3.3.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Patients who relapse after standard induction chemotherapy for AML have a poor prognosis, particularly if they do not achieve a CR, relapse within 1 year of initial therapy or after stem cell transplantation, experience AML that developed from an antecedent hematologic disorder, or experience multiple relapses (Löwenberg et al. 1989; Breems et al. 2005; Ofran and Rowe 2012). No standard regimen exists for the treatment of patients with relapsed or refractory AML, particularly for patients with initial remission duration of <1 year, whose median survival is measured in months (Breems et al. 2005). These patients urgently need more effective new therapies.

Idasanutlin is a potent and selective inhibitor of the p53-MDM2 interaction that activates the p53 pathway and induces cell cycle arrest and/or apoptosis in a variety of tumor types expressing functional p53 in vitro and in vivo. Idasanutlin given orally (PO) caused tumor growth inhibition in a variety of different dosing schedules in a human osteosarcoma cancer xenograft model. When tested in combination with cytarabine in a preclinical disseminated AML model, both the once weekly and daily for 5 days (5 days on/23 days off) schedules in combination with cytarabine demonstrated an increase in survival when compared with correlative monotherapy arms. The daily for 5 days (5 days on/23 days off) schedule of idasanutlin in combination with cytarabine was selected as the dosing regimen for clinical development (idasanutlin IB).

Meanwhile, efficacy and safety data from 122 patients from the Phase I/Ib Study NP28679 are available. Overall, 121 patients receiving idasanutlin monotherapy or combination therapy with cytarabine 1 g/m^2 were evaluable for response. Patients listed as achieving CR underwent a subsequent bone marrow assessment that confirmed continued bone marrow response approximately 28 days following the initial CR assessment (confirmed CR). For patients achieving CR, the duration of clinical response was measured until relapse or until 1 year from the start of therapy.

Across cohorts the combination with cytarabine led to a CR/CRp rate in evaluable patients of 28% (21 of 75 patients) (Section 1.2.1.1). The CR/CRp rate in evaluable patients receiving 300 mg BID of the idasanutlin SDP formulation, which is the dose selected for the present Phase III study, was 36.8% (7 of 19 patients) (Section 1.2.1.1).

Analysis of the number and type of prior regimens, exposure, and best response on study for patients treated with idasanutlin in combination with cytarabine demonstrated activity in patients who have received prior cytarabine-containing regimens and were refractory or relapsed. Ongoing analysis of characteristics of patients responding to therapy demonstrates activity in patients who have antecedent hematologic disorders and prior malignancies, as well as being refractory to initial induction therapies. One patient with AML treated with idasanutlin plus cytarabine achieved a CR despite harboring a *TP53* mutation. The median duration of response for combination therapy in patients who did not have disease progression was approximately 8.35 months (range: 1.1–11.7 months).

Cytarabine is a potent bone marrow suppressant and as such has an overlapping toxicity profile with idasanutlin. In the AML population this combination appears nevertheless desirable because the additive effect might lead to increased blast clearance and higher efficacy for the combination treatment. Preliminary efficacy data from Phase I appear to confirm this hypothesis.

Safety data from the 122 patients exposed to idasanutlin monotherapy or combination therapy in the Phase I/Ib AML Study NP28679 showed that the most common adverse events across all study groups were GI disorders, in particular diarrhea, nausea, and vomiting, all of which were clinically manageable by appropriate treatment and prophylaxis. The most frequent serious adverse events were infectious events and blood and lymphatic system disorders.

Comorbidities and characteristics such as older age, frailty, and presence of prolonged cytopenias prior to study initiation are common among relapsed/refractory AML patients. The treatment proposed in this study is anticipated and expected to lead to cytopenias rendering patients susceptible to infections. Cytopenia or aplasia may be a consequence of clearance of the bone marrow blasts, which leads to the possibility of normal hematopoietic recovery. To reduce the risk to patients enrolled, this study will rely on stringent enrollment criteria for performance status, diligent clinical observation and management (i.e., initiation of mandatory diarrhea and infectious events prophylaxis/management and guidelines for tumor lysis syndrome [TLS] management; for detailed information on toxicity management guidelines, please refer to Appendix 14), and pharmacovigilance. The safety data for patients in the study will be reviewed regularly during study conduct by an independent Data Monitoring Committee (iDMC; see Section 6.6).

Relapsed/refractory AML is a condition with high, unmet medical need. Idasanutlin in combination with cytarabine showed promising activity in Phase I AML with a manageable safety profile, therefore its benefit-risk is considered positive.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is as follows:

Within the *TP53* WT population

- To compare OS in patients with relapsed or refractory AML who have been randomized to idasanutlin in combination with cytarabine versus those who have been randomized to cytarabine and placebo

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

Within the TP53 WT population

- To compare the proportions of *complete remission (*CR*)* between treatment arms
- To compare event-free survival (EFS) between treatment arms
- *To compare ORR (defined as CR), complete remission with incomplete platelet count recovery [CRp], and complete remission with incomplete blood count recovery [CRi]) between treatment arms*
- *To compare duration of remission following CR (DOR) between treatment arms*
- To compare the proportions of allogeneic HSCT following *CR* between treatment arms
- *To assess OS and CR in clinically actionable mutation-defined AML subpopulations, including FLT3, IDH1, and IDH2*
- *To assess the safety of idasanutlin plus cytarabine as compared with cytarabine and placebo*
- *To compare the differences in disease and treatment-related symptoms and health-related quality of life between treatment arms*

Within the all-patient population

- To assess the safety of idasanutlin plus cytarabine as compared with cytarabine and placebo
- To characterize the pharmacokinetics of both idasanutlin and cytarabine
- To compare the differences in disease and treatment related symptoms and health-related quality of life between treatment arms

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

Within the all-patient population

- *To evaluate primary and secondary efficacy endpoints, including OS, CR, proportion of HSCT, EFS, and DOR in the all-patient population and OS and CR in the clinically actionable mutation-defined AML subpopulations (including FLT3, IDH1, and IDH2)*

Within the all-patient and TP53 WT populations

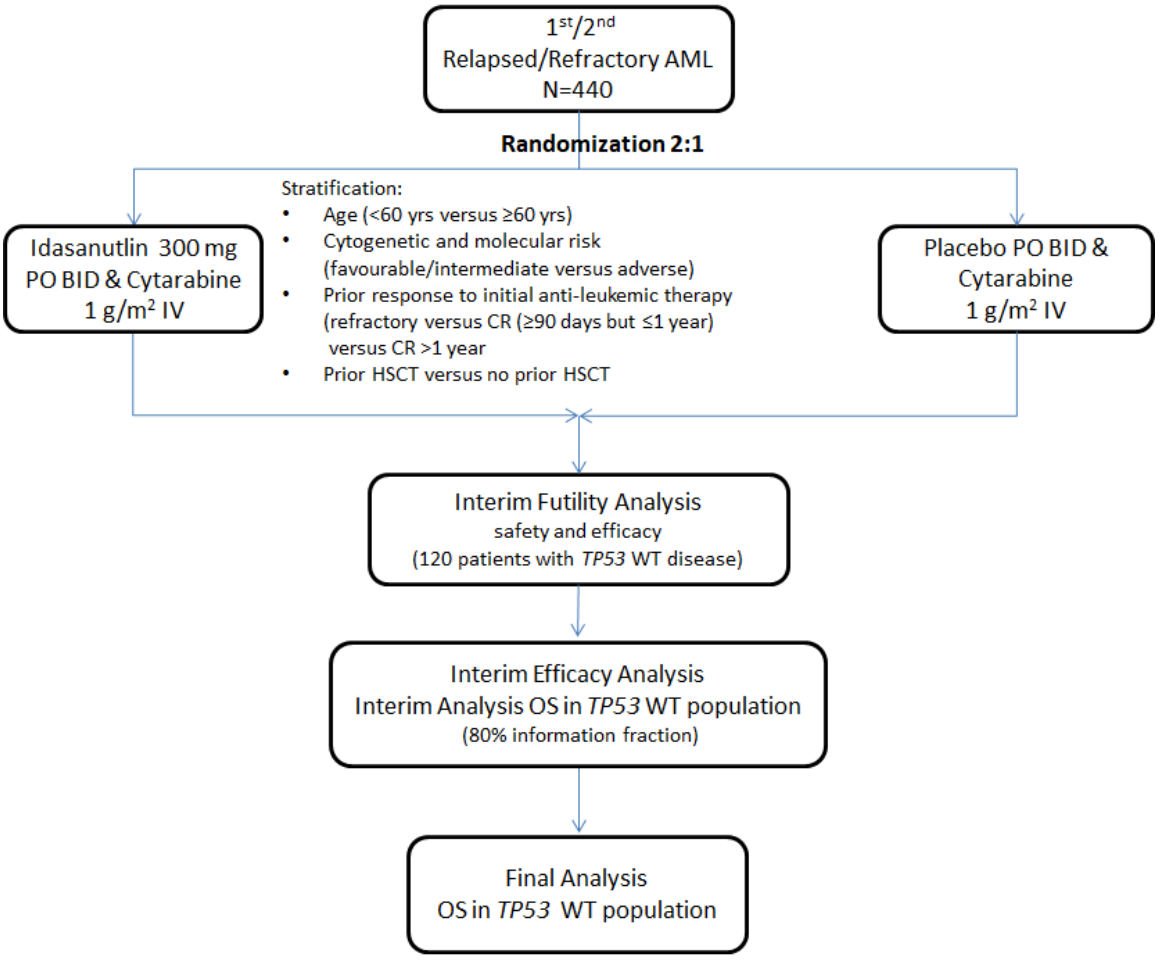
- *To evaluate efficacy endpoints, including proportion of HSCT, CR, ORR, and DOR on the basis of response assessed over entire treatment period*
- *To evaluate LFS (leukemia-free survival, or duration of OR)*
- To explore minimal/*measurable* residual disease (MRD) in bone marrow after treatment with idasanutlin plus cytarabine compared with cytarabine and placebo
- To evaluate candidate response biomarkers (gene *expression signatures*) and MDM2 protein expression in blast cells
- *To assess prognostic and predictive effect of disease-associated mutations*

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase III multicenter, double-blind, randomized, placebo-controlled study of idasanutlin in combination with cytarabine compared with cytarabine and placebo. See Study Scheme in Figure 2.

Figure 2 Study Scheme



AML = acute myeloid leukemia; BID = twice daily; CR = complete remission; HSCT = hematopoietic stem cell transplant; IV = intravenous; OS = overall survival; PO = orally; WT = wild type.

A total of 440 patients with AML who have relapsed following, or are refractory to cytarabine–containing standard induction chemotherapy after at least one and no more than two prior cytarabine–containing induction chemotherapy regimen(s) are planned to be enrolled. Relapsed patients are defined as patients with first or second relapse; first relapsed patients who are young and had a good response to initial therapy (i.e., age <60 years with first CR [CR1] duration >1 year) are excluded. Refractory patients are defined as patients with persistent leukemia after one or two induction cycles, or patients with CR1 duration of <90 days. Patients may have received prior HSCT in remission. Note that patients with prior allogenic HSCT within 90 days prior to randomization will not be eligible for this study. The *TP53* WT population will consist of patients with WT *TP53*, established centrally.

Re-screening is allowed under the conditions listed in Section 4.5.1.

Patients will be randomly assigned to each treatment arm. The arms will be stratified according to the following factors:

- Age (<60 years versus ≥60 years)
- Cytogenetic and molecular risk according to *the 2010* European LeukemiaNet (ELN) standardized reporting system at initial diagnosis (favorable/intermediate versus adverse; see Appendix 9 for full details). Cytogenetic information allowing stratification in those two groups must be available.
- Response to initial anti-leukemic therapy (refractory versus CR ≥90 days but ≤1 year; versus CR >1 year)
- Prior HSCT versus no prior HSCT

Patients will receive induction treatment with idasanutlin/placebo 300 mg BID and cytarabine 1 g/m^2 for 5 days followed by 23 days of rest (Cycle 1). For patients who achieve clinical response after induction and for whom HSCT for consolidation is not an option, it is strongly recommended to continue study medication with a maximum of two additional cycles of consolidation (Cycles 2 and 3) unless clinically contraindicated. Please refer to Sections 4.3.2.3 and 4.3.2.4 for further details.

Responding patients, including those who proceed to HSCT, will be followed for EFS and *DOR*. All patients irrespective of response to treatment will be followed for OS (see Section 6.4.2 for definition of endpoints) until the end of the study.

An interim analysis for futility based on CR, EFS, and safety is planned after 120 *TP53* WT patients are enrolled, have received at least one cycle, and confirmatory response assessment is available, to allow early stopping of the study in the event of inadequate CR, EFS, or safety concerns.

The *futility* interim analysis will be performed by an iDMC. Enrollment of patients will continue while *this* interim analysis takes place. If the Sponsor decides to stop the study based on iDMC recommendation following the *futility* interim analysis, enrollment will be discontinued.

An efficacy interim analysis on OS is planned to be conducted by iDMC to allow early testing of OS in the event of relevant efficacy. The efficacy interim analysis will be conducted when 80% of the OS events have occurred (i.e., approximately 220 events). At this time, it is anticipated that all patients will have been enrolled.

Accompanying this interim efficacy analysis, a non-binding additional futility assessment will be performed based on a hazard ratio on overall survival ≥1.

In the case of not reaching significance for OS at interim analysis, a primary analysis of OS will be performed (i.e., when 275 events have occurred).

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur 2 years after the last patient is enrolled or after 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 *5*.5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Idasanutlin Dose and Schedule

Idasanutlin dosing for this study was based on experience with an initial MBP formulation in both single agent testing (Studies NP27872 and NP28902) and from the combination with 1g/m^2 cytarabine in Study NP28679 in patients with both relapsed/refractory and elderly frontline AML. An alternative idasanutlin SDP formulation was developed, which improved the stability of the drug with regard to decreased formation of a genotoxic impurity over the shelf life, and will be used for all future studies, including this one. An integrated dose and PK exposure response analysis and a comparative safety assessment have been conducted in Study NP28679 between the two formulations. Based on this, the recommended dose of the SDP formulation is 300 mg BID (or 600 mg/day) $\times$ 5 days, which can be administered without regard to food. The dose selected, optimizes the proportion of patients ($>$90%) to achieve an efficacious exposure threshold (Day-5 area under the concentration-time curve during a 24 hour dosing interval ($AUC_{0\text{-}24h}$) $>$ 100 μg·h/mL), at which approximately 50% of patients achieved a CR, and with acceptable safety/tolerability profiles (refer to the idasanutlin IB for further details).

Idasanutlin PK exposure, pharmacodynamic effects (e.g., increased expression of serum MIC-1 as a p53 activation marker), and target-mediated hematological changes (platelet reduction in particular) were evaluated to define the optimal dosing schedule (idasanutlin IB). A comparison of MIC-1 elevation between the idasanutlin dosing schedules demonstrated limited ability to activate p53 with the weekly schedule. The daily $\times$ 3 days dose regimen did not achieve steady-state exposure, displayed shorter duration for SD (median 57 and 103 days for daily $\times$ 3-day and daily $\times$ 5-day schedules, respectively), and did not alleviate thrombocytopenia. Therefore, the daily $\times$ 5-day schedule was chosen as optimal for future clinical trials. Because thrombocytopenia in solid tumor patients and bone marrow clearance in leukemia patients share the target-mediated hematological effects, this optimal schedule found in solid tumor patients is deemed to be applicable to AML patients.

Because idasanutlin is a highly lipid-soluble small molecule, a food-effect evaluation of a high-energy/high-fat meal (1000 kcal with 50% from fat) and low-fat meal (500 kcal with 30% from fat) was explored in patients with solid tumors using the optimized SDP formulation in Study NP28902. The PK results from 19 evaluable patients (all whom received three crossover treatments) showed that the high–fat meal demonstrated equivalence in all PK exposure parameters analyzed with 90% CI values. The low-fat meal demonstrated less than 20% increase in all PK exposure parameters analyzed and was just outside the upper limit of 90% CI for equivalence, but is unlikely to be clinically significant as the inter-patient variability is approximately 50%. Thus, idasanutlin may be administered PO with or without food. Water can be given ad libitum.

3.3.2 Rationale for Patient Population

The target patient population for this Phase III study includes first or second relapsed/refractory AML patients, excluding APL (i.e., AML patients who are refractory or have relapsed following at least one and no more than two prior cytarabine–containing induction chemotherapy regimen[s]). As reflected in the current practice guidelines for AML (National Comprehensive Cancer Network Version 1. 2015, European Society for Medical Oncology, and ELN) patients who have relapsed after completion of, or are refractory to primary therapy are encouraged to participate in clinical trials.

The efficacy of study treatment is assessed based on bone marrow status. Patients with extramedullary disease with no evidence of systemic involvement are excluded from the study as their disease cannot be properly followed for response under this protocol.

Patients who have received allogeneic HSCT $\geq$ 90 days prior to randomization will be eligible for this study. No time frame applies to patients who have received autologous HSCT as consolidation therapy. HSCT should have been performed in remission and not used for salvage.

In order to control for variability in AML prognosis, and thus outcome, patients in this trial will be stratified on the basis of known prognostic factors including age, molecular

and cytogenetic risk factors, and response to initial therapy (Cheson et al. 2003; Döhner 2010). Eligible patients must have received at least one induction regimen that included cytarabine with an anthracycline (or anthracenedione). In order to determine potential benefit and protect patients unlikely to respond to therapy, patients with an extremely poor prognosis will be excluded from this trial. This includes patients who have received more than 2 prior induction regimens in their first line treatment, patients with AML secondary to a documented antecedent hematologic disorder, patients with AML secondary to prior chemotherapy, and patients who have poor performance status. Additionally, patients either refractory to or who have relapsed within 90 days of having received a course of high-dose cytarabine (HiDAC) of cumulative dose $\geqslant$18 g/m^2 will be ineligible for the proposed trial (see details in Appendix 16).

Allogeneic HSCT was shown to offer the best chance for cure of relapsed/refractory AML for patients in CR2 or greater and is therefore allowed under this protocol (Breems et al. 2005). However, the benefit of HSCT is impaired by non-relapse-related mortality, depending on the performance status, age, disease status, and transplant toxicity. HSCT-associated mortality may potentially confound the primary endpoint OS and may even risk failure to meet the primary endpoint, as observed in previous studies (Faderl et al. 2012; Ravandi et al. 2015). For this reason, the present study will rely on enrollment criteria regarding the physical status of potentially eligible patients, thereby selecting for patients with a chance to successfully undergo a later HSCT procedure.

Patients with mutations that render the p53 protein inactive are not expected to respond to an MDM2 antagonist. However, hundreds of mutations in the *TP53* gene have been described, and the relationship to the gene's functionality is not well characterized (Petitjean et al. 2007). In Study NO21279 (Phase I in AML with RO5045337), most patients treated with RO5045337 with mutant *TP53* failed to show evidence of response. Two AML patients with *TP53* mutations demonstrated clinical activity by decreased peripheral blast counts, but none had sustained clinical improvement (prolonged CRs). In NP28679 study, 1 patient with *TP53* mutation who received idasanutlin in combination with cytarabine achieved a confirmed CR (confirmatory assessment approximately 28 days following initial CR determination).

Given the uncertain role of *TP53* mutational status on p53 tumor suppressor activity, patients harboring *TP53* mutation will be allowed into this study.

The expected proportion of *TP53* mutations in the relapsed/refractory AML patient population is approximately 10% (Hu et al. 1992; Trecca et al. 1994; Wattel et al. 1994). Review of large public databases (Forbes et al. 2008; TCGA) confirms these rates. Phase I experience with both idasanutlin and RO5045337 has been consistent with *TP53* mutation rates of approximately 20%. A slightly higher rate is expected in a heavily pretreated AML population, in keeping with the larger percentage of *TP53* mutations seen in complex karyotype AML (Rucker et al. 2012).

Taking all evidence together, the mutation proportion in this study population—with fewer lines of prior therapy and excluding patients with a prior documented antecedent hematological disorder (AHD)—is expected to be approximately 15%.

Since the majority of the patients are expected to be TP53 WT (85%) and efficacy is primarily expected in the TP53 WT patients, the primary and secondary efficacy endpoints will be tested in patients who are WT for TP53 who have been randomized to idasanutlin in combination with cytarabine versus those who have been randomized to cytarabine and placebo. Efficacy in the all-patient population will be tested as exploratory endpoints.

3.3.3 Rationale for Control Group

No standard of care exists for the treatment of relapsed/refractory AML, but the most effective agent in the relapsed setting is cytarabine. Studies conducted more than three decades ago demonstrated that remission can be induced in the relapsed setting by increasing the exposure to cytarabine used in induction regimens or by prolonging the infusion duration to achieve higher intracellular concentrations (Momparler 1974). These findings have been confirmed in numerous Phase II and III studies utilizing cytarabine given in a variety of dosing regimens, including "intermediate-dose" (e.g., 1 g/m^2 Q12hour$\times$6–12 doses) and "high-dose" (e.g., $\geq$3 g/m^2 Q12hour$\times$8–12 doses), either as monotherapy or in combination with other agents (Leopold and Willemze 2002; Rudnick et al. 1979). In general, higher exposures to cytarabine produced modestly higher remission rates, but did not prolong OS, and were associated with significant and life-threatening clinical toxicities and higher rates of early death in the immediate post-treatment period. Treatment outcome was mostly influenced by patient age and the duration of CR1 and not by cytarabine dose. Similarly, patients with second or greater relapse have a worse prognosis, but can achieve remission based on cytogenetics, age and achievement of previous CR being the most important factors (Stoiser et al. 2000).

The MTD of cytarabine was found to be 3 g/m^2 per day for several days based on severe cerebellar toxicity which can be irreversible (Gottlieb et al. 1987; Herzig et al. 1987; Nand et al. 1986). The major toxicities are age-related and worsen with hepatic or renal insufficiency, such that usual clinical practice for treatment of AML at any point in therapy generally prohibits the use of repeated doses of cytarabine greater than 1–2 g/m^2 per day in patients over the age of 60 years.

Cytarabine at a dose of 1 g/m^2 rather than 2 g/m^2 was chosen as the comparator and combination partner for idasanutlin in the Phase I setting on the basis of data from the induction setting of AML therapy, where the benefit/risk of high-dose cytarabine (greater than/equal to 2 g/m^2) versus 1 g/m^2 has been questioned (Löwenberg et al. 1989; Reese and Schiler 2013; Momparler et al. 2013). Among specific cytogenetic/molecular subsets of AML in patients $<$ 60 years, there may be a benefit associated with post-remission consolidation therapy with high-dose cytarabine, but the benefit is not clear for the population overall (Byrd et al. 2002). Doses greater than 1 g/m^2 are above

the metabolic limit for cytarabine conversion to cytarabine triphosphate for the majority of patients, and thus such treatment may add only toxicity (Löwenberg 2013). This is particularly important for patients over the age of 50 years who have the greatest risk of CNS toxicity with cytarabine, and will most likely comprise the majority of the patients enrolled in this trial for relapsed/refractory disease (median age for AML onset approximately 66 years) (Herzig et al. 1987).

It is important to note that with the exclusion of first relapsed patients who are younger than 60 years of age and had a durable CR to initial therapy, a patient set is excluded where standard practice would be to use multi-agent chemotherapy (e.g., FLAG-IDA). Patients who have received more than two prior induction regimens as part of their first line treatment and those who are either refractory to or who have relapsed within 90 days after receiving HiDAC of cumulative dose $\geq 18 g/m^2$ are excluded from enrollment to limit the study population to patients with the potential to respond to cytarabine as a single agent. Furthermore, patients are randomized 2:1 from the start to the combination regimen of idasanutlin and cytarabine to limit the exposure to the control arm (Figure 2).

3.3.4 Rationale for Population Pharmacokinetic/Pharmacodynamic Analysis

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

With these PK exposure data, the exposure-response relationship of idasanutlin in combination with cytarabine on efficacy measures, such as best overall response and OS, as well as the relationship between the exposure of idasanutlin in combination with cytarabine, 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 which indicate whether sub-populations may be at increased risk will be investigated.

3.3.5 Rationale for Biomarker Assessments

This study will look at *TP53* mutation status *and other disease-associated genetic alterations, including FLT3, IDH1, and IDH2;* gene expression *signatures that* may be associated with clinical response to idasanutlin*;* flow cytometry assessment of *MDM2 expression in* blast cells*;* and MIC-1 expression levels.

Activity of idasanutlin is derived from the stabilization and accumulation of p53. *The level of MDM2* is important because MDM2 is overexpressed in approximately 50% of AML*, leading to destabilization of TP53* (Fenaux et al.1992; Hu et al. 1992; Wattel et al. 1994). This is believed to result in decreased p53 levels and activity, and *thus* p53 function could be restored by MDM2 antagonists. Activated p53 induces or inhibits the expression of multiple genes, some of which are secreted and may be useful as pharmacodynamic indicators of clinical activity of idasanutlin *(e.g., MIC-1).*

Additional biomarkers related to p53 and MDM2 activity may be evaluated as appropriate.

3.3.5.1 Mutation State of *TP53*

In AML, the *TP53* mutation rate is less than that of solid tumors, estimated to be approximately 7%–13% (Forbes et al. 2008). 16% of patients in the Phase I AML population in Study NO21279 treated with RO5045337 demonstrated a mutation in *TP53*. Leukemia cells from patients will be tested for *TP53* mutation during this study *by NGS. Mutation testing will be done retrospectively* because of the low anticipated rate of *TP53* mutation in the AML population.

3.3.5.2 MDM2 Expression Status/Predictive Gene Signatures

MDM2 protein expression in blast cells analyzed by flow cytometry is associated with response in Study NP28679 (Reis et al. 2016). MDM2 transcript (mRNA) expression from pretreatment AML patient blood specimens also trends with clinical response both in Phase I Study NO21279 with RO5045337 and in Phase I/Ib Study NP28679 with idasanutlin. However, the association is not sufficiently robust to use *MDM2* alone for selection of responsive patients. Gene expression signature(s) may provide a means of predicting patient response to MDM2 inhibitors *and a number of other gene signatures that predict response to MDM2 inhibition have been reported in the literature (Ishizawa et al. 2018). Nonclinical and* clinical data (Studies NO21279 and NP28679) suggest that an mRNA signature of four genes (*MDM2, BBC3/PUMA, XPC, and CDKN2A*) is associated with response to MDM2 antagonist RO5045337 (Zhong et al. 2015). An evaluation of this signature is also planned in this Phase III study. At the *futility* interim analysis, the iDMC will use guidelines as specified in the iDMC charter to issue a recommendation indicating the status of the gene signature.

3.3.5.3 MIC-1 Expression

MIC-1, a secreted protein that is strongly induced by activated p53, can be detected in the blood of mice bearing human tumor xenografts after treatment with doxorubicin, a genotoxic p53 activator (Yang et al. 2003). Therefore, MIC-1 may have utility as a pharmacodynamic biomarker for idasanutlin. In Study NO21279 for RO5045337 – which included patients with AML – as well as in the AML Phase I Study NP28679 for idasanutlin, MIC-1 expression has been shown to be a useful pharmacodynamic biomarker *providing evidence that the mechanism of action was engaged at a systemic level*.

3.3.5.4 Exploratory Markers

Ongoing evaluation of pharmacodynamic biomarker activity in a subset of patients in Study NO21279 has demonstrated treatment-related increases in p53 activity, particularly through the activation of p53 gene targets and induction of apoptosis (Kojima et al. 2005). On the basis of the results from this study, additional analyses on blood and/or bone marrow specimens may be performed in this trial to explore biomarkers related to p53 and MDM2 activity and the activity of idasanutlin.

3.3.5.5 AML-Relevant Markers

Additional biomarkers may also contribute to the selection of AML patients most likely to respond to idasanutlin treatment. For example, the status of one of the most commonly mutated genes in AML, *FLT3*, has been shown to be linked to the ex vivo response of AML blasts to an MDM2 inhibitor (MI2190) (*Long et al. 2010*). *In addition, FLT3, IDH1, and IDH2 are clinically actionable mutations for approved treatments (Rowe et al. 2018; Bewersdorf et al. 2019). Other mutations and genetic abnormalities have prognostic value in AML. Additional genetic analyses* include sequencing of genes associated with AML and/or those related to the mechanism of action for idasanutlin.

3.3.5.6 Minimal/*Measurable* Residual Disease Assessment in Patients with Complete Remission

The updated ELN guidelines qualify the complete remissions in AML additionally by MRD response (Döhner et al. 2017). Patients who achieve clinical remission, defined as cytomorphologic clearance of the bone marrow of leukemia (CR, CRi, or CRp, see Section 3.4.1), will undergo serial MRD assessments *in bone marrow at the time of hematologic malignancy response assessment (HMRA). These will be done primarily with flow cytometry assessments for detection of the leukemia-associated immunophenotype (LAIP) at a central laboratory. Alternative technologies (detection of disease characteristic clonal markers by NGS or polymerase chain reaction [PCR] or expression of WT-1) may be used for confirmation of the MRD response at the time of CR.* Stabilization or reduction of MRD measures *(MRD response)* could serve as a potential surrogate marker of efficacy of idasanutlin.

In patients achieving clinical remission, MRD monitoring from bone marrow aspirates will be prioritized over analysis of other exploratory markers. Other markers that may be evaluated at the time of MRD monitoring include gene sequencing to detect disease related markers.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are:

- OS
- EFS
- *DOR*
- CR
- CRp
- CRi
- Overall remission rate (ORR) (CR, CRp, and CRi)
- *Allogeneic* HSCT

For definition of response criteria (CR, CRp, CRi), see Section 4.5.8; for all other definitions, see Section 6.4.

In this study, CR or CRp achieved by induction Cycle 1 must be confirmed for the purpose of the *futility* interim analysis.

For all patients in CR or CRp who do not proceed to Cycle 2, an additional HMRA will be scheduled 30 (±3) days after the previous HMRA performed at the end of Cycle 1 (Note that this assessment will not be required after the *futility* interim analysis). For all patients proceeding to Cycle 2, the HMRA at the end of Cycle 2 will be used as the confirmatory response in the analysis. If a patient proceeds directly to HSCT in aplasia after Cycle 1 or prior to undergoing an HMRA, this will be considered confirmed CR *for the purpose of futility analysis* unless the HSCT was clearly performed in disease progression or relapse.

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are:

- Incidence and severity of adverse events and serious adverse events
- Incidence of clinically significant laboratory abnormalities
- ECGs
- Vital signs
- 30- and 60-day mortality rates

3.4.3 Pharmacodynamic/Biomarker Outcome Measures

The pharmacodynamic/biomarker outcome measures for this study are:

- *Mutation analysis in TP53, FLT3, IDH1, IDH2, and other tumor-associated genes*
- Serum MIC-1 profile (raw and/or adjusted from baseline as percentage of change)

- MDM2 expression by qRT-PCR and flow cytometry as well as gene signatures by qRT-PCR and/or RNA sequencing

3.4.4 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

- Apparent clearance (CL/F) and apparent volume of distribution (V_d/F) as well as C_{max}, steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration) [C_{trough}], area under the concentration–time curve during one dosing interval ($AUC_{0-\tau}$), AUC_{0-24h}, and $t_{1/2}$ of idasanutlin (and M4 metabolite RO6802287)
- Total clearance (CL) and volume of distribution (V_d) of cytarabine
- Effect of idasanutlin on cytarabine pharmacokinetics
- Effect of cytarabine on idasanutlin pharmacokinetics

3.4.5 Patient-Reported Outcome Measures

The patient-reported outcome (PRO) measures for this study are:

- European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
- EuroQol 5 Dimension 5-Level (EQ-5D-5L) Questionnaire

3.4.6 Exploratory Outcome Measures

The exploratory outcome measures for this study are:

- Pharmacodynamic biomarkers and other biomarkers (e.g., protein, nucleic acid, and other tumor cell–derived markers related to the mechanism of action of the study drug, which include, but are not limited to, markers of MDM2 or p53 pathway alterations) that may help predict patient subpopulations that are more likely to respond to the therapies in this study *and support a better understanding of disease biology or improvement of diagnostic assays.*
- Evaluation of MRD (LAIP, AML-specific mutations and translocations, expression of *AML*-related genes such as *WT-1*)

4. MATERIALS AND METHODS

4.1 PATIENTS

The population will include patients with first or second relapsed/refractory AML as defined in Section 4.1.1 and Section 4.1.2. At enrollment, patients should have a physical status that is considered compatible to allow for a later HSCT procedure.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age $\geq$ 18 years
- Documented/confirmed first or second refractory or relapsed AML using World Health Organization classification (Appendix 10), except acute promyelocytic leukemia. Please note that first relapsed AML patients with a CR1 duration of $>$1 year AND age $<$60 years are excluded (see Section 4.1.2).
- No more than 2 prior induction regimens (excluding prior HSCT) in their first line treatment, and one must have included cytarabine with an anthracycline (or anthracenedione).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–2
- Adequate hepatic function assessed by the following:

  Serum total bilirubin $\leq 1.5 \times$ institutional upper limit of normal (ULN), unless resulting from hemolysis, Gilbert's syndrome, or liver infiltration with leukemia

  AST/ALT $\leq 3 \times$ institutional ULN (or $\leq 5 \times$ 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) $\geq$50 mL/min
- WBC count at randomization of $\leq$50,000/mm^3

  Note: When treatment is not started immediately upon randomization, the WBC count at the start of induction therapy (Cycle 1) must remain at $\leq$50,000/mm^3. The use of hydroxyurea (HU) or leukapheresis to meet eligibility is allowed. HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $<$1% per year, during the treatment period and for up to 6 months after the last dose of study drug.

  A woman is considered to be of childbearing potential if she has not reached a postmenopausal state ($\geq$12 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, and established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  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. Barrier methods must always be supplemented with the use of a spermicide.

- For men unless permanently sterile by bilateral orchidectomy: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for up to 6 months after the last dose of study drug. Men must refrain from donating sperm during this same period.

  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.

- Ability to understand and willingness to sign a written informed consent form and comply with all study requirements including completion of PRO measures.

4.1.2 Exclusion Criteria

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

- First relapsed patients aged $<$60 years with a CR1 duration of $>$1 year
- Patients with prior documented AHD including the following: myelodysplastic syndrome, myeloproliferative disease (i.e., chronic myelomonocytic leukemia, polycythemia vera, primary myelofibrosis, and essential thrombocythemia), and aplastic anemia
- AML secondary to any prior chemotherapy unrelated to leukemia
- Patients who are either refractory to or have relapsed within 90 days of receiving a regimen containing a cumulative dose of $\geq$18 g/m^2 cytarabine
- Patients who have received allogeneic HSCT within 90 days prior to randomization. HSCT should have been performed in remission and not used for salvage (patients who have received autologous HSCT as consolidation in CR1 are eligible).
- Patients who have received immunosuppressive therapy for graft-versus-host disease or for engraftment syndrome after autologous stem cell transplantation within 2 weeks prior to randomization
- Prior treatment with an MDM2 antagonist
- Patients with clinically relevant QTc prolongation (QTcF $>$480 ms), a family history of long QT syndrome, or who are currently receiving treatment with medications that are known to prolong the QT interval (see Appendix 11; Yap and Camm 2003)

  Medications that are known to prolong the QT interval must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study medication until 5 days after the final administration of study medication (Section 4.4.2.2).

- Patients receiving any other investigational or commercial agents or therapies administered with the intention to treat their malignancy within 30 days (or 5 half-lives) from first receipt of study drug

Note: The exception is HU or leukapheresis in patients who need to continue this therapy to maintain a WBC count ≤50,000/mm^3. HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication.

- Patients with acute toxicities from any prior anti-leukemia therapy that have not resolved to Grade ≤2 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03
- Patients with a history of other malignancy within 5 years prior to screening, except for malignancy that has been in remission without treatment for at least 2 years prior to randomization
- Patients unable to temporarily 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 Table 2, Table 3, and Table 4 during the treatment phase. These agents must be discontinued 7–14 days prior to the start of study medication.
- 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) during the treatment phase. These agents must be discontinued 7 days (or 5 half-lives) prior to the start of study medication.

  Note: Treatment with or switch to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is allowed, according to local practice. However, platelet levels need to be closely monitored in these patients (see Section 4.4.2).
- Patients with a history of systemic hypersensitivity reactions ≥Grade 2 attributed to cytarabine or components of the formulated product
- Patients who have 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 III, IV), myocardial infarction ≤ 6 months prior to first study medication, and cerebrovascular accidents ≤ 6 months before study medication start

  Unstable seizure disorders

  Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study medication, such as hereditary coagulation disorders or insulin-dependent diabetes mellitus not optimally controlled with medical management (e.g., presence of ketoacidosis) or active GI conditions (e.g., Grade ≥2 graft-versus-host disease) and uncontrolled *inflammatory* bowel disease (i.e., Crohn's disease, ulcerative colitis, diverticulosis-associated colitis, and Behçet's disease).

- 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 <2 weeks of appropriate systemic antifungal therapy

    Active bacterial infection and/or bacterial infection with positive cultures in the 7 days prior to dosing

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

    History of symptomatic *Clostridium 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.

    In all cases, the patient should be afebrile (exception of AML-related fever) and hemodynamically stable for at least 72 hours at the time of study medication initiation.

- Patients with a history of active or chronic infectious hepatitis unless serology demonstrates clearance of infection

    Patients with occult or prior hepatitis B virus (HBV) infection (defined as negative hepatitis B surface antigen and positive total hepatitis B core antibody) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody after vaccination or prior but cured hepatitis B are eligible. Patients positive for hepatitis C virus antibody are eligible provided PCR is negative for HCV RNA.

- Patients who have a history of clinically significant liver cirrhosis (e.g., Child-Pugh class B and C).
- Patients with electrolyte abnormalities such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade >1 per NCI CTCAE v4.03. Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility.
- Patients with extramedullary AML with no evidence of systemic involvement
- Patients with active CNS leukemia
- Pregnant or breastfeeding patients
- HIV-positive patients
- Patients who might refuse to receive blood products and/or have a hypersensitivity to blood products.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After signed informed consent has been obtained and eligibility has been established, the study site will obtain the patient's unique identification number and treatment assignment from the interactive web response system (IWRS). Randomization will be performed through the IWRS using stratified permuted block randomization. Randomization stratification factors are age (<60 versus ≥ 60 years), cytogenetic and molecular risk (favorable/intermediate versus adverse, see Appendix 9 for definitions) at initial diagnosis, prior response to initial anti-leukemic therapy (refractory versus CR ≥ 90 days but ≤ 1 year versus CR > 1 year) and prior HSCT versus no prior HSCT. Randomization will be 2:1 (higher probability to be in the idasanutlin plus cytarabine arm).

This is a double-blind trial, that is, neither the patient nor the treating physician will know the assigned treatment arm. The randomization code may however be made available to the Bioanalytical manager to facilitate the analysis of PK samples.

An iDMC will be established to monitor patient safety and efficacy and will assess the outcome of the interim *analyses*. All analyses for the iDMC's reviews will be prepared by an independent Data Coordinating Center (IDCC). Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of study results. iDMC membership and procedures to be followed for the study will be detailed in an iDMC charter.

In general, treatment codes should not be broken, except in emergency situations. If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IWRS. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event). Unblinding should not result in the withdrawal of a patient from the study. Every effort should be made to retain unblinded patients in the study.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Idasanutlin and Placebo

Idasanutlin and matching placebo will be supplied by the Sponsor. Idasanutlin will be supplied as 300 mg tablets. For information on the formulation, packaging, and handling of idasanutlin see the idasanutlin IB.

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.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Idasanutlin and Placebo

Idasanutlin/placebo will be administered at 300 mg BID PO for 5 days, without regard to meals. Water can be given ad libitum. During induction the first (morning) dose of idasanutlin/placebo should be administered immediately before cytarabine infusion starts and the second (evening) dose should be administered 10–14 hours after the first dose. In case the patient proceeds to consolidation therapy, only 50% of idasanutlin should be given (300 mg QD in the morning) for 5 days.

Guidelines for dosage modification for efficacy are provided in Section 4.3.2.4. Guidelines for dosage modification and treatment interruption or discontinuation for safety reasons are provided in Section 5.1.2.5.

4.3.2.2 Cytarabine

Cytarabine will be administered at a dose of 1 g/m^2 QD for 5 days as a 1–3 hour IV infusion (local practice applicable within this guideline). 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 8. Guidelines for dosage modification for efficacy are provided in Section 4.3.2.4. Guidelines for dosage modification and treatment interruption or discontinuation for safety reasons are provided in Section 5.1.2.5.

4.3.2.3 Guidelines for Induction Therapy (Cycle 1)

Induction therapy must begin ≤3 days after randomization. For patients who need to continue HU or leukapheresis during the screening period to maintain a WBC count ≤50,000/mm^3, HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication.

Patients will be treated for an initial 28-day induction cycle (5 days PO idasanutlin or placebo [Days 1–5] plus IV cytarabine for 5 days [Days 1–5] followed by 23 days off treatment [Days 6–28]). In patients achieving CRp or CRi up to 28 additional days (up to Day 56) following treatment are allowed for blood count recovery, if needed. Patients must receive antibiotic, anti-diarrheal, and anti-emetic prophylaxis during the treatment and recovery periods (see Appendix 14). Patients should receive appropriate anti-TLS prophylaxis during the treatment and recovery periods according to patient's TLS risk factors and investigator's clinical judgement (see Appendix 14).

Induction therapy in this study is limited to a single cycle, as there are very limited data indicating any benefit of an additional induction cycle based on Phase I studies. For

patients achieving a good partial remission (PR) however, a second cycle of induction therapy at the same dose level as Cycle 1 may be allowed on a case-by-case basis after discussion and agreement with the Sponsor.

4.3.2.4 Guidelines for Consolidation Therapy (Cycles 2 and 3)

Responding patients (CR/CRp or CRi with neutrophil recovery [$\geq 0.5 \times 10^9$/L]) who do not proceed to transplant, directly or at all, are recommended to continue with consolidation therapy with cytarabine and idasanutlin or placebo for a maximum of two additional cycles if not medically contraindicated. Mandatory prophylaxis must be adhered to in the same manner as in Cycle 1.

Continuation of study medication into consolidation therapy is determined based on the presence of clinical response at the end of Cycle 1 (see Appendix 4). Once CR/CRp/CRi with neutrophil recovery ($\geq 0.5 \times 10^9$/L) is observed, consolidation therapy should begin within 7 days from the day that clinical response is observed. If Cycle 2 is started $>$7 days after clinical response is observed (e.g., due to prolonged toxicity), weekly blood counts must be performed to confirm that the patient remains in clinical remission. If relapse is suspected, a bone marrow aspirate must be taken and an HMRA performed as an unscheduled assessment. These same rules apply when patients move from Cycles 2 to 3.

It was observed in Study NP28679 that patients who continued on full doses of treatment following achievement of CR frequently required additional time for blood count recovery. Therefore, the daily dose of idasanutlin/placebo (300 mg BID in Cycle 1) will be reduced to 50% (300 mg QD for subsequent cycles) for consolidation because a 50% dose reduction was tolerated for multiple cycles in leukemia patients with a minimum of dosing delays.

- Patients with CR at the Day 28 HMRA may proceed immediately to consolidation therapy with 50% idasanutlin (300 mg QD in the morning) and 100% cytarabine (1 g/m^2).
- For patients with CRp/CRi at the Day 28 weekly blood counts should be obtained between the Day 29 and Day 42. As soon as blood counts recovered and CR/CRp is observed (but latest at Day 42), patients may start Cycle 2 with 50% idasanutlin (300 mg QD in the morning) and 100% cytarabine (1 g/m^2).
- For patients remaining in CRi until Day 42 weekly blood counts should be obtained up to Day 56. As soon as blood counts recovered and CR, CRp or CRi with ANC $\geq 0.5 \times 109$/L is observed (but latest at Day 56), patients may start Cycle 2 with 50% idasanutlin (300 mg QD in the morning) and 50% cytarabine (0.5 g/m^2). Once the cytarabine dose is reduced, the dose reduction should be maintained for the remainder of the cycles.

For more detailed instructions on continuation of study medication based on response criteria see Appendix 4. For guidelines on mandatory and recommended prophylaxis regimens, consult Appendix 14.

4.3.3 Prophylactic Medication

The use of oral or IV prophylactic anti-emetics, anti-diarrheals, and antimicrobials is mandatory in all patients (see Appendix 14). As outlined in regulatory guidelines, mandatory prophylaxis is considered a non-investigational medicinal product (NIMP). Administration of an NIMP must be recorded on the Concomitant Medication electronic Case Report Form (eCRF). Side effects associated with an overdose or incorrect administration of an NIMP must be recorded as an adverse event in the eCRF. The potential causality to NIMPs must be assessed by the investigator for any adverse event. Please refer to Table 1 for a complete list of NIMPs.

Table 1 Non-Investigational Medicinal Products

NIMP
5-HT_3-receptor antagonists (e.g., palonosetron[a] and granisetron)
Dexamethasone
Levofloxacin
Loperamide
Posaconazole

NIMP = non-investigational medicinal product.

[a] Palonosetron is the recommended option due to its efficacy against delayed nausea and lack of QT interval prolonging effects.

4.3.4 Investigational Medicinal Product Accountability

Idasanutlin and matching placebo as well as cytarabine are considered investigational medicinal products (IMPs) in this trial. Idasanutlin and matching placebo required for completion of this study will be provided by the Sponsor. Cytarabine and NIMPs will be provided from local sources.

The study site will acknowledge receipt of idasanutlin and placebo, using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator is responsible for the control of drugs under investigation.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed, and provided that adequate storage and integrity of drug has been confirmed. The site's method of IMP destruction must be agreed to by the

Sponsor in advance. The site must obtain written authorization from the Sponsor before any 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.

Accountability and patient compliance with IMPs will be assessed by adequately tracking "drug dispensing" and returned bottles at each site.

These records must contain the following information:

- Documentation of drug shipments received from the Sponsor (date received and quantity)
- Disposing of all unused study drug not dispensed to patients

A Drug Dispensing Log must be kept current and should contain the following information:

- The identification number of the patient to whom the study medication was dispensed
- The date and quantity of the study drug dispensed to the patient
- The date and quantity of the study drug returned by the patient

All records and drug supplies must be available for inspection by the Roche Clinical Trial Monitor at every visit.

4.3.5 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 website:

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

4.4 CONCOMITANT THERAPY AND FOOD

4.4.1 Permitted 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., red blood cells [RBCs] and platelets) used by a patient from 28 days prior to screening up to the study drug completion/discontinuation visit. All such therapy 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).

The use of antimicrobials, anti-emetics, and anti-diarrhea prophylaxis for patients taking idasanutlin/placebo in combination with cytarabine is mandatory (see Section 4.3.3 and Appendix 14 for guidance). Their use must be documented in the eCRF.

The use of TLS prophylaxis and/or treatment is recommended according to the guidelines in Appendix 14. Growth factors may be used according to local guidelines and/or usual practice at the study site. Their use must be documented in the eCRF.

Treatment with or switch to LMWH or UFH is allowed, according to local practice. Importantly, platelet levels need to be closely monitored in these patients (see Section 4.4.2.3).

4.4.2 Prohibited Therapy

4.4.2.1 Drugs Prohibited Due to Potential Drug-Drug Interaction

Oral or parenteral use of the following drugs will be prohibited during the treatment phase in order to prevent undesirable DDIs (see Section 1.2.2.3).

- Strong/moderate inducers or inhibitors of CYP2C8, including gemfibrozil, which is also an inhibitor of UGT1A3 (Table 2)
- CYP2C8 (Table 2) or OATP1B1/3 (Table 4) substrates
- Strong inducers of CYP3A4 (Table 3)

Substrates and inhibitors listed in Table 2 and Table 4 must be discontinued 7 days prior to start of study treatment.

Inducers listed in Table 2 and Table 3 must be discontinued 14 days prior to start of study treatment.

Drugs listed in Table 2, Table 3, and Table 4 may be re-initiated per protocol after the study drug completion/discontinuation visit.

Table 2 List of Prohibited CYP2C8 Substrates, Inhibitors, and Inducer

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 3 List of Prohibited CYP3A4 Inducers

Inducers (Strong)
Carbamazepine
Cyproterone
Efavirenz
Etravirine
Modafinil
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin
Rifampicin
St. John's wort

Table 4 List of Prohibited OATP1B1/3 Substrates

OATP1B1/3 Substrates
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.

The above lists of 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

4.4.2.2 Drugs Known to Prolong the QT Interval

Medications that are known to prolong the QT interval (see Appendix 11) must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study medication until 5 days after the final administration of study medication.

Patients will require azole drugs for prophylactic or treatment purposes (see Appendix 14). Oral fluconazole and ketoconazole are known to prolong the QT interval (see Appendix 11); therefore, other members of the azole class (i.e., posaconazole, itraconazole, and voriconazole) should be used in lieu of oral fluconazole and

ketoconazole as indicated for the specific disease and/or fungal pathogen (see Appendix 14 for antifungal prophylaxis guidance).

4.4.2.3 Oral or Parenteral Anticoagulant/Anti-Platelet Agents

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. Clinical data on thrombocytopenia severity and duration in AML are limited. In Study NP28679, the time to platelet recovery was highly variable, with a mean time to recovery for platelet counts (Kaplan-Meier estimates) of 34 days in patients who responded to idasanutlin and cytarabine combination therapy.

Therefore, due to the potential severity and duration of thrombocytopenia induced by study treatment, patients in clinical need for chronic treatment with oral or parenteral anticoagulant/anti-platelet agents (e.g., warfarin, chronic daily treatment with aspirin [$>$ 325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban) are excluded from this study. In patients considered eligible for the study because they are able to tolerate anticoagulant/anti-platelet treatment interruption, these agents must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study medication. After the study drug completion/discontinuation visit, treatment with anticoagulant/anti-platelet agents may be re-initiated for patients with transfusion-independent adequate platelet levels as clinically indicated.

Thrombocytopenic patients are not devoid of risk for thrombosis. Although patients with low platelet counts are at decreased risk for venous thrombosis compared to patients with normal platelet counts, thrombosis may still occur. Hence, in patients remaining transfusion-dependent or patients with an adverse event requiring anti-thrombotic therapy during the study treatment period, the clinical benefit of using anticoagulation therapy (acute risk of thromboembolism/stroke) should be carefully weighed against its risks (acute risk of hemorrhage/uncontrolled bleeding) and only initiated if anticoagulant/anti-platelet use is acutely required and use cannot be postponed until after the study drug completion/discontinuation visit. Close monitoring of platelet levels is recommended. Frequent measurement of peak anti-Xa levels and tight maintenance between 0.5 and 1.0 IU/ml are advised and may improve the risk/benefit ratio (Rickels et al. 2007). The maintenance of anti-thrombotic treatment should be continuously reassessed. Sustained use over time must be clinically warranted. Treatment of central venous catheter–related venous thromboembolisms may not always require anticoagulants, since many of these thrombi resolve spontaneously in patients with acute leukemia following removal of the catheter. Anti-thrombotic treatment should be reserved for those patients with established conditions, such as venous thromboembolism. LMWH preparations or UFH with doses adjusted to platelet levels are allowed and would be the preferred therapeutic intervention. LMWH and UFH are

recommended for patients who do not have contraindications to anticoagulant use (see Khorana et al. 2007).

4.4.3 Prohibited Food

None.

4.5 STUDY ASSESSMENTS

The schedule of assessments performed during the study is detailed in Appendix 1, Appendix 2, and Appendix 3.

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 randomization. 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.

Screening and pretreatment assessments will be performed within 14 days prior to Cycle 1/Day 1 unless otherwise specified. Test results or examinations (except for the bone marrow aspirate) performed as standard of care prior to obtaining informed consent and within the protocol-defined screening 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 9) must be available from initial diagnosis prior to randomization of the patient to allow stratification by risk category. At a minimum cytogenetic information allowing stratification into the risk categories favorable/intermediate versus adverse needs to be available. Additional information on molecular markers is desirable and should be entered into the eCRF.

Those patients who fail the screening due to organizational reasons moving them out of the screening window (e.g., long waiting times for results, wash-out period, technical reasons) will be allowed to be re-screened once. Additionally, those patients who fail the screening for previously identified infection, for ECOG greater than 2, for acute toxicities from any prior anti-leukemia therapy, for previous electrolyte abnormalities, or patients pregnant or breastfeeding will also be allowed to be re-screened once upon resolution of the excluding criterion. Results of screening tests within the protocol-defined screening window (prior to randomization/Cycle 1, Day 1) may be used rather than repeating required tests.

Written informed consent must be obtained again before performing any re–screening tests or evaluations.

4.5.2 Assessments during Treatment and Follow-Up

All assessments must be performed as outlined in Appendix 1, Appendix 2, Appendix 3 Assessments scheduled on the day of study medication administration should be performed prior to administration of study medication, unless otherwise noted in the schedule of assessments. All other assessments, including hematology and biochemistry assessments scheduled on non-study medication dosing days, should be performed on the day of the specified visit within a window of ±2 days. Please see Appendix 4 for a detailed description of bone marrow sampling for HMRAs and biomarker assessments, and the underlying algorithm governing continuation of study medication into consolidation therapy.

Treatment Phase (Cycle 1 [Induction] and Cycles 2 and 3 [Consolidation])

Assessments should be collected on the day and time period required as per the schedule of assessments (Appendix 1).

If the specified screening assessments found in Appendix 1 are performed up to 72 hours prior to Cycle 1, Day 1, these assessments do not have to be repeated on Cycle 1, Day 1 except for hematology and biochemistry, which must be performed 1 day prior to Cycle 1, Day 1. Note: Hematology assessments should be obtained and checked PRIOR to randomization.

At the end of each cycle, the response to treatment will be determined. Patients in CRp/CRi by Day 28 will be allowed a maximum of an additional 28 days (until Day 56) for blood counts to recover before proceeding with consolidation therapy. The end of cycle is hence defined as either Day 28 or the day of the best peripheral blood count recovery, up until Day 56.

Please see Appendix 1 and Appendix 4 for detailed instructions on bone marrow collection and HMRA assessment during the treatment phase.

Note that the *futility* interim analysis will include a comparison of the proportion of confirmed CR/CRp between study arms (see Section 3.4.1). For patients proceeding to Cycle 2, the best response at the end of Cycle 2 will be used as the confirmed response. For patients not proceeding to Cycle 2, the response observed at the end of Cycle 1 must be confirmed 30 days (± 3 days) later.

Sampling timepoints for bone marrow aspirate and/or blood for HMRA are outlined in Appendix 1.

Study Drug Completion/Discontinuation Visit

Once a patient completes study treatment or discontinues study drug for any reason, the Study Drug Completion/Discontinuation eCRF page must be completed. To allow for this, patients will be asked to return to the clinic 28 days (+28 day window) after the last dose of study medication is administered.

In the event that the decision to withdraw from further therapy on the study occurs after 28 days from the last dose of idasanutlin/placebo (e.g., due to an interruption of an intended cycle continuation due to an adverse event), then the study drug discontinuation visit should occur on the date of withdrawal.

For a patient in remission after induction who is not continuing on to consolidation after the allowed recovery period for blood counts (up until Day 56), the study drug completion/discontinuation visit and the confirmatory response assessment visit may occur during the same time window. Please consult Appendix 1 for guidance on data entry into the eCRF in this scenario.

Follow-Up

Patients in CR/CRp/CRi after terminating study treatment will be followed for EFS, DOR, $and\ LFS$. HMRAs will be performed monthly ($\pm$5 days) until disease progression/relapse is noted or until the patient moves to HSCT. Every 3 months HMRAs will include assessment of bone marrow aspirate; in all other instances, HMRA will be based on peripheral blood counts only.

In the event of relapse, a HMRA based on a bone marrow aspirate is required. In addition, whole blood in EDTA for biomarker analysis should be obtained.

For patients who move to HSCT, an HMRA based on a bone marrow aspirate should be performed to document the bone marrow status prior to the start of conditioning therapy. The quantity of the bone marrow aspirate should also allow for exploratory biomarker analyses (MRD/Flow, EDTA, and Paxgene), and the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score (Sorror et al. 2005; Sorror 2013) should be obtained to document the patient's health status prior to the start of conditioning therapy.

All patients will be followed every 3 months for study treatment-related serious adverse events, fatal adverse events, subsequent anti-cancer therapies, and survival status. Survival follow-up ends with death or end of study. Adverse events should be followed as outlined in Section 5.3.1 and Section 5.6. Please see Appendix 1 for the schedule of follow-up assessments.

4.5.3 Hematopoietic Stem Cell Transplant

For patients who proceed to undergo HSCT after completion/discontinuation of study medication, data regarding the health status (HCT-CI score [Appendix 15]), leukemia status (HMRA) within 28 days prior to start of conditioning, date of transplant, type of transplant (allogeneic versus autologous, peripheral blood versus bone marrow versus cord blood, matched sibling versus matched unrelated donor, or mismatched donor or haploidentical donor), and conditioning (myeloablative versus reduced) will be collected. Information on engraftment status and survival will be requested every 3 months. Note: Donor lymphocyte infusion is allowed under this protocol and should be recorded in the eCRF as an anti-cancer therapy.

4.5.4 Medical History and Demographic Data

Medical history includes clinically significant diseases within the last 5 years, surgeries, AML cancer history (including prior cancer therapies and procedures, cytogenetics, and leukemia markers) and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the screening visit.

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

4.5.5 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological 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), limited, symptom-directed physical examinations should be performed. 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.

4.5.6 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 12.

4.5.7 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.

4.5.8 Hematologic Malignancy Response Assessment

The following criteria should be used to determine hematologic malignancy response (Cheson et al. 2003; Döhner et al *2017*; NCCN guidelines):

- CR: Bone marrow blasts < 5%, absence of blasts with Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9$/L; platelets $\geq 100.0 \times 10^9$/L
- CRi: All CR criteria except for residual neutropenia (ANC $< 1.0 \times 10^9$/L) or thrombocytopenia (platelets $< 100.0 \times 10^9$/L)
- CRp: All CR criteria except for thrombocytopenia (platelets $< 100.0 \times 10^9$/L)
- Treatment failure:

  Resistant disease:
  Failure to achieve CR, CRi, or CRp; only includes patients surviving $\geq$ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.

  PR and SD/hematologic improvement (HI) will be considered treatment failure.

  PR $\geq$ 50% decrease in bone marrow blasts

  SD/HI = decreased peripheral blast percentage, decreased frequency of transfusions, improvement in peripheral cell counts

  Death in aplasia:
  Deaths occurring $\geq$7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia

  Deaths from indeterminate cause:
  Deaths occurring before completion of therapy, or $<$7 days following its completion; or deaths occurring $\geq$7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
- Relapse of Disease: $\geq$5% bone marrow blasts; or reappearance of blasts in the blood, or development of extramedullary disease.

HMRAs require sampling of blood and bone marrow as indicated. Bone marrow aspirates are required, but if bone marrow biopsies are performed, the biopsy results should be provided. Depending on timepoint in the schedule of assessments the HMRA is established based on 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/relapses outside of the scheduled visit, an unscheduled HMRA must be provided.

If a bone marrow aspirate is performed at any unscheduled timepoint while on 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 exploratory analyses (MRD by flow cytometry, EDTA, Paxgene) and amount taken should be taken into consideration (Section 4.5.10.6).

Throughout the Study

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, 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 (See Appendix 1, Appendix 3, and Appendix 4 for further details).

Bone marrow and blood will be required for HMRA after Cycle 1 for all patients. Depending on blood count recovery, this will be between Day 28 and Day 56 latest. Patients with CR or CRp by Day 42 may proceed with Cycle 2 (50% idasanutlin [300 mg QD in the morning], 100% cytarabine [1 g/m^2]). Patients remaining in CRi up to Day 42 will need to undergo another HMRA to determine response status. Based on this, patients with CR, CRp, or CRi with ANC $\geq 0.5 \times 10^9$/L may continue with Cycle 2 (50% idasanutlin [300 mg QD in the morning], 50% cytarabine [0.5 g/m^2]). Once the cytarabine dose is reduced, the dose reduction should be maintained for the remaining cycles. With respect to continuation with Cycle 3 different criteria apply before and after the $futility$ interim analysis (please see below). Refer to the schedule of assessments (Appendix 1) and the treatment algorithm (Appendix 4) for further details.

During the follow-up of patients who remain in CR, CRp, or CRi after treatment, blood will be required every month and a bone marrow aspirate will be required every 3 months to allow for HMRA until relapse or HSCT. Refer to Appendix 1 and Appendix 3 for further details.

Before $Futility$ Interim Analysis

The $futility$ interim analysis will include a comparison of the proportion of confirmed CR or CRp between study arms. If a patient proceeds to Cycle 2, then the HMRA at the end of Cycle 2 (on Days 28–56 of Cycle 2) will be used as confirmation of response. If a patient does not receive a second cycle of therapy then the response from Cycle 1 should be confirmed 30 days ($\pm$ 3 days) later. In both cases confirmation of response requires bone marrow aspirate.

The decision criteria to continue with Cycle 3 are the same as applied in Cycle 1 for Cycle 2. Refer to the schedule of assessments (Appendix 1) and the treatment algorithm (Appendix 4) for further details.

After *Futility* Interim Analysis

After the *futility* interim analysis bone marrow aspirate for confirmation of response is no longer required. However, HMRA including bone marrow assessment needs to be available for the last cycle received, that is, if a patient stops study medication after Cycle 2, then a HMRA including bone marrow aspirate is required; if a patient continues with Cycle 3 HMRA based on blood counts only is sufficient and HMRA based on bone marrow will be performed at the end of Cycle 3.

The decision to continue with Cycle 3 will no longer be based on bone marrow data, but on blood counts only. Refer to the schedule of assessments (Appendix 1) and the treatment algorithm (Appendix 4) for further details.

4.5.9 Laboratory Assessments

Normal ranges for the study laboratory parameters must be submitted to Roche **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 (glucose, urea or BUN, serum creatinine, creatinine clearance [at screening only determined by Cockcroft-Gault Formula], AST, ALT, LDH, alkaline phosphatase, 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.
- Serum pregnancy test in females of child bearing potential and postmenopausal females with less than 1 year of amenorrhea.
- Bone marrow aspirate (total cells counted, absolute mature neutrophils, mature eosinophils, mature basophils, monocytes, lymphocytes, blasts, promyelocytes, myelocytes, metamyelocytes, plasma cells, pronormoblasts, normoblasts, nucleated erythrocytes)
- Bone marrow biopsy (leukemia histology, cellularity, percent cellularity, percent blasts)

4.5.10 Mandatory Samples for Pharmacokinetic, Pharmacodynamics, and Exploratory Biomarkers

All samples listed below will be collected according to the Schedule of Assessments outlined in Appendix 1, Appendix 2, and Appendix 3. Unscheduled PK samples matched to ECG recordings may be required in case any prolongation of the QTc interval or other adverse cardiac findings are identified (see Section 4.5.11 for details). For PK analysis, it is of utmost importance to record dosing and blood sampling times accurately.

Allowed sampling time windows are as follows:

- Predose (before idasanutlin/placebo morning dose): Within 2 hours prior to dosing of cytarabine
- End of cytarabine infusion: within 5 minutes after the ECG at end of cytarabine infusion
- 6 hours post idasanutlin/placebo morning dose: $\pm$0.5 hours

For sampling procedures, storage conditions, and shipment instructions see the Laboratory Manual(s).

4.5.10.1 Pharmacokinetic

PK blood samples will be collected in all patients in Cycle 1 on Days 1, 2, 5, and 8 for idasanutlin/placebo and in Cycle 1 on Days 1, 2, and 5 for cytarabine to measure the amount of study drug and relevant metabolites in the blood. An additional PK blood sample for idasanutlin/placebo will be collected on Cycle 1 on Day 10 until approximately 80 samples are received for this timepoint (Appendix 2).

Patients that receive more than Cycle 1 of treatment will have additional blood sampling for PK analyses (Cycles 2 and 3 on Days 2 and 5 for idasanutlin/placebo, Cycles 2 and 3 on Day 2 for cytarabine). Note: The PK blood sample for idasanutlin/placebo on Day 5 will only be collected until the $futility$ interim analysis.

The placebo-treated samples will also be collected (due to blinding) but will not be analyzed. A safe-guard procedure will be in place to maintain integrity of blinding.

All PK samples will be collected from the arm (limb) which is not being used during the administration of cytarabine (i.e., from the alternate arm). If cytarabine is 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.

4.5.10.2 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. *Analyses* include, but are not limited to:

- Quantification of MIC-1 *by ELISA-based assay*
- *Determination of the TP53 mutation status and transcriptome* and/or genome sequencing of cancer-related genes including *TP53*
- Measurement of transcript gene expression signatures that may predict response to MDM2 antagonists
- MRD will be monitored on the basis of aberrant immunophenotypes *(flow),* AML-specific mutations/translocations *(NGS/PCR),* or aberrant gene expression *of WT-1 (qRT-PCR).*
- *WT-1 mRNA expression will be analyzed by qRT-PCR, and mutations/translocations will be analyzed as AML-specific clonal markers by PCR/sequencing.*
- *MDM2 protein expression level in AML blasts will be analyzed by flow cytometry.*
- *A 4-gene signature (including MDM2 gene expression) will be analyzed by qRT-PCR. The predictive or prognostic value of these markers will be analyzed at futility interim analysis (gene signature) and at the time of OS primary analysis. For protein expression and 4–gene signature evaluations at futility interim analysis, see Section 6.11.3.*

Mutations in TP53 have been reported in approximately 15% of patients with AML, including single nucleotide variants, truncations, and frameshifts, with mutations found throughout the gene (Haferlach et al. 2008). Therefore, mutation analysis for TP53 requires sequencing the entire coding sequence of TP53 by a next generation sequencing (NGS) method.

The TP53 mutation status determination in Study WO29519 was initially performed using a laboratory-developed test (LDT). In September 2018, the Sponsor decided to switch to the investigational use only F1CDx assay from Foundation Medicine, Inc. (FMI) in a central Clinical Laboratory Improvement Amendment (CLIA) certified laboratory to include the assessment of other mutations with clinical relevance in AML, including FLT3, IDH1, and IDH2. Technical information on the assay is available on the FMI website:

https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx

F1CDx is a comprehensive NGS assay that can detect genomic alterations in 324 genes. These include IDH1, IDH2, and FLT3 that have been shown to be prognostically relevant and clinically actionable for patients with AML. The assay has comparable sensitivity to the LDT for TP53 status determination (5% mutant allele frequency).

F1CDx has gone through analytical and clinical validation to become FDA approved as a CDx assay for multiple therapies for solid tumors using formalin-fixed paraffin-embedded tissues as input. Bone marrow specimen and blood have been shown in pilot studies to be equally usable as input material for DNA extraction and sequencing analysis. Additional analytical validation is being performed to fully qualify bone marrow aspirate and peripheral blood samples for use with this assay. Retrospective testing of all available specimens previously analyzed with the LDT is also conducted.

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. Samples could be used for validation of assays. Additional markers may be measured in case a strong scientific rationale for these analyses develops. Based on continuous analysis of biomarker data (blinded to the treatment arm) any analysis, timepoint, or sample type not considered to be critical for safety may be stopped at any time if the data does not support a strong scientific justification to continue. Some samples that are collected may not be analyzed. Some analysis may not occur in placebo patients (e.g., clinical genotyping). Furthermore, some analysis may depend on patient's molecular status or response to treatment.

Unless specified, samples will be destroyed within 7 years after the clinical study report (CSR) is finalized.

4.5.10.3 Whole Blood

Whole blood will be collected to evaluate candidate biomarkers related to MDM2 and/or p53 pathways as well as other biomarkers related to treatment response, dose response or re-treatment.

- **EDTA whole blood:** analysis to include, but not be limited to, sequencing of *TP53* and genes in MDM2 and p53 pathways and disease-related markers such as gene mutations and rearrangements
- **Paxgene whole blood RNA:** analysis to include, but not limited to, sequencing of gene fusions that are frequent in AML, gene expression analysis for predictive gene signature and MRD monitoring by measuring *WT-1* transcript levels.
- **Whole blood for Flow Cytometry:** analysis to include protein expression of MDM2 in peripheral blood *in* AML blast cells

4.5.10.4 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

4.5.10.5 Serum Biomarker (Prior to *Futility* Interim Analysis Only)

Blood samples for analysis of Serum MIC-1 will be collected up until only the *futility* interim analysis. These samples may also be evaluated for the presence of candidate biomarkers of the proposed mechanism of action of idasanutlin. Exploratory assessments may include, but are not limited to, markers of cell death and apoptosis, circulating microRNA, as well as exploratory studies of circulating tumor specific DNA.

4.5.10.6 Bone Marrow

Bone marrow samples will be collected to evaluate candidate biomarkers related to MDM2 and/or p53 pathways as well as other biomarkers related to treatment response, dose response or re-treatment. Evaluations may include proteomic tests, gene expression analyses, and nucleic acid sequencing of mechanism or disease-related markers.

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, Appendix 2, Appendix 4, and Section 4.5.8). 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:** analysis will include determination of abnormal cell phenotypes by flow cytometry.

  After screening, the bone marrow for MRD flow cytometry is the priority sample.

- **EDTA bone marrow:** analysis to include, but not be limited to, sequencing of *TP53* and genes in MDM2 and p53 pathways, and analysis of gene mutations, rearrangements, and fusions commonly seen in AML patients (potentially to be used for MRD monitoring).

  Sample for DNA is the priority bone marrow sample at screening.

- **Paxgene bone marrow:** analysis to include, but not be limited to, gene expression analysis for predictive gene signature. MRD monitoring by measuring *WT-1* transcript levels *will be assessed prior to futility interim analysis.*

  Bone marrow RNA is the last bone marrow sample at all timepoints.

For patients who proceed to transplant, pretransplant 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.

In case a patient consents to optional exploratory research the remainder of the bone marrow sample(s) will be stored in the Roche Clinical Repository (RCR), (see Section 4.5.13.1) for up to 15 years after the date of final closure of the clinical database.

4.5.11 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints, as outlined in the Schedule of Assessments (Appendix 1 and Appendix 2). Additional ECG recordings may be performed at unscheduled timepoints as clinically indicated. Please note that the time points of ECG recordings are matched to PK sampling time points and should be performed sequentially as indicated in Section 4.5.10.

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). 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 the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: ECG abnormality (including waveform), heart rate; PQ, PR, RR, QRS intervals; 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 postdose 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, severe bradycardia) and provide this information to the eCRF. In case a patient presents with an episode of grade $\geq$2 supraventricular arrhythmia (atrial fibrillation, atrial flutter, sinus tachycardia, etc.), an unscheduled ECG should be recorded. Standard-of-care treatment may be instituted per the discretion of the

investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained.

If at a particular postdose timepoint in Cycle 1 the mean QTcF is $>$500 ms and/or 60 ms longer than the baseline value, then ECG assessments at time points as in Cycle 1 are to be repeated in all following cycles.

Allowed ECG sampling assessment windows are as follows:

- Predose assessment: within 2 hours prior to idasanutlin morning dosing
- Assessments end of cytarabine infusion: up to 10 minutes after infusion
- Assessments 6 hours after idasanutlin morning dosing: $\pm$18 minutes
- Assessments 24 hours (equivalent to Day 2 predose idasanutlin): $\pm$2 hours

4.5.12 Patient-Reported Outcomes

PRO data will be collected via electronic questionnaires to more fully characterize the clinical profile of idasanutlin. The questionnaires will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study medication.

The EORTC QLQ-C30 is a validated and reliable self-reporting measure (Fayers et al. 2001) consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and a global health status/global quality-of-life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The EORTC QLQ-C30 questionnaire takes 5 minutes to complete. The EORTC QLQ-C30 will be conducted using electronic patient-reported outcome (ePRO) prior to treatment across all cycles on Days 1, 8, 15, and 28, and between Days 29–56, if applicable. Additionally, the EORTC QLQ-C30 will be collected during study drug completion/discontinuation visit and every 3 months until relapse during long-term follow-up of patients in clinical remission. An additional EORTC QLQ-C30 questionnaire must also be completed after progressive disease (PD).

The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (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 visual analogue scale that measures overall health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L questionnaire takes

5 minutes or less to complete, and assessments are made at the same time as the EORTC QLQ-C30. An additional EQ-5D-5L questionnaire is also required to be completed after PD.

Patients will use an ePRO device to capture PRO data for the above two 5-minute surveys. The ePRO device and/or instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via transmission method (wireless daily) automatically to a centralized database at the ePRO vendor. The data can be accessed by appropriate study personnel securely via the Internet.

4.5.13 Samples for Roche Clinical Repository

4.5.13.1 Overview of the Roche Clinical Repository

The RCR 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 and analysis of RCR specimens 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.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- 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

4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

4.5.13.3 Sample Collection

If RCR consent is provided, any mandatory bone marrow material (cells, RNA, and DNA) remaining after protocol defined analysis will be stored for up to 15 years in the RCR.

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Blood for serum isolation on Day 1, Day 5, and at disease relapse (in those patients who have hematological response).
- Blood for plasma isolation on Day 1, Day 5, and at disease relapse (in those patients who have hematological response).

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood for DNA isolation will be collected on Day 1. If the sample is missed on Day 1, it can be collected at any time in the study.

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.13.4 Confidentiality

Confidentiality for All RCR Specimens

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

Patient medical information associated with RCR specimens 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.

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

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The

aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.13.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens 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 RCR specimens. 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 by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant’s death or loss of competence, the participant’s specimens and data will continue to be used as part of the RCR research.

4.5.13.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient’s wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RCR 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 specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from this study.

4.5.13.7 Monitoring and Oversight

RCR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. 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 RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 determines it is in the best interest of the patient
- Patient non-compliance, defined as unable or unwilling to complete the required study dosing or assessments

In the case that the patient decides to prematurely discontinue study medication ("refuses treatment"), all efforts should be undertaken to keep the patient in the study for further follow-up. In case the patient does not wish to return for study assessments or follow up, he/she should be asked if he/she can still be contacted every 3 months to collect survival information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If necessary, the investigator should contact the subject or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study.

Patients who withdraw from the study will not be replaced.

4.6.2 Study Drug Discontinuation

Patients must discontinue study medication 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 who discontinue study medication prematurely will not be replaced. Patients discontinuing study medication will be followed as per Schedule of Assessment (Appendix 1 and Appendix 3).

After the study drug completion/discontinuation visit, adverse events should be followed as outlined in Section 5.3.1 and Section 5.6.

4.6.3 Study and Site 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.

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 Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Safety Risks of Idasanutlin and Cytarabine in Leukemia

Patient well-being and safety will be protected by applying stringent exclusion criteria specified in Section 4.1.2, applying the toxicity management guidelines detailed in Appendix 14, and through pharmacovigilance/safety monitoring of all adverse events and laboratory assessments and will be graded according to the CTCAE v4.03 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. In addition to the oversight provided by the Medical Monitor and drug safety personnel for this trial, an iDMC will review safety data on a regular and unblinded basis. 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. More details on the frequency and content of the iDMC meetings can be found in the iDMC charter.

Information related to the risks associated with idasanutlin treatment is described in the idasanutlin IB. Potential risks associated with idasanutlin include GI toxicity, cytopenias, TLS, electrolyte abnormalities, and infectious complications. Given the clinical need for effective treatment for patients with AML, the benefit-risk relationship for idasanutlin is acceptable. Many of the toxicities experienced by patients were manageable with appropriate prophylaxis and supportive therapy and/or were reversible with discontinuation of idasanutlin. As a result, stringent toxicity management recommendations were introduced and are detailed in Appendix 14. Refer to the current idasanutlin IB for details on the safety data from previous idasanutlin studies and for additional information on idasanutlin warnings and precautions.

5.1.1.1 Gastrointestinal Toxicity

GI adverse events reported in Phase I idasanutlin studies were primarily diarrhea, nausea, vomiting, abdominal pain, constipation, and anorexia. Diarrhea was the most common adverse event and was observed in $>$90% of patients in the AML Study NP28679 (mostly Grade 1 and Grade 2 in severity). Nausea and vomiting were also frequently reported but to a lesser extent, and the majority of adverse events were Grade 1 and Grade 2. In addition to institutional guidelines, specific instructions for the management of GI side effects are provided in Section 5.1.2.1 and in Appendix 14.

5.1.1.2 Cytopenias

Cytopenias, including myelosuppression, are expected under the anti-leukemia treatment proposed, and the therapeutic effect is expected to be associated with toxicity on normal bone marrow progenitors. Bone marrow toxicity may manifest as cytopenias (i.e., pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, and anemia). In Study NP27872, which evaluated idasanutlin in patients with solid tumors, possible

exposure-dependent neutropenia and thrombocytopenia were observed; these events were reversible and able to be monitored. In leukemia patients, drug-induced myelosuppression is expected during idasanutlin treatment, and idasanutlin administered in combination with cytarabine may prolong the aplasia window. In Study NP28679, the time to platelet and neutrophil recovery were highly variable, and the mean time to recovery for platelet and leukocyte counts (Kaplan-Meier estimates) were 34 days in patients who responded to idasanutlin and cytarabine administered in combination.

5.1.1.3 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. Five cases with laboratory evidence of TLS were reported in Study NP28679 as an idasanutlin-related event. Of these 5 cases, a single case with clinical abnormalities was reported. The patient was subsequently treated for TLS and recovered. To date, there have been no other cases of TLS among the $>$282 patients exposed to idasanutlin.

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 14.

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 included 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 Management of Patients Who Experience Specific Adverse Events

5.1.2.1 Gastrointestinal Events

GI adverse events are the most common toxicity observed during idasanutlin therapy. All enrolled patients will be evaluated at regular intervals clinically and with standard laboratory tests before and during their participation in this study. Frequent monitoring and supportive treatment (including hydration and electrolyte monitoring and correction) are strongly encouraged. Prophylactic treatment to mitigate GI toxicity is mandatory during the treatment phase after the initial toxicity assessment is made (ASCO, ESMO, and NCCN; Roila et al. 2010; Ettinger et al. 2012; Hesketh et al. 2016).

Prophylaxis guidelines for moderately emetogenic chemotherapy must be followed.

Diarrhea was the most common adverse event observed, occurring in $>90\%$ of patients in Study NP28679. Mandatory prophylaxis with antidiarrheal agents must therefore be implemented in all patients. Close clinical monitoring for signs of diarrhea is required. Patients who develop diarrhea should have other or concomitant causes ruled out (including infection due to *C. difficile*). Once other or concomitant causes of diarrhea are evaluated, prompt treatment with anti-diarrheal agents must be administered to prevent severe diarrhea during study treatment. See Appendix 14 for specific recommendations and guidelines on anti-emesis and anti-diarrheal prophylaxis, adverse event management, and *C. difficile* infection.

Please note that diarrhea adverse events (Grade ≥ 2) and *C. difficile* infection (Grade ≥ 2) are considered adverse events of special interest for idasanutlin (see Section 5.2.3).

5.1.2.2 Myelosuppression

For patients who are neutropenic and thrombocytopenic at baseline due to their underlying leukemia, elimination of leukemic blasts is essential for normal bone marrow recovery. Idasanutlin was associated with myelosuppression in Study NP28679, but normal bone marrow recovery was observed in patients showing a clinical response. Additive effects from idasanutlin administered in combination with cytarabine on normal bone marrow progenitors (including early progenitors) are possible.

In anticipation of a potential extended period of myelosuppression, the standard precautions for neutropenia, thrombocytopenia, and anemia will be used for patients in the trial. In this study, blood counts will be monitored closely throughout treatment (see Appendix 1). Administration of growth factors will be permitted for neutropenic sepsis according to local practice, and patients will be monitored and treated promptly should infection occur. Patients will be excluded from study participation if they are unwilling to

undergo supportive blood transfusion therapy. Please refer to Appendix 14 for guidelines for hematological toxicity management.

Please note that events of febrile neutropenia Grade ≥ 3 and thrombocytopenia Grade ≥ 3 (if associated with hemorrhage or bleeding) are considered adverse events of special interest for idasanutlin (see Section 5.2.3).

5.1.2.3 Infections

Infections of various etiologies have been reported in patients with AML in Study NP28679. Drug-induced myelosuppression and AML-linked cytopenia increases the risk for infectious complications. In addition, AML is associated with impaired immune function and an increased susceptibility to infection. Assessment of causality in these cases can be difficult, and it is unclear whether or how much the incidence of infection may be increased due to idasanutlin treatment.

Prophylactic antimicrobial and antifungal therapy are mandatory for all patients in the study. Prophylaxis for *Pneumocystis carinii* infection will be administered according to local and institutional guidelines. Patients receiving antimicrobial agents with a therapeutic intent, as described in the exclusion criteria (Section 4.1.2), are not permitted to start study medication. Patients should be carefully screened for evidence of active or uncontrolled infection or other uncontrolled disorder prior to enrollment. Patients in this study will be closely monitored for infection, and prompt therapy will be instituted as necessary. In any patient with uncontrolled and/or severe diarrhea, the presence of *C. difficile* infection should be investigated. **See Appendix 14 for specific recommendations and guidelines for antimicrobials, antifungals, and *C. difficile* infection.**

Please note that *C. difficile* infection (Grade ≥2) is considered an adverse events of special interest for idasanutlin (see Section 5.2.3).

5.1.2.4 Tumor Lysis Syndrome

There is a potential for TLS in patients treated with idasanutlin. Patients with an initial WBC count at randomization of >50,000/mm^3, as described in the inclusion criteria (Sections 4.1.1), are not permitted to start study medication. Treatment to decrease the WBC count (e.g., HU or leukapheresis) is permitted prior to randomization and up to 24 hours prior to the start of study medication to meet eligibility criteria. The risk of TLS should be assessed prior to initiating study medication, and standard institutional guidelines for TLS prophylaxis for leukemia patients should be followed. The following clinical laboratory parameters will be monitored in all patients receiving study medication: sodium, potassium, chloride, calcium, carbonate, BUN, uric acid, serum creatinine, LDH, and phosphorus. In the event that clinical laboratory abnormalities arise that are suggestive of TLS, in addition to following institutional guidelines, study-specific guidelines are provided in Appendix 14. **Please refer to Appendix 14 for further guidance on TLS management.**

Per the Howard criteria, clinical tumor lysis syndrome (CTLS) is defined as laboratory evidence of metabolic changes concomitant with significant clinical toxicity requiring clinical intervention, that is, the presence of laboratory TLS (LTLS) and one or more clinical manifestations of TLS such as seizures, cardiac arrhythmia, and renal abnormality (see Appendix 13). Due to the life-threatening nature of CTLS, this condition is considered an adverse event of special interest for idasanutlin (see Section 5.2.3).

5.1.2.5 Dose Modification due to Toxicity

Reasons for dose modifications or delays to the start of the next cycle, the supportive measures taken, and the outcome, will be documented in the patient's chart and recorded in the eCRF.

As a general rule, all study medication should be held and resumed together to remain synchronized when toxicity resulting from any component of the regimen occurs. Missed doses of study medication cannot be administered at a later timepoint in the case of treatment interruption.

All treatment-related toxicities should be resolved to Grade ≤ 1 or the baseline grade prior to beginning the next cycle. Patients will be allowed a maximum of an additional 28 days (up until Day 56) for recovery of toxicities to Grade ≤ 1 or the baseline grade. In the event that a non-hematologic toxicity occurs prior to the start of a subsequent cycle until Day 56, the case may be discussed with the medical monitor or designee, who may allow an additional recovery period.

Continuation on study medication is gated by the clinical response observed at the end of a cycle (see Appendix 4). Once clinical response is observed and continuation is allowed per Appendix 4, the next cycle should be initiated. A delay >7 days from clinical response is considered a delay of therapy. In such cases, weekly blood counts must be performed to confirm that the patient remains in clinical remission. Upon suspicion of relapse, a bone marrow aspirate must be taken and an HMRA performed as an unscheduled assessment. Reduction/interruption of dosing of cytarabine due to adverse events (other than hematologic toxicities) should be according to available National Prescribing Information, Summary of the Product Characteristics, or other relevant documents and institutional practice.

Reduction of exposure to idasanutlin/placebo may be managed by reducing the dose to 50% (i.e., 300 mg dose administered in the morning only). As a further step, the treatment length may be shortened (i.e., 3 days instead of 5 days of study drug administration); however, all efforts should be undertaken by using optimal premedication to allow all patients completion of Cycle 1, Day 1–5.

Hematological toxicity Grade 3, 4:

- Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia that worsens after initiation of study medication.
- Administer RBCs or platelets as required (see Appendix 14).
- For patients targeted to receive consolidation Cycles 2 and/or 3, follow dosing guidelines based on blood counts depicted in Appendix 4.

AST, ALT, or bilirubin increase Grade 3, 4:

- For Grade 3 AST/ALT elevation, study medication may be continued without interruption and/or dose reduction at the discretion of the investigator per institutional practice.
- For Grade 4 AST/ALT elevation, study medication must be withheld until the severity of the AST/ALT elevation is Grade ≤ 1.
- If improvement to Grade ≤ 1, resume idasanutlin/placebo and cytarabine with original dose and schedule.
- Permanently discontinue study medication if Hy's Law criteria (defined in Section 5.3.5.6) are met, AST/ALT elevation does not resolve to Grade ≤ 1 within 28 days, or if Grade 4 AST/ALT elevation recurs.

Diarrhea, nausea, or vomiting:

- Please refer to Appendix 14 for specific recommendations.

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.

Patients will be evaluated for adverse events (all grades according to the NCI CTCAE v4.03), serious adverse events, and any adverse events requiring treatment interruption or discontinuation. Patients who have an ongoing adverse event leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, the patient undergoes HSCT, or the patient starts a different anti-tumor therapy.

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), except as described in Section 5.3.5.9
- 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:

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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 (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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 criteria; 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 include the following:

- 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 13)
- Febrile neutropenia (Grade ≥3)
- Thrombocytopenia (Grade ≥3 if associated with hemorrhage or bleeding)

  Reporting of this adverse event of special interest requires two separate forms: one form to report thrombocytopenia and one form to report hemorrhage/or bleeding.
- Diarrhea (Grade ≥2)
- Clostridium difficile infection (Grade ≥2)

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. Hematological adverse events of special interest 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 drug, 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 drug until 56 days after the last dose of study drug, all adverse events should be reported. Patients who, at 56 days after the last dose of study medication is administered, have an ongoing adverse event will be followed until the event resolves or the patient is lost to follow-up.

After informed consent has been obtained until 6 months after the last dose of study medication is administered, adverse events of special interest are reportable with the exception of hematological adverse events of special interest arising as a result of confirmed relapsed disease (see Section 5.2.3 for adverse event of special interest definition).

After 56 days from the last dose of study drug until the end of the study, the investigator should only report any serious adverse events that are believed to be related to the prior administration of study drug treatment or any fatal adverse events. Those should be reported on the eCRF Adverse Event page over the course of the study (see Section 5.6).

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 timepoints. Examples of non-directive questions include the following:

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

"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 v4.03 will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 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]

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

Note: Based on the most recent version of NCI CTCAE v4.03, 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 or not 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, considering especially 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, including mandatory prophylactic medication.

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

For all adverse events, 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. 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/intermittent 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 should be considered clinically significant and only reported as an adverse event if it meets at least one of the following criteria:

- Is accompanied by clinical symptoms *(e.g., Grade ≥3 thrombocytopenia accompanied by bleeding)*
- Results in a change in investigational study medication (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
- Meets serious adverse event criteria as defined in Section 5.2.2

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., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF. If the laboratory abnormality is related to the underlying disease (for example neutropenia, thrombocytopenia or pancytopenia is a clinical manifestation of leukemia), the laboratory abnormality would not be required to be reported as an adverse event. In the event that a patient achieves a CR with recovery of peripheral blood counts, then subsequent hematologic toxicities should be reported as adverse events.

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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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:

- Accompanied by clinical symptoms
- Results in a change in investigational study medication (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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. 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 the primary 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 AML should be recorded only on the Study Discontinuation eCRF. All other on study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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").

All deaths, including those attributed to disease progression, will be monitored by the iDMC in an unblinded manner and analyzed by the iDMC with recommendations of those analyses reported to the Sponsor as described in the iDMC charter.

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 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 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

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

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study medication is not itself an adverse event, but it may result in an adverse event.

All adverse events associated with an overdose or incorrect administration of study medication should be recorded on the Adverse Event eCRF.

If the associated adverse event fulfills serious 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).

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 study drug:

- Serious adverse events (defined in Section 5.2.2)
- Adverse events of special interest (defined in Section 5.2.3)
- Pregnancies (see Section *5.4.3* 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

Primary Contact

Medical Monitor: [redacted], *Ph.D.*

Telephone No.: [redacted]

Secondary Contact

Medical Monitor/*Roche Medical Responsible*: [redacted], *M.D., DMSc*

Telephone No.: [redacted]

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 and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events

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. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, all serious adverse events irrespective of drug-event relationship will be reported until 56 days after the last dose of study drug. Thereafter only *adverse events of special interest and* serious adverse events related to study drug should be reported as per guidance in Section 5.6. Please note that this is not applicable to fatal adverse events who should be reported as serious adverse events irrespective of study drug relationship and be recorded on the Adverse Event eCRF until the end of the study. 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, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events 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 last dose of study drug. A 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 drug 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 last dose of study drug. A 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 drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should 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

A spontaneous 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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)*. A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug 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).

5.5 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 of the event 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. Hematological 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, electronic mail, 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 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the study, if the event is believed to be related to the prior study medication.

Adverse events of special interest are reportable until 6 months after the last dose of study medication is administered, with the exception of hematological adverse events of special interest arising as a result of confirmed relapsed disease (refer to Section 5.2.3 for adverse events of special interest definitions).

The investigator should report these events directly to Roche Safety Risk Management either by faxing or by scanning and emailing the Serious Adverse Event/ Adverse Event of Special Interest Reporting Form using the fax number or email address provided by the Sponsor.

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 IB
- Cytarabine Summary of Product Characteristics

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

A mechanistic simulation model was used to determine the sample size in this event-driven study, based on the following global assumptions:

- Final analysis for OS in patients with *TP53* WT disease based on two-sided log-rank test at 0.05 level of significance
- 85% power to detect an OS hazard ratio for idasanutlin + cytarabine versus cytarabine + placebo of 0.67 in patients with *TP53* WT disease, corresponding to an improvement in median OS from 6 to 9 months (50%)
- Proportion of long term survivors of 8.0% in the cytarabine + placebo arm and 16.1% in the idasanutlin + cytarabine arm

To compute the necessary number of events, we $simulated$ OS times based on the following assumptions:

- All simulated OS times for patients not considered long-term survivors are exponentially distributed
- Probability of being a complete responder in the cytarabine + placebo arm is 0.16
- Probability of being a complete responder in the idasanutlin + cytarabine arm is 0.323, implying an odds ratio for CR comparing the idasanutlin + cytarabine versus the cytarabine + placebo arm of 2.5
- Probability for a complete responder to be a long-term survivor is 0.5 in either arm

- An annual dropout rate of 5% (every effort will be made to contact patients for survival information in case of study withdrawal or loss to follow-up)

To have the targeted 85% power, 275 events *in patients with TP53 WT disease* are required. The minimum detectable hazard ratio in a 2:1 randomized trial corresponding to 275 events and a significance level of 0.05 amounts to 0.78, corresponding to a minimal detectable median improvement from 6 to 7.7 months assuming exponentiality.

All patients*, regardless of TP53 mutation status*, will be randomized to this *study. Assuming 85% of patients will have TP53 WT disease and 15% will have TP53 mutant disease, approximately 440* patients will be enrolled over approximately 29 months, corresponding to an estimated number of 374 patients *with TP53 WT disease.*

In Version 6 of the protocol, an interim analysis for efficacy on OS of TP53 WT patients was added. The sample size assumptions above remain unchanged other than the recruitment time (now estimated at 41 months). The interim analysis will occur at an information fraction of 80%, providing a maximum power of 83% for the final OS analysis (see Section 6.11.2).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations, and study drug administration will be summarized by treatment arm. Patient disposition will be summarized by treatment arm and will include whether treatment was completed or discontinued early, and the reason for early treatment discontinuation.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and disease status, will be summarized by treatment arm. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum and maximum, and number of observations. Descriptive summaries of discrete data will include frequencies and percentages.

6.4 EFFICACY ANALYSES

Patients will be analyzed according to the treatment arm to which they were randomized. *The TP53 WT population is the efficacy population and refers to all randomized TP53 WT patients as identified by a central laboratory test (see Section 4.5.10.2).*

Description of efficacy analysis in this section is valid for both interim and primary analysis.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint, OS, is defined as the time from randomization to death due to any cause. OS for patients who have not died at the time of the analysis will be censored at the date last known alive.

The primary OS analysis of the study will assess the null hypothesis of equality of OS functions in the idasanutlin in combination with cytarabine (MDM2-chemo) arm versus the cytarabine given with a placebo (chemo) arm in the *TP53* WT population as follows:

H0: $OS_{MDM2\text{-}chemo} = OS_{chemo}$ versus H1: $OS_{MDM2\text{-}chemo} \neq OS_{chemo}$

A formal treatment comparison will be made using a two-sided stratified log-rank test at a significance level *defined using the O´Brien-Fleming alpha-spending function with overall Type I error rate at 0.05 corresponding to available information (see Section 6.11.2).* Stratification factors that will be used are the same as for randomization, that is, age (<60 versus ≥ 60 years), cytogenic and molecular risk (*favorable*/intermediate versus adverse), prior response to initial anti-leukemic therapy (refractory versus CR ≥ 3 months but ≤ 1 year versus CR > 1 year) and prior HSCT versus no prior HSCT.

Survival curves in each treatment arm will be estimated using Kaplan−Meier estimates. The Kaplan–Meier estimates will provide a visual description of the survival curves and the difference across treatment arms. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% CI. To further describe and quantify OS, estimated median OS per arm and 1-year and 2-year survival probabilities, all including 95% CI, will be given. The effect of prognostic factors on OS will be assessed in an exploratory analysis using Cox multivariate regression.

6.4.2 Secondary Efficacy Endpoints

The following secondary endpoints will be tested for the TP53 WT population, as described in the Statistical Analysis Plan:

- *CR proportion*
- EFS
- ORR (CR, CRp, and CRi)
- *DOR (duration of remission following CR)*
- Proportion of HSCT *following CR*
- *CR proportion and OS in clinically actionable mutation-defined subpopulation (FLT3, IDH1, and IDH2)*

Patients with no response assessments (for any reason) will be considered non-CR.

Difference in proportions of CR will be assessed between the two treatment arms using Cochran–Mantel–Haenszel test stratified by randomization stratification factors. In addition, proportions and 95% CI will be reported for each treatment arm. The effect of prognostic factors on CR will be assessed in an exploratory analysis using logistic regression.

EFS is defined for all patients and measured from the date of randomization. It is measured until treatment failure, relapse from CR, or death from any cause, whichever occurs first. For patients with none of these events before *time of analysis*, EFS is censored at the date of the patient's last response assessment.

DOR is defined for patients achieving CR and is the time from achieving CR until relapse or death from any cause, whichever occurs first. For patients with none of these events before time of analysis, DOR is censored at the date of the patient's last response assessment.

EFS and *DOR* will in general be analyzed using the same statistical methods as those described for OS. If only very few patients qualify for *DOR* analysis, only descriptive statistics will be given.

ORR (CR, CRp, and CRi) and proportion of HSCT will be compared between the two treatment arms using the same statistical methods as those described for CR.

6.4.3 Exploratory Efficacy Endpoints

Primary and secondary efficacy endpoints (OS, CR, ORR, HSCT, EFS, and DOR) in the all-patient population, as well as OS and CR in the subpopulation of FLT3, IDH1, and IDH2, will be analyzed.

The following endpoints will be assessed in the all-patient and TP53 WT populations: CR and ORR over entire treatment period; LFS; and HSCT in patients with OR (CR/CRp/Cri) and all patients. CR over entire treatment period will also be assessed in the subpopulation of FLT3, IDH1, and IDH2.

Biomarker analyses are described in Section 6.8.

6.5 SENSITIVITY ANALYSES

The following sensitivity analyses for OS will be performed in the *TP53* WT population:

- An unstratified log-rank test.
- To assess the relevance of HSCT against other long-term effects, OS will be alternatively defined with censoring at date of HSCT and analyzed using the same methods as for the primary endpoint.
- *Discontinuation of assessments or patient lost to follow up considered as an event*

6.6 SAFETY ANALYSES

All safety analyses will be based on *both the TP53 WT population (defined here as TP53 WT patients who have received any study medication at least once) and* the complete safety analysis population (defined as all patients who have received any study medication at least once), and patients will be analyzed according to the treatment received (patients receiving idasanutlin at least once will be analyzed in the idasanutlin arm). Safety analyses will include, but not be limited to, incidence rates for adverse events including mortality, adverse event severity, seriousness, and adverse events leading to discontinuation. In addition, abnormalities of clinical laboratory tests and vital signs assessed during the study treatment period and post-treatment follow-up will be assessed. Exposure to study medication will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics.

This trial is designed to allow for early termination or a modification of the protocol for safety concerns or lack of efficacy, based on the advice of an iDMC. The iDMC will be incorporated into the study to review safety data on a regular basis, including adverse events of special interest. Both the Sponsor and the iDMC can request ad hoc iDMC meetings if potential safety concerns arise. Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm as a result of safety reasons. The iDMC will also perform a safety review at the preplanned interim analyses for futility and efficacy.

6.7 ELECTROCARDIOGRAMS

Incidence of clinically significant ECG abnormalities will be reported in patient listings and change from baseline summarized in tables by treatment arm. ECG QT and QTcF intervals will be summarized by descriptive statistics.

6.8 PHARMACODYNAMIC AND BIOMARKER ANALYSES

The following pharmacodynamic parameters will be presented by listings and descriptive summary statistics.

- Blood samples analyzed for MIC-1
- Analysis of *TP53, FLT3, IDH1, and IDH2* mutation status
- *MDM2 protein expression level in AML blasts*
- *A 4-gene signature (including MDM2 gene expression)*
- *MRD*

6.9 PHARMACOKINETIC ANALYSES

Key PK parameter values (CL/F and Vd/F) of idasanutlin and cytarabine (CL and Vd) will be estimated using a popPK approach. The influence of covariates such as gender, race/ethnicity, weight, hematological parameters at baseline, renal/hepatic impairment, and degree of underlying disease will be investigated. Other PK parameters such as C_{max}, C_{trough}, $AUC_{0-\tau}$, AUC_{0-24h}, and $t_{1/2}$ will be derived from the individual post hoc predictions. Details of the population analysis will be described in the Modeling and Simulation Analysis Plan. Results of this analysis will be reported separately.

If appropriate, an exploratory PK/pharmacodynamic analysis may be performed post hoc. The primary focus will be exploration of the relationship between measures of exposure to idasanutlin in combination with cytarabine (C_{max}, C_{trough}, and AUC_{0-24h}) and ECG, drug-related adverse effects as well as clinical efficacy parameters.

6.10 PATIENT-REPORTED OUTCOME ANALYSES

Scoring for the EORTC QLQ-C30 questionnaire will be based on the scoring manual. Consistent with the user manual, prorated scores will be computed for a subscale if more than 50% of the constituent items have been completed for that subscale. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Summary statistics of the EORTC QLQ-C30 scales and their changes from baseline will be calculated at each assessment timepoint for both study arms. Analysis details of these PROs will be provided in the Statistical Analysis Plan.

Health utility scores, as assessed by the EQ-5D-5L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-5L assessment that generate a score. Scores at baseline and change from baseline scores for each timepoint will be quantified using descriptive statistics. The results will be used for more complete health economic data analysis.

6.11 INTERIM *ANALYSES*

6.11.1 *Futility*

A non-binding interim analysis for safety and futility will be performed by an iDMC after 120 patients with *TP53* WT have been enrolled and assessed for response. For the purposes of the *futility* interim analysis, CR is defined as confirmed CR (see definition in Section 3.4.1). Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of study results. The iDMC may recommend stopping the study for futility if:

- the observed odds ratio for CR in the cytarabine and idasanutlin arm versus the cytarabine and placebo arm in the population of patients WT for *TP53*, is < 2.0,

- or the observed odds ratio for CR in the cytarabine and idasanutlin arm versus the cytarabine and placebo arm in the population of patients WT for *TP53,* is < 2.5 and the hazard ratio for EFS > 1.

To compute stopping probabilities for the *futility* interim analysis, the following additional assumptions are made within *TP53* WT patients and the simulation model is extended accordingly:

- Median OS for non-responders in cytarabine arm is 5.1 months
- Median OS for responders, but short-term survivors in cytarabine arm is 7.5 months
- EFS follows an exponential distribution
- Median EFS times for non-responders and CR short-term responders is assumed to be shorter by a factor 2.5 compared to OS in these same subpopulations
- The correlation between uncensored EFS and OS times is 0.5
- Hazard ratio for a comparison of idasanutlin + cytarabine versus cytarabine +placebo in both non-responders and short-term responders is 0.8

Using these assumptions, we expect 63 EFS events at the *futility* interim analysis under the alternative hypothesis. The probability of early stopping due to futility is 89.9% if the null hypothesis of equal OS survival functions is true and 31.9% if the alternative assumption of an increase in median OS from 6 to 9 months is true.

The analysis in both the *TP53* WT population and in the overall population will be provided to the iDMC.

The iDMC may recommend stopping the study for safety at the *futility* interim analysis if any of the following criteria are met (note: early death is defined as any death within the first 30 days after randomization):

- The proportion of GI toxicity (nausea, vomiting, diarrhea) events in the experimental arm (idasanutlin + cytarabine): Grade 3 $>$ 40% or Grade 4 $>$ 15%
- The proportion of early deaths in the experimental arm (idasanutlin + cytarabine) is $\geq$ 10 percentage points greater than in the control arm (cytarabine + placebo)
- $>$ 20% of early deaths overall in the treatment arm

More details on the interim analysis are provided in the iDMC charter.

6.11.2 *Efficacy*

An interim analysis for efficacy on OS is planned to be conducted by iDMC. The efficacy interim analysis will be conducted when 80% of the OS events have occurred (i.e., approximately 220 events). At this time, it is anticipated that all patients will have been enrolled (see Section 6.1).

For the interim efficacy analysis of OS, the significance level will be determined using the O'Brien-Fleming alpha-spending function with overall type I error rate at 0.05 level. At the time of the interim efficacy analysis, it is expected that 80% of the OS events will have occurred, corresponding to an alpha spending of 0.025 for the interim and 0.043 for the final OS analysis leading to a power of 83% for the final analysis.

The iDMC will test OS for efficacy and check if there is a significant difference (alpha level 0.025 or as assessed based on actual number of OS events) in OS in favor of the experimental arm.

Accompanying this interim efficacy analysis, a non-binding additional futility assessment will be performed and the iDMC may recommend stopping the study for futility if the hazard ratio on OS is greater than or equal to one.

Further details of the interim analyses will be described in the iDMC Charter and Statistical Analysis Plan.

6.11.3 Biomarker Recommendation

The iDMC will use guidelines as specified in the iDMC charter for making a recommendation for the gene signature and MDM2 expression on the basis of the interim futility analysis.

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. 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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME

ePRO data will be collected through use of an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The ePRO device data are available for view access only via secure access to a web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, PROs, 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 7.6.

To facilitate source data verification, 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.

7.5 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

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 *applicable* 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 European Union or European Economic

Area will comply with the E.U. Clinical Trial Directive (2001/20/EC*) and applicable local, regional, and national laws.*

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's 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.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens 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 allow any remaining specimens to be used for exploratory research. 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.

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 investigational new drug 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.

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

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.

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 study is sponsored by F. Hoffmann-La Roche Ltd. Study centers will participate in this study globally, enrolling a total of approximately 440 patients. An IWRS will be used to manage site drug supply and to randomize patients to study drug.

Plasma samples for PK assessment will be sent to a central laboratory for sample storage and to an external vendor for analysis. Plasma and serum will be sent to a central laboratory for analysis and sample storage. Sample analysis will be performed by an external vendor or the Sponsor.

An iDMC will review unblinded data on a regular basis at predefined timepoints during the study. The iDMC will review results from the analyses of unblinded accumulating safety data and make recommendations to the Sponsor regarding continuation and/or modification of the study. The final decision on the iDMC recommendation will be made by the Sponsor. The details of the composition, roles, and responsibilities of the iDMC will be documented in detail in the iDMC charter, and submitted to Health Authorities as applicable. An IDCC will perform statistical analyses of accumulated safety data every

6 months (deaths and serious adverse events every 3 months) during the study for review by the iDMC.

A Steering Committee including trial investigators will provide scientific and medical advice during the study will regularly review blinded reports on study conduct, efficacy and safety and will help to ensure accurate and complete data collection. Details on member selection, roles and responsibilities are outlined in the Steering Committee Charter.

9.5 PUBLICATION 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, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

http://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 CSR. 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 Assessments

Table 1 Cycle 1

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days									Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29 – 42**	**43 – 56** [h]	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
Informed Consent [a]	x												
Demographics, Medical History, Determination of cytogenetic and molecular risk [b], Physical Examination, Height, Chest X Ray (or Chest CT) [c]	x												
Idasanutlin/placebo Dosing		x	x	x	x	x							

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days									Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–42**	**43–56 [h]**	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
Cytarabine Dosing		x	x	x	x	x							
Symptom Directed Physical Examination		x [d]					x	x	x	x	x	x	
Vital Signs [e], Weight, ECOG	x	x [d]					x	x	x	x	x	x	
ECG (repeated) [f]	x	x	x			x							
Urinalysis	x	x [d]											
ePRO Assess-ments [g]		x					x	x		x	x [n]	x [n]	

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days									Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–42**	**43–56 [h]**	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
Serum Pregnancy Test	x	x [d]											
Concomitant Medication	x	x											
Adverse Events and Serious Adverse Events	x	x											
Biochemistry [i]	x	x	x				x	x	x	x	x (weekly blood counts latest up to D42)	x (weekly blood counts latest up to D56)	

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days								Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–42**	**43–56** [h]	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
Hematology [i]	x	x	x				x	x	x	x	x (weekly blood counts latest up to D42)	x (weekly blood counts latest up to D56)	x
HMRA										x perform if peripheral blasts present OR if blood counts recovered	x perform if peripheral blasts present OR as soon as blood counts recovered. If no recovery, perform at D42	x perform if peripheral blasts present OR if blood counts recovered by Day 56	x

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days								Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–42**	**43–56** [h]	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
BM sampling for HMRA [i]	x									x if peripheral blasts present OR if blood counts recovered	x if peripheral blasts present OR as soon as blood counts recovered. If no recovery, sample at D42	x if peripheral blasts present OR if blood counts recovered by Day 56	x

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days								Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–42**	**43–56 [h]**	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
BM sampling [l] • MRD/Flow • EDTA • Pax-gene	x									x [k]	x [k]	x [k]	x [k]
Whole blood sampling • Flow • EDTA • Clinical Genotyping		x [m]											

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

	APPLICABLE TO ALL PATIENTS											APPLICABLE TO PATIENTS NOT CONTINUING TO CYCLE 2 (UNTIL *fIA*)
	Screening	Cycle 1 (Induction)										Confirmation of Response
		Treatment Period Cycle—28 days								Only Applicable in Case of Incomplete Blood Count Recovery by D28	Only Applicable in Case of Incomplete Blood Count Recovery by D42 [h]	Only Applicable to Patients with CR, CRp
Cycle Day	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–42**	**43–56** [h]	**30 Days after CR or CRp in Cycle 1 HMRA (±3 days)**
Whole blood sampling Paxgene		x	x			x				x [o]	x [o]	x [o]	

AML = acute myeloid leukemia; BM = bone marrow; CR = complete remission; CRp = complete remission with incomplete platelet count recovery; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EDTA = ethylenediaminetetraacetic acid; ePRO = electronic patient-reported outcome; *fIA = futility* interim analysis; HMRA = Hematologic Malignancy Response Assessment.

Note: Results of screening tests or examinations (except for the bone marrow aspirate) performed as standard of care prior to obtaining informed consent and within the protocol-defined screening window (prior to randomization/Cycle 1, Day 1) may be used rather than repeating required tests.

Note: All assessments scheduled on study drug administration days must be performed PRIOR to first dose of study drug.

See Table 2 and Table 3 for additional visits during Cycles 2 and 3 and post-treatment, respectively.

[a] *For re-screening, written informed consent must be obtained again before performing any re- screening tests or evaluations.*

[b] From initial AML diagnosis.

Appendix 1
Schedule of Assessments (cont.)

Table 1 Cycle 1 (cont.)

[c] If a Chest CT is performed up to 28 days prior to study drug administration, a chest x-ray is not required.

[d] If performed within 72 hours before the first study drug administration, the assessment does not have to be repeated on the first day of Cycle 1.

[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] Time points:
- Cycle 1, Days 1: predose idasanutlin, end of cytarabine infusion, 6, and 24 (equivalent to Day 2, predose) hours post dose idasanutlin (a.m.)
- Cycle 1, Day 5: predose idasanutlin, end of cytarabine infusion and 6 hours post dose idasanutlin (a.m.)

[g] ePRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-ePRO assessments and the administration of study medication. ePRO questionnaires need to be completed only once during each of the recovery periods D29-42 and D43-56, if applicable.

[h] If patient is eligible to continue with consolidation therapy, be aware that a maximum of 56 days is allowed for recovery between cycles.

[i] All hematology and biochemistry assessments may be performed up to 1 day prior to the scheduled timepoint. Results must be reviewed by the investigator (or designee) PRIOR to study drug administration.

[j] 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 should be performed at the discretion of the investigator.

[k] 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.

[l] At screening, the priorities for bone marrow samples are EDTA > MRDFlow > Paxgene. At subsequent timepoints the priorities are MRD/FLOW > EDTA > Paxgene.

[m] If clinical genotyping sample is missed on Day 1, sample can be collected at any point in the study.

[n] If assessment is within time window of confirmation of response or Study Drug Completion/Discontinuation visit, then assessment does not need to be repeated.

[o] Whenever bone marrow is sampled for HMRA assessment.

Appendix 1
Schedule of Assessments (cont.)

Table 2 Cycles 2 and 3

	Cycles 2 and 3 (Consolidation)									
	Treatment Period Cycle—28 days									Only Applicable in Case of Incomplete Blood Count Recovery by D28[a]
Cycle Day	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–56**
Idasanutlin/ placebo Dosing	x	x	x	x	x					
Cytarabine Dosing	x	x	x	x	x					
Symptom Directed Physical Examination	x					x	x	x	x	x
Vital Signs [b], Weight, ECOG	x					x	x	x	x	x
ECG [c] (repeated, in triplicate)	x	x								
Urinalysis	x									
ePRO Assessments [d]	x					x	x		x	x
Serum Pregnancy Test	x									
Concomitant Medication	x									
Adverse Events and Serious Adverse Events	x									
Biochemistry [e]	x	x				x	x	x	x	x (weekly blood counts, latest up to D56)
Hematology [e]	x	x				x	x	x	x	x (weekly blood counts, latest up to D56)

Appendix 1
Schedule of Assessments (cont.)

Table 2 Cycles 2 and 3 (cont.)

	Cycles 2 and 3 (Consolidation)									
	Treatment Period Cycle—28 days									Only Applicable in Case of Incomplete Blood Count Recovery by D28[a]
Cycle Day	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**28**	**29–56**
HMRA									x	x if blood counts do not recover, perform latest by D56
BM sampling for HMRA [f]									x [j]	x [j] if blood counts do not recover, sample latest by D56
BM sampling [g] • MRD/Flow • EDTA • Paxgene									x [h]	x [h]
Whole blood sampling Paxgene									x [i, k]	x [j]

BM=bone marrow; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EDTA=ethylenediaminetetraacetic acid; ePRO=electronic patient-reported outcome; $fIA = futility$ interim analysis; HMRA=Hematologic Malignancy Response Assessment.

Note: All assessments scheduled on study drug administration days must be performed PRIOR to first dose of study drug.

See Table 3 for additional visits during post-treatment.

[a] if patient is eligible to continue with consolidation therapy, be aware that maximally 56 days are allowed between cycles. For rules to continue with Cycle 3, please consult Appendix 4.

[b] Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

Appendix 1
Schedule of Assessments (cont.)

Table 2 Cycles 2 and 3 (cont.)

[c] Time points:
- Day 1: predose idasanutlin, end of cytarabine infusion, 6, and 24 (equivalent to Day 2, predose) hours post-dose idasanutlin (only if there is QT prolongation found in Cycle 1 measurements)

[d] ePRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-ePRO assessments and the administration of study medication. ePRO questionnaires need to be completed only once during the recovery period D29-56 if applicable.

[e] All hematology and biochemistry assessments may be performed up to 1 day prior to the scheduled timepoint. Results must be reviewed by the investigator (or designee) PRIOR to study drug administration.

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

[g] The priorities for bone marrow sampling are MRD/Flow > EDTA > Paxgene.

[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.

[i] Collect whenever bone marrow is sampled for HMRA assessment.

[j] In Cycle 2, required up to *futility* interim analysis OR after *futility* interim analysis; if patient does not proceed to Cycle 3, please see Appendix 4 for additional details.

[k] After *futility interim analysis*, sample should be collected for all patients regardless if bone marrow is being collected.

Appendix 1
Schedule of Assessments (cont.)

Table 3 Post-Treatment Phase

	Applicable to All Patients	Applicable to Patients in Remission (CR, CRp, CRi)				Applicable to Patients with Treatment Failure/ After Relapse/ After HSCT
	Study Drug Completion/ Discontinuation Visit	Follow-Up after Last Dose of Study Drug		Relapse	Pre-HSCT	Survival Follow-Up
Cycle Day	28 Days after Last Dose of Idasanutlin/ Placebo (+28 Days)	Q1m	Q3m			
Symptom directed physical exam	x					
Vital signs [a], weight, ECOG	x					
ECG (repeated, in triplicate)	x					
Urinalysis	x					
ePRO assessments [b]	x [c]		x [b, d]			x [b]
Serum pregnancy test	x					
Concomitant medication	x					
Adverse events and serious adverse events	x	x [e]	x			x [e]
Survival, HSCT, subsequent anti-cancer therapies			x			x

Appendix 1
Schedule of Assessments (cont.)

Table 3 Post-Treatment Phase (cont.)

Biochemistry [f]	x [c]		x [g]			
Hematology [f]	x [c]	x [g]		x		
HMRA		x [g]		x	x	
BM sampling for HMRA [h]			x [g]	x		
BM sampling [i] • MRD/Flow • EDTA • Paxgene			x [g, j]	x [j]	x	
Whole blood sampling EDTA				x		
Whole blood sampling Paxgene		x [g, k]		x		

AE = adverse event; BM = bone marrow; CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet count recovery; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EDTA = ethylenediaminetetraacetic acid; ePRO = electronic patient-reported outcome; HMRA = Hematologic Malignancy Response Assessment; HSCT = hematopoietic stem cell transplant; MRD = minimal residual disease; PD = progressive disease; Q1m = every month; Q3m = every 3 months; SAE = serious adverse event.

Note: All assessments scheduled on study medication administration days must be performed PRIOR to the first dose of study medication.

[a] Vital signs include body temperature, systolic and diastolic blood pressure, pulse rate, and respiration rate.

[b] ePRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-ePRO assessments and the administration of study medication. An additional ePRO assessment is also required to be completed after PD.

[c] If assessment is within time window of confirmation of response or extended recovery period D29-56, then assessment does not need to be repeated.

[d] Until relapse.

[e] Only SAEs related to study treatment or fatal AEs.

Appendix 1
Schedule of Assessments (cont.)

Table 3 Post-Treatment Phase (cont.)

[f] All hematology and biochemistry assessments may be performed up to 1 day prior to the scheduled timepoint.

[g] While patient remains in remission or until HSCT.

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

[i] The priorities are MRD/Flow >EDTA >Paxgene.

[j] Bone marrow MRD/Flow, EDTA, and Paxgene to be collected at the 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.

[k] Whenever bone marrow is sampled for HMRA assessment.

Appendix 2
Schedule of PK/PD Sampling

Cycle	**1 (Induction)**									**2 (Consolidation)**			**3 (Consolidation)**	
Cycle Day	**1**			**2**	**5**			**8**	**10** [a]	**1**	**2**	5[b]	**2**	**5**[b]
Time	Pre-dose [c]	End of cytarabine infusion (within 5 minutes from ECGs at end of cytarabine infusion)	Post-idasanutlin/ placebo morning dose 6 hours (± 30 min)	Pre-dose [c]	Pre-dose [c]	Post ECG at end of cytarabine infusion (± 5 min)	Post-idasanutlin/ placebo morning dose 6 hours (± 30 min)	any time	any time	Pre-dose [c]	Pre-dose [c]	Pre-dose [c]	Pre-dose [c]	Pre-dose [c]
PK-idasanutlin/placebo	x	x	x	x	x	x	x	x	x		x	x	x	x
PK-cytarabine	x	x	x	x	x	x	x				x		x	
Serum Biomarker [b]	x				x	x	x			x		x		

PD = pharmacodynamics; PK = pharmacokinetics.

[a] Sample collection will stop once we have approximately 80 samples.

[b] Until *futility* interim analysis.

[c] Predose (before idasanutlin morning dose) and within 2 hours prior to dosing of cytarabine.

Appendix 3
Schedule of Optional RCR Sampling

Cycle	**1 (Induction)**		**Relapse**
Study Day [a]	**1**	**5**	
DNA	x [b]		
Plasma	x	x	x
Serum	x	x	x

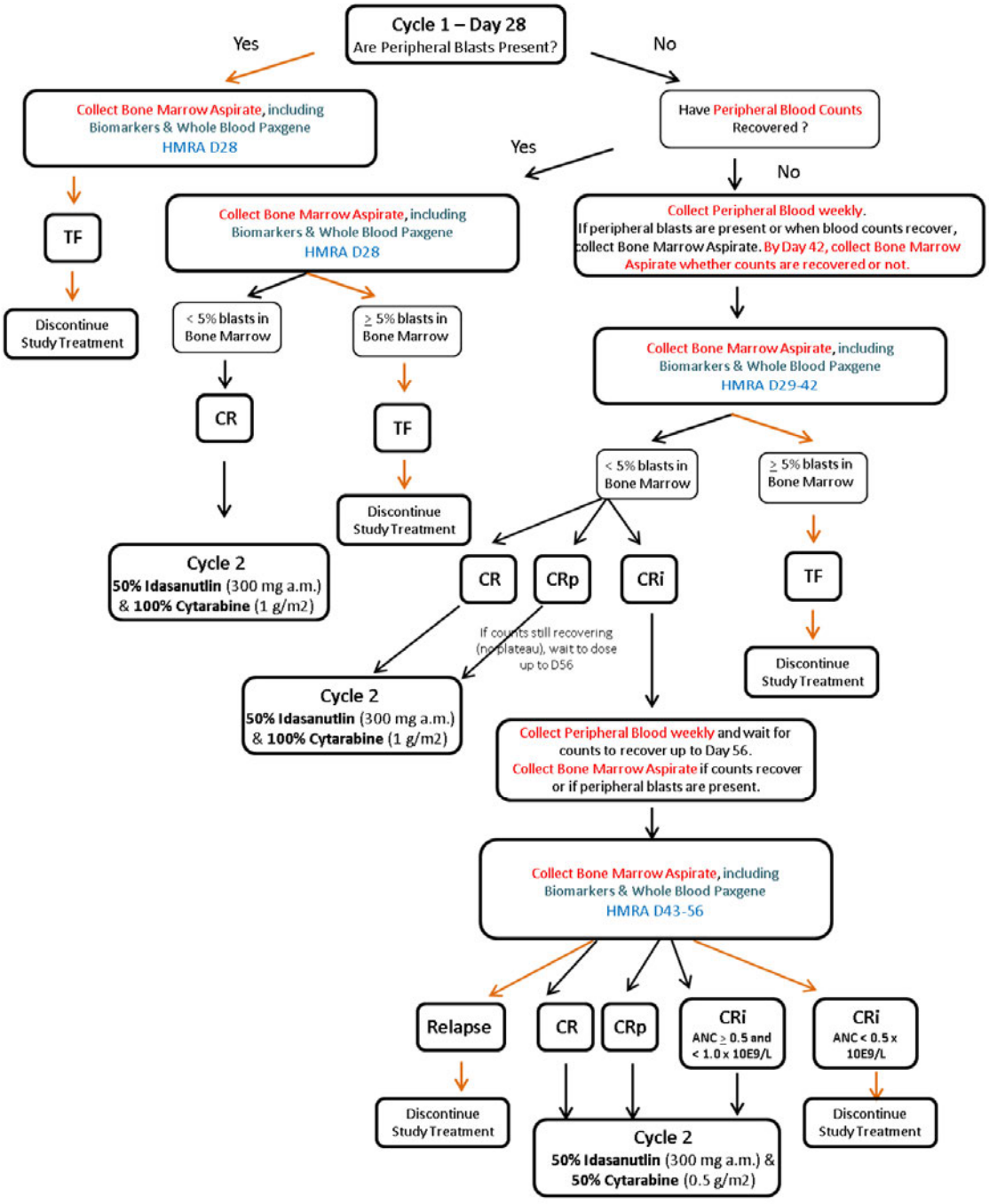
RCR = Roche Clinical Repository

[a] Predose (before idasanutlin morning dose) and within 2 hours prior to dosing of cytarabine

[b] If missed on Day 1, can be collected at any point in the study.

Appendix 4
Algorithm Guiding Bone Marrow Collection and Study Medication Continuation

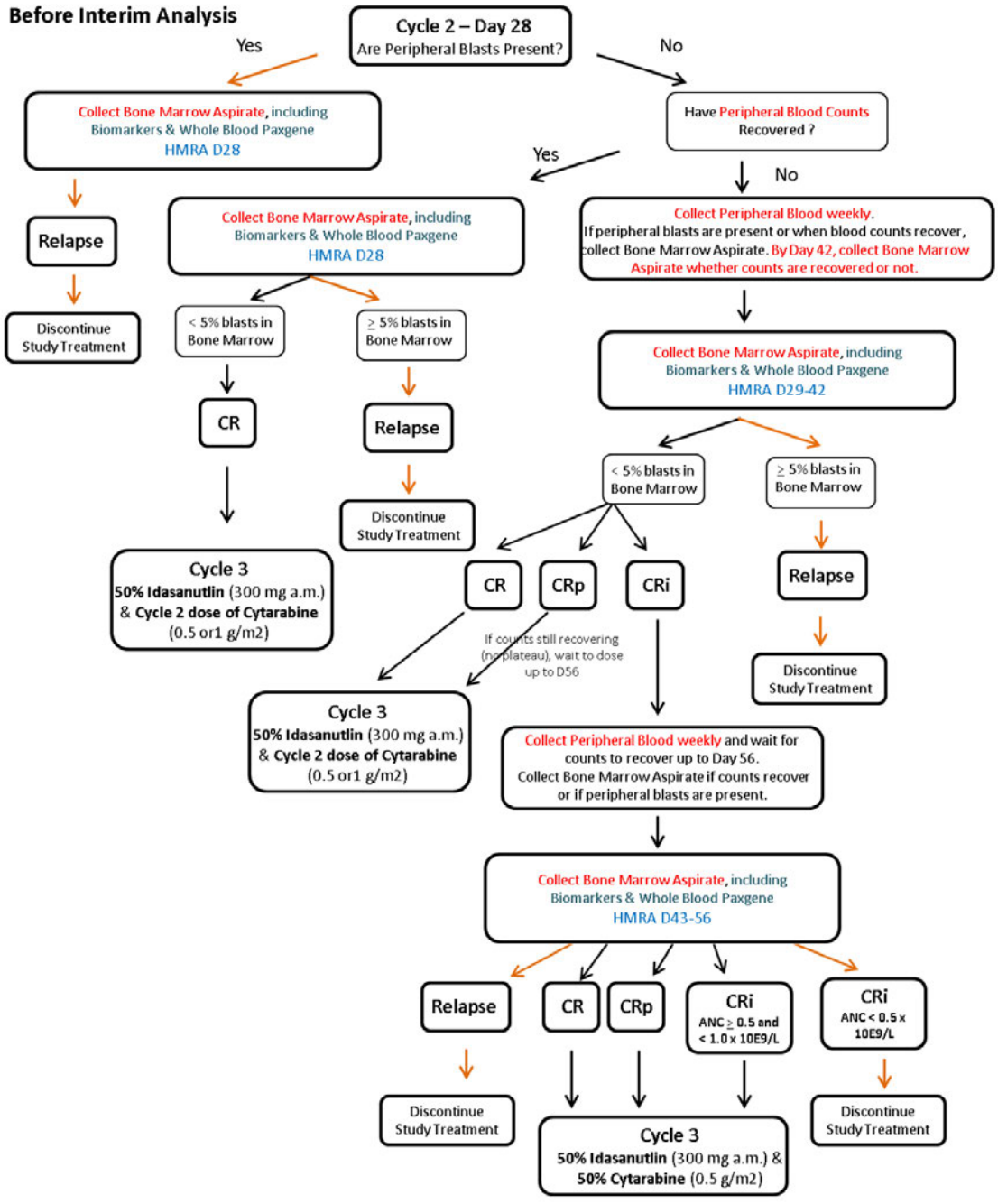
Figure 1 Response Treatment Decision Tree Cycle 1



CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; HMRA = Hematologic Malignancy Response Assessment; Idasanutlin = idasanutlin or placebo; TF = treatment failure.

Appendix 4
Algorithm Guiding Bone Marrow Collection and Study Medication Continuation (cont.)

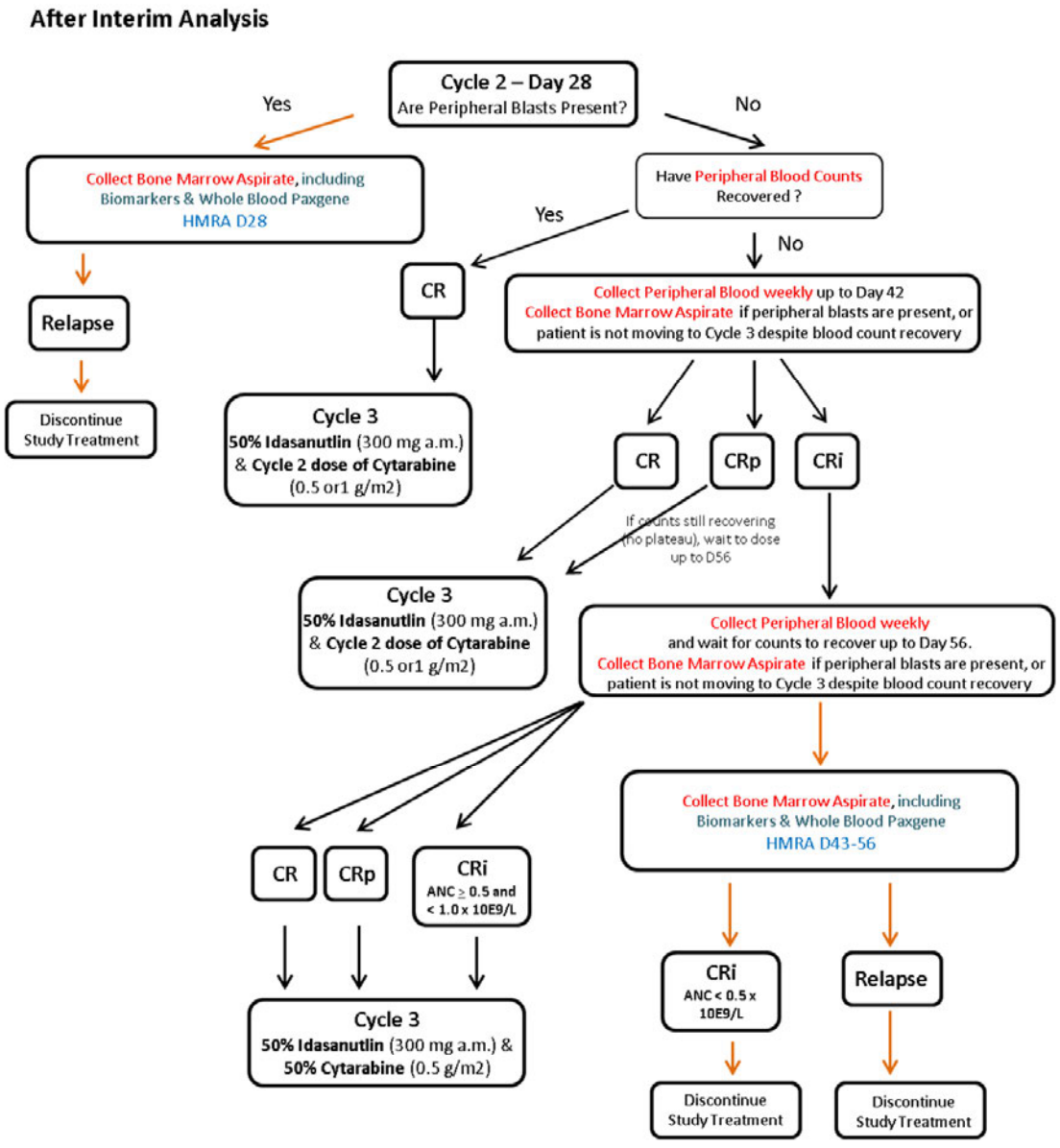
Figure 2 Response Treatment Decision Tree Cycle 2 (Before *Futility* Interim Analysis)



CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; HMRA = Hematologic Malignancy Response Assessment; Idasanutlin = idasanutlin or placebo.

Appendix 4
Algorithm Guiding Bone Marrow Collection and Study Medication Continuation (cont.)

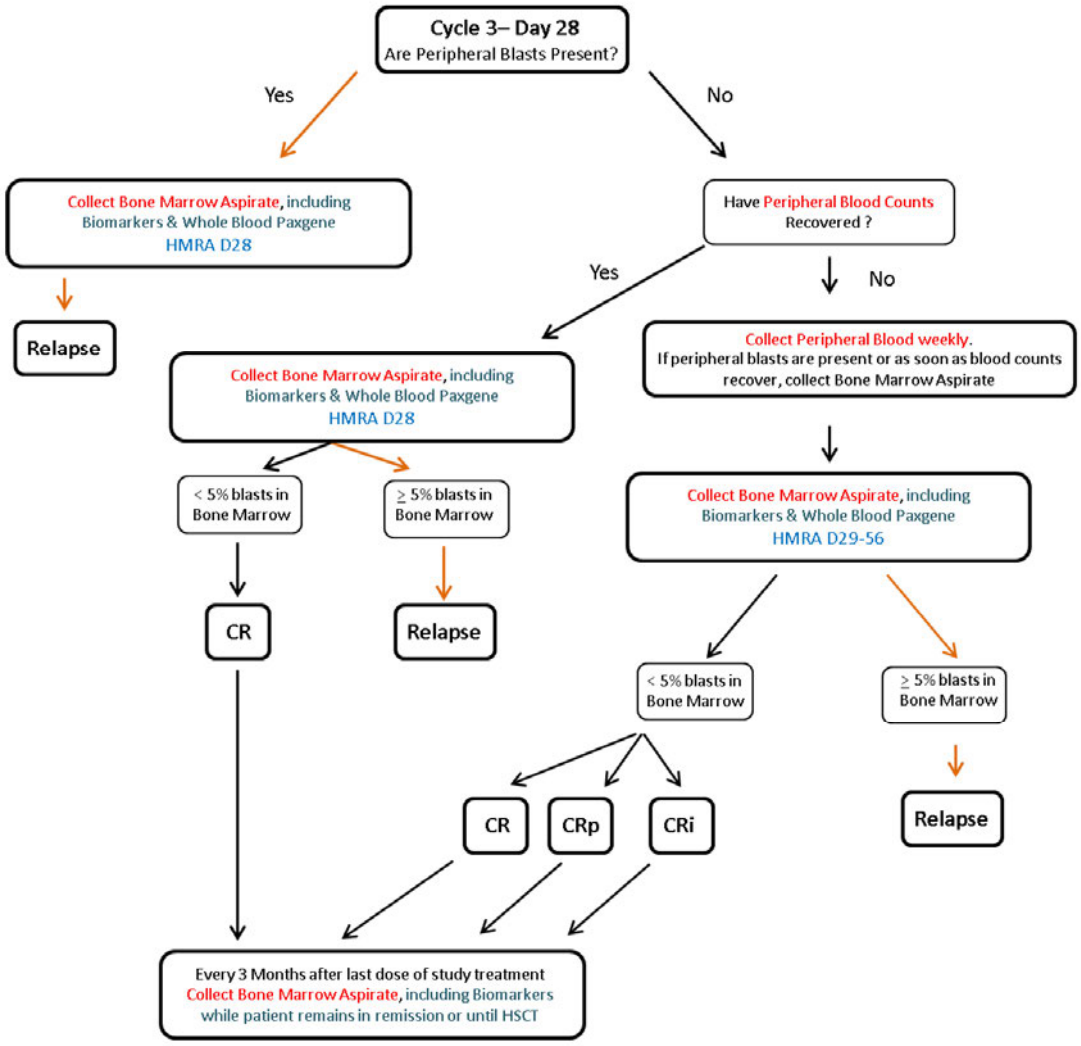
Figure 3 Response Treatment Decision Tree Cycle 2 (After *Futility* Interim Analysis)



CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; HMRA = Hematologic Malignancy Response Assessment; Idasanutlin = idasanutlin or placebo.

Appendix 4
Algorithm Guiding Bone Marrow Collection and Study Medication Continuation (cont.)

Figure 4 Recovery Follow-up Decision Tree Cycle 3



CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; HSCT = hematopoietic stem cell transplant; Idasanutlin = idasanutlin or placebo.

Appendix 5
Cockcroft Gault Formula for Calculation of Creatinine Clearance

Calculation of Creatinine Clearance

Creatinine Clearance (ml/min) for ***Males***:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age (years)}) \times \text{body weight (kg)}}{(72 \times (\text{serum creatinine (mg/dL)}))}$$

Creatinine Clearance (ml/min) for ***Females***:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age (years)}) \times \text{body weight (kg)}}{(72 \times (\text{serum creatinine (mg/dL)}))} \times 0.85$$

Appendix 6
Fridericia's Formula for Corrected QT interval

$$QTcF = QT/RR^{0.33}$$

Appendix 7
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 8
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 kg

Height in cm

Appendix 9
European Leukemia Net Standardization Reporting System

Table 4. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

Frequencies, response rates, and outcome measures should be reported by genetic group, and, if sufficient numbers are available, by specific subsets indicated; excluding cases of acute promyelocytic leukemia.

*Includes all AMLs with normal karyotype except for those included in the favorable subgroup; most of these cases are associated with poor prognosis, but they should be reported separately because of the potential different response to treatment.

†For most abnormalities, adequate numbers have not been studied to draw firm conclusions regarding their prognostic significance.

‡Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3); indicate how many complex karyotype cases have involvement of chromosome arms 5q, 7q, and 17p.

Source: Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115:453–74.

Appendix 10
Classification of Acute Myeloid Leukemia (World Health Organisation, 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

Appendix 10
Classification of acute myeloid leukemia (World Health Organisation, 2016 revision) (cont.)

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

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

Appendix 11
List of Drugs That Can Prolong QT Interval and Torsades De Pointes

This table has been adapted from Yap and Camm (2003). Please note that this list is not comprehensive.

Antiarrhythmic drugs	Type 1A (TdP reported in all)
	Quinidine (TdP reported)
	Procainamide (TdP reported)
	Disopyramide (TdP reported)
	Ajmaline (TdP reported)
	Type 1C (increase QT by prolonging QRS interval)
	Encainide
	Flecainide
	Type 3 (TdP reported in all)
	Amiodarone
	Sotalol
	d-Sotalol
	Bretylium
	Ibutilide
	Dofetilide
	Amakalant
	Semantilide
Calcium channel blockers	Prenylamine (TdP reported, withdrawn)
	Bepridil (TdP reported, withdrawn)
	Terodiline (TdP reported, withdrawn)
Psychiatric drugs	Thioridazine (TdP reported)
	Chlorpromazine (TdP reported)
	Haloperidol (TdP reported)
	Droperidol (TdP reported)
	Amitriptyline
	Nortriptyline
	Imipramine (TdP reported)
	Desipramine (TdP reported)
	Clomipramine
	Maprotiline (TdP reported)
	Doxepin (TdP reported)

Appendix 11
List of Drugs That Can Prolong QT Interval and Torsades De Pointes (cont.)

Psychiatric drugs (cont.)	Lithium (TdP reported)
	Chloral hydrate
	Sertindole (TdP reported, withdrawn in the U.K.)
	Pimozide (TdP reported)
	Ziprasidone
Antihistamines	Terfenadine (TdP reported, withdrawn in the U.S.A.)
	Astemizole (TdP reported)
	Diphenhydramine (TdP reported)
	Hydroxyzine
	Ebastine
	Loratadine
	Mizolastine
Antimicrobial and antimalarial drugs	Erythromycin (TdP reported)
	Clarithromycin (TdP reported)
	Ketoconazole
	Fluconazole
	Pentamidine (TdP reported)
	Quinine
	Chloroquine (TdP reported)
	Halofantrine (TdP reported)
	Amantadine (TdP reported)
	Sparfloxacin
	Grepafloxacin (TdP reported, withdrawn in the U.K. and U.S.A.)
	Pentavalent antimonial meglumine
Serotonin agonists/antagonists	Ketanserin (TdP reported)
	Cisapride (TdP reported, withdrawn in the U.K. and U.S.A.)
Immunosuppressant	Tacrolimus (TdP reported)
Antidiuretic hormone	Vasopressin (TdP reported)
Other agents	Adenosine
	Organophosphates
	Probucol (TdP reported)
	Papaverine (TdP reported)
	Cocaine

TdP = Torsades de pointes; U.K. = United Kingdom; U.S.A. = United States of America.

Appendix 11
List of Drugs That Can Prolong QT Interval and Torsades De Pointes (cont.)

REFERENCE

Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart 2003;89:1363–72.

Appendix 12
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 13
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/hours 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).

Appendix 13
Howard Definition and Classification of Tumor Lysis Syndrome (Howard et al. 2011) (cont.)

REFERENCES

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

Levin A, Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis. 2007;50:1–4.

Appendix 14
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 idasanutlin (Study NP28679). The following provisions should be strictly followed:

- 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's disease) prior to enrollment. Patients with active GI conditions as noted in the exclusion criteria are not permitted to start treatment (see Section 4.1.1 and Section 4.1.2)

  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 medication as follows:

  Loading dose of loperamide 4 mg orally 30 minutes before first administration of study medication *(applicable to all treatment cycles)*

  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 hours.

  Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, and antacids), Clostridium 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 intravenous (IV) fluids as clinically indicated and aim at all times for electrolyte correction.

Appendix 14
Toxicity Management Guidelines (cont.)

Table 1 Diarrhea Management According to CTCAE Grade

Diarrhea Grade	Recommended Actions
Grade 1/2	• See all supportive recommendations indicated above (i.e., loperamide, symptomatic management, dietary counselling, rehydration, and electrolyte correction). • No change in study medication dose will be implemented for Grade $\leq$2 diarrhea; patients should receive maximal supportive care as described above. • If diarrhea persists after 48 −72 hours despite administration of the maximum recommended daily loperamide dose (16 mg/24 hours), second-line agents may be considered.
Grade 3	• 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 hours). • If no improvement is observed within 24 hours, test for CDI. • If, despite adequate supportive care, Grade 3 diarrhea persists $>$ 48 hours without responding to loperamide at the maximum recommended daily dose (16 mg/24 hours), reduction of the idasanutlin/placebo dose to 50% may be considered. • If clinical characteristics have NOT improved to Grade $\leq$ 1 or baseline by 28 days despite the patient receiving maximal supportive care, idasanutlin/placebo must be permanently discontinued. • If the diarrhea recurs at Grade 3 despite supportive care and idasanutlin dose reduction, idasanutlin/placebo must be permanently discontinued.
Grade 4	• If, despite prophylaxis and adequate supportive care, Grade 4 diarrhea is diagnosed, idasanutlin/placebo must be permanently discontinued. • 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 hours). • If no improvement is observed within 24 hours, test for CDI.

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

Appendix 14
Toxicity Management Guidelines (cont.)

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). Regardless, prophylactic anti-microbial therapy MUST be administered to all patients (see Section 4.3.3).

- 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 (see Section 4.1.1 and Section 4.1.2).

  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.

Appendix 14
Toxicity Management Guidelines (cont.)

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 administered idasanutlin in combination with cytarabine. International guidelines on antiemesis prophylaxis for moderately emetogenic agents MUST be followed (Roila et al. 2010; NCCN Clinical Practice Guidelines in Oncology V.1 2012; Hesketh et al. 2016).

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 *(applicable to all treatment cycles)*. Emesis should be managed symptomatically throughout the study conduct.

- 30 –60 minutes before administration of study medication

  Preferably long acting 5-HT3-receptor antagonist (RA) orally (PO) or IV on *Day 1 of the treatment cycle (*palonosetron IV 0.25 mg or PO 0.5 mg*); otherwise, short-acting 5-HT3-RA PO or IV on Days 1–5*

  Dexamethasone 12 mg PO/IV on Day 1 then 8 mg PO on Days 2–5 (may also reduce cytarabine-induced skin toxicity)

  Rescue medication: Consider adding a NK-1 RA (aprepitant 125 mg PO on Day 1, then 80 mg PO daily, fosaprepitant 150 mg IV on Day 1 or switch to PO fixed-combination netupitant/palonosetron [dexamethasone dose should be adjusted if netupitant/palonosetron is administered]).

  Administer IV fluids and correct electrolytes as clinically required.

- 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 (see Section 4.4.2 for information on prohibited concomitant medication).

- Prior to first administration of study medication

Appendix 14
Toxicity Management Guidelines (cont.)

Patients should be carefully screened for evidence of active/uncontrolled infections prior to enrollment. Patients receiving antimicrobial agents with therapeutic intent (as noted in the exclusion criteria) are not permitted to begin treatment (see Section 4.1.1 and Section 4.1.2)

- Mandatory antifungal prophylaxis *(applicable to all treatment cycles)*

  Recommended: 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.

- Mandatory antibacterial prophylaxis *(applicable to all treatment cycles)*

  Recommended: 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; refer to Section 4.4.2).

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 (see Schedule of Assessments in Appendix 1).

- 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). The hemoglobin level should be maintained at >9 g/dL in patients with documented cardiac insufficiency (ejection fraction $<50\%$).

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 (Flowers et al. 2013; de Naurois et al. 2010; Montesinos et al. 2008).

TUMOR LYSIS SYNDROME MANAGEMENT GUIDELINES

Five cases with laboratory evidence of tumor lysis syndrome (TLS) have been reported in AML patients 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 (see Section 4.1.2).

- 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 $\geq$7.0 mmol/L and/or symptoms of hyperkalemia (e.g., muscle cramps, arrhythmias, paresthesia, and nausea)

  Serum uric acid (SUA) $\geq$10 mg/dL (595 µmol/L) or SUA $\geq$ 8.0 mg/dL (476 µmol/L) with a 25% increase and a creatinine increase $\geq$0.3 mg/dL from baseline

  Nephrology assessment warrants initiating dialysis

Appendix 14
Toxicity Management Guidelines (cont.)

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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Appendix 15
Hematopoietic Cell Transplantation-Specific Comorbidity Index

Comorbidity [a]	Definitions of Comorbidities Included in the New HCT-CI	HCT-CI Weighted Scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac [b]	Coronary artery disease, [c] congestive heart failure, myocardial infarction, or EF $\leq$ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance [d]	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild [b]	Chronic hepatitis, bilirubin > ULN to 1.5 $\times$ ULN, or AST/ALT > ULN to 2.5 $\times$ ULN	1
Obesity [d]	Patients with a body mass index > 35 kg/m^2	1
Infection [d]	Requiring continuation of antimicrobial treatment after Day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal [b]	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary [b]	DL_{CO} and/or FEV_1 66%–80% or dyspnea on slight activity	2
Prior solid tumor [b]	Treated at any timepoint in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary [b]	DL_{CO} and/or $FEV_1 \leq$ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic [b]	Liver cirrhosis, bilirubin > 1.5 $\times$ ULN, or AST/ALT > 2.5 $\times$ ULN	3

CCI = Charlson Comorbidity Index; CTD = connective tissue disease; DL_{CO} = diffusion capacity of carbon monoxide; EF = ejection fraction; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; ULN = upper limit of normal.

Note: To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.

[a] Definitions of comorbidities included in the original CCI are defined in the appendix of a prior publication (Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-

Appendix 15
Hematopoietic Cell Transplantation-Specific Comorbidity Index (cont.)

383.).

[b] Comorbidities with modified definitions compared with the original CCI.

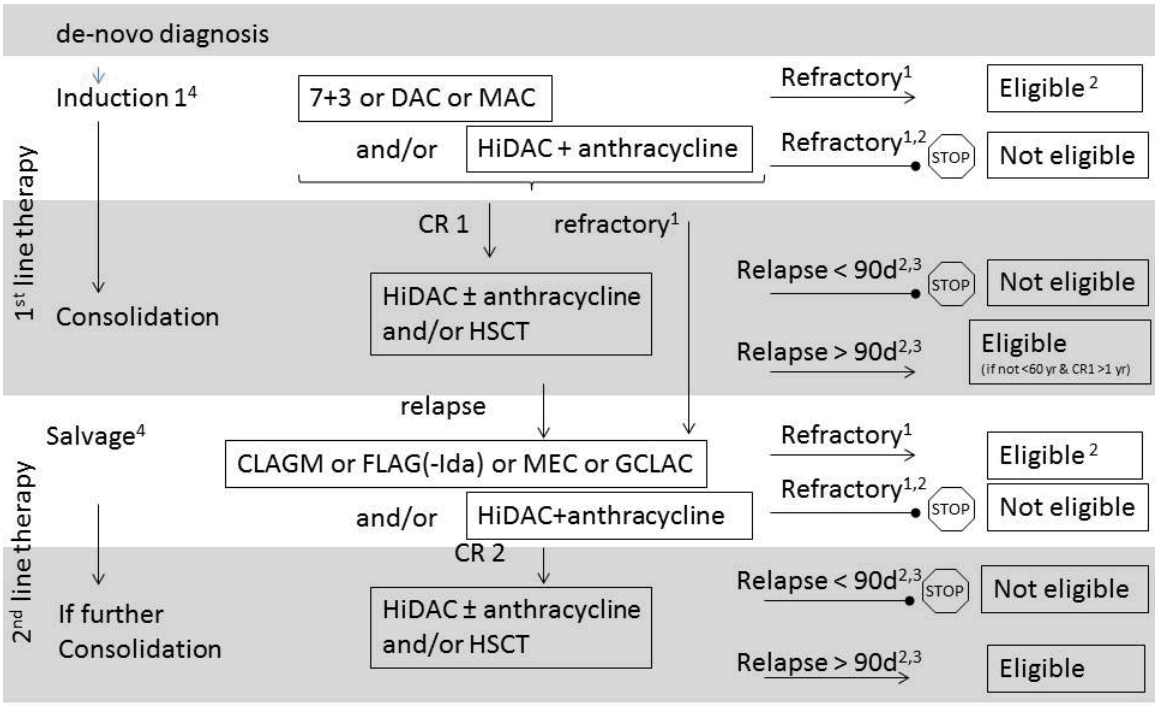
[c] One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

[d] Newly investigated comorbidities.

Adapted from Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106(8):2912–9.

Appendix 16
Eligibility Flow Chart for Prior Lines of Therapy

This flow chart provides guidance on how prior lines of therapy may impact eligibility. The regimens shown are examples commonly used in clinical practice. Please note that to be eligible a patient must comply with all eligibility criteria as listed in Sections 4.1.1 and 4.1.2.



1: Refractory includes persistent Leukemia after 1 or 2 induction cycles, or CR1 duration <90 days
2: excluding patients who are refractory to or relapse <90 days from HiDAC (≥ 18 g/m2 cumulative dose) as part of their induction or consolidation regimen
3: excluding patients who have received allogeneic HSCT within 90 days prior to randomization
4: patients responding to (Re-)Induction 1 cycle may receive additional induction cycles, also with different drug combinations, before moving to consolidation
Note: eligible patients must have received no more than 2 prior induction regimens (excl. prior HSCT) for their 1st line treatment and one must have included cytarabine with an anthracycline (or anthracenedione)

Appendix 16
Eligibility Flow Chart for Prior Lines of Therapy (cont.)

Table 1 Conventional and Novel Cytotoxic Salvage Chemotherapy Regimens Utilized in Patients with Relapsed/Refractory Acute Myeloid Leukemia

Regimen	Agents
HIDAC	Cytarabine 3 g/m^2 every 12 h days 1–6
FLAG FLAG-IDA	Fludarabine 30 mg/m^2 days 1–5 Cytarabine 2 g/m^2 days 1–5 G-CSF 5 mcg/kg day 0 until ANC recovery Fludarabine 30 mg/m^2 days 1–5 Cytarabine 2 g/m^2 days 1–5 G-CSF 300 mcg day 0 until ANC recovery Idarubicin 8 mg/m^2 days 1–3
FLA	Fludarabine 30 mg/m^2 days 1–5 Cytarabine 2 g/m^2 days 1–5
CLAG CLAG-M	Cladribine 5 mg/m^2 days 2–6 Cytarabine 2 g/m^2 days 2–6 G-CSF 300 mcg days 1–6 Cladribine 5 mg/m^2 days 1–5 Cytarabine 2 g/m^2 days 1–5 G-CSF 300 mcg days 0–5 Mitoxantrone 10 mg/m^2 days 1–3
MEC	Mitoxantrone 6 mg/m^2 days 1–6 Etoposide 80 mg/m^2 days 1–6 Cytarabine 1 g/m^2 days 1–6 Mitoxantrone 8 mg/m^2 days 1–5 Etoposide 100 mg/m^2 days 1–5 Cytarabine 1 mg/m^2 days 1–5

Appendix 16
Eligibility Flow Chart for Prior Lines of Therapy (cont.)

Table 1 Conventional and Novel Cytotoxic Salvage Chemotherapy Regimens Utilized in Patients with Relapsed/Refractory Acute Myeloid Leukemia (cont.)

Regimen	Agents
MEC/Decitabine	Decitabine 20 mg/m^2 days 1–10
	Mitoxantrone 8 mg/m^2 days 16–20
	Etoposide 100 mg/m^2 days 16–20
	Cytarabine 1 mg/m^2 days 16–20
EMA-86	Mitoxantrone 12 mg/m^2 days 1–3
	Cytarabine 500 mg/m^2 CI days 1–3 & 8–10
	Etoposide 200 mg/m^2 CI days 8–10
MAV	Mitoxantrone 10 mg/m^2 days 4–8
	Cytarabine 100 mg/m^2 CI days 1–8
	Etoposide 100–120 mg/m^2 days 4–8
FLAD	Fludarabine 30 mg/m^2 days 1–3
	Cytarabine 2 g/m^2 days 1–3
	Liposomal daunorubicin 100 mg/m^2 days 1–3
FLAM	Flavopiridol 50 mg/m^2 days 1–3
	Cytarabine 2 g/m^2/72 h starting day 6
	Mitoxantrone 40 mg/m^2 day 9
Hybrid FLAM	Flavopiridol 30mg/m^2 bolus, 60 mg/m^2 over 4 h days 1–3
	Cytarabine 2 g/m^2/72 h starting day 6
	Mitoxantrone 40 mg/m^2 day 9
Clofarabine Cytarabine	Clofarabine 40 mg/m^2 days 2–6
	Cytarabine 1 g/m^2 days 1–5
	Clofarabine 40 mg/m^2 days 1–5; Cytarabine 1 g/m^2 days 1–5
	Clofarabine 22.5 mg/m^2 days 1–5; Cytarabine 1 g/m^2 days 1–5
GCLAC	Clofarabine 25 mg/m^2 days 1–5; Cytarabine 2 g/m^2 days 1–5; G-CSF 5 mcg/kg day 0 until ANC recovery

Appendix 16
Eligibility Flow Chart for Prior Lines of Therapy (cont.)

Table 1 Conventional and Novel Cytotoxic Salvage Chemotherapy Regimens Utilized in Patients with Relapsed/Refractory Acute Myeloid Leukemia (cont.)

HAA	Homoharringtonine 4 mg/m^2 days 1–3 Cytarabine 150 mg/m^2 days 1–7 Aclarubicin 12 mg/m^2 days 1–7
CPX 351	CPX 351 101 units/m^2 days 1, 3, and 5 CPX 351 100 units/m^2 days 1, 3, 5 (first induction) and days 1 and 3 (second induction and consolidation)

CI = continuous infusion; G-CSF = granulocyte colony stimulating factor; HIDAC = high-dose arabinoside cytarabine.

Adapted from Ramos NR, Mo CC, Karp JE, et al. Current approaches in the treatment of relapsed and refractory acute myeloid leukemia. Journal of Clinical Medicine 2015 4(4): 665-695.

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