PROTOCOL

TITLE: **A PHASE I/II, MULTICENTER, OPEN-LABEL, MULTI-ARM STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PRELIMINARY ACTIVITY OF IDASANUTLIN IN COMBINATION WITH EITHER CHEMOTHERAPY OR VENETOCLAX IN THE TREATMENT OF PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED/REFRACTORY ACUTE LEUKEMIAS OR SOLID TUMORS**

PROTOCOL NUMBER: GO40871

VERSION NUMBER: 4

EUDRACT NUMBER: 2018-004579-11

IND NUMBER: 117005

NCT NUMBER: *NCT04029688*

TEST PRODUCT: Idasanutlin (RG7388; RO5503781-020)
Venetoclax (GDC-0199; ABT-199; RO5537382)

MEDICAL MONITOR: [redacted] M.D., Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

APPROVAL DATE: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
19-Mar-2021 15:10:36	Company Signatory	[redacted]

CONFIDENTIAL

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PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	Date Final	Country	Version	Date Final
4	see electronic date stamp on title page	—	—	—
3	15 June 2020	—	—	—
2	19 July 2019	France	2	4 October 2019
1	11 January 2019	—	—	—

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

The idasanutlin development program in adults has been discontinued following a negative read out in the pivotal study in adults with relapsed/refractory acute myeloid leukemia. While efficacy data were negative (no improvement in overall survival with idasanutlin/cytarabine vs placebo/cytarabine), no new safety signal has been identified for idasanutlin. Based on promising preclinical data and different disease biology in pediatric cancers as well as an ongoing positive benefit risk assessment, the pediatric development of idasanutlin continues. However, adaptations of the ongoing GO40871 have been made. Changes to the protocol, along with a rationale for each change, are summarized below:

- Initiation of the safety run-in cohorts for the planned combinations in neuroblastoma may occur asynchronously (Figure 1). Thus, the randomization of patients with neuroblastoma in study Part 2 to either chemotherapy or venetoclax has been removed (Section 3.1.2).
- An early efficacy gate was added at the end of the safety run-in (Gate 1b) for the neuroblastoma cohorts, which will include patients treated at the recommended Phase II dose (RP2D). This gate allows for discontinuation of a cohort at an earlier point should there be a lack of efficacy observed (Section 3.1.1.2).
- A requirement for a minimum of 6 patients treated at the RP2D in neuroblastoma safety run-in has been added. This change allows more certainty in the determination of the RP2D and allows for the early efficacy gate noted above (Section 3.1.1.2).
- Patients with TP53 wild-type neuroblastoma treated at the RP2D in the safety run–in will also be included in the ten patients for the efficacy analysis at Gate 2 (Section 3.1.1.2).
- Initiation of the leukemia cohorts may start asynchronously relative to the neuroblastoma cohorts (Figure 1)
- The nomenclature for the various study parts has been revised to coincide with the current study design (Section 3.1).
- The pre-defined maximum dose of idasanutlin has been eliminated. As there is not a clearly defined efficacious exposure in adults and the tolerability of idasanutlin may differ between adults and children, there is no reason to arbitrarily limit the dose of idasanutlin in the pediatric population if it is well tolerated (Section 3.1.1.1).
- In order to minimize the risk of neutropenia, the prophylactic use of granulocyte stimulating factor support is now recommended for all solid tumor patients receiving combination with cyclophosphamide and topotecan (Sections 3.1.1.1 and 4.3.3).
- The definition of dose-limiting toxicities has been revised to accommodate the known and manageable toxicities of the chemotherapy combination agents, as well as to be more consistent with the standards used in other pediatric clinical trials (Section 3.1.1.3).

- The inclusion criterion on the ability to swallow tablets or liquid has been removed since the administration of idasanutlin via nasogastric tube is possible (Section 4.1.1).
- Dosing of topotecan and cyclophosphamide is now based on body weight rather than body surface area for patients weighing less than 12 kg. This is more consistent with standard dosing for this regimen (Section 4.3.2.3).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.4).
- The guidelines for dose modifications due to hematologic toxicity have been revised to include modification of the combination agents as well as idasanutlin, as cytopenias are risk factors for both (Section 5.1.5.1).
- Addition of mucosal inflammation as an adverse event of special interest (Section 5.2.3).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.10).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- A new section has been added to describe the implementation of a system to manage the quality of the study (Section 9.3).
- Language has been modified to clarify that Roche's global policy on data sharing does not have requirements that must be met before study results can be made available. The name of a Roche policy on data sharing has been corrected (Section 9.6).

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I/II, MULTICENTER, OPEN-LABEL, MULTI-ARM STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PRELIMINARY ACTIVITY OF IDASANUTLIN IN COMBINATION WITH EITHER CHEMOTHERAPY OR VENETOCLAX IN THE TREATMENT OF PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED/REFRACTORY ACUTE LEUKEMIAS OR SOLID TUMORS**
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MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or designee.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I/II, MULTICENTER, OPEN-LABEL, MULTI-ARM STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PRELIMINARY ACTIVITY OF IDASANUTLIN IN COMBINATION WITH EITHER CHEMOTHERAPY OR VENETOCLAX IN THE TREATMENT OF PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED/REFRACTORY ACUTE LEUKEMIAS OR SOLID TUMORS**
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TEST PRODUCT:	Idasanutlin (RG7388; RO5503781-020) Venetoclax (GDC-0199; ABT-199; RO5537382)
PHASE:	Phase I/II
INDICATION:	Relapsed/refractory acute leukemias and solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, tolerability, and pharmacokinetics of idasanutlin as a single agent and the safety, tolerability, pharmacokinetics, and preliminary efficacy of idasanutlin in combination with either chemotherapy or venetoclax in children and young adults with acute leukemias or solid tumors that are recurrent or refractory to standard therapy.

In this protocol, "study treatment" refers to the single agent or combination of treatments assigned to patients as part of this study (i.e., idasanutlin with or without chemotherapy or venetoclax).

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

Safety Objectives

The safety objectives for this study are to evaluate the safety and tolerability of idasanutlin as a single agent, in combination with chemotherapy, and in combination with venetoclax; to determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) of idasanutlin administered as a single agent; and to define the recommended Phase 2 dose (RP2D) of idasanutlin in combination with either chemotherapy or venetoclax on the basis of the following endpoints:

- Incidence and severity of adverse events with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0)
- Changes from baseline in physical findings
- Changes from baseline in targeted clinical laboratory test results and ECG parameters

- Incidence of dose-limiting toxicities (DLTs) assessed during the first cycle of study treatment of single-agent idasanutlin and again with idasanutlin in combination with chemotherapy or venetoclax

The exploratory safety objective for this study is to evaluate the impact of idasanutlin as a single agent and in combination with chemotherapy and venetoclax on growth and development on the basis of the following endpoints:

- Changes from baseline in growth patterns (relative to age-specific standards for height and weight)
- Changes from baseline in development patterns (relative to onset of menarche [for females] and pubertal changes)

Pharmacokinetic Objectives

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

- To characterize the PK profile of idasanutlin as a single agent and in combination with chemotherapy or venetoclax on the basis of the following endpoints:
  - Plasma concentration of idasanutlin (and M4 metabolite RO6802287, where relevant) as a single agent at specified timepoints
  - Plasma concentration of idasanutlin in combination with chemotherapy or venetoclax at specified timepoints
- To characterize the PK profile of venetoclax in combination with idasanutlin on the basis of the following endpoint:
  - Plasma concentration of venetoclax at specified timepoints

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study (Study Parts $1b$, 2, and 3) is to evaluate the anti-cancer activity of idasanutlin in combination with chemotherapy or venetoclax on the basis of the following endpoints:

Neuroblastoma

- Objective response rate (ORR), defined as the proportion of patients with complete response or partial response (PR) at any time during study treatment, on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to INRC for patients with neuroblastoma.

Primary $efficacy$ analysis will be conducted on patients with *TP53* wild-type (WT) tumors in Study Parts $1b$, 2, and 3.

Leukemia

- Complete remission rate (CRR), defined as the proportion of patients with morphologic complete remission, complete remission with incomplete blood count recovery (CRi) or complete remission with incomplete platelet count recovery (CRp), within 2 cycles of study treatment
- For patients with acute lymphocytic leukemia (ALL): minimal residual disease (MRD)-negative rate, defined as the proportion of patients with ALL who have an MRD value $<$ 0.01%, as measured by next-generation sequencing (NGS), within 2 cycles of study treatment

Primary $efficacy$ analyses will be conducted on patients with *TP53* WT tumors in Study Parts 2 and 3.

Secondary Efficacy Objective

The secondary efficacy objective for this study (Study Parts 1, 2, and 3) is to evaluate the anti-cancer activity of idasanutlin as single agent, in combination with chemotherapy, and in

combination with venetoclax (in patients with *TP53* WT tumors, as well as in all patients regardless of mutation status) on the basis of the following endpoints:

Solid tumors (including Neuroblastoma)

- Clinical benefit rate (CBR), defined as the proportion of patients achieving confirmed complete response, PR, or SD on two consecutive occasions ≥ 4 weeks apart during the total study period
- Duration of objective response (DOR), defined as the time from the first tumor assessment that supports a patient's objective response to the time of disease progression or death from any cause (whichever occurs first), as determined by the investigator using INRC for patients with neuroblastoma or RECIST v1.1 for patients with other solid tumors
- Progression-free survival (PFS), defined as the time from initiation of study drug to the first documented occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator using INRC for patients with neuroblastoma and RECIST v1.1 for patients with other solid tumors
- Overall survival (OS), defined as the time from initiation of study drug to death from any cause
- ORR of efficacy-evaluable population irrespective of *TP53* mutation status

Leukemia

- Number of patients receiving transplant after study treatment
- DOR, defined as the time from the first tumor assessment that supports the patient's objective response (CR, CRp, CRi) to the time of relapse, or death from any cause, whichever occurs first
- EFS, defined as the time from initiation of study drug to the first documented occurrence of M3 marrow after Cycle 1, failure to achieve CR/CRp/CRi after Cycle 2, disease progression, relapse subsequent to achieving CR/CRp/CRi, or death from any cause, whichever occurs first.
- OS, defined as the time from initiation of study drug to death from any cause
- CRR of efficacy-evaluable population irrespective of *TP53* mutation status
- For patients with acute myeloid leukemia (AML): MRD-negative rate, defined as the proportion of patients with AML who are MRD negative within 2 cycles of study treatment

Exploratory Biomarker Objectives

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to idasanutlin as a single agent or in combination with chemotherapy or venetoclax; are early surrogates of efficacy; are associated with progression to a more severe disease state (i.e., prognostic biomarkers); are associated with acquired resistance to idasanutlin as a single agent or in combination with chemotherapy or venetoclax; are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers); can provide evidence of idasanutlin activity (i.e., pharmacodynamic biomarkers) as a single agent or in combination with chemotherapy or venetoclax; or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers identified in blood versus tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate the acceptability and palatability of idasanutlin on the basis of the following endpoint:

- Acceptability Survey scores at Cycle 1, Day 5

Study Design

Description of Study

The study is divided into three parts:

- **Study Part 1:**
  - *Part 1a:* Dose escalation to assess safety, tolerability, and pharmacokinetics of idasanutlin as a single-agent treatment in the pediatric population with relapsed or refractory solid tumors; to identify the single-agent MTD/MAD; and to characterize DLTs. Patients in dose escalation after one cycle will either continue single-agent idasanutlin or start early combination of idasanutlin with chemotherapy (for precise rules, see protocol).
  - *Part 1b:* Following single-agent MTD/MAD identification, separate safety run-in cohorts *will be conducted* in neuroblastoma with newly enrolled patients to identify the RP2Ds of idasanutlin in combination *with cyclophosphamide and topotecan and in combination with venetoclax. These cohorts will also provide early efficacy assessments of these combinations in the patients with TP53 WT tumors treated at the RP2Ds. Additional safety run-in cohorts will be conducted in AML to identify the RP2D of idasanutlin in combination with fludarabine and high-dose cytarabine (FLA) and in AML and ALL to identify the RP2D of idasanutlin in combination with venetoclax in patients with leukemia.*

- **Study Part 2:** *In cohorts that pass the safety and efficacy criteria for Part 1b (Gate 1b), e*valuation of safety and efficacy of idasanutlin in combination with chemotherapy or venetoclax *will be continued* in neuroblastoma, AML, and*/or* ALL at *the* RP2D*(s) for the combinations*.
- **Study Part 3:** Potential expansion of idasanutlin combination cohorts in neuroblastoma, AML, *and/*or ALL meeting the pre-defined efficacy criteria for expansion *(Gate 2)*, also taking into account practical considerations (e.g., enrollment feasibility), nonclinical findings, biomarker analysis, safety profiles, and any other relevant information.

In Study Part 1*a*, only patients < 18 years of age will be enrolled. In Study Parts *1b,* 2*,* and 3, pediatric and young adult patients with neuroblastoma or acute leukemias (age: birth to < 30 years) will be enrolled.

Idasanutlin will be administered orally to patients once daily for Days 1–5 of each cycle, followed by 23 days of rest, for a total cycle duration of 28 days. All patients will be closely monitored for adverse events (regardless of relationship to study drug) throughout the study and for at least 30 days after the last dose of study treatment or until initiation of a new anti-cancer therapy, whichever comes first.

Patients will be enrolled regardless of their *TP53* mutation status, as not all *TP53* mutations may be inactivating; therefore, responses may still be observed in some patients with *TP53* mutations. A pre-idasanutlin tumor biopsy of current disease within 6 months of screening and after the last anti-cancer therapy is required for patients with solid tumors *unless approved by the Medical Monitor*. A bone marrow aspirate (BMA) specimen is required within the screening period for patients with leukemia. Samples will be analyzed for *TP53* mutation status by centralized molecular testing. If available, sites must also report any local molecular testing results for *TP53* mutation status in the eCRF.

An internal monitoring committee and external scientific oversight committee (IMC/SOC) will be established for safety monitoring at pre-defined study milestones and approximately every 6 months.

Study Part 1*a*—Single-Agent Dose Escalation

The study will begin with a dose-escalation phase with idasanutlin in patients with solid tumors using the modified continual reassessment method of escalation with overdose control (mCRM-EWOC) to identify the single-agent MTD/MAD. Approximately 9–*24 DLT-evaluable* patients are anticipated to be enrolled in this phase. Based on *physiologically*-based pharmacokinetic (PBPK)-predicted exposures in children, the starting dose *in this escalation cohort* is defined as 2 mg/kg/day (dose level 1). Dose-level escalation or de-escalation (if required) will be decided following review of PK and safety data.

The single-agent DLT window will be 28 days (one cycle duration) and until ANC $\geq 0.75 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L are achieved. Following the first cycle, patients will undergo response and DLT assessment. Any delay > 14 days in treatment due to delayed platelet recovery will also be considered a DLT; therefore, DLT assessment may extend until platelet count recovery.

- Patients who do not experience a DLT or progressive disease will have the option (with investigator approval) to continue single-agent idasanutlin or start combination therapy with cyclophosphamide/topotecan with a dose reduction in idasanutlin of 20%.
- Patients who do not experience a DLT but do experience progressive disease may continue idasanutlin (with a 20% dose reduction) in combination with cyclophosphamide/topotecan with investigator and Medical Monitor approval, but will not be permitted to continue idasanutlin monotherapy.
- Patients who experience a DLT but have CR, PR, or SD will have the option to continue single-agent treatment (dose reduced by 20%) upon adequate recovery from toxicities and depending on the nature of the specific toxicity, as jointly judged by investigator and the Medical Monitor.
- Patients who experience a DLT and progressive disease will permanently discontinue study therapy.

Patients will start subsequent cycles of therapy after Day 28 and when ANC $\geq 0.75 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L are achieved. Patients who remain on study therapy (single agent or combination) will continue until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, or patient/guardian or investigator decision to discontinue treatment.

Study Part 1*b*—Combination Therapy Safety Run-In

Once the idasanutlin single-agent MTD/MAD has been identified, a safety run-in phase with newly enrolled pediatric patients will be conducted to identify RP2Ds for idasanutlin in combination with chemotherapy or venetoclax in separate neuroblastoma, AML, and ALL combination cohorts. The safety run-in phase will start at a maximum of 80% of the idasanutlin MTD/MAD identified in the dose-escalation phase, combined with the following regimens in the listed diseases:

- Idasanutlin + chemotherapy:
  - Neuroblastoma: cyclophosphamide + topotecan
  - AML: fludarabine + cytarabine
- Idasanutlin + venetoclax:
  - Neuroblastoma
  - ALL and AML, with different DLT rules for hematologic toxicity

Assignment of patients to either the chemotherapy or venetoclax cohort will be at the investigator's discretion and in accordance to the availability of open slots for enrollment.

The DLT criteria (disease-type dependent) are modified from those used in the single-agent dose escalation cohort in order to determine more appropriately the RP2D in the setting of combinations with agents that have anticipated effects on bone marrow suppression. Dose-escalation decisions will be dependent on pharmacokinetics and totality of data. Only the idasanutlin dose will be escalated, while chemotherapies or venetoclax doses will not be escalated. *However, idasanutlin, chemotherapy, and/or venetoclax doses may be de-escalated based on the totality of the data as determined by the Medical Monitor.*

For each combination cohort, the first patient at the first dose level must complete at least 5 days of treatment without a DLT before subsequent patients can be treated at the same dose level. Dose modifications will be conducted according to design similar to a 3+3 design, except with additional restrictions: a maximum of one higher dose level from the starting dose-level cohort, or *one* lower dose-level cohorts of idasanutlin, will be permitted. If *one* dose level below the starting dose of idasanutlin is considered intolerable, the combination will be discontinued.

As the safety profile of idasanutlin may differ among combinations, the idasanutlin RP2D may also differ among cohorts.

Upon identification of the appropriate RP2D, patients treated at lower dose levels (including those patients treated in the single-agent dose escalation who go on to receive combination therapy with cyclophosphamide/topotecan) will be allowed to escalate to the RP2D.

Patients will be treated with combination therapy until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, study termination, or patient/guardian or investigator decision to discontinue treatment, except in the following instances:

- Patients with AML treated with FLA) will receive up to 2 cycles of combination therapy, followed by idasanutlin monotherapy in subsequent cycles.
- Patients with leukemia who 1) do not meet criteria for progression or relapse but have M3 marrow after Cycle 1 of therapy or 2) fail to achieve morphologic CR/CRi/CRp after 2 cycles of therapy will be required to discontinue study therapy unless the investigator views the benefit–risk ratio of continued therapy as favorable (and with approval of the Medical Monitor). Patients will still be recorded as having had an event for EFS analysis.

Study Part 2—Initial Expansion for Early Efficacy Evaluation

The preliminary efficacy for the RP2D idasanutlin combinations will be evaluated in Study Part 2. Upon *determination* of the appropriate idasanutlin RP2D *and passage of Gate 1b* for each disease *and* combination*, additional patients will be enrolled in Study Part 2. For neuroblastoma cohorts, approximately 4–6 patients will be added to reach a total of 10 patients with TP53 wild type (WT) tumors (including those patients enrolled in Study Part 1b at the RP2D).*

For AML*, patients* will be randomly allocated between two combination arms (*FLA* versus venetoclax) and evaluated for safety and preliminary efficacy. *For these AML arms, ten patients with TP53 WT AML will be enrolled per arm, not counting those enrolled in Study Part 1b. For* ALL*, patients* will be non-randomly assigned to receive idasanutlin plus venetoclax. Ten patients with *TP53* WT *ALL* will be required for *this cohort. On the basis of the frequency of TP53 mutations in the selected tumor types, the overall number of patients enrolled in each individual cohort is not expected to exceed approximately 20% more than the target minimum of 10 patients.* Patients enrolled in the study whose *cancers* are found to have *TP53* mutations will be allowed to continue study therapy but will be replaced for efficacy analysis. The different *cancer* types will be evaluated independently of one another.

Patients included in the safety run-in phase will not be included in the 10-patient initial response assessment *for the leukemia arms.*

Study Part 3—Additional Expansion Phase

A minimum number of responders among the 10 patients with TP53 WT enrolled in Study Part*s 1b and* 2 *for the neuroblastoma cohorts or Study Part 2 for the leukemia cohorts* will be required for cohort expansion and advancement to the additional response assessment (Study Part 3). The minimum number of responders is defined separately for each disease and is based on an expected observation of improvement over response rates to backbone therapies. A decision to expand a cohort will take into account safety and tolerability of the combination regimen in addition to the number of responders. Practical considerations will also be taken into account, such as enrollment feasibility, nonclinical findings, biomarker analysis, safety profiles, and any other relevant information. In general, cohorts will not expand if the minimum number of responders is not met. However, the study team (only with endorsement of the IMC/SOC) will be permitted to expand a cohort even if the minimum number of responders is not met, if the totality of the efficacy and other data support cohort expansion. The maximum number of additional patients enrolled in any tumor cohort in Study Part 3 will range from 20–30 patients with *TP53* WT tumors. Tumor assessments will be performed utilizing the same response criteria used in Study Part 2.

Number of Patients

Approximately *15–108* patients will be enrolled in the Study Parts 1 and 2. After completion of the initial response assessment, an additional 20–30 patients may be enrolled for a combination regimen in each tumor type, up to a total sample size of approximately *183* patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent before any study-specific screening procedures are conducted, and age-appropriate assent when considered appropriate according to local, regional, or national guidelines
- Age *< 18 years at the time of signing informed consent for Part 1a,* <30 years at time of signing informed consent *for Parts 1b, 2, and 3*

  *Note: T*he Sponsor may decide to stop enrollment of patients who are ≥ 18 years at any time during the study to ensure adequate enrollment of patients who are < 18 years.
- Study Part 1*a* (single-agent therapy dose escalation): histologically confirmed diagnosis of neuroblastoma or other solid tumor that has progressed or recurred despite standard therapy, and for which there is no therapy proven to prolong survival with an acceptable quality of life
- Study Part 1*b* (safety run-in), Study Part 2, and Study Part 3: histologically confirmed diagnosis of neuroblastoma, AML, or precursor-B ALL that has progressed or recurred despite, or is refractory to, standard therapy
- Adequate performance status:

  Patients < 16 years of age: Lansky ≥ 50%

  Patients ≥ 16 years of age: Karnofsky ≥ 50%

- Adequate end-organ function defined by the following laboratory results obtained within 28 days prior to initiation of study drug:

  Renal and liver function

  - Creatinine ≤ 1.5 ULN for age; if higher, an estimate GFR based on the Schwartz equation (Schwartz et al. 2017) or as per institutional guidelines must be ≥ 60mL/min/1.73 m^2
  - Bilirubin ≤ 1.5 × ULN for age (or ≤ 2.5 × ULN if liver infiltrated with leukemia or metastases)
  - AST *and* ALT ≤ 3 × ULN for age (or ≤ 5 × ULN if liver infiltrated with leukemia or metastases)

  Cardiac function

  - Fractional shortening (FS) ≥ 28% or left ventricular ejection fraction (LVEF) ≥ 50%, as determined by echocardiography or multigated acquisition scan (MUGA) within 28 days prior to initiation of study therapy

    Depending on institutional standard, either FS or LVEF is adequate for enrollment if only one value is measured; if both values are measured, then both values must meet the above criteria.

- For females of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, agreement to refrain from donating eggs, as defined below:

  Females must remain abstinent or use two methods of contraception with a failure rate of < 1% per year during the treatment period and for 6 weeks after the final dose of idasanutlin, 30 days after the final dose of venetoclax, 12 months after final treatment for patients receiving cyclophosphamide/topotecan (or longer if required according to national prescribing information), 6 months after final treatment for patients receiving FLA (or longer if required according to national prescribing information), or in accordance with national prescribing information guidance regarding abstinence, contraception, and egg donation for any non-Investigational Medicinal Products listed in the protocol. Females must refrain from donating eggs during this same period.

A female is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

A barrier method may be used as the second contraceptive method.

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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For males: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, males must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of idasanutlin, 12 months after final treatment with cyclophosphamide/topotecan (or longer if required according to national prescribing information), 6 months after final treatment with fludarabine to avoid exposing the embryo (or longer if required according to national prescribing information), or in accordance with national prescribing information guidance regarding abstinence, contraception, and sperm donation for any non-Investigational Medicinal Products listed in the protocol. Males 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

<u>Additional Inclusion Criteria for Patients with Solid Tumors (including Neuroblastoma)</u>

- At least one evaluable or measurable radiological site of disease as defined by standard criteria for the patient's tumor type (e.g., INRC), or measurable bone marrow disease by morphology
- Adequate end-organ hematologic function, as specified in the following parameters:
  - Hemoglobin ≥ 8 g/dL (transfusion allowed)
  - Peripheral ANC ≥ 0.75×10^9/L (no G-CSF support for 72 hours)
  - Platelet count ≥ 75×10^9/L (unsupported for 72 hours)
- Tumor tissue from relapsed disease, obtained subsequent to last anti-cancer therapy regimen administered and obtained within 6 months prior to study enrollment, or willingness to undergo a core or excisional biopsy sample collection prior to enrollment
  - Patients must submit a tissue block or 15 slides containing unstained, freshly cut, serial sections available for submission.
  - Fine needle aspirations, brush biopsies, bone metastasis samples, and lavage samples are not acceptable.

- Patients with < 15 slides available, or whose tumor tissue does not otherwise meet criteria above, may be eligible for study entry after Medical Monitor approval has been obtained. See protocol for detailed tissue requirements.

- Life expectancy ≥ 12 weeks, in the investigator's judgment

Additional Inclusion Criteria for Patients with Leukemia

- Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
- Available bone marrow aspirate or biopsy from screening

Exclusion Criteria

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

- Primary CNS tumors
- Symptomatic CNS metastases that result in a neurologically unstable clinical state or require increasing doses of corticosteroids or local CNS-directed therapy to control the CNS disease
- CNS3 leukemia (total nucleated cell count ≥ 5/μL with blasts on cytocentrifuge in an atraumatic lumbar puncture, or clinical signs of CNS leukemia including cranial nerve palsy)
- Acute promyelocytic leukemia
- White blood cell count > 50×10^9/L
  - Prior cytoreduction with leukapheresis or hydroxyurea (HU) is allowed to meet this criterion. HU must be discontinued at least 24 hours prior to the initiation of study treatment.
  - Prior cytoreduction with leukapheresis or hydroxyurea is allowed in patients with a WBC count ≤ 50×10^9/L if the patient is symptomatic from hyperleukocytosis, or if consistent with institutional guidelines.
- Down syndrome, Li-Fraumeni syndrome, history of severe aplastic anemia, or any known bone marrow failure predisposition syndrome (including, but not limited to, Fanconi anemia or dyskeratosis congenita)
- Burkitt-type acute lymphoblastic leukemia (mature B-cell)
- T-cell lymphoblastic leukemia
- Prior treatment with an MDM2 antagonist
- Prior treatment with venetoclax (if potential for enrollment in a venetoclax arm)
- Infection considered by the investigator to be clinically uncontrolled or of unacceptable risk to the patient upon induction of neutropenia, including patients who are, or should be, on antimicrobial agents for the treatment of active infection such as the following:
  - Fungal infection, other than mucosal candidiasis, with < 2 weeks of appropriate systemic antifungal therapy
  - 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
  - Neutropenic fever considered infection-related within 72 hours prior to dosing
  - History of symptomatic *Clostridium difficile* (*C. difficile*) infection that required treatment within 1 month prior to dosing

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

- Pregnant or breastfeeding, or intending to become pregnant during the study

  Females of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
- Active GI disease (e.g., gut graft-versus-host disease, Crohn's disease, ulcerative colitis) or GI conditions that may significantly alter drug absorption of oral drugs (e.g., uncontrolled vomiting, diarrhea, or malabsorption syndrome)
- Active viral hepatitis or human immunodeficiency virus (HIV) infection
- Presence of any CTCAE $\geq$ Grade 2 clinically significant treatment-related toxicity with the exception of alopecia, ototoxicity, peripheral neuropathy and parameters otherwise permitted in the inclusion criteria (e.g., hematological criteria)
- Clinically relevant QTc prolongation (QTcF $>$ 450 ms using the Fridericia correction)
- Any uncontrolled medical condition or other identified abnormality that precludes the patient's safe participation in and completion of the study, as judged by the investigator
- Systemic anticancer therapy within 28 days or 5 half-lives, whichever is shorter, prior to initiation of study treatment
  - Requirement may be waived at the investigator's request, with approval of the Medical Monitor, if the patient has recovered from therapeutic toxicity to the degree specified in the protocol.
  - Intrathecal chemotherapy per protocol prior to starting study therapy is permissible.
- Treatment with monoclonal antibodies, antibody drug conjugates, or cellular therapy (e.g., CAR-T cell infusion) for anti-neoplastic intent within 30 days prior to initiation of study treatment
- I-131 MIBG therapy within 6 weeks prior to initiation of study treatment
- Myeloablative therapy with autologous or allogeneic hematopoietic stem cell rescue within 100 days of study treatment initiation
- Immunosuppressive therapy for treatment of graft-versus-host disease within 2 weeks of study treatment initiation
- Radiotherapy (non-palliative) within 3 weeks prior to study treatment initiation
- Known hypersensitivity to any study drug or component of the formulation that could potentially be allocated according to tumor type
- Received the following within 7 days prior to initiation of study treatment:
  - Strong CYP2C8 inhibitors
  - CYP2C8 substrates
  - OATP1B1/3 substrates
- Received strong CYP2C8 and strong CYP3A4 inducers within 14 days prior to the initiation of study treatment
- For patients assigned or randomized to venetoclax arms:
  - Strong or moderate CYP3A4 inhibitors or moderate inducers or P-gp inhibitors within 7 days of study drug initiation
  - Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days prior to the initiation of study treatment
  - Vaccination with a live vaccine $\leq$28 days prior to randomization
- Received anti-coagulant or anti-platelet agent within 7 days or 5 half-lives prior to study treatment initiation

- Underwent major surgical procedure within 21 days of study treatment initiation, or anticipate need for major surgical procedure during the course of the study

  Gastrostomy, tumor biopsy, and insertion of central venous access devices are not generally considered major surgery, but the Medical Monitor should be notified of these or other minor procedures prior to initiating therapy.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or 1 year after the last patient is enrolled, whichever occurs first. For an individual patient, the completion of the study (i.e., the last visit) will occur when the patient withdraws consent, has been lost to follow-up, dies, or when the study is stopped.

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 years.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are idasanutlin, venetoclax, cyclophosphamide, topotecan, fludarabine, and cytarabine.

Test Product (Investigational Drug)

Idasanutlin

Idasanutlin will be supplied as 5-mg and 20-mg dispersible tablets. The dispersible tablets can either be swallowed or used to prepare a suspension (ad hoc) for patients not able to swallow tablets. Idasanutlin will be administered as an oral medication once daily on Days 1–5 of a 28-day cycle. The starting daily dose of idasanutlin in the dose-escalation phase of the study will be 2 mg/kg/day and will be modified according to the protocol.

Venetoclax

Venetoclax (GDC-0199/ABT-0199) will be supplied as oral film-coated tablets of 10-mg, 50-mg, and 100-mg strength. Venetoclax will also be provided as 2.5-mg, 10-mg, and 25-mg tablets for oral suspension for patients not able to swallow tablets.

Venetoclax (in combination with idasanutlin) will be administered at the adult dose equivalent (adjusted by body weight) of 400 mg in patients with neuroblastoma and the adult dose equivalent of 600 mg in patients with leukemia once daily on Days 1–28 of a 28-day cycle. For patients with *neuroblastoma*, venetoclax will ramp-up to the target dose over 2 days (200 mg equivalent Day 1 to 400 mg equivalent Day 2). Patients with neuroblastoma receiving venetoclax should be hospitalized during the ramp-up phase until the target dose has been administered. For patients with leukemia, venetoclax will ramp-up to the target dose over 3 days (150 mg equivalent Day 1; 300 mg equivalent Day 2; 600 mg equivalent Day 3). If lower doses of venetoclax are required, intermediate doses for the ramp up will be proportionally adapted based on the duration of ramp-up period (2 or 3 days), the final dose to be achieved, and the available formulation dose strength. For guidance on dose reductions in case of co-administration with CYP3A4 or P-gp, refer to protocol.

Chemotherapy

For patients assigned to arms combining idasanutlin with chemotherapy, chemotherapy should be administered at the doses prescribed below. Infusion duration, prophylactic medications, and monitoring guidelines should be managed in accordance with institutional standard unless specified in the protocol.

Neuroblastoma

Cyclophosphamide and topotecan will be administered once daily on Days 1–5 of each 28-day cycle at the following doses:

- Cyclophosphamide 250 mg/m^2 *(8.33 mg/kg for patients <12 kg)* as an intravenous (IV) infusion over 1 hour
- Topotecan 0.75 mg/m^2 *(0.025 mg/kg for patients <12 kg)* as an IV infusion over 1 hour

Acute Myeloid Leukemia

FLA (fludarabine and high-dose cytarabine) chemotherapy will be administered during each 28-day combination treatment cycle as per the following regimen:

- Fludarabine 30 mg/m^2 IV Days 1 to 5 over 30 minutes
- Cytarabine 2000 mg/m^2 IV Days 1 to 5 over 4 hours

  Note: Cytarabine infusion is administered 4 hours after the start of the fludarabine infusion.

Non-Investigational Medicinal Products

The non-IMPs in the study include the prophylactic medications (anti-diarrheal agents, antibiotics, anti-fungal agents, uric acid reducing agents, anti-PCP therapy, *growth factors,* and 5-HT3-receptor antagonists) and the intrathecal chemotherapy agents (intrathecal cytarabine, methotrexate, and hydrocortisone).

Statistical Methods

Safety Analyses

Safety will be characterized by incidence of adverse events and DLTs, as well as change from baseline in ECG parameters and clinical laboratory results. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All safety analyses will be based on the safety-evaluable population, which includes all patients who received any amount of the study treatment, whether prematurely withdrawn from the study or not.

Incidence and nature of DLTs assessed during the first cycle of study treatment will be summarized using descriptive statistics. All DLT analyses will be based on the DLT-evaluable population, which includes all patients enrolled in Part 1 and Part 2 who either have completed at least 80% of the prescribed dose of idasanutlin in Cycle 1 or have experienced a DLT in Cycle 1 of the dose-escalation phase.

An mCRM-EWOC model will be utilized to inform decision-making regarding the MTD of idasanutlin in Study Part I*a*. The MTD is defined as the dose that maximizes the posterior probability of a DLT being in the targeted toxicity interval of 20%–35%, while controlling the probability of a DLT being in the excessive toxicity interval of 35%–100% to be < 25%.

The mCRM-EWOC model will adaptively estimate the MTD after gathering cumulative DLT data including newly completed cohorts and calculate a recommended next dose for the next cohort.

Determination of Sample Size

The sample size for the dose-escalation phase of this study is based on the mCRM-EWOC design. The study will enroll approximately 9–*24 DLT–evaluable* patients in dose escalation to reach the MTD/MAD and approximately 3–9 patients in each cohort in the safety run-in phase to reach RP2D. Explicit power and type I error considerations are not factored into the design of the MTD/MAD or RP2D determination, as the dose-escalation and safety run-in phases are designed to obtain preliminary safety and PK information for the study drug.

An early response assessment (Gate 1B), will be performed for the neuroblastoma cohorts at the end of Study Part 1b after six patients have been treated at the RP2D for the combination. Additional response assessments of patients enrolled in Part 2 (also including patients treated at the RP2D in Part 1b for the neuroblastoma cohorts) (Gate 2) and of patients enrolled in Part 2 and Part 3 (again including patients treated at the RP2D in Part 1b for the neuroblastoma cohorts) (Gate 3) are planned in order to make a preliminary assessment of the efficacy of the study drug.

At least 50% of patients with TP53 wild-type tumors treated at the RP2D in Study Part 1b for the neuroblastoma cohorts (Gate 1b) must have an observed objective response prior to advancing to Part 2 of the study. If this benchmark is not reached, the *cohort will be discontinued for futility.* The minimum number of patients in the response assessment *at* Gate 2 and the minimum number of responders required for advancement to the additional response assessment *(Part 3)* are presented by tumor type in the protocol, taking into account historical control ORRs for neuroblastoma and CRR for leukemias. For neuroblastoma and AML, up to one combination regimen may advance to Part 3 for each tumor type, taking into account the preliminary efficacy, safety, biomarker data, and enrollment feasibility. The ALL cohort will be considered for expansion similarly, if either morphologic response or MRD-negative response criteria are met.

The sample size and minimum number of responders for the additional response assessment for each tumor type cohort were determined based on 90% confidence interval (CI) for the appropriate response rate parameter for each disease cohort. Part 3 of this trial will be able to detect a large benefit of the idasanutlin in combination with chemotherapy or venetoclax in terms of the appropriate response rate for the disease. For example, an observed response rate of 45% in 40 patients with neuroblastoma will have a 90% confidence interval excluding the 32% historical response rate. Similarly, an observed CRR of 53% in 30 patients with ALL will have a 90% confidence interval excluding 40%.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
AUC	area under the concentration–time curve
BCL-2	B-cell lymphoma 2
BID	twice a day
BMA	bone marrow aspirate
C. difficile	*Clostridium difficile*
CAR	chimeric antigen receptor
CBR	clinical benefit ratio
CI	confidence interval
CLL	chronic lymphocytic leukemia
COG	Children's Oncology Group
CR	1. (morphologic) complete remission in context of leukemia 2. complete response in the context of solid tumor cancer
CRc	composite complete remission
Cri	incomplete blood count recovery
CRp	complete remission with incomplete platelet count recovery
CRR	complete remission rate
CTCAE	common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DE	DLT-evaluable
DLT	dose-limiting toxicity
DOR	duration of objective response
EC	ethics committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FLAG	Fludarabine, cytarabine, and G-CSF
FLA	Fludarabine *and high-dose* cytarabine
FS	fractional shortening

Abbreviation	Definition
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HU	hydroxyurea
ICH	International Council for Harmonisation
IMC	internal monitoring committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INRC	International Neuroblastoma Response Criteria
IRB	Institutional Review Board
IT	intrathecal
ITT	intent-to-treat
IxRS	interactive voice/web-based response system
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MBP	microprecipitated bulk powder
mCRM-EWOC	modified continual reassessment method of escalation with overdose control
MDM2	murine double minute 2
MIBG	meta-iodobenzylguanidine
MIC-1	macrophage inhibitory cytokine-1
MLL	mixed—lineage leukemia
MM	multiple myeloma
MN	mobile nursing
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal product
ORR	objective response rate
OS	overall survival
PBPK	*physiologically*-based pharmacokinetic
PD	pharmacodynamic*s*
PE	polyethylene

Abbreviation	Definition
PFS	progression-free survival
PK	pharmacokinetic
PPTP	Pediatric Preclinical Testing Program
PR	partial response
PRO	patient-reported outcome
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RP2D	recommended Phase II doses
SD	stable disease
SDP	spray-dried product
SE	safety evaluable
SOC	scientific oversight committee
$t_{1/2}$	terminal half-life
TLS	tumor lysis syndrome
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
WT	wild-type

1. BACKGROUND

1.1 BACKGROUND ON NEUROBLASTOMA

Neuroblastoma is the most common extra-cranial solid tumor in children and remains a major cause of pediatric mortality (Maris 2007). Patient prognosis and therapy are determined by a number of risk factors, with less favorable risk features including tumor metastasis, patient age $>$18 months, poor tumor differentiation, presence of MYCN amplification or 11q aberration, and DNA diploidy (Cohn et al. 2009). Patients classified as high risk, based on a combination of these features (including the majority of patients $>$18 months of age), require frontline multimodal therapy that includes chemotherapy, surgery of the primary tumor, high-dose therapy with hematopoietic stem cell rescue, radiation to the primary tumor site, differentiation therapy, and immunotherapy (Pinto et al. 2015). Despite such therapy, the long-term survival rates for patients with high-risk disease remain unsatisfactory at 50%–55% (Kreissman 2013; Ladenstein 2017).

Novel agents are thus necessary in the treatment of neuroblastoma. The recent addition of maintenance immunotherapy with chimeric anti-GD2 monoclonal antibody has shown some promise. Early efficacy results from a Children's Oncology Group trial of high-risk patients given dinutuximab in combination with interleukin-2 and granulocyte-macrophage colony-stimulating factor in maintenance showed an improvement in 2-year event-free survival (EFS) from 46% to 66% and in 2-year overall survival (OS) from 75% to 86% (Yu et al. 2010). Lower long-term OS was reported in high-risk patients who received a similar molecule, dinutuximab beta, in the European Union, where the 3-year OS rate has been 71%–72% in patients without disease at initiation of therapy and 54%–63% in patients who did not achieve complete response prior to initiation of dinutuximab beta therapy (Qarziba SmPC). Patients with disease relapse fare substantially worse; 5-year OS in relapsed neuroblastoma has been reported to be between 12% and 20% (London et al. 2011; Basta et al. 2016).

Additionally, patients who have received intensive multimodal therapy face significant long-term toxicity with an increased mortality rate, a risk of second malignant neoplasms, and a higher rate of chronic health conditions, including hearing loss (49% of patients), renal impairment (16%), and endocrine complications (28%) (Lavedière et al. 2009; Moreno et al. 2013). These findings, combined with the apparent plateau in survival rates, suggest that the tolerable ceiling of traditional therapy has been reached and fine-tuning of conventional treatment is unlikely to solve the remaining clinical challenges. Innovative therapies targeting a different mechanism of action are urgently required.

1.2 BACKGROUND ON ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a rare childhood cancer, with an incidence of approximately 7 children per million annually (Zwaan et al. 2015), but AML remains a significant cause of childhood cancer mortality. All major cooperative groups report similar outcomes for childhood AML, with an EFS around 50%–60% and an OS of

65%–75% (Zwaan et al. 2015; Rubnitz 2017), which reflects an improvement over time. This improvement is most likely due to intensification of chemotherapy, more precise risk classification based on the biology of the leukemia and response to treatment, and improvements in supportive care. However, the cumulative incidence of relapse remains unacceptably high at 25%–40% (Hasle et al. 2012; Creutzig et al. 2013; Pession et al. 2013; Tomizawa et al. 2013; Gamis et al. 2014), with relapsed disease being the most common cause of death in AML. Five-year OS in relapsed AML has been reported to be between 23% and 37% (Sander et al. 2010; Kaspers et al. 2013; Nakayama et al. 2014; Karlsson et al. 2017).

Treatment remains largely based on non-specific cytotoxic drugs (anthracyclines and nucleoside analogues) delivered as 4–5 courses of intensive therapy, with hematopoietic stem cell transplant—and its significant associated co-morbidities—reserved for high-risk patients with unfavorable cytogenetic abnormalities or a poor response to therapy (Rubnitz 2017). Novel agents are clearly required to tackle the outstanding challenges of this disease. Most notably in the last decade, a Phase III study of gemtuzumab ozogamicin demonstrated improved 3-year disease-free survival in patients with AML receiving gemtuzumab ozogamicin in addition to standard of care compared with those who received standard of care alone, albeit with a modest improvement from 55% to 61% (Gamis et al. 2014).

1.3 BACKGROUND ON ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for approximately 30% of all pediatric malignancies in industrialized countries (Ries et al. 1999; Stiller 2009). Significant improvements in outcome have been achieved; the overall cure rate reported by most cooperative groups is approaching 90%, with an outstanding cure rate of 98% in certain subsets (Pui et al. 2012; Cooper et al. 2015). This progressive improvement has been largely attributed to accurate identification of prognostic factors and more precise risk stratification based on these factors to enable appropriate treatment intensity choice, as well as improved supportive care (Cooper and Brown 2015; Lee and Cho 2017). Populations with poor prognosis have been clearly defined and include patients <1 year and >10 years of age, patients with overt CNS disease at diagnosis, patients with unfavorable genomic alterations, and patients with induction failure or minimal residual disease (MRD) positivity at end of induction (Ceppi 2015; Cooper and Brown 2015). Notably, infants harboring translocations in the mixed-lineage leukemia (*MLL*) oncogene experience shorter remission durations and markedly lower survival rates of $<50\%$ (Pieters 2007). Traditional cytotoxics delivered in multi-agent regimens are the mainstay of frontline treatment that consists of remission induction, consolidation, maintenance, and CNS-directed therapy, with an overall duration of 2–3 years (Cooper and Brown 2015). Despite the steady improvements in outcome, ALL remains one of the leading causes of pediatric malignant deaths (Curtin et al. 2016), with survival post-relapse strongly associated with duration of first CR and site of relapse (Ko et al. 2010; Oskarsson et al. 2016). Re-induction of patients with

relapsed ALL commonly includes conventional agents largely identical to those used at initial diagnosis, with hematopoietic stem cell transplant frequently used as consolidation therapy. Successful re-induction of remission becomes increasingly challenging with subsequent relapses, and mortality in second or greater relapse is high. Five-year OS in patients with relapsed ALL has been reported to be $<$40%, with 5-year OS of approximately 20% in patients who relapse within 18 months of initial diagnosis, and worse 5-year OS in second and third relapses of 27% and 15%, respectively (Einsiedel et al. 2005; Nguyen et al. 2008; Ko et al. 2010).

Novel agents and cellular therapies have recently come to the fore as highly active in the relapse setting. Most notable among these is the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel, which when tested in patients with relapsed/refractory disease demonstrated an overall remission rate of 82% (all of whom were negative for MRD), and 12-month EFS and OS of 50% and 76%, respectively (Maude et al. 2018). Also notable are results observed with the CD19-targeting bispecific T-cell engager blinatumomab. In a Phase II label–enabling study in patients with relapsed/refractory pre-B ALL, 39% of patients treated with single-agent blinatumomab achieved morphologic CR, and of these responders, 52% achieved MRD-negative status (von Stackelberg et al. 2016). Even despite these robust response rates, a high percentage of patients do not achieve durable remission, thus necessitating continued evaluation of new agents in ALL.

1.4 BACKGROUND ON THE TEST PRODUCTS

1.4.1 Idasanutlin

The tumor suppressor p53 is a powerful growth suppressive and pro-apoptotic protein that plays a central role in protection from tumor development. The protein p53 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 (Harris and Levine 2005). The p53 protein is regulated through a negative feedback loop by murine double minute 2 (MDM2), which binds to p53, blocks its transactivation domain, and targets p53 for ubiquitin-dependent degradation in the proteasome. Some tumors overexpress MDM2, thus disabling the effective function of p53, leading to inefficient growth arrest or apoptosis.

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

delivered as a single agent in an established osteosarcoma xenograft model and in combination with cytarabine in an AML model in immunodeficient mice.

Refer to the Idasanutlin Investigator's Brochure for additional details on nonclinical studies.

1.4.1.1 Clinical Studies of Idasanutlin in Adults

Idasanutlin has been investigated in adult patients with solid tumors (Phase I Studies NP27872, NP28902, NP29910, and NP39051); in adult patients with AML (Phase I Study NP28679); in combination with cytarabine and daunorubicin in adult patients with newly diagnosed, previously untreated AML (Phase Ib/II GO40800); and in combination with cytarabine in adult patients with relapsed/refractory AML (Phase III Study WO29519). In parallel, the Phase Ib/II Study GH29914 explored the combination of idasanutlin and venetoclax in a chemotherapy-free regimen for older patients with relapsed/refractory AML. Administration of idasanutlin in patients with non-Hodgkin lymphoma (NHL) was explored in two Phase Ib/II trials, in combination with obinutuzumab or rituximab, either with or without venetoclax (Studies BH39147 and BH29812, respectively). Other studies included a bio-equivalence study in patients with solid tumors (Study NP39051) and a Phase I/II, single-agent study in patients with polycythemia vera (Study NP39761).

Pharmacokinetics and Recommended Doses

Two different formulations of idasanutlin have been developed: a microprecipitated bulk powder (MBP) and a spray-dried product (SDP) formulation. Pharmacokinetic (PK) data in adult patients treated with idasanutlin in Studies NP27872, NP28902, and NP28679 show that half-life ($t_{1/2}$) was approximately 1 day and that there was apparent dose-proportionality for the daily schedule (Days 1–5 in a 28-day cycle) in patients with solid tumors or AML. The SDP formulation is 2-fold more bioavailable than the MBP formulation 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, and idasanutlin is not excreted through urine. There was no major impact of a strong CYP3A inhibitor, posaconazole, or concomitant cytarabine on idasanutlin pharmacokinetics.

Different maximum tolerated doses (MTDs) were identified depending on the disease and combination therapy, as detailed below.

- Study NP27872 evaluated idasanutlin as a single agent in adult patients with solid tumors using a legacy MBP formulation. For daily administration regimens, MTDs for idasanutlin were identified as 500 mg daily × 5 days or 500 mg twice a day (BID) × 3 days (duration of all cycles was 28 days). Thrombocytopenia and decreased platelet count were the most commonly reported dose-limiting toxicity (DLT) events, followed by neutropenia, febrile neutropenia, pancytopenia, and diarrhea.

- Study NP28679 evaluated idasanutlin as a single agent and in combination with cytarabine in adult patients with AML. Less stringent DLT rules for hematologic adverse events were utilized in this study, given the need for dose intensity in AML therapy. The dose-escalation phase of the study utilized the MBP formulation. The MTD was not formally reached, but a decision to halt further dose escalation was made due to concerns over increased frequency and severity of adverse events, in particular diarrhea, at doses $>$600 mg BID MBP. A bridging cohort (n$=$29 patients) subsequently explored the safety/PK profile of a new SDP idasanutlin in combination with cytarabine. The 300 mg BID SDP schedule (administered to 16 patients) was better tolerated than higher doses and had comparable PK exposure as the 600 mg BID MBP schedule. Thus, the relative bioavailability of SDP is approximately twice that of MBP.
- Study GH29914 $evaluated$ idasanutlin SDP in combination with venetoclax in patients $\geq$ 60 years of age with relapsed/refractory AML. Although a recommended idasanutlin dose was not identified $prior\ to\ study\ closure$, significant clinical responses $were$ observed at substantially lower idasanutlin doses (150–200 mg SDP daily) in combination with venetoclax than were assessed in Study NP28679, and higher doses of idasanutlin (up to 400 mg daily) $were$ not considered tolerable in this combination.

Safety

As of 13 September 2019, a total of 216 adult patients with solid tumors have been treated with idasanutlin in four studies. Across the solid tumor studies, 98.6% of patients had at least one adverse event. The most common adverse events were diarrhea and nausea (each 64%), vomiting (48%), decreased appetite (34%), and fatigue (33%) being the most frequently reported adverse events. The most common ($\geq$30%) related adverse events were diarrhea (63%), nausea (61%), and vomiting (43%).

Grade $\geq$3 adverse events were reported in 56% of patients, most commonly within the system organ classes of blood and lymphatic system disorders, metabolism and nutrition disorders, gastrointestinal (GI) disorders, and investigations. Thrombocytopenia, anemia, neutropenia, hypokalemia, and nausea were the most common ($\geq$5% of patients) Grade $\geq$3 adverse events.

Serious adverse events were reported in 27% of patients in the pooled dataset, most commonly ($\geq$2% of patients) thrombocytopenia (6.0%), febrile neutropenia (2.3%), and pyrexia (2.3%). In 14% of patients, serious adverse events were considered related to idasanutlin, with the most commonly reported ($\geq$2% of patients) being thrombocytopenia (6.0%) and febrile neutropenia (2.3%).

A total of 14 patient deaths were recorded across all four studies, of which 10 deaths were attributed to progressive disease. Of the remaining 4 deaths, 1 death was considered remotely related to idasanutlin (pulmonary embolism); the other 3 deaths were considered unrelated (intracranial hemorrhage, intra-abdominal hemorrhage with concurrent pulmonary embolism, and aspiration pneumonia).

As of 13 September 2019, a total of 122 patients with AML have received idasanutlin as monotherapy or in combination with cytarabine in Study NP28679, 49 patients have received combination therapy with venetoclax and idasanutlin in Study GH29914, and 5 patients have received idasanutlin in combination with cytarabine and daunorubicin in Study GO40800. As of 1 November 2019, a total of 290 patients have received idasanutlin in combination with cytarabine in Study WO29519. A summary of the safety data from Studies NP28679, GH29914, GO40800, and WO29519 is presented.

In Study NP28679 the most frequently reported adverse events were diarrhea, nausea, hypokalemia, vomiting, and decreased appetite. The most common Grade ≥ 3 adverse events were from system organ classes infections and infestations; blood and lymphatic system disorders; metabolism and nutrition disorders; GI disorders; and general disorders and administrative site conditions. The types of adverse events of patients treated with idasanutlin monotherapy were similar to those of patients treated with idasanutlin in combination with cytarabine; however, an increase in the frequency of adverse events in combination therapy versus monotherapy (at the same idasanutlin dose) suggests an additive effect of cytarabine. Serious adverse events were reported in 59% of patients in Study NP28679, most commonly from infections and infestations. Twenty-seven patients died in Study NP28679; 11 of the 29 deaths were attributed to disease progression, and 16 deaths were associated with serious adverse events. Most of the deaths associated with serious adverse events were due to infectious processes, including 5 deaths due to sepsis and 2 deaths due to neutropenic sepsis.

In Study GH29914, four dosing cohorts have been evaluated to date: 6 patients received 400/200 mg (venetoclax/idasanutlin), 13 patients received 600/150 mg, 21 patients received 600/200 mg, and 9 patients received 400/400 mg. Similar to other idasanutlin trials, the most common adverse events were reported from system organ classes GI disorders, blood and lymphatic system disorders, infections and infestations, and metabolism and nutrition disorders. Serious adverse events were reported in 40 patients, of which 19 patients experienced serious adverse events considered related to idasanutlin and 19 patients experienced serious adverse events considered related to venetoclax. Death was reported in 38 patients: 29 deaths were due to progressive disease, 5 deaths were due to adverse events of cardio-respiratory arrest, nervous system disorder, respiratory failure, hemophagocytic lymphohistiocytosis, and sepsis; and the remaining 4 deaths were due to other reasons (unspecified causes other than adverse event or disease progression).

In Study GO40800, the most common adverse events (≥ 3 patients) were diarrhea, nausea, thrombocytopenia, febrile neutropenia, anemia, dyspepsia, and leukopenia. Four serious adverse events were reported in 3 patients, of which three of the serious adverse events in the 3 patients were considered related to idasanutlin: febrile neutropenia (2 patients) and respiratory failure (1 patient). One patient died due to an adverse event of respiratory failure (related to idasanutlin).

In Study WO29519, there were no new safety concerns identified.

For additional information on clinical safety, please refer to the current Idasanutlin Investigator's Brochure.

Efficacy

In the adult AML dose-escalation study (NP28679), bone marrow clearance, demonstrated by CR, complete remission with incomplete platelet count recovery (CRp), incomplete blood count recovery (CRi), and MLFS responses, was seen across all patients throughout different dose levels and formulations (MBP and SDP) in an all comer population (p53 WT and mutant). The best overall response rate included 4 CR (8.7%) and 3 CRi (6.5%) for a composite complete remission (CRc) rate of 15.2% for monotherapy. With regard to combination therapy, there were 20 CR (26.7%), 1 CRp (1.3%), and 1 CRi (1.3%), for a CRc rate of 29.3% across all patients treated with combination therapy with cytarabine.

Across all adult solid tumor studies, the best overall response to single-agent idasanutlin observed was stable disease (SD); there were no objective responses according to Response Evaluation in Solid Tumors (RECIST) criteria. In Study NP27872, which investigated idasanutlin in advanced solid malignancies, the rate of SD was 30.6% with a median overall duration of SD of 72.5 days (range: 8–696 days).

In study WO29519 *(MIRROS),* idasanutlin showed *minimal* clinical activity as seen in increased overall remission*; however, a* lack of *improvement in* OS *was observed with idasanutlin plus cytarabine versus placebo plus cytarabine*.

Please refer to the current Idasanutlin Investigator's Brochure for additional details on the efficacy results.

1.4.2 Venetoclax

B-cell lymphoma 2 (BCL-2) family proteins are important regulators of the intrinsic apoptosis pathway. The BCL-2 family of genes encodes closely related proteins that possess either pro-apoptotic or anti-apoptotic activity, the latter mediated by BCL-2, BCL-XL, BCL-W, A-1, and MCL-1. The ratio of pro-apoptotic to anti-apoptotic proteins is associated with the outcome of cell survival or programmed cell death. In contrast to other known oncoproteins, BCL-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of pro-apoptotic stimuli, including cytotoxic drugs, cytokine withdrawal, irradiation, heat, and deregulated oncogenes (Souers et al. 2013).

Venetoclax is a potent, selective, orally bioavailable small molecule BCL-2 inhibitor. It binds to BCL-2 with $>$500-fold higher affinity (Ki $<$ 0.010 nM) than other BCL-2 family members, including BCL-XL (Ki ~48 nM) and BCL-w (Ki ~245 nM) (Souers et al. 2013). Over-expression of anti-apoptotic BCL-2 family proteins enables cancer cell survival.

Antagonism of these proteins may enhance response to chemotherapeutic agents or trigger apoptosis directly in certain tumor cells.

Two pediatric studies are currently evaluating venetoclax as a single agent in pediatric and young adult patients with relapsed or refractory malignancies (Study M13-833, Clinicaltrials.gov identifier NCT03236857, EudraCT 2017-000439-14), and in combination with navitoclax and chemotherapy in patients with relapsed/refractory ALL or relapsed/refractory lymphoblastic lymphoma >4 years of age (Study M16-106, NCT03181126).

Please refer to the current version of the Venetoclax Investigator's Brochure, Karol et al. (2019), and Goldsmith et al. (2020) for additional details regarding the adult and pediatric clinical studies.

Pharmacokinetics and Recommended Doses

PK data for venetoclax are available from studies in patients with cancer (chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL], AML, NHL, multiple myeloma [MM]), healthy subjects, and patients with hepatic impairment. Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained 5–8 hours after dosing. The harmonic mean $t_{1/2}$ ranged from 17–41 hours following a single oral dose of venetoclax. In patients with CLL, venetoclax showed minimal accumulation, and steady-state AUC increased proportionally over the dose range of 150–800 mg. Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with unbound fraction (fu) <0.01 and is primarily eliminated as metabolites in feces with negligible renal elimination ($<0.1\%$). Drug–drug interaction studies of venetoclax with ketoconazole, rifampin, warfarin, ritonavir, azithromycin, and digoxin were conducted to provide dosing recommendations for patients concomitantly taking CYP3A and/or P-gp inhibitors, inducers, and/or warfarin. PK studies were conducted in healthy Chinese subjects and Japanese subjects to provide dosing recommendations for those specific populations. Additionally, a dedicated study to evaluate the pharmacokinetics of venetoclax in patients with hepatic impairment is ongoing. Based on the population PK analysis, age, sex, race, weight, mild and moderate renal or hepatic impairment do not have an effect on venetoclax clearance.

Safety

The safety profile of venetoclax for each indication has been consistent with that of the overall population. Common treatment-emergent adverse events across indications and across monotherapy and combination therapy include Grades 1–2 GI toxicities (nausea and diarrhea) and Grades 3–4 hematologic toxicities (neutropenia, febrile neutropenia, thrombocytopenia, and anemia) (see Section 5.1.2).

Refer to the current version of the Venetoclax Investigator's Brochure for additional clinical safety information. The observed risks of venetoclax and the safety management guidelines for these risks are described in Section 5.1.2.

Efficacy

Venetoclax is approved for the treatment of adult patients with CLL or SLL. In the United States, venetoclax is also approved in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. In addition, preliminary efficacy results are available for patients with AML, NHL, and MM, showing promising efficacy results in oncology patient populations (Kumar et al. 2017; deVos et al. 2018; Zelenetz et al. 2019).

For additional information on clinical efficacy, please refer to the current Venetoclax Investigators' Brochure.

1.4.3 Nonclinical Activity of Idasanutlin as Single Agent and in Combination with Chemotherapy and Venetoclax in Pediatric Cancers

1.4.3.1 Idasanutlin as Single Agent and in Combination in Neuroblastoma

Neuroblastoma, even in the relapse setting, does not have frequent mutations in p53 or downstream effectors. Approximately 15% of relapsed neuroblastomas harbor a p53 mutation; a greater number of p53-inactivating abnormalities in neuroblastoma occur upstream of p53 (Carr-Wilkinson et al. 2010). Thus, targeting this negative regulator has been hypothesized to be a potential, and relevant, pro-apoptotic therapeutic approach. A predecessor MDM2 inhibitor to idasanutlin, nutlin-3a, was cytotoxic in neuroblastoma cell lines (Van Maerken et al. 2006) and sensitized cells to chemotherapy-induced apoptotic cell death (Barbieri et al. 2006).

Idasanutlin has subsequently been shown to have nonclinical activity in vitro and in vivo in nonclinical models of neuroblastoma as a single agent and in combination with chemotherapy agents and with venetoclax. As a single agent, idasanutlin potently decreases cell proliferation in multiple neuroblastoma cell lines and xenografts. In one study evaluating 16 *TP53* wild-type (WT) cell lines, the mean concentration at which idasanutlin induced 50% growth inhibition was 68.2 nM (range 14.8–140.3 nM). Cell cycle arrest and apoptosis, p53 stabilization, and induction of p53 downstream targets were also observed in treated cell lines (Chen et al. 2015). Furthermore, idasanutlin-induced tumor growth inhibition was consistently observed in *TP53* WT neuroblastoma cell line xenografts (range 59%–75%) (Lakoma et al. 2015).

When combined with chemotherapy or venetoclax, idasanutlin leads to synergistic outcomes. Specifically, combining idasanutlin with cisplatin, doxorubicin, topotecan, temozolomide, or busulfan in vitro induced greater cell growth inhibition in *TP53* WT cell lines than with either agent alone. Median effect analysis demonstrated that this effect

was at least moderately synergistic in all agents tested, and combinations also led to greater levels of p53 stabilization, pathway activation, and apoptosis (Chen et al. 2015). In vitro cell line combination studies of idasanutlin with 15 targeted agents considered relevant in neuroblastoma biology (including the BET inhibitor JQ1, the ALK inhibitor crizotinib, the mTOR inhibitor rapamycin, the histone deacetylase inhibitor vorinostat, and the reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome bortezomib) identified that combining with the dual BCL2/BCL-XL inhibitor navitoclax was strongly synergistic and yielded the highest level of synergy of any combination tested. Expansion of this cohort to include a larger number of cell lines recapitulated strong synergy when combining idasanutlin with either navitoclax or venetoclax.
To assess the effect of the combination of idasanutlin and venetoclax in vivo, orthotopic xenograft tumors of SMS-KCNR/luc human neuroblastoma cells in nude mice were treated with vehicle, idasanutlin, venetoclax, or idasanutlin plus venetoclax for 2 weeks. In the combination cohort, mean tumor weight at the end of the treatment period was 4% of that observed in the vehicle group, and tumors were significantly smaller than those in cohorts treated with either drug alone (van Goethem et al. 2017), demonstrating a profound effect of this combination on neuroblastoma tumor growth.

1.4.3.2 Idasanutlin as Single Agent and in Combination in Acute Myeloid Leukemia

Pediatric AML has a low mutation rate relative to other cancers, and mutations in *TP53* are particularly uncommon. Although *TP53* mutations are measurably present in approximately 8% of adult AML, they were present at a rate of approximately 1% in newly diagnosed pediatric AML in a nearly 1,000-patient series (Boulouri et al. 2018). Although clonal evolution at relapse has not been reported to result in acquisition of novel *TP53* mutations (Farrar et al. 2016), a recent study identified *TP53* mutations in 12% (9 of 73) of AML samples, likely obtained in the relapse setting, as these were obtained from samples submitted for gene sequencing as part of clinical care (Chmielecki et al. 2017).

Activity of idasanutlin as a single agent and in combination with cytarabine was established utilizing an AML cell line xenograft model.

Idasanutlin and venetoclax have complementary mechanisms of action. In nonclinical testing restoration of p53 tumor-suppressor activity through MDM2 antagonism by idasanutlin, combined with induction of mitochondrial apoptosis by inhibiting Bcl-2 inhibition with venetoclax, delivers enhanced anti-tumor activity in AML. In vitro, the combination of idasanutlin and venetoclax demonstrated synergistic anti-apoptotic and anti-tumor activity, and superior activity over either agent alone, in the MV4-11 cell line (established from a 10-year old male) and the MOLM-13 cell line (established from a 20-year old male). Subcutaneous MV4-11 xenografts treated with idasanutlin plus venetoclax led to partial tumor regression (55%) relative to control, while tumor regressions were not observed with either single agent alone. Compared with the

single-agent treatments, combination treatment resulted in superior tumor growth inhibition (>100 %) in MV4-11 xenografts (Lehmann et al. 2016).

1.4.3.3 Idasanutlin as Single Agent and in Combination in Acute Lymphoblastic Leukemia

TP53 mutations occur in a small percentage of patients at diagnosis of ALL, but occur in up to 11% of patients at relapse, with $>$ 50% of these mutations acquired subsequent to diagnosis (Hof et al. 2011). Overexpression of MDM2 has been observed in a significant proportion of both pediatric ALL cell lines and primary leukemic cells expressing WT p53 (Zhou et al. 1995; Gustafsson et al. 1998) and has been associated with a poorer treatment outcome (Zhou et al. 1995; Gustafsson et al. 1998). Given this degree of expression, MDM2 is a rational target in ALL.

Nonclinical testing of an early generation MDM2 antagonist, nutlin-3, showed dose-dependent cytotoxic activity in 9 of 9 *TP53* WT pediatric ALL cell lines tested and 29 of 29 *TP53* WT primary pediatric ALL samples tested. A significant positive correlation was noted between MDM2 expression levels and nutlin-3–induced cytotoxicity (Gu et al. 2008).

Marked activity of RG7112 (predecessor to idasanutlin) was demonstrated in patient-derived ALL systemic-disease xenograft models in immunocompromised mice (Carol et al. 2013). All seven evaluable pediatric ALL xenografts showed leukemia regression (5 complete responses, 1 maintained complete response, and 1 partial response) and a significant prolongation of EFS in all complete responders. Notably, the only xenograft to achieve a maintained complete response was an *MLL*-rearranged xenograft derived from an infant. Evaluation of 6 additional infant *MLL*-rearranged ALL models showed that RG7112 induced a prolonged complete remission in all 6 xenografts with leukemia growth delay ranging from 17.1–44.7 days (Richmond et al. 2015). In the same study, synergy was observed with the addition of idasanutlin to an induction-type regimen of vincristine, dexamethasone, and *L*-asparaginase, with significant extension of disease remission in two MLL-ALL xenografts.

Venetoclax has demonstrated robust single-agent activity in nonclinical pediatric ALL studies. Khaw et al. (2016) showed that venetoclax significantly delayed leukemia progression in 11 of 19 (58%) xenografts established from pediatric ALL biopsies, with superior activity in MLL-rearranged ALL relative to other subtypes. This, in combination with the superior nonclinical activity of dual MDM2/BCL2 targeting in other disease areas, and the known clinical activity and tolerability of idasanutlin in combination with venetoclax in AML, supports further investigation of the combination in pediatric ALL.

1.4.3.4 Idasanutlin as Single Agent in Other Solid Tumors

Besides neuroblastoma, idasanutlin and related nutlin compounds (such as nutlin-3 or RG7112) have demonstrated preclinical efficacy in a number of different pediatric solid tumor models including:

- Rhabdomyosarcoma. Nutlins have shown activity in pediatric preclinical models as a single agent and as combination therapy. Single-agent RG7112 demonstrated CR in an alveolar rhabdomyosarcoma PDX model tested in the NCI Pediatric Preclinical Testing Program (PPTP), and significant tumor growth inhibition was observed in 4/7 rhabdomyosarcoma models tested (Carol et al. 2013). Nutlin-3 induced cell cycle arrest and apoptosis, and demonstrated synergy with vincristine and dactinomycin, when tested in TP53 wild-type rhabdomyosarcoma cell lines (Miyachi et al. 2009). Embryonal rhabdomyosarcoma cell line xenografts treated with idasanutlin showed radiosensitization when treated with idasanutlin in combination with radiotherapy, as opposed to radiotherapy alone (Phelps et al. 2015).
- Rhabdoid tumor. Targeting of MDM2 has recently been identified as a key vulnerability in malignant rhabdoid tumor. Pooled-format RNAi identified that TP53 inhibition significantly promoted cell survival, and unbiased CRISPR-Cas9 screens identified MDM2 inactivation as the strongest vulnerability evaluated. In vitro testing resulted in upregulation of p53 signaling, and in vivo testing in cell line xenografts resulted in tumor regression of all xenografts tested and a 50% complete response rate (Howard et al. 2019). Significant tumor growth inhibition was also observed in all three rhabdoid tumor xenografts treated with RG7112 by the PPTP, with tumor shrinkage and survival prolongation observed in one model (Carol et al. 2013).
- Ewing sarcoma. Significant tumor growth inhibition was observed in three out of four tumor xenografts treated with RG7112 by the PPTP, with tumor shrinkage and survival prolongation observed in one model (Carol et al. 2013).
- Wilms tumor. Partial tumor regression was observed in the one Wilms tumor xenograft model treated with RG7112 by the PPTP (Carol et al. 2013).
- Osteosarcoma. Idasanutlin was tested in SJSA osteosarcoma cell line xenografts and demonstrated tumor growth inhibition, regression, and improved mouse survival in a dose dependent manner (Filipovic et al. 2011).
- Retinoblastoma. Administration of nutlin-3a has been identified to induce retinoblastoma regressions in genetically engineered mouse models of the tumor (Brennan et al. 2011, Laurie et al. 2006).

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Given the compelling nonclinical efficacy of idasanutlin as a single agent and in combination with chemotherapy or venetoclax in several pediatric tumor types (neuroblastoma, AML, and ALL), idasanutlin represents a strong candidate for clinical evaluation in single agent and combination in children and young adults.

This trial has the primary aims of identifying the MTD/maximum administered dose (MAD), safety, and pharmacokinetics of idasanutlin in children with relapsed/refractory

cancer; the recommended Phase II dose(s) (RP2D[s]) of idasanutlin in combination with chemotherapy or venetoclax; and the preliminary efficacy for idasanutlin in combination with either chemotherapy or venetoclax in neuroblastoma, AML, or ALL.

Based on the superior results combining idasanutlin with chemotherapy or venetoclax in all of these diseases in nonclinical models, initiation of combination cohorts is justified in patients with relapsed/refractory disease *after* an MTD/MAD *is* identified *for idasanutlin*, including:

- Idasanutlin + cyclophosphamide + topotecan in neuroblastoma
- Idasanutlin + fludarabine and cytarabine in AML
- Idasanutlin + venetoclax in AML, ALL, and neuroblastoma

The combination chemotherapy regimens proposed are supported not only by evidence of synergy between idasanutlin and at least one agent contained in the regimen, but also by the established benefit–risk ratio of these chemotherapy regimens in children (see Section 3.3.1 for details about tolerability in pediatric regimen).

Venetoclax is an approved therapy in certain adults with CLL and AML, but has not been approved for use in children or in any of the indications proposed in this study. Venetoclax has shown activity in clinical trials in AML; in a Phase Ib study, adult chemotherapy-ineligible patients treated with venetoclax plus azacitidine or decitabine had CR + CRi rates of 67%, significantly higher than in studies of any of these agents singly (DiNardo et al. 2018). Given the nonclinical results in combination studies of idasanutlin and venetoclax described above, *and given the differences in biology between pediatric and adult AML (Conneely and Rau 2020),* evaluation of this combination is warranted.

The study is designed to identify response rates in a disease-appropriate manner. In neuroblastoma, the primary response endpoint will be objective response rate using International Neuroblastoma Response Criteria (INRC). In leukemias, inducing morphologic complete remission following relapse is well recognized as a critical step in achieving a long-term cure. A deeper remission, evidenced by MRD negativity, provides a better bridge to transplant and a higher probability of long-term survival. Achievement of CR and MRD negativity will be co-primary endpoints in ALL given the extensive literature supporting MRD as a relevant clinical endpoint in early-phase ALL trials, and MRD will be a secondary endpoint in AML. Although progression-free survival (PFS) in solid tumors, EFS in leukemias, and OS in all patients will be evaluated as secondary endpoints, this study is not designed to definitively identify a survival benefit associated with idasanutlin in pediatrics.

Adult studies have shown idasanutlin to have an acceptable toxicity profile both as a single agent and in combination with chemotherapy (cytarabine) and venetoclax. The most commonly reported adverse events for idasanutlin monotherapy include GI toxicity

(diarrhea, nausea, and vomiting), with the majority of events Grade 1 or 2, as well as hematological events (thrombocytopenia, anemia, and neutropenia) and infections such as sepsis and pneumonia. Refer to the Idasanutlin Investigator's Brochure for more details on the safety data observed to date in humans. The anticipated and potential safety issues associated with the administration of idasanutlin in combination with venetoclax or chemotherapy, and the measures that are intended to avoid or to minimize such toxicities in this study, are described in detail in Section 5.1.

Both venetoclax and the proposed combination chemotherapy regimens are myelosuppressive and, as such, have an overlapping toxicity profile with idasanutlin. In the hematological malignancy populations, this risk of this degree of myelosuppression might prove to be outweighed by increased clearance of blasts and deeper responses for the combination treatment. In evaluating idasanutlin in solid tumors (as single agent and in combination), more stringent DLT rules are implemented for hematologic toxicities. As a result, lower idasanutlin RP2Ds are expected in solid tumors relative to leukemias.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and pharmacokinetics of idasanutlin as a single agent and the safety, tolerability, pharmacokinetics, and preliminary efficacy of idasanutlin in combination with either chemotherapy or venetoclax in children and young adults with acute leukemias or solid tumors that are recurrent or refractory to standard therapy.

In this protocol, "study treatment" refers to the single agent or combination of treatments assigned to patients as part of this study (i.e., idasanutlin with or without chemotherapy or venetoclax).

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

2.1 SAFETY OBJECTIVES

The safety objectives for this study are to evaluate the safety and tolerability of idasanutlin as a single agent, in combination with chemotherapy, and in combination with venetoclax; to determine the MTD/MAD of idasanutlin administered as a single agent; and to define the RP2D of idasanutlin in combination with either chemotherapy or venetoclax on the basis of the following endpoints:

- Incidence and severity of adverse events with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0)
- Changes from baseline in physical findings
- Changes from baseline in targeted clinical laboratory test results and ECG parameters

- Incidence of DLTs assessed during the first cycle of study treatment of single-agent idasanutlin and again with idasanutlin in combination with chemotherapy or venetoclax

The exploratory safety objective for this study is to evaluate the impact of idasanutlin as a single agent and in combination with chemotherapy and venetoclax on growth and development on the basis of the following endpoints:

- Changes from baseline in growth patterns (relative to age-specific standards for height and weight)
- Changes from baseline in development patterns (relative to onset of menarche [for females] and pubertal changes)

2.2 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are as follows:

- To characterize the PK profile of idasanutlin as a single agent and in combination with chemotherapy or venetoclax on the basis of the following endpoints:
  - Plasma concentration of idasanutlin (and M4 metabolite RO6802287, where relevant) as a single agent at specified timepoints
  - Plasma concentration of idasanutlin in combination with chemotherapy or venetoclax at specified timepoints
- To characterize the PK profile of venetoclax in combination with idasanutlin on the basis of the following endpoint:
  - Plasma concentration of venetoclax at specified timepoints

2.3 EFFICACY OBJECTIVES

2.3.1 Primary Efficacy Objective

The primary efficacy objective for this study (Study Parts *1b,* 2*,* and 3) is to evaluate the anti-cancer activity of idasanutlin in combination with chemotherapy or venetoclax on the basis of the following endpoints:

Neuroblastoma

- Objective response rate (ORR), defined as the proportion of patients with complete response or partial response (PR) at any time during study treatment, on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to INRC for patients with neuroblastoma

Primary *efficacy* analysis will be conducted on patients with *TP53* WT tumors in Study Parts *1b,* 2*,* and 3.

Leukemia

- Complete remission rate (CRR), defined as the proportion of patients with morphologic CR, CRi, or CRp (see Appendix 7 and Appendix 8), within 2 cycles of study treatment

- For patients with ALL: MRD-negative rate, defined as the proportion of patients with ALL who have an MRD value $< 0.01\%$, as measured by next-generation sequencing (NGS), within 2 cycles of study treatment

Primary *efficacy* analyses will be conducted on patients with *TP53* WT tumors in Study Parts 2 and 3.

2.3.2 Secondary Efficacy Objective

The secondary efficacy objective for this study (Study Parts 1, 2, and 3) is to evaluate the anti-cancer activity of idasanutlin as single agent, in combination with chemotherapy, and in combination with venetoclax (in patients with *TP53* WT tumors, as well as in all patients regardless of mutation status) on the basis of the following endpoints:

Solid tumors (including Neuroblastoma)

- Clinical benefit rate (CBR), defined as the proportion of patients achieving confirmed CR, PR, or SD on two consecutive occasions ≥ 4 weeks apart during the total study period
- Duration of objective response (DOR), defined as the time from the first tumor assessment that supports a patient's objective response to the time of disease progression or death from any cause (whichever occurs first), as determined by the investigator using INRC for patients with neuroblastoma or RECIST v1.1 for patients with other solid tumors
- PFS, defined as the time from initiation of study drug to the first documented occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator using INRC for patients with neuroblastoma and RECIST v1.1 for patients with other solid tumors
- OS, defined as the time from initiation of study drug to death from any cause
- ORR of efficacy-evaluable population irrespective of *TP53* mutation status

Leukemia

- Number of patients receiving transplant after study treatment
- DOR, defined as the time from the first tumor assessment that supports the patient's objective response (CR, CRp, CRi; see Appendix 7 and Appendix 8) to the time of relapse, or death from any cause, whichever occurs first
- EFS, defined as the time from initiation of study drug to the first documented occurrence of M3 marrow after Cycle 1, failure to achieve CR/CRp/CRi after Cycle 2, disease progression, relapse subsequent to achieving CR/CRp/CRi, or death from any cause, whichever occurs first.
- OS, defined as the time from initiation of study drug to death from any cause
- CRR of efficacy-evaluable population irrespective of *TP53* mutation status
- For patients with AML: MRD-negative rate, defined as the proportion of patients with AML who are MRD negative within 2 cycles of study treatment

2.4 EXPLORATORY BIOMARKER OBJECTIVES

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to idasanutlin as a single agent or in combination with chemotherapy or venetoclax; are early surrogates of efficacy; are associated with progression to a more severe disease state (i.e., prognostic biomarkers); are associated with acquired resistance to idasanutlin as a single agent or in combination with chemotherapy or venetoclax; are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers); can provide evidence of idasanutlin activity (i.e., pharmacodynamic biomarkers) as a single agent or in combination with chemotherapy or venetoclax; or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers identified in blood versus tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.5 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate the acceptability and palatability of idasanutlin on the basis of the following endpoint:

- Acceptability Survey scores at Cycle 1, Day 5

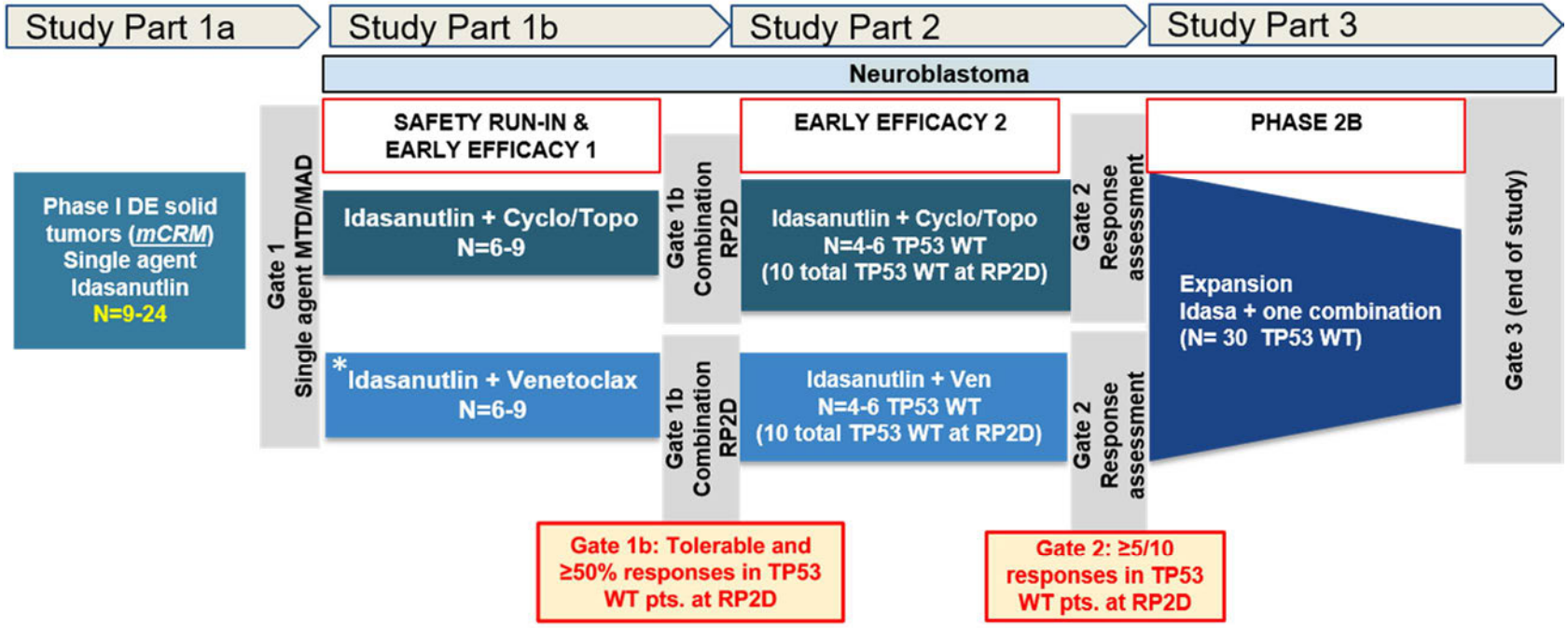
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

The study is a Phase I/II, multicenter, open-label, multi-arm study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of idasanutlin in pediatric and young adult patients with acute leukemias or solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable. Idasanutlin will be administered as a single agent or in combination with chemotherapy or venetoclax.

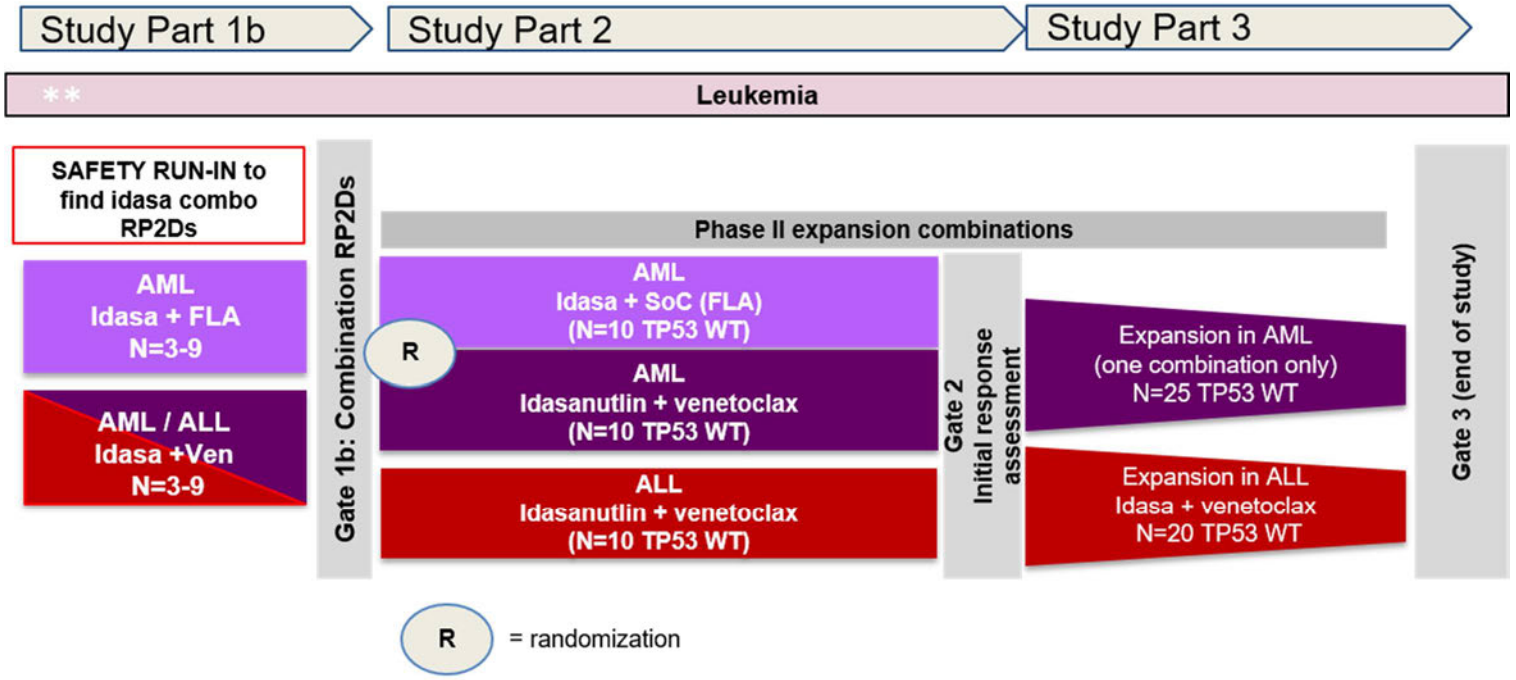
Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1, Appendix 2, and Appendix 3.

Figure 1 Study Schema



* Initiation of the safety run-in cohorts for the planned combinations in neuroblastoma may occur asynchronously.

Figure 1 Study Schema (cont.)



** Initiation of the leukemia cohorts may start asynchronously relative to the neuroblastoma cohorts.

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; *DE=DLT-evaluable;* DLT = dose-limiting toxicity; *FLA=fludarabine and high-dose cytarabine;* mCRM-EWOC = modified continual reassessment method of escalation with overdose control; NBL = neuroblastoma; RP2D = recommended Phase II dose; WT = wild-type.

Note: *TP53* mutation status will not be taken into account when enrolling patients in the study. Study Part 3 requires at least 30, 25, and 20 patients with *TP53* WT tumors in the NBL, AML, or ALL cohorts, respectively.

The study is divided into three parts:

- **Study Part 1:**
  - *Part 1a:* Dose escalation to assess safety, tolerability, and pharmacokinetics of idasanutlin as a single-agent treatment in the pediatric population with relapsed or refractory solid tumors; to identify the single-agent MTD/MAD; and to characterize DLTs. Patients in dose escalation after one cycle will either continue single-agent idasanutlin or start early combination of idasanutlin with chemotherapy (for precise rules, see Section 3.1.1.1).
  - *Part 1b:* Following single-agent MTD/MAD identification, separate safety run-in cohorts *will be conducted* in neuroblastoma with newly enrolled patients to identify the RP2Ds of idasanutlin in combination *with cyclophosphamide and topotecan and in combination with venetoclax. These cohorts will also provide early efficacy assessments of these combinations in the patients with TP53 WT tumors treated at the RP2Ds (see Section 3.1.1.2). Additional safety run-in cohorts will be conducted in AML to identify the RP2D of idasanutlin in combination with FLA and in AML and ALL to identify the RP2D of idasanutlin in combination with venetoclax in patients with leukemia.*

- **Part 2:** *In cohorts that pass the safety and efficacy criteria for Part 1b (Gate 1b),* evaluation of safety and efficacy of idasanutlin in combination with chemotherapy or venetoclax *will be continued* in neuroblastoma, AML, and/*or* ALL -at *the* RP2D*(s) for the combinations* (see Section 3.1.2).
- **Study Part 3:** Potential expansion of idasanutlin combination cohorts in neuroblastoma, AML, *and/*or ALL meeting the pre-defined efficacy criteria for expansion *(Gate 2)*, also taking into account practical considerations (e.g., enrollment feasibility), nonclinical findings, biomarker analysis, safety profiles, and any other relevant information (see Section 3.1.3).

In Study Part 1*a*, only patients $<$18 years of age will be enrolled. In Study Parts *1b,* 2*,* and 3, pediatric and young adult patients with neuroblastoma or acute leukemias (age: birth to $<$30 years) will be enrolled.

Idasanutlin will be administered orally to patients once daily for Days 1–5 of each cycle, followed by 23 days of rest, for a total cycle duration of 28 days. All patients will be closely monitored for adverse events (regardless of relationship to study drug) throughout the study and for at least 30 days after the last dose of study treatment or until initiation of a new anti-cancer therapy, whichever comes first.

Patients will be enrolled regardless of their *TP53* mutation status, as not all *TP53* mutations may be inactivating; therefore, responses may still be observed in some patients with *TP53* mutations. A pre-idasanutlin tumor biopsy of current disease within 6 months of screening and after the last anti-cancer therapy is required for patients with solid tumors *unless approved by the Medical Monitor*. A bone marrow aspirate (BMA) specimen is required within the screening period for patients with leukemia. Samples

will be analyzed for *TP53* mutation status by centralized molecular testing. If available, sites must also report any local molecular testing results for *TP53* mutation status in the eCRF.

An internal monitoring committee and external scientific oversight committee (IMC/SOC) will be established for safety monitoring at pre-defined study milestones and approximately every 6 months (see Section 3.1.4).

3.1.1 Study Part 1—Dose Escalation and Safety Run-In

3.1.1.1 *Study Part 1a:* Single-Agent Dose Escalation

The study will begin with a dose-escalation phase with idasanutlin in patients with solid tumors using the modified continual reassessment method of escalation with overdose control (mCRM-EWOC) to identify the single-agent MTD/MAD. Approximately 9–*24 DLT-evaluable* patients are anticipated to be enrolled in this phase. Based on *physiologically*-based pharmacokinetic (PBPK)-predicted exposures in children, the starting dose is defined as 2 mg/kg/day (dose level 1) (Section 3.3.1.1). Dose-level escalation or de-escalation (if required) will be decided following review of PK and safety data.

Due to the limitations of predicting exposure in children <2 years of age, patients <2 years of age require investigator discussion with, and approval of, the Medical Monitor for enrollment until at least 6 patients have completed one cycle of treatment. Exposure data from the first 6 patients will be used to refine predictions for patients <2 years of age. The first patient at each dose level must complete at least 5 days of treatment without a DLT before subsequent patients can be treated at the same dose level.

The single-agent DLT window will be 28 days (one cycle duration; see Section 4.3.2.1) and until ANC $\geq 0.75 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L are achieved. Adverse events identified as DLTs will be reported to the Sponsor within 24 hours. Following the first cycle, patients will undergo response and DLT assessment. Any delay >14 days in treatment due to delayed platelet recovery will also be considered a DLT; therefore, DLT assessment may extend until platelet count recovery.

- Patients who do not experience a DLT or progressive disease will have the option (with investigator approval) to continue single-agent idasanutlin or start combination therapy with cyclophosphamide/topotecan (dose defined in Section 4.3.2) with a dose reduction in idasanutlin of 20%.
- Patients who do not experience a DLT but do experience progressive disease may continue idasanutlin (with a 20% dose reduction) in combination with cyclophosphamide/topotecan with investigator and Medical Monitor approval, but will not be permitted to continue idasanutlin monotherapy.
- Patients who experience a DLT but have CR, PR, or SD will have the option to continue single-agent treatment (dose reduced by 20%) upon adequate recovery

from toxicities and depending on the nature of the specific toxicity, as jointly judged by investigator and the Medical Monitor.

- Patients who experience a DLT and progressive disease will permanently discontinue study therapy.

Patients will start subsequent cycles of therapy after Day 28 and when ANC $\geq 0.75 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L are achieved. Patients who remain on study therapy (single agent or combination) will continue until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, or patient/guardian or investigator decision to discontinue treatment.

All patients who experience a DLT will be DLT evaluable. Patients who discontinue from the study prior to completing the DLT assessment window or who complete less than 80% (i.e., less than 4 doses) of the prescribed therapy for that cycle for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD/MAD assessments. DLT non-evaluable patients will be replaced, unless the Medical Monitor determines that replacement is not necessary for a dose escalation or reduction decision. The Medical Monitor will review all patients who ingest prohibited therapies, foods, or supplements (see Section 4.4), or who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described below as part of the DLT definition) to determine DLT-evaluability and whether they will be replaced.

Patients who experience a DLT during the assessment window (i.e., in the first 28 days) are not permitted to continue drug at their current dose. The investigator should use guidance in Section 5.1.5 (and if guidance is not specified, investigator discretion) to determine whether the patient should permanently discontinue study drug or withhold study drug until adequate toxicity resolution.

All patients in the dose-escalation phase, irrespective of diagnosis, will be eligible for combination therapy with cyclophosphamide/topotecan after the DLT assessment window provided they meet the above criteria. Patients treated with combination therapy will be closely monitored for safety for the duration of treatment (i.e., no fixed DLT period/assessment). Dose reductions *of idasanutlin and/or cyclophosphamide/topotecan* can be applied based on the patient's clinical status, as jointly judged by investigator and Medical Monitor. The Medical Monitor may also mandate dose reductions for all patients treated with combination in this phase of the study based on the combination dose-finding rules established in Section 3.1.1.2. Any emerging safety data will inform the starting dose of the combination safety run-in cohorts.

The dose-escalation phase will utilize the mCRM-EWOC design to inform decision-making regarding the MTD of idasanutlin. The MTD is defined as the dose that maximizes the posterior probability of a DLT being in the targeted toxicity interval of 20%

to 35%, while keeping the overdose probability below 25%. A minimum of 3 patients will be initially enrolled per dose level. Before declaring MTD, a minimum of 6 patients will be enrolled in that dose level. The mCRM-EWOC model will adaptively estimate the MTD after gathering cumulative DLT data from newly completed cohorts and will calculate a recommended next dose for the next cohort. The maximum allowable dose increase to the next dose level will be 50%. The mCRM-EWOC design parameters and operating characters are described in Appendix 11. Because the mCRM-EWOC model does not take into account the type and grade of DLT and non-DLT adverse events, clinical judgment will always override model estimates when selecting the next dose. Thus, decisions to dose escalate must be approved by the Medical Monitor. On the basis of an ongoing review of safety data and available PK data, increases in dose level may be halted by the Sponsor as deemed appropriate, even if the model estimates that MTD has not been exceeded.

3.1.1.2 *Study Part 1b:* Combination Therapy Safety Run-In

Once the idasanutlin single-agent MTD/MAD has been identified, a safety run-in phase with newly enrolled pediatric patients will be conducted to identify RP2Ds for idasanutlin in combination with chemotherapy or venetoclax in separate neuroblastoma, AML, and ALL combination cohorts (see *Section 4.2* for treatment assignment information). The safety run-in phase will start at a maximum of 80% of the idasanutlin MTD/MAD identified in the dose-escalation phase, combined with the following regimens in the listed diseases:

- Idasanutlin + chemotherapy:
  - Neuroblastoma: cyclophosphamide + topotecan
  - AML: fludarabine + cytarabine
- Idasanutlin + venetoclax:
  - Neuroblastoma
  - ALL and AML, with different DLT rules for hematologic toxicity, as described in Section 3.1.1.3

Assignment of patients to either the chemotherapy or venetoclax cohort will be at the investigator's discretion and in accordance to the availability of open slots for enrollment.

The DLT criteria (disease-type dependent) are modified from those used in the single-agent dose escalation cohort in order to determine more appropriately the RP2D in the setting of combinations with agents that have anticipated effects on bone marrow suppression. Dose-escalation decisions will be dependent on pharmacokinetics and totality of data. Only the idasanutlin dose will be escalated, while chemotherapies or venetoclax doses will not be escalated (see also Section 4.3.2.2). *However, idasanutlin, chemotherapy, and/or venetoclax doses may be de-escalated based on the totality of the data as determined by the Medical Monitor.*

For each combination cohort, the first patient at the first dose level must complete at least 5 days of treatment without a DLT before subsequent patients can be treated at the same dose level. After the first 3 patients at a particular dose level have completed 1 cycle of therapy (28 days), recruitment will be paused, and safety and tolerability will be evaluated as described below:

- Should no patients experience DLTs and the regimen is otherwise considered tolerable, dose escalation to the next dose level may be considered. Alternatively, 3 additional patients may be enrolled at the same dose or*, for the leukemia cohorts,* an RP2D may be declared with endorsement by the IMC/SOC.
- Should 1 of the first 3 patients experience a DLT, dose reduction *of idasanutlin and/or chemotherapy/venetoclax* or additional enrollment of 3 patients at the same dose will be considered.
- Should more than 1 patient experience a DLT or the regimen is otherwise considered intolerable based on the totality of the data, the dose of idasanutlin *and/or chemotherapy/venetoclax* will be reduced.

If 3 additional patients are enrolled in a dose-level cohort, safety and tolerability will be evaluated as described below:

- If 0 or 1 total patients experience a DLT and the regimen is considered tolerable, dose escalation to the next dose level may be considered or an RP2D may be declared with endorsement by the IMC/SOC. *A minimum of 6 patients are required to be treated at a dose level prior to it being declared the RP2D for the neuroblastoma cohorts.*
- If more than 1 patient experiences a DLT or the regimen is otherwise considered intolerable based on the totality of the data, the dose of idasanutlin *and/or chemotherapy/venetoclax* will be reduced.

The degree of dose escalation or reduction in each cohort (if necessary) will be determined by the Medical Monitor. For dose escalations, the degree of escalation may not exceed 25% of the previously administered dose. For dose reductions, the degree of reduction must be at least 20% of the previous dose.

Although safety and tolerability will be the primary determinants of dose recommendation, identification of an RP2D may also be informed by observed idasanutlin drug exposures or efficacy. At each dose level cohort, the process of dose selection will restart as described above. A maximum of one higher dose level from the starting dose-level cohort, or *one* lower dose-level cohorts of idasanutlin, will be permitted. If *one* dose level~~s~~ below the starting dose of idasanutlin is considered intolerable, the combination will be discontinued. As the safety profile of idasanutlin may differ among combinations, the idasanutlin RP2D may also differ among cohorts.

Upon identification of the appropriate RP2D, *evaluation of the combination will proceed to Study Part 2; however, the neuroblastoma cohorts will not proceed unless ≥ 50% of*

the TP53 wild-type patients treated at the RP2D have an objective response by INRC. If this criterion for Gate 1b is passed, the safety and preliminary efficacy for the RP2D idasanutlin combinations will *continue to* be evaluated in Study Part 2, *where* enrollment will proceed until *a total of* 10 *TP53*-wild type (WT)-evaluable patients per disease cohort are enrolled *(See Section 3.1.2)*.

Once the appropriate RP2D is identified, patients treated at lower dose levels (including those patients treated in the single-agent dose escalation who go on to receive combination therapy with cyclophosphamide/topotecan) will be allowed to escalate to the RP2D.

Patients will be treated with combination therapy until the occurrence of disease progression as determined by the investigator, death, unacceptable toxicity, study termination, or patient/guardian or investigator decision to discontinue treatment, except in the following instances:

- Patients with AML treated with fludarabine and high-dose cytarabine (FLA) will receive up to 2 cycles of combination therapy, followed by idasanutlin monotherapy in subsequent cycles.
- Patients with leukemia who 1) do not meet criteria for progression or relapse but have M3 marrow after Cycle 1 of therapy or 2) fail to achieve morphologic CR/CRi/CRp after 2 cycles of therapy will be required to discontinue study therapy unless the investigator views the benefit–risk ratio of continued therapy as favorable (and with approval of the Medical Monitor). Patients will still be recorded as having had an event for EFS analysis.

Patients with neuroblastoma will start subsequent cycles of therapy after Day 28 when ANC is $\geq 0.75 \times 10^9$/L and platelet count is $\geq 75 \times 10^9$/L. Patients with AML and ALL will start subsequent cycles of therapy after Day 28 when ANC is $\geq 0.5 \times 10^9$/L and platelet count is $\geq 75 \times 10^9$/L (or at Day 56 when ANC is $\geq 0.5 \times 10^9$/L irrespective of platelet counts).

3.1.1.3 Definition of Dose-Limiting Toxicity

During the dose-escalation phase, safety run-in phase, and initial cohort expansion phase (Study Parts 1 and 2), any one of the following events will be considered a DLT if it occurs during the DLT assessment window and is assessed by the investigator to be related or possibly related to idasanutlin (rules for attributing causality are defined in Section 5.3.4). Adverse events identified as DLTs, as defined below, must be reported to the Sponsor within 24 hours.

Single-Agent Dose Escalation (Solid Tumors, including Neuroblastoma)

The DLT period will be defined as 28 days (1 cycle) plus any additional time required for count recovery sufficient to start the next cycle of therapy. The following will be considered a DLT:

- Any treatment-related death

- Elevation of serum hepatic transaminase (ALT/ AST) $\geq 5 \times$ the upper limit of normal (ULN) lasting for > 72 hours, or $> 20 \times$ ULN lasting for any duration of time not attributable to disease progression
- Severe liver injury, in the absence of cholestasis or other causes of hyperbilirubinemia, as defined by Hy's law:
  - Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
  - Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with clinical jaundice
- Any non-hematologic toxicity Grade ≥ 3 except for the following:
  - Grade 3 fatigue, generalized muscle weakness, fever, anorexia, or constipation
  - Grade 3 laboratory abnormality (except elevations of hepatic transaminases) that is asymptomatic and deemed not clinically significant by both the investigator and Medical Monitor.
- Nausea, vomiting, and/or diarrhea if Grade 3 severity lasts greater than 24 hours after initiation of supportive care measures or if Grade 4 or higher
- Hematologic toxicity (not applicable for patients with bone marrow involvement at baseline):
  - Grade 4 neutropenia (i.e., neutrophil count $< 0.5 \times 10^9$/L) lasting at least 7 days

    Treatment with *granulocyte colony stimulating factors* is acceptable if patient has Grade 4 neutropenia *and prophylactic use of granulocyte colony stimulating factors is recommended for patients who receive idasanutlin in combination with cyclophosphamide and topotecan starting in Cycle 2.*
  - Febrile neutropenia: Grade 4 neutropenia (i.e., neutrophil count $< 0.5 \times 10^9$/L) with a temperature ≥ 38.5°C or documented infection
  - Grade 4 anemia
  - Grade 4 thrombocytopenia (i.e., platelet count $< 25.0 \times 10^9$/L) or any thrombocytopenia requiring platelet transfusion
  - Delay in starting Cycle 2 > 14 days ($>$ Day 42) due to slow recovery from thrombocytopenia (platelet count $< 75 \times 10^9$/L) or neutrophil count $< 0.75 \times 10^9$/L

    Delays will be taken into account for subsequent dosing decisions.
- Any related event that results in a dose delay beyond Day 42

Combination Safety Run-in and Expansion (**Neuroblastoma**)

The DLT period will be defined as 28 days (1 cycle) plus any additional time required for count recovery sufficient to start the next cycle of therapy. The following will be considered a DLT:

- Any treatment-related death

- Elevation of serum hepatic transaminase (ALT/ AST) $\geq 5 \times$ the ULN lasting for > 72 hours, or $> 20 \times$ ULN lasting for any duration of time not attributable to disease progression
- Severe liver injury, in the absence of cholestasis or other causes of hyperbilirubinemia, as defined by Hy's law:
  - Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
  - Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with clinical jaundice
- Any non-hematologic toxicity Grade ≥ 3 except for the following:
  - Grade 3 fatigue, generalized muscle weakness, fever, anorexia, or constipation
  - Grade 3 laboratory abnormality (except elevations of hepatic transaminases) that is asymptomatic and deemed not clinically significant by both the investigator and Medical Monitor.
- Nausea, vomiting, and/or diarrhea if Grade 3 severity lasts greater than 24 hours after initiation of supportive care measures or if Grade 4 or higher
- Hematologic toxicity (not applicable for patients with bone marrow involvement at baseline):
  - Grade 4 neutropenia (i.e., neutrophil count $< 0.5 \times 10^9$/L) lasting at least 14 days

    Prophylactic use of granulocyte colony stimulating factors is *recommended per institutional standards*

    Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.
  - Grade 4 anemia
  - Grade 4 thrombocytopenia (i.e., platelet count $< 25.0 \times 10^9$/L) lasting at least 14 days *with assessments on at least two separate days or requiring a platelet transfusion on 2 separate days*
  - Delay in starting Cycle 2 > 14 days ($>$ Day 42) due to slow recovery from thrombocytopenia (platelet count $< 75 \times 10^9$/L) or neutrophil count $< 0.75 \times 10^9$/L

    Delays will be taken into account for subsequent dosing decisions.
- Any related event that results in a dose delay beyond Day 42

Combination Safety Run-in and Expansion (**Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia**)

The DLT period will be defined as 28 days (1 cycle) plus any additional time required for count recovery sufficient to start the next cycle of therapy for consideration of DLT.

The following will be considered a DLT:

- Any treatment-related death

- Elevation of serum hepatic transaminase (ALT/ AST) $\geq 5 \times$ the ULN > 72 hours or $> 20 \times$ ULN lasting for any duration of time
- Severe liver injury, in the absence of cholestasis or other causes of hyperbilirubinemia, as defined by Hy's law:
  - Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
  - Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with clinical jaundice
- Any non-hematologic toxicity Grade ≥ 3 except for the following:
  - Grade 3 fatigue, generalized muscle weakness, anorexia, or constipation
  - Grade 3 laboratory abnormality that is asymptomatic or can be controlled with medical interventions (e.g., electrolyte disturbances due to chemo-induced diarrhea) and deemed to be not clinically significant by both the investigator and the Medical Monitor
  - Grade 3 or 4 fever *or febrile neutropenia*
  - Infection, bleeding, or other expected direct complication of cytopenias due to active underlying AML/ALL
  - Tumor lysis syndrome (TLS) if it is successfully managed clinically and resolves within 7 days without end-organ damage
- Nausea, vomiting, and/or diarrhea if Grade 3 severity lasts greater than 24 hours after initiation of supportive care measures or if Grade 4 or higher
- Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) or Grade $\geq$2 thrombocytopenia (platelets $< 75 \times 10^9$/L) in absence of evidence of active leukemia (i.e., < 5% blasts in the bone marrow) lasting $\geq$ 42 days

  Myelosuppression and associated complications are expected as events during leukemia therapy and are part of the treatment success (marrow emptying of leukemia cells). Therefore, myelosuppression and associated complications such as fever, infections, bleeding, and related hospitalization will be reported in the study summary.
- Any related event that results in a dose delay beyond Day 42

3.1.1.4 Dose-Limiting Toxicity Re-Treatment Criteria

In the single-agent dose-escalation phase of Study Part 1*a*, if DLT occurs, study treatment must be suspended.

- For patients with CR/PR/SD at end of Cycle 1, re-start idasanutlin monotherapy at a 20% reduced dose (see Section 3.1.1.1) once DLT has resolved to Grade ≤ 1 or baseline. Resumption of idasanutlin may also be considered if approved by the investigator and Medical Monitor.
- For patients with PD, permanently discontinue study treatment.

For the safety run-in phase of Study Part 1*b*, if DLT occurs, study treatment must be suspended.

- Re-start combination treatment (with idasanutlin at a reduced dose) once DLT has resolved to Grade ≤1 or baseline. *Dose reduction of combination agents may also be considered with approval of Medical Monitor.* Resumption of study treatment may also be considered if approved by the investigator and Medical Monitor.

For Study Part 2, if a DLT occurs, study treatment must be suspended.

- Re-start treatment once the event has resolved to ≤Grade 1 or baseline. Resumption of study treatment may also be considered if approved by the investigator and Medical Monitor.

See Sections 5.1.5.1 and 5.1.5.4 for additional guidance on dose modifications and management of specific adverse events.

3.1.2 Study Part 2—Initial Expansion for Early Efficacy Evaluation

Upon *determination* of the appropriate idasanutlin RP2D *and passage of Gate 1b* for each disease *and* combination, *additional patients will be enrolled in Study Part 2. For neuroblastoma cohorts, approximately 4–6 patients will be added to reach a total of 10 patients with TP53 WT tumors (including those patients enrolled in Study Part 1b at the RP2D).* For AML*, patients* will be randomly allocated between two combination arms *FLA* versus venetoclax) and evaluated for safety and preliminary efficacy. *For these AML arms, ten patients with TP53 WT AML will be enrolled per arm, not counting those enrolled in Study Part 1b. For* ALL*, patients* will not undergo randomization, as only one treatment combination (idasanutlin plus venetoclax) will be evaluated. Ten patients with *TP53* WT *ALL* will be required for *this cohort. On the basis of the frequency of TP53 mutations in the selected tumor types, the overall number of patients enrolled in each individual cohort is not expected to exceed approximately 20% more than the target minimum of 10 patients.* Patients enrolled in the study whose *cancers* are found to have *TP53* mutations will be allowed to continue study therapy but will be replaced for efficacy analysis. The different *cancer* types will be evaluated independently of one another.

Patients included in the safety run-in phase will not be included in the 10-patient initial response assessment *for the leukemia arms*.

Response criteria, assessment timepoints, and primary efficacy endpoints for each disease are listed in Table 1.

Table 1 Response Criteria, Assessment Timepoints, and Primary Efficacy Endpoints

Disease	Response Criteria	Assessment Timepoint	Primary Efficacy Endpoint for Determination of Subsequent Cohort Expansion
Solid tumors (non-neuroblastoma)	RECIST v1.1. for patients with other solid tumors (see Appendix 6)	Part 1*a* (single-agent dose escalation): Cycles 1, 3, 5, and 7 and every fourth cycle thereafter	*N/A*
Neuroblastoma	International Neuroblastoma Response Criteria (INRC) (see Appendix 5)	Part 1*a* (single-agent dose escalation): Cycles 1, 3, 5, and 7 and every fourth cycle thereafter	*N/A*
		Part 1b (combination safety run-in), Part 2, and Part 3: Every two cycles from Cycle 1 through Cycle 8 and then every fourth cycle thereafter	*Objective response rate*
AML	See Appendix 7	After the first and second cycles of therapy, and every 2 cycles thereafter	CR within two cycles
ALL	See Appendix 8	After the first and second cycles of therapy, and every 2 cycles thereafter	CR within two cycles; MRD negative within two cycles

ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CR = complete response; INRC = International Neuroblastoma Response Criteria; MRD = minimal residual disease; RECIST = Response Evaluation Criteria in Solid Tumors.

Although Part 2 of the study is not dose finding, DLTs will be reported and analyzed in conjunction with the efficacy evaluation. The DLT collection period will take place during Cycle 1, lasting 28 days for each patient plus any additional time required for count recovery sufficient to start the next cycle of therapy. The same DLT criteria will be used as during the safety run-in portion of Part 1*b* as defined in Section 3.1.1.3.

Upon completion of enrollment in the initial expansion for efficacy in Part 2, an additional safety analysis will be performed at the time of response assessment for all patients enrolled in a cohort. If more than 35% of patients experience a DLT in Part 2, the combination may stop enrollment, after taking into account the discussions with investigators as well as IMC/SOC recommendation.

For example, if the true toxicity rate is 20% at a certain combination dose level, there is a 12% probability of observing DLTs in more than 35% of 10 patients. On the other hand, if the true toxicity rate is 40%, there is a 62% probability of observing DLTs in more than 35% of 10 patients.

3.1.3 Study Part 3—Additional Expansion Phase

As defined in Section 6.1, a minimum number of responders among the 10 patients with *TP53* WT enrolled in Study Part*s 1b and* 2 *for the neuroblastoma cohort or Study Part 2 for the leukemia cohorts* will be required for cohort expansion and advancement to the additional response assessment (Study Part 3). The minimum number of responders is defined separately for each disease and is based on an expected observation of improvement over response rates to backbone therapies (see Section 3.3.7). A decision to expand a cohort will take into account safety and tolerability of the combination regimen in addition to the number of responders. Practical considerations will also be taken into account, such as enrollment feasibility, nonclinical findings, biomarker analysis, safety profiles, and any other relevant information. In general, cohorts will not expand if the minimum number of responders is not met. However, the study team (only with endorsement of the IMC/SOC) will be permitted to expand a cohort even if the minimum number of responders is not met, if the totality of the efficacy and other data support cohort expansion. The maximum number of additional patients enrolled in any tumor cohort in Study Part 3 will range from 20–30 patients with *TP53* WT tumors. Tumor assessments will be performed utilizing the same response criteria used in Study Part 2 (see Table 1).

3.1.4 Stopping Rules by Cohort

3.1.4.1 Temporary Halt

A temporary dosing halt will be applied in the event that excessively prolonged marrow aplasia or deaths attributable to study drug occur in Part 1 of the study (single-agent dose-escalation and combination therapy safety run-in). If any of the applicable adverse events described below occur, all patients must stop dosing unless evidence of clinical benefit is demonstrated (e.g., decreased tumor-related symptoms, reduced tumor burden, or evidence of stable disease) and has already been observed in the

investigator's opinion. For relevant events in a combination therapy cohort, because toxicity is anticipated to be different with different drug combinations, the stopping rule will apply only to the disease and drug combination cohort in which the toxicity occurred:

- Single-agent cohort
  - Any Grade 4 neutropenia or Grade 4 thrombocytopenia lasting beyond Day 56 of any cycle, attributable to study drug
  - Any Grade 5 event attributable to study drug
- Combination cohorts
  - Solid tumor combinations with chemotherapy or venetoclax:
    - $>$1 episode of Grade 4 neutropenia or Grade 4 thrombocytopenia lasting beyond Day 56 of any cycle, attributable to study drug
    - Any Grade 5 event attributable to study drug
  - Leukemia combinations with chemotherapy or venetoclax:
    - $>$1 episode of Grade 4 neutropenia or Grade 4 thrombocytopenia lasting beyond Day 56 of any cycle, attributable to study drug, AND not attributable to disease
    - $>$1 episode of any Grade 5 infection in the setting of drug-induced neutropenia
    - Any other Grade 5 event attributable to study drug

Dosing may not resume in the patients unless and until the IMC/SOC recommend resumption of dosing after review of the adverse event(s).

3.1.4.2 Temporary Pause in Enrollment

In study Part 1 (single-agent or combination), if the first patient in a dose level cohort has a DLT within 5 days, enrollment will pause in that cohort. Enrollment will be permitted to resume at a lower dose level. Subsequent enrollment in the specific cohort where the DLT event occurred (i.e., at the same dose level as the DLT event occurred) may not resume unless and until the IMC/SOC recommend resumption of enrollment after review of the adverse event.

For patients in study Parts 2 and 3, meeting the criteria for temporary halting of the cohort (see Section 3.1.4.1) will not result in a halt to dosing. Only enrollment in the specific cohort where the event(s) occurred $will\ pause$ until the IMC/SOC recommend resumption of enrollment after review of the adverse event(s).

Additional guidance for stopping enrollment related to DLTs in Part 2 is provided in Section 3.1.2.

3.1.4.3 Final End of Dosing by Cohort

In addition to the regular safety reviews planned every 6 months, the IMC/SOC may request an ad hoc meeting to review the safety data as needed (see Section 3.1.5 and

IMC/SOC Charter). The IMC/SOC may recommend permanent discontinuation of dosing in some or all treatment cohorts based on their findings.

3.1.5 Internal Monitoring Committee and Scientific Oversight Committee

An IMC will be established to monitor patient safety throughout the study, to provide recommendations on the single-agent MTD/MAD and combination RP2Ds of idasanutlin, and to provide recommendations on which cohorts qualify to proceed to the study expansion phase. The IMC will include Sponsor representatives from clinical science, biostatistics, safety science, and clinical pharmacology. IMC members will not have regular contact with the sites as part of their responsibilities.

In addition to the ongoing assessment by the investigator and the Medical Monitor of the incidence and nature of DLTs, adverse events (particularly Grades ≥ 3), serious adverse events, deaths, and laboratory abnormalities, the IMC will review all necessary cumulative data approximately every 6 months during the study. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to obtain IMC recommendations on management of any new safety issues.

An SOC, which will consist of experts external to the Sponsor (including at least 2 pediatric oncologists), will also be established for this study. The SOC will leverage external experts' scientific expertise by providing advice on data interpretation as well as advice on which cohorts qualify to proceed to the expansion phase. The SOC will function as a consultative body to the Sponsor, providing individual expert opinions.

Specific operational details—such as committee composition, frequency and timing of meetings, and member roles and responsibilities—will be detailed in an IMC and SOC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or 1 year after the last patient is enrolled, whichever occurs first. For an individual patient, the completion of the study (i.e., the last visit) will occur when the patient withdraws consent, has been lost to follow-up, dies, or when the study is stopped.

The Sponsor reserves the right to present interim data to *H*ealth *A*uthorities for compliance purposes. The primary analysis will be conducted after the enrollment has been completed and all enrolled patients have been followed for at least 6 months. A Clinical Study Report will be submitted to *H*ealth *A*uthorities by the Sponsor according to local/regional regulations.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Study Treatment Dose and Schedule

3.3.1.1 Idasanutlin

The traditional starting dose for pediatric oncology Phase I studies of cytotoxic agents is 80% of the adult dose (Lee et al. 2005). Furthermore, according to the evaluation of toxicity profiles of targeted agents around 80%–100% of the adult dose appears to be a safe starting dose (Paoletti et al. 2013). As noted in Section 1.4.1.1, different MTDs have been identified based on the formulation used (MBP versus SDP), the relevant DLT rules used for hematologic toxicity in solid tumors versus leukemia, and the combination partner used (i.e., cytarabine versus venetoclax).

The single-agent dose finding in this study aims to achieve an MTD of SDP formulation *in pediatric patients. It is anticipated that the pediatric MTD will achieve at least* similar exposures as adults with solid tumors on Study NP27872. A pediatric PBPK model was used to identify *the* dose to achieve the *initial* target exposure AUC_{0-24h} of 70 μg h/mL observed as the median value after 500-mg MBP formulation daily for 5 days in adult patients with solid tumors who participated in Study NP27872. Simulations with 500 virtual children age 0–18 years indicated that an SDP formulation dose of 2 mg/kg/day × 5 days would achieve the target exposure.

In the idasanutlin dose-escalation phase, the starting dose for idasanutlin will be 2 mg/kg. Accounting for the estimated 2-fold increased bioavailability of idasanutlin SDP over MDP, this dose equates to 56% of the predicted SDP solid tumor dose of 3.6 mg/kg/day (500 mg/day MBP divided by 70 kg, divided by a*n* SDP/MBP formulation correction factor of 2). Thus, this starting dose provides a sufficient safety margin below the adult MTD for initiation of dose finding, while *based on PBPK results,* also being likely to match drug exposure *in adults at the MTD for adult solid tumor patients*.

The rationale for idasanutlin dosing in the combination safety run-in is provided in Section 3.3.6.

3.3.1.2 Venetoclax

Venetoclax is approved for use in adults with CLL or SLL at a dose of 400 mg daily (see Venetoclax U.S. Package Insert). In diseases where a higher degree of marrow toxicity is necessary as part of therapy, such as AML and NHL, venetoclax has been evaluated in adults at doses as high as 1200 mg daily without exceeding the MTD in combination with other anti-cancer therapies, although recommended doses have been capped at 800 mg daily in these studies (DiNardo et al. 2018; de Vos et al. 2018).

The pediatric dose for venetoclax is under investigation in a Phase I trial evaluating monotherapy followed by the addition of chemotherapy (Place et al. 2018; trial registration: EudraCT 2017-000439-14, NCT03236857). The starting dose in this study was an adult exposure-equivalent dose of 800 mg daily, adjusted for weight. Preliminary

data from this study by Abb*V*ie indicate that venetoclax administered at this dose exceeded the MTD when used in combination with chemotherapy (topotecan/ cyclophosphamide) in patients with solid tumors due to prolonged neutropenia; at the current time, the optimal dosing for this combination is still being evaluated (S. Kim, personal communication; Goldsmith, et al. 2020). Based on this information, the dose of venetoclax administered in combination with idasanutlin in this study will not exceed 400 mg daily (adjusted for weight) in patients with neuroblastoma.

Because a higher degree of marrow toxicity is tolerated in patients with leukemia in order to adequately treat the bone marrow, a higher starting dose of venetoclax will be utilized in patients with ALL or AML relative to patients with solid tumors in this study. In the ongoing adult study combining idasanutlin with venetoclax in adults with AML (NCT02670044), venetoclax doses ranging from 400 to 600 mg have been evaluated without exceeding the MTD (Daver et al. 2017). A dose of venetoclax higher than 600 mg is not currently planned; as such, the dose of venetoclax on this study will not exceed 600 mg adjusted for weight in patients with leukemia.

Further dosing information is provided in Section 4.3.2.2.

3.3.2 Rationale for Patient Population

The aim of this Phase I/II trial will be to evaluate idasanutlin safety, tolerability and pharmacokinetics in pediatric patients with relapsed/refractory solid tumors, neuroblastoma, AML, and ALL and to derive direct evidence of its efficacy in combination treatment.

The safety risk mitigation plan for all parts of this study will include management measures for adverse events of relevance for idasanutlin. Mitigation and monitoring measures are in place to also cover potential overlapping risks associated with chemotherapy or venetoclax (see Section 5.1.4).

Given the nonclinical activity of idasanutlin in the diseases eligible for this study (outlined in Section 1.4.3), it is anticipated that the benefits of idasanutlin in combination with chemotherapy or venetoclax will outweigh its potential risks, particularly given the poor prognosis of patients with relapsed/refractory solid tumors, neuroblastoma, AML, and ALL who have failed standard-of-care regimens.

Significant focus will be put on preventing highly relevant toxicities from idasanutlin combination therapy through strict adherence to exclusion criteria, rigorous monitoring, and prophylactic treatments to ensure that any and all adverse events remain manageable.

3.3.2.1 Patients with *TP53* Mutations

Patient tumors with mutations that render the p53 protein inactive are not expected to respond to an MDM2 antagonist. However, the exact impact of any given *TP53*

mutation and possible heterozygosity cannot be fully predicted for the clinical setting (Petitjean et al. 2007).

In Study NO21279, a Phase I study of RG7112 (a predecessor MDM2 inhibitor to idasanutlin) in adult AML and ALL, patients with mutant *TP53* exhibited only SD or progressive disease. Two patients with AML with *TP53* mutations demonstrated clinical activity by decreased peripheral blast counts, but none had sustained clinical improvement (prolonged CRs) (Andreef et al. 2016). In the completed Study NP28679, 1 patient with AML with a *TP53* mutation who received idasanutlin in combination with cytarabine achieved a confirmed CR (confirmatory assessment approximately 28 days following initial CR determination) (Reis et al. 2016).

Given the uncertain role of *TP53* mutation status on p53 tumor suppressor activity, patients with tumors harboring *TP53* mutations will be allowed into this study. Due to the possibility of lower efficacy of idasanutlin treatment in these patients, the primary efficacy analyses will be based on patients whose tumors are *TP53* wild type.

Taking all evidence together, the mutation proportion in this study population is not expected to exceed 15%–20%. In addition, results from the Sponsor's clinical studies of MDM2 antagonists in patients with AML suggest that *TP53* mutations are not necessarily predictive of lack of treatment response and a better measure of p53 functionality is needed.

3.3.2.2 Adolescent and Young Adult Patients

The Sponsor expects that the majority of enrolled patients will be < 18 years of age. However, there may be young adult patients with "pediatric-type" tumors who are treated in pediatric oncology facilities. In a specific analysis of adolescent and young adult patients in the United States, limited clinical trial participation correlated with the relative lack of improvement in survival prolongation and cancer death rates (Bleyer et al. 2006). The lower participation of adolescent and young adult patients in clinical trials has created significant knowledge gaps with respect to cancer biology, treatment, and other factors affecting their survival. As part of the Sponsor's commitment to the development of personalized medicine, adolescent and young adult patients up to 30 years of age will be included in *Study Parts 1b, 2, and 3*.

3.3.3 Rationale for Biomarker Assessments

This study will assess *TP53* mutation status, *MDM2* amplification and expression status, serum MIC-1 expression levels, and—in the AML and ALL cohorts—MRD.

Idasanutlin activity is derived from the stabilization and accumulation of p53 that can function only if it retains its conformation and transcriptional activity. Therefore, the intact status of p53 in cancer cells is important in achieving the desirable pharmacodynamic (PD) effects in vivo (that is, inhibition of cancer cell growth and apoptosis). Furthermore, MDM2 amplification/overexpression is believed to result in

decreased p53 levels and activity, and 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 PD indicators of idasanutlin clinical activity.

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

Venetoclax inhibits the ability of cancer cells to evade cell death, or apoptosis, by blocking the activity of the anti-apoptotic protein Bcl-2. Previous nonclinical and clinical studies have demonstrated a pattern of response to venetoclax based on the levels of Bcl-2 family proteins. High levels of Bcl-2 and low levels of Bcl-XL and Mcl-1 are generally associated with response to this drug both in vitro and in patients. In addition, high levels of at least one pro-apoptotic "sensor" such as Noxa or Bim is required.

3.3.3.1 *TP53* Mutations and p53 Activity

As a single agent, idasanutlin has demonstrated anti-tumor activity in cultured tumor cells harboring WT *TP53*. At the same concentrations, idasanutlin is approximately 300-fold less active in cultured cells with mutated *TP53*. Nevertheless, not all *TP53* mutations may disrupt p53 downstream activity. For example, in Studies NO21279 and NP28769, patients with leukemia who exhibited a CR ($n=1$) or peripheral blast reduction ($n=2$) harbored *TP53* mutations, as did patients in studies of solid tumors.

In adult tumors, with the exception of a few "hotspot" alterations (e.g., mutations at codon R248), *TP53* mutations are distributed across the length of the gene. This spectrum is similarly observed in pediatric tumor types (Chmielecki et al. 2017). In neuroblastoma, the rate of *TP53* mutations is reported to be approximately 15% at relapse (Carr-Wilkinson et al. 2010). In pediatric AML and ALL relapse/refractory disease, *TP53* alterations are expected to occur in 12%–18% of such malignancies (Chmielecki et al. 2017).

Sites are strongly encouraged to provide patients' *TP53* mutation status as per local molecular testing results, if available. For central confirmation of *TP53* mutation status, pre-treatment biopsies from patients with neuroblastoma or other solid tumors, and pretreatment BMAs from patients with AML and ALL will be retrospectively tested via NGS. The primary response assessment prior to Gate 2 will be performed on patients whose tumors are centrally confirmed to be *TP53* wild type. Furthermore, these data will be used to evaluate the role of *TP53* mutations toward response to idasanutlin in pediatric malignancies.

3.3.3.2 MDM2 Expression and Idasanutlin Efficacy

Unlike other gene-to-protein relationships, the correlation of *MDM2* amplification with MDM2 mRNA and/or protein expression is unclear. *MDM2* amplification is extremely rare in pediatric neuroblastomas (approximately 3%–4%) and is purportedly non-existent in pediatric AML and ALL (Chmielecki et al. 2017). However, in a study of pediatric

neuroblastoma, investigators observed that patients whose tumors exhibited MDM2 mRNA expression above the study median exhibited a statistically shortened EFS rate in comparison to patients with below-median MDM2 expression in their tumors ($p < 0.001$) (Inomistova et al. 2015). An older nonclinical study interrogating MDM2 mRNA expression of 19 pediatric ALL cell lines and 1 pediatric AML cell line showed that 15 of the 20 cell lines (75%) expressed MDM2 mRNA (Zhou et al. 1995). In the same study, a similar analysis of primary ALL cells from 7 patients showed that leukemic cells in 3 of the 7 patients (43%) exhibited MDM2 mRNA expression levels at or above that observed in normal bone marrow mononuclear cells (Zhou et al. 1995).

MDM2 transcript expression from pretreatment blood specimens from patients with AML 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 the selection of responsive patients. In Study NP28679, MDM2 protein expression in blast cells analyzed by flow cytometry revealed a stronger association with response (Reis et al. 2016). Gene expression signatures may also provide a means of predicting patient response to MDM2 inhibitors. Both nonclinical and clinical data (Studies NO21279 and NP28679) suggest that an mRNA gene expression signature consisting of the genes *MDM2*, *BBC3/PUMA*, *XPC*, and *CDKN2A* may be associated with response to MDM2 antagonist RO5045337 (Zhong et al. 2015).

The significance of these biomarkers to pediatric tumor response to idasanutlin is still unknown. As such, this study (GO40871) may assess *MDM2* gene amplification and gene expression, as well as candidate gene expression signatures and protein expression on blasts (flow cytometry) on an exploratory basis.

3.3.3.3 MIC-1 Expression in Serum

When activated, p53 binds to consensus sites on the promoter of MIC-1, a secreted protein, to induce expression. In mice bearing human tumor xenografts, increased levels of MIC-1 protein were detected in the blood following treatment with doxorubicin, a genotoxic p53 activator (Yang et al. 2003). In the completed Phase I Study NP28679 and the ongoing Phase III Study WO29519, MIC-1 serves as a surrogate biomarker of idasanutlin exposure; correlation of MIC-1 expression with patient response is still under investigation. In Study NO21279 for RG7112, which included patients with AML, elevated MIC-1 serum levels were observed with RG7112 plasma concentrations of > 2 mg/mL; however, the magnitude of elevation did not correlate with patient response (Andreef et al. 2016). In line with these efforts, Study GO40871 will assess MIC-1 serum levels in all patients prior to and during idasanutlin exposure by an established ELISA as an exploratory PD biomarker.

3.3.3.4 Additional Exploratory Biomarker Analyses

In patients enrolled in any of the idasanutlin plus venetoclax combination cohorts, BMA, bone marrow biopsy (BMB), and/or formalin-fixed tissue samples taken at baseline, on-treatment, or end-of-treatment may be analyzed for venetoclax-relevant biomarkers

including, but not limited to, Bcl-2, Bcl-XL, and Mcl-1 by IHC or NGS, depending on sample availability.

Other exploratory biomarkers may include, but will not be limited to, NGS of circulating tumor DNA (ctDNA) throughout the course of therapy, NGS of RNA and/or DNA from tumor tissues and BMAs (leukemia cohorts), and B-cell receptor repertoire sequencing from peripheral blood cells.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.4 Rationale for Efficacy Endpoints

The primary endpoints for this study will be related to response to therapy. As this is a Phase I/II study primarily designed to interrogate whether drug activity is present, survival endpoints (i.e., PFS, EFS, OS) will be secondary.

3.3.4.1 Neuroblastoma

Response assessments will be conducted in accordance with the updated INRC (Park et al. 2017) (see Appendix 5). Compared with the last published INRC revision defined in 1993 (Brodeur et al. 1993), these endpoints more clearly incorporate ^{123}I-meta-iodobenzylguanidine (MIBG) or fluorodeoxyglucose-positron emission tomography (FDG-PET) into disease assessments, refine definitions of bone marrow disease, and remove urine catecholamines as a measure of response.

3.3.4.2 Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia

As the goal of re-induction therapy is to induce a complete remission, the primary outcome measure for patients with AML or ALL will be morphologic CRR within 2 cycles of therapy.

Criteria for response in patients with AML are based on published and widely accepted International Working Group criteria (Cheson et al. 2003).

For patients with ALL, morphologic complete remission encompasses all patients who experience CR, CRp, or CRi, based on criteria defined by a 2007 American Society of Hematology workshop (Appelbaum et al. 2007). These criteria have been utilized in subsequent pediatric ALL trials including a recent trial of tisagenlecleucel in relapsed/refractory disease (Maude et al. 2018) that led to drug approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency.

3.3.4.3 Minimal Residual Disease Assessments for Leukemia Cohorts

Patients with AML or ALL will undergo additional serial assessments for MRD detection. MRD assessments can be made with the use of multiple technologies (e.g., polymerase chain reaction technologies) to detect disease-specific translocations or mutations, and/or by flow cytometry for abnormal cell phenotypes.

Particularly in pediatric ALL, MRD has been established as a strong predictor of likelihood of relapse both in the upfront setting after induction therapy (Borowitz et al. 2008) and in the pre- and post-transplant setting (reviewed in Campana et al. 2013; Lovisa et al. 2018). Risk stratification of patients and therapy intensification or reduction based on MRD status in pediatric ALL and AML has been widely implemented (Campana et al. 2013). MRD has been used as a surrogate endpoint for drug approval in relapsed pediatric ALL, including the approvals of tisagenlecleucel and blinatumomab. As such, MRD will be a co-primary endpoint in evaluating ALL efficacy. Although MRD is used for risk stratification and treatment decisions in AML, MRD has not been used previously as a surrogate endpoint for survival in AML because of limited data to date supporting its use (Schuurhuis et al. 2018). Therefore, MRD will be a secondary endpoint in AML.

Leukemia-associated aberrant immunophenotypes relevant for MRD assessment will be interrogated via flow cytometry or NGS from BMAs. MRD will be monitored in patients with AML and ALL achieving clinical remission using BMAs at subsequent scheduled hematologic malignancy assessments.

BMA analysis to monitor MRD will be prioritized over other exploratory markers requiring BMA material. BMA material from patients with ALL will be assessed using nucleic acid-based methods including, but not limited to, NGS. For patients with AML, standard flow cytometric methods will be used for MRD (see Section 2.3.1 for further details on MRD assessment as an efficacy endpoint). Nucleic acid-based methods may also be explored depending on sample availability.

3.3.5 Rationale for Combination Therapies

Idasanutlin will be combined either with chemotherapy backbone regimens that have been well established in pediatric oncology or with venetoclax.

3.3.5.1 Cyclophosphamide/Topotecan Combination in Patients with Neuroblastoma and Other Solid Tumors

In neuroblastoma, the combination of cyclophosphamide and topotecan has been shown to be tolerable and is anticipated to be acceptable from a safety perspective in combination with idasanutlin; no specific risks have been identified beyond the known potential overlapping toxicities that relate to the majority of standard cytotoxic agents, namely myelosuppression and infection risk. This chemotherapy combination has shown activity in neuroblastoma with an ORR (complete, partial, and mixed responses) reported at 47%–63% of patients in first relapse or progression of high-risk disease and

a 3-year progression-free and overall survival of 11% and 17%–33%, respectively (London et al. 2010; Ashraf et al. 2013). Other studies have utilized cyclophosphamide and topotecan as a chemotherapy backbone for combination with other novel agents in early phase studies, including sorafenib in relapsed/refractory NBL (NCT02298348) and bevacizumab in relapsed/refractory NBL and Ewing sarcoma (NCT01492673).

Additionally, this combination has been shown to be tolerable with evidence of activity in other relapsed/refractory pediatric solid tumors including Ewing sarcoma and rhabdomyosarcoma. Patients with solid tumors may be enrolled in Part 1a of the study up to the idasanutlin single-agent MTD identification (Saylors et al. 2001). Therefore, safety and PK data gained throughout this study may inform exploration of the combination in other pediatric malignancies in the future.

3.3.5.2 Fludarabine and Cytarabine in Patients with Acute Myeloid Leukemia

In AML, the combination of fludarabine, cytarabine, and G-CSF (FLAG) has long been established as an appropriate therapy for inducing remissions in the relapse setting. Among pediatric patients in first relapse or primary refractory disease, it has been shown to deliver a CRR after 2 cycles of 59% and a 4-year OS of 36% (Kaspers et al. 2013). This combination has subsequently served as a backbone for evaluating novel agents in the relapse setting. The study of liposomal daunorubicin given in combination with FLAG established the tolerability of adding a further myelosuppressive agent to the regime. No marked toxicity differences were seen between the groups (Kaspers et al. 2013).

Although G-CSF has been added to fludarabine and cytarabine in many trials theoretically to boost the percentage of cells in cell cycle prior to and during chemotherapy administration, and thus enhance cytotoxicity, its value in clinical practice is debatable. No significant benefit of adding G-CSF to fludarabine and cytarabine has been clinically observed in adults with AML (Estey et al. 1994), and in vitro studies indicate no added effect of G-CSF on the cytotoxicity of FLA (Hubeek et al. 2004). As G-CSF may increase the risk of hyperleukocytosis, and given the known risk of TLS associated with idasanutlin, G-CSF will not be included as a therapeutic component in this study.

3.3.5.3 Venetoclax Combination in Patients with Neuroblastoma, Acute Lymphoblastic Leukemia, and Acute Myeloid Leukemia

The combination of idasanutlin and venetoclax has shown more substantial nonclinical activity in neuroblastoma and AML than either agent alone (see Section 1.4.3), and both idasanutlin and venetoclax have demonstrated substantial single-agent activity in ALL, in many cases eliciting complete tumor responses. The combination $was\ evaluated$ in adult patients $\geq$60 years of age with relapsed or refractory AML who $were$ not eligible for cytotoxic therapy (GH29914, [NCT02670044]). Preliminary results from the study were presented at the American Society of Hematology's annual meeting in 2017. As of 25 April 2017, 20 patients were safety evaluable. Reported DLTs included generalized

muscle weakness, diarrhea, acute coronary syndrome, and elevated bilirubin (1 instance each). Grade ≥3 events occurring in more than 1 patient were febrile neutropenia (30%), decreased appetite (15%), diarrhea (10%), fatigue (10%), and hypokalemia (10%). At a dose of 600 mg venetoclax and 200 mg idasanutlin daily for 5 days, 3 of 8 (38%) patients experienced a complete remission (with or without complete count recovery) (Daver et al. 2017). A complete description of the effects in humans to date can be found in the combination therapy investigator's brochure (RO5537382 venetoclax [GDC-0199/ABT-199] in combination with RO5514041 cobimetinib [GDC-0973/XL518] or RO5503781 idasanutlin [RG7388]).

3.3.6 Rationale for Safety Run-In Design

The primary objective of the safety run-in component of the study is to identify RP2Ds of the individual combination arms across the diseases evaluated. *For neuroblastoma, this part of the study will also provide an early efficacy assessment.* Patients will not be randomized between different regimens because the relative safety profiles of idasanutlin in the proposed combination regimens will not yet have been characterized. During the safety run-in phase, treatment assignment will be at the discretion of the investigator unless the required number of patients to evaluate the RP2D dose is achieved, or the RP2D dose of a specific combination arm has been declared.

A formal dose-escalation approach will not be conducted for idasanutlin in the combination regimens proposed here, but an approach focused on dose reduction in the event of DLTs will be implemented. To ensure patient safety, the following principles will be adhered to:

- A modified 3+3 design is being implemented for dose reductions. Enrollment will pause after every 3 patients to review totality of data. Dose reductions will be required if 2 patients at a dose level experience a DLT, and to determine whether dose reductions should be implemented even in the absence of DLTs. *A dose reduction may be implemented for idasanutlin and/or the combination agent(s) based on the attribution of the observed toxicities as determined by the Medical Monitor.*
- Idasanutlin dosing will be initiated at 80% of its single-agent MTD/MAD in all combinations to provide a safety margin for combination initiation. *A decrease in the starting dose of the combination agents may also be implemented as determined by the Medical Monitor in consultation with the IMC/SOC.*
- An early discontinuation rule has been implemented if after a dose reduction idasanutlin still is not tolerated in combination with other agents.
- The IMC/SOC will review all decisions to declare a recommended dose for a particular combination.

3.3.7 Rationale for Randomization *in AML C*ohorts, Initial Response Assessment, and Target Effect Size

Based on the nonclinical and clinical data supporting the use of idasanutlin in the combinations proposed, clinical equipoise exists as to whether idasanutlin combinations with chemotherapy or venetoclax are the most appropriate development approach for this molecule *in pediatric AML*. To ensure unbiased distribution of patients to inform focused development of one combination, patients *with AML in Study Part 2* will be randomized to either chemotherapy or venetoclax combinations. This study does not formally test the question of whether idasanutlin combinations with chemotherapy or venetoclax are superior. However, a randomized approach in a limited patient population, followed by an initial response assessment based on efficacy and safety data, will inform which combination is more likely to meet the study objective of identifying an idasanutlin regimen *in AML* with acceptable tolerability and a potential signal of efficacy.

After 10 patients with *TP53* WT *cancers* are efficacy evaluable in each combination arm for a disease, the study team in consultation with the IMC/SOC will determine *which, if any,* combinations meet the predefined efficacy threshold for cohort expansion and whether to expand a cohort (see Section 6.2). The minimum number of responders in the initial response assessment for each disease approximates the number of patients that would be expected to respond if the desired level of improvement over backbone therapy is present, although the study is not powered to definitively detect a difference at this stage.

The control *response* rate is defined from the following backbone therapies:

- For neuroblastoma, the ORR observed with the cyclophosphamide/topotecan backbone is 32% (London et al. 2010). For the initial response assessment, this study is targeting an ORR of 47%, a 15–percentage point improvement.
- For AML, the CRR observed with the FLAG regimen is 59% in patients in first relapse or with primary refractory disease (Kaspers et al. 2013); as this study will allow enrollment of patients in later relapse, a lower baseline response rate is expected. For initial response assessment, the study is targeting a 15-percentage point improvement over predicted response rate of 55% of backbone therapy in this study's AML population.
- For ALL, the CRR with re-induction therapy in the second or greater relapse (reflective of the patient population to be enrolled here) is expected to be 40% (Ko et al. 2010). This is comparable to the CRR observed with single-agent blinatumomab (von Stackelberg et al. 2016). Given the large number of ALL therapies recently approved or in development in the relapse setting, a large effect size (20–percentage point improvement) will be targeted. As MRD is a co-primary endpoint, this study will target a 20-point improvement over the MRD-negative rate of 20% observed in a Phase I/II trial of blinatumomab in pediatric patients at any stage of relapse (von Stackelberg et al. 2016).

Because the number of targeted responders in the initial response assessment is not statistically fully powered to detect the target difference, the study team (only with endorsement of the IMC/SOC) will be permitted to expand a cohort even if the minimum number of responders is not met, if the totality of the efficacy and data support cohort expansion.

3.3.8 Rationale for Additional Response Assessment and Target Effect Size

An idasanutlin combination cohort that is selected for expansion will enroll enough patients to determine whether the desired effect size is present with a two-sided alpha of $\leq$10%. The number of patients needed for the additional response assessment will also take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information.

Targets for effect size will be the same as in initial response assessment, except that a higher bar for positive effect size will be set for AML given the availability of superior combinations of FLAG with another agent, liposomal daunorubicin (Kaspers et al. 2013). In this setting, the idasanutlin combination will be compared with the best available relapse therapy, FLAG plus liposomal daunorubicin (69% CR), with a target effect size of 5 points (74% CR).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately *15–108* patients will be enrolled in the Study Parts 1 and 2. After completion of the initial response assessment, an additional 20–30 patients may be enrolled for a combination regimen in each tumor type, up to a total sample size of approximately *183* patients.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent before any study-specific screening procedures are conducted, and age-appropriate assent when considered appropriate according to local, regional, or national guidelines
- Age *<18 years at the time of signing informed consent for Part 1a;* <30 years at time of signing informed consent *for Parts 1b, 2, and 3*

  *Note: T*he Sponsor may decide to stop enrollment of patients who are ≥18 years at any time during the study to ensure adequate enrollment of patients who are <18 years.
- Study Part 1*a* (single-agent therapy dose escalation): histologically confirmed diagnosis of neuroblastoma or other solid tumor that has progressed or recurred despite standard therapy, and for which there is no therapy proven to prolong survival with an acceptable quality of life

- Study Part 1b (safety run-in), Study Part 2, and Study Part 3: histologically confirmed diagnosis of neuroblastoma, AML, or precursor-B ALL that has progressed or recurred despite, or is refractory to, standard therapy
- Adequate performance status:

  Patients $<$ 16 years of age: Lansky $\geq$ 50%

  Patients $\geq$ 16 years of age: Karnofsky $\geq$ 50%

- Adequate end-organ function defined by the following laboratory results obtained within 28 days prior to initiation of study drug:

  Renal and liver function

  – Creatinine $\leq$ 1.5 ULN for age; if higher, an estimate GFR based on the Schwartz equation (Schwartz et al. 2017) or as per institutional guidelines must be $\geq$ 60mL/min/1.73 m^2
  – Bilirubin $\leq 1.5 \times$ ULN for age (or $\leq 2.5 \times$ ULN if liver infiltrated with leukemia or metastases)
  – AST and ALT $\leq 3 \times$ ULN for age (or $\leq 5 \times$ ULN if liver infiltrated with leukemia or metastases)

  Cardiac function

  – Fractional shortening (FS) $\geq$ 28% or left ventricular ejection fraction (LVEF) $\geq$ 50%, as determined by echocardiography or multigated acquisition scan (MUGA) within 28 days prior to initiation of study therapy

    Depending on institutional standard, either FS or LVEF is adequate for enrollment if only one value is measured; if both values are measured, then both values must meet the above criteria.

- For females of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, agreement to refrain from donating eggs, as defined below:

  Females must remain abstinent or use two methods of contraception with a failure rate of $<$ 1% per year during the treatment period and for 6 weeks after the final dose of idasanutlin, 30 days after the final dose of venetoclax, 12 months after final treatment for patients receiving cyclophosphamide/topotecan (or longer if required according to national prescribing information), 6 months after final treatment for patients receiving FLA (or longer if required according to national prescribing information), or in accordance with national prescribing information guidance regarding abstinence, contraception, and egg donation for any non-Investigational Medicinal Products listed in Section 4.3. Females must refrain from donating eggs during this same period.

  A female is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not

permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

A barrier method may be used as the second contraceptive method.

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. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For males: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, males must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of idasanutlin, 12 months after final treatment with cyclophosphamide/topotecan (or longer if required according to national prescribing information), 6 months after final treatment with fludarabine to avoid exposing the embryo (or longer if required according to national prescribing information), or in accordance with national prescribing information guidance regarding abstinence, contraception, and sperm donation for any non-Investigational Medicinal Products listed in Section 4.3. Males 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.1 Additional Inclusion Criteria for Patients with Solid Tumors (including Neuroblastoma)

- At least one evaluable or measurable radiological site of disease as defined by standard criteria for the patient's tumor type (e.g., INRC), or measurable bone marrow disease by morphology
- Adequate hematologic end-organ function, as specified in the following parameters:
  - Hemoglobin ≥ 8 g/dL (transfusion allowed)
  - Peripheral ANC $\geq 0.75 \times 10^9$/L (no G-CSF support for 72 hours)

  - Platelet count $\geq 75 \times 10^9$/L (unsupported for 72 hours)
- Tumor tissue from relapsed disease, obtained subsequent to last anti-cancer therapy regimen administered and obtained within 6 months prior to study enrollment, or willingness to undergo a core or excisional biopsy sample collection prior to enrollment
  - Patients must submit a tissue block or 15 slides containing unstained, freshly cut, serial sections available for submission.
  - Fine needle aspirations, brush biopsies, bone metastasis samples, and lavage samples are not acceptable.
  - Patients with < 15 slides available, or whose tumor tissue does not otherwise meet criteria above, may be eligible for study entry after Medical Monitor approval has been obtained. See Section 4.5.5.1 for detailed tissue requirements.
- Life expectancy ≥ 12 weeks, in the investigator's judgment

4.1.1.2 Additional Inclusion Criteria for Patients with Leukemia

- Bone marrow with $\geq 5\%$ lymphoblasts by morphologic assessment at screening
- Available bone marrow aspirate or biopsy from screening

4.1.2 Exclusion Criteria

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

- Primary CNS tumors
- Symptomatic CNS metastases that result in a neurologically unstable clinical state or require increasing doses of corticosteroids or local CNS-directed therapy to control the CNS disease
- CNS3 leukemia (total nucleated cell count $\geq 5/\mu$L with blasts on cytocentrifuge in an atraumatic lumbar puncture, or clinical signs of CNS leukemia including cranial nerve palsy)
- Acute promyelocytic leukemia
- White blood cell count $> 50 \times 10^9$/L
  - Prior cytoreduction with leukapheresis or hydroxyurea (HU) is allowed to meet this criterion. HU must be discontinued at least 24 hours prior to the initiation of study treatment.
  - Prior cytoreduction with leukapheresis or hydroxyurea is allowed in patients with a WBC count $\leq 50 \times 10^9$/L if the patient is symptomatic from hyperleukocytosis, or if consistent with institutional guidelines.
- Down syndrome, Li-Fraumeni syndrome, history of severe aplastic anemia, or any known bone marrow failure predisposition syndrome (including, but not limited to, Fanconi anemia or dyskeratosis congenita)
- Burkitt-type acute lymphoblastic leukemia (mature B-cell)

- T-cell lymphoblastic leukemia
- Prior treatment with an MDM2 antagonist
- Prior treatment with venetoclax (if potential for enrollment in a venetoclax arm)
- Infection considered by the investigator to be clinically uncontrolled or of unacceptable risk to the patient upon induction of neutropenia, including patients who are, or should be, on antimicrobial agents for the treatment of active infection such as the following:
  - Fungal infection, other than mucosal candidiasis, with <2 weeks of appropriate systemic antifungal therapy
  - 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
  - Neutropenic fever considered infection-related within 72 hours prior to dosing
  - History of symptomatic *Clostridium difficile* (*C. difficile*) infection that required treatment within 1 month prior to dosing

    Upon clinical response to *C. difficile* treatment, the stool consistency and frequency must have returned to normal.
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Females of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
- Active GI disease (e.g., gut graft-versus-host disease, Crohn's disease, ulcerative colitis) or GI conditions that may significantly alter drug absorption of oral drugs (e.g., uncontrolled vomiting, diarrhea, or malabsorption syndrome)
- Active viral hepatitis or human immunodeficiency virus (HIV) infection
- Presence of any CTCAE $\geq$ Grade 2 clinically significant treatment-related toxicity with the exception of alopecia, ototoxicity, peripheral neuropathy and parameters otherwise permitted in the inclusion criteria (e.g., hematological criteria)
- Clinically relevant QTc prolongation (QTcF >450 ms using the Fridericia correction)
- Any uncontrolled medical condition or other identified abnormality that precludes the patient's safe participation in and completion of the study, as judged by the investigator
- Systemic anticancer therapy within 28 days or 5 half-lives, whichever is shorter, prior to initiation of study treatment
  - Requirement may be waived at the investigator's request, with approval of the Medical Monitor, if the patient has recovered from therapeutic toxicity to the degree specified in the protocol.
  - Intrathecal chemotherapy per Section 4.3.2.1.1 prior to starting study therapy is permissible.

- Treatment with monoclonal antibodies, antibody drug conjugates, or cellular therapy (e.g., CAR-T cell infusion) for anti-neoplastic intent within 30 days prior to initiation of study treatment
- I-131 MIBG therapy within 6 weeks prior to initiation of study treatment
- Myeloablative therapy with autologous or allogeneic hematopoietic stem cell rescue within 100 days of study treatment initiation
- Immunosuppressive therapy for treatment of graft-versus-host disease within 2 weeks of study treatment initiation
- Radiotherapy (non-palliative) within 3 weeks prior to study treatment initiation
- Known hypersensitivity to any study drug or component of the formulation that could potentially be allocated according to tumor type
- Received the following within 7 days prior to initiation of study treatment (see Table 3):
  - Strong CYP2C8 inhibitors
  - CYP2C8 substrates
  - OATP1B1/3 substrates
- Received strong CYP2C8 and strong CYP3A4 inducers within 14 days prior to the initiation of study treatment (see Table 3)
- For patients assigned or randomized to venetoclax arms:
  - Strong or moderate CYP3A*4* inhibitors or moderate inducers or P-gp inhibitors within 7 days of study drug initiation (see Table 3 and Table 4)
  - Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days prior to the initiation of study treatment
  - Vaccination with a live vaccine ≤28 days prior to randomization
- Received anti-coagulant or anti-platelet agent within 7 days or 5 half-lives prior to study treatment initiation
- Underwent major surgical procedure within 21 days of study treatment initiation, or anticipate need for major surgical procedure during the course of the study

  Gastrostomy, tumor biopsy, and insertion of central venous access devices are not generally considered major surgery, but the Medical Monitor should be notified of these or other minor procedures prior to initiating therapy.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. Patients will be assigned to dose levels in the order in which they are enrolled in Study Parts 1*a* and *1b*. *For patients with neuroblastoma or AML enrolled in Part 1b, assignment to either the chemotherapy or venetoclax cohort will be at the investigator's discretion and in accordance to the availability of open slots for enrollment.*

In Study Part 2, for patients in the AML cohorts, after written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the interactive voice/web-based response system (IxRS). Patients will be randomized in a 1:1 ratio to either idasanutlin plus chemotherapy or idasanutlin plus venetoclax. The investigator, patient, and the contract research organization will not be blinded to treatment assignment.

The patients in the ALL cohort in Study Part*s 1b and* 2 will not be randomized and will be assigned to receive idasanutlin in combination with venetoclax.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are idasanutlin, venetoclax, cyclophosphamide, topotecan, fludarabine, and cytarabine.

The non-IMPs in the study include the prophylactic medications stated in Section 4.3.3 (anti-diarrheal agents, antibiotics, anti-fungal agents, uric acid reducing agents, anti-PCP therapy, *growth factors* and 5-HT3-receptor antagonists) and the intrathecal (IT) chemotherapy agents stated in Section 4.3.2.4 (IT cytarabine, methotrexate, and hydrocortisone).

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Idasanutlin

Idasanutlin will be supplied as 5-mg and 20-mg dispersible tablets. The dispersible tablets can either be swallowed or used to prepare a suspension (ad hoc) for patients not able to swallow tablets. Idasanutlin will be packaged in high-density polyethylene (PE) plastic bottles to accommodate the study design.

Idasanutlin is a weak acidic drug and high lipophilicity (logP5.6) without clinically significant food-effect (both low-fat and high-fat meals) on pharmacokinetics in comparison with fasting. Therefore, it is expected that suspensions prepared from the 5- and 20-mg dispersible film-coated tablets will not have significant bioavailability differences compared to the film-coated tablets utilized in the Phase III adult trial WO29519. This expectation will be *evaluated* with the PK and tolerability analysis during dose escalation from the current study.

For information on the formulation and handling of idasanutlin, see the pharmacy manual and the Idasanutlin Investigator's Brochure.

4.3.1.2 Venetoclax

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 10-mg, 50-mg, and 100-mg strength.

Venetoclax tablets will be packaged in high-density PE plastic bottles to accommodate the study design. Venetoclax tablets must be stored at 15°C–25°C (59°F–77°F). Venetoclax will also be provided as 2.5-mg, 10-mg, and 25-mg tablets for oral suspension for patients not able to swallow tablets.

The decision on which formulation to use for each individual patient is at investigator's discretion. One unique formulation should be used throughout the study conduct for each individual patient. Patients may be permitted to switch formulations during the course of therapy if there is sufficient medical justification or if a switch is warranted to ensure study treatment compliance. Any potential switch in formulation must be discussed with the Medical Monitor.

For information on the formulation and handling of venetoclax, see the pharmacy manual and the Venetoclax Investigator's Brochure.

4.3.1.3 Chemotherapy

For information on the formulation, packaging, and handling of cyclophosphamide, topotecan, fludarabine, and cytarabine, as well as intrathecally administered therapy, see the local prescribing information.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

At applicable sites, study treatment may be administered by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in mobile nursing (MN) visits.

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

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.5.1.

4.3.2.1 Idasanutlin

Idasanutlin will be administered as an oral medication once daily on Days 1–5 of a 28-day cycle. The starting daily dose of idasanutlin in the dose-escalation phase of the study will be 2 mg/kg/day and will be modified according to Section 5.1.5.1. All administered doses of idasanutlin will be recorded in a patient diary, whether or not the doses are administered at the investigational site. Idasanutlin should be administered at the same time daily. Idasanutlin should be administered immediately prior to any daily doses of combination chemotherapies or venetoclax.

Note that no clinically meaningful food effect was found with idasanutlin, which can be administered with or without a meal.

Idasanutlin must be administered orally. If the patient vomits within 15 minutes of taking idasanutlin, the drug may be re-administered. If the patient vomits more than 15 minutes after drug administration, no additional dose should be taken that day and the next dose should be taken at the usual time the next day.

Administration via nasogastric tube is allowed with specific restrictions as outlined in the Pharmacy Manual.

If a dose of idasanutlin is missed by less than 8 hours, the dose should be taken right away. The next dose should be taken at the usual time the next day. If a dose of idasanutlin is missed by more than 8 hours, the dose should not be taken that day. The next dose should be taken at the usual time the next day. The time of each drug administration will be recorded to the nearest minute in the patient's diary.

4.3.2.1.1 Dose Modifications after Clearance of Leukemia from Bone Marrow

Patients with leukemia who achieve morphologic CR/CRi/CRp after Cycles 1 or 2 who are able to continue therapy will receive idasanutlin at a 50% reduction in dose in subsequent cycles. This adjustment accounts for the observation in Study NP28679 that patients who continued on full doses of treatment following achievement of CR frequently required additional time for blood count recovery. The duration of idasanutlin treatment has no maximum predefined duration and will be at investigator discretion, provided other criteria necessitating study drug discontinuation are not met.

4.3.2.2 Venetoclax

Venetoclax (in combination with idasanutlin) will be administered at the adult dose equivalent (adjusted by body weight) of 400 mg in patients with neuroblastoma and the adult dose equivalent of 600 mg in patients with leukemia once daily on Days 1–28 of a 28-day cycle (see Appendix 14). The rationale for starting dose is provided in Section 3.3.1.2. Although the dose of venetoclax is not intended to be modified during the safety run-in phase of the study, the study team (in consultation with the IMC/SOC) may advise sites to use a lower dose of venetoclax.

For patients with *neuroblastoma*, venetoclax will ramp-up to the target dose over 2 days (200 mg equivalent Day 1 to 400 mg equivalent Day 2). Patients with neuroblastoma receiving venetoclax should be hospitalized during the ramp-up phase until the target dose has been administered. For patients with leukemia, venetoclax will ramp-up to the target dose over 3 days (150 mg equivalent Day 1; 300 mg equivalent Day 2; 600 mg equivalent Day 3 (Appendix 14). If lower doses of venetoclax are required, intermediate doses for the ramp up will be proportionally adapted based on the duration of ramp-up period (2 or 3 days), the final dose to be achieved, and the available formulation dose

strength. For guidance on dose reductions in case of co-administration with CYP3A4 or P-gp, refer to Section 4.4.3.

Patients should self-administer venetoclax at approximately the same time each morning. Oral venetoclax should be taken with water within 30 minutes after a meal. The tablets for oral suspension should be taken within 30 minutes after completion of any meal. Venetoclax administration should follow idasanutlin administration. On days in which predose PK sampling is required, dosing will occur in the morning at the clinic to facilitate PK sampling.

If the patient vomits within 15 minutes of taking venetoclax and all expelled tablets are still intact, the dose may be re-administered. If the patient vomits more than 15 minutes after taking venetoclax, no additional dose should be taken that day and the next dose should be taken at the usual time the next day.

If a dose of venetoclax is missed by less than 8 hours, the dose should be taken right away with food. The next dose should be taken at the usual time the next day. If a dose of venetoclax is missed by more than 8 hours, the dose should not be taken that day. The next dose should be taken at the usual time the next day. The time of each drug administration will be recorded to the nearest minute in the patient's diary.

The venetoclax dose may be reduced or interrupted to manage toxicities.

4.3.2.3 Chemotherapy

For patients assigned to arms combining idasanutlin with chemotherapy, chemotherapy should be administered at the doses prescribed below. Infusion duration, prophylactic medications, and monitoring guidelines should be managed in accordance with institutional standard unless specified in the protocol.

Neuroblastoma

Cyclophosphamide and topotecan will be administered once daily on Days 1–5 of each 28-day cycle at the following doses:

- Cyclophosphamide 250 mg/m^2 *(8.33 mg/kg for patients <12 kg)* as an intravenous (IV) infusion over 1 hour
- Topotecan 0.75 mg/m^2 *(0.025 mg/kg for patients <12 kg)* as an IV infusion over 1 hour

Acute Myeloid Leukemia

FLA (fludarabine and high-dose cytarabine) chemotherapy will be administered during each 28-day combination treatment cycle as per the following regimen:

- Fludarabine 30 mg/m^2 IV Days 1 to 5 over 30 minutes
- Cytarabine 2000 mg/m^2 IV Days 1 to 5 over 4 hours

Note: Cytarabine infusion is administered 4 hours after the start of the fludarabine infusion.

4.3.2.4 Intrathecal Chemotherapy in Patients with Leukemia

All patients with leukemia, irrespective of arm, will receive IT chemotherapy with each cycle (see Appendix 15 for appropriate age-based dosing). For patients on Cycle 3 or greater who are in CR/CRp/CRi, lumbar puncture and IT therapy may be deferred by the investigator.

Acute Myeloid Leukemia

The following CNS-directed IT chemotherapy will be used:

- CNS negative or unknown CNS status: cytarabine at age-adjusted doses by IT administration on Day 1. May be administered up to 1 week prior to Day 1 of each cycle.
- If blasts present in CSF at screening or traumatic lumbar puncture occurs: methotrexate, cytarabine, and hydrocortisone at age-adjusted doses by IT administration on Day 1 and then every 7 days until complete clearance of leukemic blasts. In subsequent cycles, patients should receive treatment as CNS-negative.

  Investigators may use this triple IT therapy in CNS-negative patients if consistent with institutional standard.

Acute Lymphoblastic Leukemia

The following CNS-directed IT therapy will be used:

- CNS-negative or unknown CNS status: IT administration of methotrexate (age-based dosing) on Day 1. May be administered up to 1 week prior to Day 1 of each cycle.
- If blasts present in CSF at screening or traumatic lumbar puncture occurs: methotrexate, cytarabine, and hydrocortisone at age-adjusted doses by IT administration on Day 1 and then every 7 days until complete clearance of leukemic blasts. In subsequent cycles, patients should receive treatment as CNS-negative.

  Investigators may use this triple IT therapy in CNS-negative patients if consistent with institutional standard.

4.3.3 Prophylactic Medication

The use of oral or IV prophylaxis to mitigate GI toxicity, infections, and TLS is mandatory in all patients if permitted according to a patient's age and standard institutional practice (see Section 4.4.1). *In addition, the use of prophylactic therapy with granulocyte colony stimulating factors to mitigate the risk of neutropenia is recommended in solid tumor patients receiving i*dasanutlin and chemotherapy according to standard institutional practice. Administration of a prophylactic medication must be recorded on the Concomitant Medication eCRF.

4.3.3.1 Gastrointestinal Toxicity

Prophylactic treatment to mitigate GI toxicity is mandatory during study treatment. Patients should be instructed on warning signs (e.g., bloody stools, associated fever, and dizziness).

Prophylactic anti-diarrheal therapy is to be instituted for all patients based on age and local institutional practice, unless waived by Medical Monitor. Loperamide (per local dosing standard) is recommended therapy in patients if permitted according to the regional label or if consistent with institutional standard. Use of pro-kinetic agents such as metoclopramide should be avoided.

Prophylactic antiemetic medication should be given 30–60 minutes before administration of study treatment. The patient should receive a 5-HT3-receptor antagonist (e.g., ondansetron, granisetron, or palonosetron) on Days 1–5 if permitted according to local institutional practice based on the patient's age.

4.3.3.2 Tumor Lysis Syndrome

Prior to first administration of study treatment, investigators should:

- Assess the risk for TLS based on a clinical assessment and comorbidities (e.g., presence of renal dysfunction or cardiac failure)

  Note: Risk factors for TLS risk are not unique to idasanutlin or venetoclax and are multifactorial (i.e., WBC count $\geq$ 25,000/mm^3, serum uric acid $>$ 7.5 mg/dL, and LDH $>$ 4 $\times$ ULN).
- Correct pre-existing 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.

For patients with leukemia, the following guidance should be followed for the first dose in Cycle 1:

- Per the exclusion criterion, WBC counts should be $\leq 50 \times 10^9$/L prior to starting therapy. HU or leukapheresis is allowed to meet this criterion. HU must be discontinued at least 24 hours prior to initiating study treatment.
- Hospitalization is required until completion of idasanutlin per Section 5.1.5.3.
- Uric acid reducing agent (such as allopurinol) is required, preferably starting 1 day before dosing of study therapy
- TLS chemistry (calcium, phosphorus, BUN (or urea), creatinine, potassium, uric acid) (Day 0 [pre-dose and 4, 8, and 24 hours postdose]).

  See Section 5.1.5.4 for additional information on TLS prophylaxis and monitoring plan.

4.3.3.3 Infections

Anti-PCP prophylaxis is required in all patients, according to local/institutional guidelines. Trimethoprim is NOT a permitted therapy.

Anti-fungal and anti-bacterial prophylaxis is required in neutropenic patients with leukemia unless waived by the Medical Monitor, and is recommended in neutropenic patients with solid tumors.

Ciprofloxacin or other appropriate antibiotic prophylaxis for neutropenic patients should be administered according to local/institutional guidelines from Day 1 until neutrophil recovery or until IV antibiotic treatment is administered (whichever occurs first).

Fungal prophylaxis for neutropenic patients should be administered per institutional standard and per guidance below 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. Fluconazole is permitted, but patients receiving venetoclax should receive 50% dose reduction of venetoclax, as fluconazole is a moderate CYP3A inhibitor. Echinocandins (e.g., caspofungin, micafungin) are permitted. Strong CYP3A inhibitors, including voriconazole and posaconazole are permitted as prophylaxis. However, patients receiving venetoclax require a 4-fold venetoclax dose reduction when receiving strong CYP3A4 inhibitors, such as voriconazole, and a 6-fold venetoclax dose reduction specifically for posaconazole. For further guidance on prohibited or allowed concomitant medications please refer to Section 4.4, Table 3, and Table 4.

Table 2 Prophylactic Medication

Timepoint	Patients Requiring *M*edication	*M*edication	Administration
Cycle 1, Day 1	• All patients	• Anti-diarrheal [a]	
	• All neutropenic patients with leukemia; recommended in neutropenic patients with solid tumors	• Anti-fungal [c]	From Day 1 until neutrophil recovery
	• All neutropenic patients with leukemia (unless waived by the Medical Monitor); recommended in neutropenic patients with solid tumors	• Ciprofloxacin or other appropriate antibiotic per local/institutional guidelines	From Day 1 until neutrophil recovery or until IV antibiotic treatment is administered (whichever occurs first)
	• Patients with leukemia	• Uric acid reducing agent (such as allopurinol), along with IV hydration • Required for patients with leukemia; recommended for other patients at risk for TLS	Should be initiated 1 day before administration of study drug
	• All patients	• Anti-PCP therapy per institutional guidelines [d]	Continuous while on study therapy.
All cycles, Days 1–5	• All patients	• 5-HT3-receptor antagonist [b]	Administer at least 30–60 minutes prior to study drug administration
All cycles, Day 6+	• *Solid tumor patients receiving idasanutlin and chemotherapy*	• *G-CSF per institutional guidelines*	

Table 2 Prophylactic Medication (cont.)

IRR = infusion-related reaction; TLS = tumor lysis syndrome.

[a] Treat with prophylactic anti-diarrheal based on patient age and local institutional practice, unless waived by Medical Monitor. Loperamide (per local dosing standard) is recommended therapy in patients if permitted according to the regional label or if consistent with institutional standard.

[b] For example, ondansetron, granisetron, or palonosetron. Administer 5-HT3-receptor antagonist if permitted according to local institutional practice based on the patient's age.

[c] Fluconazole is permitted, but patients receiving venetoclax should receive 50% dose reduction of venetoclax, as fluconazole is a moderate CYP3A inhibitor. Echinocandins (e.g., caspofungin, micafungin) are permitted. Strong CYP3A inhibitors, including voriconazole and posaconazole, are permitted as prophylaxis. However, patients receiving venetoclax require a 4-fold venetoclax dose reduction when receiving strong CYP3A4 inhibitors, such as voriconazole, and a 6-fold venetoclax dose reduction specifically for posaconazole. For further guidance on prohibited or allowed concomitant medications, please refer to Section 4.4, Table 3, and Table 4.

[d] Trimethoprim is prohibited therapy on this study.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (idasanutlin, venetoclax, cyclophosphamide, topotecan, fludarabine, and cytarabine) will be provided by the Sponsor where required by local regulations. *The study site (i.e., investigator or other authorized personnel [e.g., mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.*

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. *The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

Refer to the pharmacy manual and/or the idasanutlin and venetoclax Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Idasanutlin and Venetoclax

Currently, the Sponsor does not have any plans to provide Roche IMPs (idasanutlin and venetoclax) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing idasanutlin and venetoclax 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, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to 30 days after final dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- Palliative radiotherapy for uncontrollable pain or imminent threat to a vital organ, with approval by the Medical Monitor.

  The decision to continue or suspend study therapy temporarily will be made by the Medical Monitor. Patients who undergo palliative radiation will not be evaluable for response by tumor assessments but will be assessed for progressive disease.
- Intrathecal steroids and/or chemotherapy in patients with leukemia as specified by the protocol
- Premedication administered as described in Section 4.3.3

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Associated with QT Prolongation

The previous or concurrent use of medications known to be associated with QT prolongation is permitted in the study but should be used with caution.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) within 7 days or 5 half-lives prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal

therapy) for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details)

- 5-Fluorocytosine should not be co-administered with cytarabine, as the therapeutic efficacy of 5-Fluorocytosine has been shown to be abolished during co-administration with this therapy
- Traditional herbal or homeopathic medicines

  Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug–drug interactions that may cause or confound assessment of toxicity.
- Vaccination with live-attenuated vaccines
- Oral or parenteral use of the following drugs during the treatment phase (see Table 3):
  - Strong/moderate inducers or inhibitors of CYP2C8, including gemfibrozil, which is also an inhibitor of UGT1A3
  - CYP2C8 or OATP1B1/3 substrates
  - CYP3A strong inducers
- Patients receiving venetoclax will be prohibited from the following agents during the treatment phase (see Table 3)
  - Strong inducers of CYP3A
  - Moderate inducers of CYP3A
- For patients receiving venetoclax, moderate or strong CYP3A inhibitors or P-gp inhibitors (see Table 3 and Table 4) are prohibited unless concurrent use is considered necessary to treat or prevent a serious medical condition and the following dose reduction instructions are followed:
  - For concurrent use of moderate CYP3A inhibitors, reduce the cohort-designated dose of venetoclax by 50%. No dose adjustment is needed for idasanutlin. After discontinuation of the moderate CYP3A inhibitors, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.
  - For concurrent use of strong CYP3A inhibitors, reduce the cohort-designated dose of venetoclax by 4-fold. No dose adjustment is needed for idasanutlin.

    For concurrent use of posaconazole, reduce the cohort-designated dose of venetoclax by 6-fold. No dose adjustment is needed for idasanutlin.

    After discontinuation of CYP3A inhibitors, including posaconazole, wait 3 days before increasing venetoclax dose back to the initial maintenance/target dose.

  - For patients who require treatment with P-gp inhibitors following venetoclax dose ramp-up, use the medications with caution and reduce the venetoclax dose by at least 50%.

- For patients receiving venetoclax, P-gp substrates are prohibited unless concurrent use of P-gp substrates is considered necessary to treat or prevent a serious medical condition.

  - For concurrent use of P-gp substrates, the P-gp substrate should be administered at least 6 hours before venetoclax administration.

Substrates and $strong\ CYP2C8$ inhibitors listed in Table 3 and Table 4 (except for P-gp substrates) must be discontinued 7 days prior to start of study treatment, while the listed $strong$ inducers must be discontinued 14 days prior to start of study treatment. All drugs listed in Table 3 and Table 4 may be re-initiated per protocol after the study drug completion/discontinuation visit.

Table 3 List of CYP2C8, CYP3A4, or OATP1B1/3 Inhibitors, Inducers, or Substrates

CYP2C8 Inducer	CYP2C8 Inhibitors	CYP2C8 Substrates	OATP1B1/3 Substrates	Strong CYP3A4 Inducers	Moderate CYP3A4 Inducers	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
Rifampicin	Clopidogrel	Amodiaquine	Atorvastatin	Avisimbe	Bosentan	Boceprevir	Amprenavir
	Deferasirox	Montelukast	Atrasentan	Carbamazepine	Efavirenz	Clarithromycin	Aprepitant
	Gemfibrozil	Paclitaxel	Bosentan	Cyproterone	Etravirine	Cobicistat	Atazanavir
	Quercetin	Pioglitazone	Ezetimibe	Efavirenz	Modafinil	Danoprevir/ritonavir	Cimetidine
	Teriflunomide	Repaglinide	Fluvastatin	Enzalutamide	Nafcillin	Conivaptan	Ciprofloxacin
	Telithromycin	Rosiglitazone	Glyburide	Etravirine		Diltiazem	Clotrimazole
	Trimethoprim[a]	Torasemide	Irinotecan	Hyperforin		Elvitegravir/ritonavir	Crizotinib
			Olmesartan	Mitotane		Idelalisib	Cyclosporin
			Pitavastatin	Modafinil		Indinavir	Darunavir/ritonavir
			Pravastatin	Nevirapine		Itraconzole	Dronedarone
			Repaglinide	Oxcarbazepine		Ketoconazole	Erythromycin
			Rifampicin	Phenobarbital		Mibefradil	Fluconazole
			Rosuvastatin	Phenytoin		Lopinavir/ritonavir	Fluvoxamine
			Simvastatin Acid	Rifampicin		Nefazodone	Fosamprenavir
			Telmisartan	St. John’s wort		Nelfinavir	Imatinib
			Valsartan			Ritonavir	Isavuconazole
						Paritaprevir/ritonavir	Tofisopam
						Posaconazole	Verapamil
						Saquinavir	
						Telaprevir	

Table 3 List of CYP2C8, CYP3A4, or OATP1B1/3 Inhibitors, Inducers, or Substrates (cont.)

CYP2C8 Inducer	CYP2C8 Inhibitors	CYP2C8 Substrates	OATP1B1/3 Substrates	Strong CYP3A4 Inducers	Moderate CYP3A4 Inducers	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
						Telithromycin	
						Troleandomycin	
						Voriconazole	

Note: The current list may not be exhaustive. If the concomitant medication is not included in the list, please contact the Medical Monitor for guidance.

[a] *Trimethoprim is a weak CYP2C8 inhibitor; however, use is not permitted while on study treatment.*

Table 4 List of P-gp Inhibitors or Substrates

P-gp	
Substrates	**Inhibitors** [a]
aliskiren	amiodarone
ambrisentan	azithromycin
colchicine	captopril
dabigatran etexilate	carvedilol
digoxin	felodipine
everolimus	propafenone
fexofenadine	quercetin
lapatinib	quinidine
loperamide	ranolazine
maraviroc	ticagrelor
nilotinib	
ranolazine	
saxagliptin	
sirolimus	
sitagliptin	
talinolol	
tolvaptan	
topotecan	

[a] P-gp inhibitors are allowed if the patient has completed the venetoclax dose ramp-up period. The appropriate dose reduction for venetoclax must be implemented. See Section 4.4.3 for details.

4.4.4 Prohibited Food

For patients receiving venetoclax, use of the following foods is prohibited as described below:

- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit (potent CYP3A4 enzyme inhibitor) during the study and for 30 days after the final dose of study treatment.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1, Appendix 2, and Appendix 3) will specify the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent, and assent when applicable, for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms and Child's Informed Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Re-screening following screening failure is allowed.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies, current cancer stage, and procedures), menstrual history, fertility history, and puberty history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient in addition to protocol-mandated treatment within 7 days prior to initiation of study treatment until 30 days after the final dose of study drug will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by local regulations).

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. 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.

The Lansky Performance Status should be performed for patients who are <16 years old, and the Karnofsky Performance Status should be performed for patients who are ≥ 16 years old.

4.5.4 Growth and Development Assessments

During the treatment period, weight will be measured at the beginning of each cycle. During the follow-up period, weight should be measured every 3 months.

During the treatment period, height, head circumference (until the age of 3 years), and Tanner stage should be measured every 3 cycles (approximately every 3 months). During the follow-up period, height, head circumference, and Tanner stage should be measured every 3 months. Tanner staging should be performed until the patient has reached Tanner Stage V or the end of the study.

4.5.5 Tumor and Response Evaluations

4.5.5.1 Tumor Assessments

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Baseline tumor assessments should be performed within

28 days prior to initiation of study drug (Day 1 of Cycle 1); subsequent tumor assessments should be performed in accordance with the Schedule of Assessments. At the investigator's discretion, unscheduled tumor assessments may be performed at any time if progressive disease is suspected.

Response will be assessed by the investigator on the basis of physical examinations, bone marrow biopsy and/or aspirate, CT scans, MRI scans, FDG-PET scans, or MIBG scans, as appropriate. Tumor assessment imaging should include all areas of known disease. For solid tumors including neuroblastoma, an objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation. The same imaging techniques and procedures used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

Patients with neuroblastoma must have an MIBG scan and BMAs and BMBs done at least at two sites each for disease evaluation. If the enrollment BMA and BMB tissue samples are negative for disease, subsequent BMA and BMB tissue samples are not needed. Patients with evidence of bone marrow disease at screening require bone marrow evaluation with scheduled disease evaluations until they have had two consecutive evaluations that are negative for disease.

Patients with other solid tumors who have a clinical suspicion of bone marrow involvement should also have bilateral BMAs and/or BMBs performed at screening. Patients who have documented bone marrow involvement at screening should have subsequent bone marrow evaluations performed with each response assessment until the first negative bone marrow evaluation.

Patients with leukemia are required to undergo bone marrow evaluation via aspiration (and biopsy if clinically indicated) prior to starting therapy and after Cycles 1 and 2 of therapy. Patients are required to undergo lumbar puncture at the same timepoints as bone marrow evaluations. Subsequent bone marrow evaluations and lumbar punctures should be conducted based on the clinical judgment of the investigator and at any time that recurrent or progressive disease is suspected based on laboratory or clinical findings. At baseline/screening, a BMB and BMA are required of patients. For postbaseline collections, if BMA cannot be obtained or is not evaluable (e.g., dry tap or no spicules are obtained), then a BMB is required.

4.5.5.1.1 Timing of Leukemia Bone Marrow Aspirates and Hematology Assessments

Patients with leukemia will have a BMA on Day 28 (± 3 days) of Cycles 1 and 2 if blood counts have recovered sufficiently (ANC $\geq 0.5 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L) to resume therapy. Patients will also have a BMA at this time if peripheral blasts are present, irrespective of count recovery.

For patients who do not have count recovery by Day 28, peripheral blood counts should be collected weekly until ANC $\geq 0.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L, up to Day 56. A BMA should be performed once patient's counts have recovered, once peripheral blood blasts are present, or by Day 42, whichever occurs first. Patients who do not have blood count recovery by Day 42 should undergo repeat BMA prior to Day 56.

This guidance is applicable to Cycles 3 and greater, except that the investigator may reduce the frequency of bone marrow evaluations if considered in the patient's best interest.

4.5.5.2 Response Criteria

All tumors will be evaluated for disease response and progressive disease according to the following criteria:

- Neuroblastoma: INRC
- Other solid tumors: RECIST v1.1
- Leukemia (morphologic response): per standard criteria outlined in Appendix 7 and Appendix 8
- Leukemia (MRD-negative response): per flow cytometry results, defined as the percentage of patients who achieve MRD levels $< 0.01\%$ by the end of two cycles

Patients who enroll with evaluable but not measurable disease will have a modified response assessment. For such patients, PR cannot be determined; therefore, response will be limited to CR, SD, or progressive disease.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Assessments that require blood draws should be monitored closely to ensure that regional or institutional guidance regarding total blood volume taken for samples is maintained. In situations where no regional or institutional guidance is available, no more than 1% of the total blood volume should be taken at one time and no more than 3% of the total blood volume should be taken over a 30-day period (total blood volume is defined as 80 mL/kg). Institutions should use micro-sampling systems to minimize the amount of blood drawn when able. In situations where the total amount will exceed the amount stated above, clinical laboratory assessments should be prioritized. Any remaining blood should be sent for PK analysis followed by biomarker and PD analyses.

Laboratory tests results must meet the inclusion criteria and not meet the exclusion criteria at the time of screening. If laboratory tests are performed again prior to the first dose, they must continue to meet the inclusion criteria and not meet the exclusion criteria.

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, blasts, and other cells)
- Serum chemistry: bicarbonate (or total carbon dioxide), sodium, potassium, chloride, glucose, BUN or urea, creatinine, albumin, magnesium, phosphate, calcium, total bilirubin [if abnormal, fractionate sample for direct and indirect], alkaline phosphatase, ALT, AST, uric acid, and LDH
- Creatinine clearance as clinically indicated

  If radioisotope glomerular filtration rate is routinely performed at the institution to measure patients' creatinine clearance, this test can be used to assess renal function at screening, per the eligibility criteria. Otherwise, serum creatinine is sufficient to document renal function at screening.

- Coagulation: INR, aPTT, and PT
- Pregnancy test

  All females of childbearing potential will undergo a serum pregnancy test at screening (prior to Cycle 1) within 1 week prior to first dose. Urine or serum pregnancy test will be performed prior to all subsequent cycles.

- Viral serology: HIV, hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, and hepatitis C antibody

  If a patient is positive for hepatitis B core antibody at screening, a test for hepatitis B virus DNA should be performed prior to Day 1 of Cycle 1.

  If a patient is positive for hepatitis C antibody at screening, a test for hepatitis C virus RNA should be performed prior to Day 1 of Cycle 1.

The following assessments will be conducted for patients with solid tumors or leukemia requiring bone marrow evaluation:

- BMA: total cells counted, absolute mature neutrophils, mature eosinophils, mature basophils, monocytes, lymphocytes, blasts, promyelocytes, myelocytes, metamyelocytes, plasma cells, pronormoblasts, normoblasts, nucleated erythrocytes
- BMB: leukemia histology, cellularity, percent cellularity, percent blasts, and fibrosis (if applicable)
- For patients with leukemia:
  - Conventional cytogenetics and molecular markers from bone marrow at the time of diagnosis and from most recent bone marrow assessment prior to the start of study
  - If sites perform MRD assessments locally or collect mutational data (any timepoint), sites are requested to please provide the results in the eCRF.

The following samples will be sent to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis
- BMA, BMB, blood, plasma, and serum for biomarker analyses

  If a BMA is not evaluable, a BMB should be sent.

- For patients with solid tumors, including neuroblastoma, tumor tissue from relapsed/refractory disease or from a newly collected tumor sample at baseline/screening for patients in the neuroblastoma cohorts for exploratory research on biomarkers. Tumor tissue must have been collected from patients no earlier than 6 months prior to study treatment initiation and subsequent to the most recent anti-cancer therapy.

  A representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10−14 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 20% tumor cell content that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspirations (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusions, lavages, and samples from bones metastases are not acceptable.

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Exploratory biomarker research may include, but will not be limited to, analysis of somatic mutations and gene signatures associated with disease type (i.e., MLL-1 rearrangement in leukemia), apoptosis, MDM2, and p53 signaling, as well as evaluation of candidate biomarkers of response to idasanutlin (i.e., MIC-1) and/or venetoclax (Bcl-2). Research may involve extraction of DNA, circulating tumor DNA, or RNA, analysis of mutations, and genomic profiling through use of comprehensive NGS. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research

purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

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

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

- Plasma samples collected for PK analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma, serum, and whole blood samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue will be returned to the site no later than 6 weeks after eligibility determination.
- Bone marrow aspirates and biopsies collected for MRD analysis and biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.

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

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

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

4.5.7 Clinical Outcomes Assessment—Acceptability Survey

To better understand the acceptability of idasanutlin, a survey will be administered immediately following administration of idasanutlin on Day 5 of Cycle 1. Patients will be advised to rinse their mouths prior to taking the medication; after taking the medication, patients should complete the survey before rinsing or drinking water.

For patients who have not yet developed the cognitive ability to provide detailed feedback on the acceptability of a medication, the parent or guardian will complete the Acceptability Survey based on their observation of their child's reaction and facial expression following the medication intake. Patients able to provide feedback will complete the survey with reading support from their parents or the clinical staff as needed. Study staff and patient's caregiver possibly present during the assessment should remain neutral. If a patient is having difficulty with selecting a score, patients may be asked the interview question first and then redirected to complete the assessment score. Parents or caregivers will be asked about their ease of experience of administering the suspension at home.

The survey will document specific aspects of the acceptability of idasanutlin, including swallowability and palatability (Kozarewicz 2014). The survey is required regardless of tablet size or whether the tablets are administered whole or dispersed in water.

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3), and may be obtained at unscheduled timepoints as indicated.

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 are recommended to be performed prior to other procedures scheduled at that same time (e.g., blood draws) and after the patient has been resting in a supine position for at least 10 minutes. 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.

The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF 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 Medical Monitor should be notified. 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. A decision on study drug discontinuation should be made, as described in Section 5.1.5.1. 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).

In case a patient presents with an episode of Grade ≥2 supraventricular arrhythmia (atrial fibrillation, atrial flutter, sinus tachycardia, etc.), an unscheduled ECG should be recorded and study treatment should be withheld.

4.5.9 Cardiac Function

Cardiac echocardiograms or MUGA will be performed during screening to assess baseline cardiac function. Studies should be performed in accordance with institutional guidelines. While on study therapy, routine cardiac function monitoring will not be conducted except at the discretion of the investigator. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo a cardiac function assessment.

FS or LVEF should be determined within 28 days prior to initiation of study drug by either echocardiography or MUGA scan.

4.5.10 Optional Tumor Tissue Samples

For patients enrolled to solid-tumor cohorts, if deemed clinically safe and feasible, tumor tissue samples obtained postbaseline (e.g., on-treatment or at the time of progression) may be collected and submitted to the Sponsor or a designee for exploratory biomarker research.

- Tissue amounts and requirements for postbaseline biopsies are the same as for mandatory baseline/screening biopsies above.
- Biopsies collected at the time of progression should be performed within 28 days (1 cycle) after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.6 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

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

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

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

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.11.3 Sample Collection

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

- Mandatory and optional leftover blood, serum, plasma, BMA, BMB, frozen tumor tissue and FFPE tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites upon request) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

4.5.11.4 Confidentiality

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

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

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

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

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

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

4.5.11.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

- Use of an anti-cancer therapy not permitted or required per protocol
- Symptomatic deterioration attributed to disease progression, except in patients treated with single-agent idasanutlin who proceed to combination therapy per Section 3.1.1.1
- Confirmed disease progression per investigator assessment according to *response criteria*
- Any adverse event that meets permanent discontinuation instructions as described in Table 5

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment may be replaced at the discretion of the Medical Monitor.

Patients will return for a treatment discontinuation visit 28 (±30) days after the final dose of study drug (see Appendix 1, Appendix 2, and Appendix 3). This may be done at the clinical visit where clinical or radiographic progression is first noted.

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for patient discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study may be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study or any arm thereof 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 or any arm thereof.

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Idasanutlin and venetoclax are not approved for pediatric use, and clinical development is ongoing in adults for different indications, including both hematologic and solid malignancies. The safety plan for patients in this study is based on nonclinical data and clinical experience with idasanutlin and venetoclax in completed and ongoing adult studies. The anticipated important safety risks for idasanutlin and venetoclax are outlined below. Please refer to the respective Investigator's Brochures for a complete summary of safety information for both molecules.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1.2). In addition, patients will undergo safety monitoring throughout the study (see Appendix 1, Appendix 2, and Appendix 3).

As detailed in Section 3.1, during the dose-escalation, safety run-in, and initial expansion cohort (Part 2), patients will be assessed for DLTs, and study treatment will be interrupted and subsequently modified following the occurrence of a DLT. Section 5.1.5.3 also outlines mandatory hospitalization periods.

An IMC and SOC will monitor patient safety throughout the study. The IMC will also provide a recommendation on the dose to be taken forward into the expansion stage after completion of the dose-escalation stage.

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, and laboratory measurements (hematology, chemistry).

Finally, guidelines for managing selected adverse events, including criteria for dosage modification and treatment interruption or discontinuation, have been provided (see Section 5.1.5). These guidelines apply to patients in the dose-escalation and expansion stages; however, the guidelines are not intended to replace clinical judgment or dictate care of individual patients.

5.1.1 Risks Associated with Idasanutlin

Information related to idasanutlin-associated risks is based mainly on review of data from Phase I experience in patients with solid-tumor cancer and AML (Studies NP27872, NP28902, and NP28679, respectively) as described in Section 1.4.1 and in the Idasanutlin Investigator's Brochure.

Risks include GI toxicity, cytopenias, TLS, infectious complications, and electrolyte abnormalities. Many of the toxicities experienced appear to be manageable with supportive therapies and/or reversible with discontinuation of idasanutlin. Refer to the current Idasanutlin Investigator's Brochure for details on the safety data from these 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 with AML in 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 Table 5.

Diarrhea is also a common adverse event with venetoclax and the proposed chemotherapy regimens; therefore, it may occur more frequently or may take longer to recover with combination therapy.

Before beginning study treatment, individual patients' normal bowel function should be established and patients should be instructed on warning signs of GI toxicity (e.g., bloody stools, associated fever, and dizziness).

5.1.1.2 Cytopenias

Bone marrow toxicity may manifest as cytopenias (i.e., pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, and anemia). Combined effects of idasanutlin and venetoclax or chemotherapy on normal bone marrow progenitors are possible. Study NP27872 evaluating idasanutlin in patients with solid tumors has shown possible exposure-dependent neutropenia and thrombocytopenia. These can be reversible and monitorable. In patients with leukemia who are neutropenic and thrombocytopenic as part of their disease process at baseline, elimination of leukemic blasts is essential for normal marrow recovery. Idasanutlin was associated with myelosuppression in AML Study NP28679, but normal marrow recovery was observed in patients showing a clinical response. In patients with leukemia, drug-induced myelosuppression is expected during idasanutlin treatment, and idasanutlin administered in combination with venetoclax 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. In this study, blood counts will be monitored closely throughout study treatment (see Appendix 1, Appendix 2, and Appendix 3).

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. To date across all idasanutlin studies, the overall incidence of TLS is 1.7%, with all cases occurring in the AML setting. The large majority of cases were Grade 3 or above (although by definition, TLS should be at least a Grade 3 event). TLS is also an important identified risk for venetoclax, although this has primarily been observed in CLL and mantle cell lymphoma (see Section 5.1.2.1).

5.1.1.4 Infections

Infections of various types (including fatal fungal infections) have occurred in patients treated with idasanutlin, most commonly in the AML setting (Studies NP28679 and WO29519). AML itself is associated with impaired immune function and higher susceptibility to infections. Assessment of causality for these cases can be difficult, and it is unclear whether or how much the incidence could be increased due to idasanutlin treatment. Infectious diarrhea, 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. There were 13 deaths associated with infectious processes in Phase I patients with relapsed or refractory AML treated with idasanutlin (either monotherapy or combination therapy). The deaths were attributed to the following causes: sepsis (5 patients), pneumonia (3 patients), neutropenic sepsis (2 patients), and *C. difficile* infection, neutropenic colitis, and scedosporium infection (1 patient each). Infections are also a risk with venetoclax and the proposed

chemotherapy treatments; therefore, patients may be at greater risk of developing infections when treated with idasanutlin in combination with venetoclax or chemotherapy compared to each treatment alone.

For additional information on risks of infection, refer to the current Idasanutlin Investigator's Brochure.

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 Testicular Toxicity

In studies in juvenile animals (rats), there were adverse effects on the male reproductive organs, including unpalpable testes and lower testicular weight, at doses of idasanutlin $>$10/50 mg/kg/day (doses of the two treatment cycles of 10 days each; from Days 7–16 post partum and from Days 35–44 post partum, with 18 days off treatment in between). Seminiferous tubular degeneration/atrophy was seen at 30/200 mg/kg/day at the end of the treatment period, and at $>$10/50 mg/kg/day at the end of the recovery period (only considered adverse at $>$15/100 mg/kg/day). Males given 30/200 mg/kg/day showed delayed sexual development, reduced fertility after mating, and decreased sperm counts and motility. The findings in testes did not reverse after the 13-week recovery period and are considered an on-target effect on dividing Sertoli cells that express high levels of MDM2 in the developing testis.

Due to the risk of testicular toxicity, male patients considering preservation of fertility should bank sperm before treatment with idasanutlin and should agree to refrain from donating sperm during the treatment period and for at least 90 days after the last dose of idasanutlin.

5.1.1.7 Other Adverse Events

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

5.1.2 Risks Associated with Venetoclax

Information related to venetoclax-associated risks is based mainly on review of data from Phase I–III studies (see the Venetoclax Investigator's Brochure) in CLL and Phase I–II data in AML (Studies M14-212, M14-358, GH29914, and M14-387). Venetoclax is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible. Risks include tumor lysis syndrome, infectious complications,

cytopenias, effects on fertility, treatment-emergent malignancies (second primary malignancies), and food effect.

There is currently limited data on the use of venetoclax in pediatric patients. Study M13-833 is an ongoing study investigating the use of venetoclax in pediatric and young adult patients with relapsed or refractory malignancies. No new safety signals have been identified from review of the available data. The most commonly reported events included febrile neutropenia, vomiting, and diarrhea.

Refer to the current Venetoclax Investigator's Brochure for details on the safety data from these studies and for additional information on venetoclax warnings and precautions.

5.1.2.1 Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk for venetoclax in oncology studies, especially in CLL and mantle cell lymphoma. The available data suggest that in indications other than CLL or mantle cell lymphoma, the risk of TLS is low but present.

To date, the principal adverse reaction associated with venetoclax in the single-agent Phase I dose-escalation Study M12-175 of CLL has been tumor lysis syndrome (primarily, but not exclusively related to, the first dose). These include cases of tumor lysis syndrome that have led to clinical sequelae including death in 2 patients. Among the non-chronic lymphocytic leukemia studies, 6 patients with NHL experienced Grade 3–4 adverse events of laboratory tumor lysis syndrome. Although several events of hyperphosphatemia and two events of rising potassium have been observed in relapsed or refractory AML study (Study M14-212), no patients experienced tumor lysis syndrome during administration of venetoclax. Safety data from 94 patients treated on three venetoclax studies in AML (M14-212, M14-358, M14-387) demonstrated no events of clinical tumor lysis syndrome. Five events of laboratory TLS have been reported across all studies of AML, including two events (one in Study M14-212, one in Study M14-387) that occurred after the patients had discontinued venetoclax and started another line of therapy. The remaining three events were protocol-defined laboratory TLS that occurred among the 92 patients in Study M14-387 during treatment with venetoclax in combination with low dose cytarabine. All three cases of laboratory TLS were transient and managed with standard-of-care measures. No events of TLS were reported in combination Study M14-358 (venetoclax plus hypomethylating agents).

Because of the known background risk of tumor lysis syndrome in this study population, patients in the study are being actively monitored and managed to prevent potential tumor lysis syndrome, and dose ramp-up is implemented (see Section 5.1.5.4 for tumor lysis syndrome prophylaxis and monitoring plan).

5.1.2.2 Neutropenia

Neutropenia is an important identified risk for venetoclax, specifically in chronic lymphocytic leukemia. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among patients who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. For the oncology studies, neutropenia management guidelines are provided in the protocol. Granulocyte colony stimulating factors can be used for supportive measures; however, the guidance for their use in non-chronic lymphocytic leukemia indications, especially in AML, is per routine local oncology practice, as well as protocol-specific.

5.1.2.3 Infections

Serious infections are an important identified risk for venetoclax. Most common infections reported with venetoclax include pneumonia, sepsis, upper respiratory tract infections, and urinary tract infections. Fatalities resulting from pneumonia and sepsis have been reported in patients receiving venetoclax. Infections of various types have occurred in patients with AML in the completed M14-212 study and in ongoing studies M14-358 and M14-387. AML itself is associated with impaired immune function and increased infections, and it is unclear whether or how much the incidence could be increased owing to venetoclax treatment.

See Section 5.1.5.4 and Table 5 for management of infections.

5.1.2.4 Cytopenias

Anemia has been reported with slightly higher frequency in some oncology studies in which venetoclax is combined with other chemotherapeutic agents; however, most of the events were non-serious and confounded by disease factors and prior therapies. The dataset in non-chronic lymphocytic leukemia indications is small.

Thrombocytopenia adverse events have been reported in oncology studies, with slightly higher frequency in studies in which venetoclax is combined with other chemotherapeutic agents. However, most of the events were non-serious and assessment of these events is confounded by the patients' underlying disease state, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several patients. The dataset in non-chronic lymphocytic leukemia indications is small.

Lymphopenia has been observed in nonclinical studies. Although opportunistic infections have been reported in the clinical program, data are confounded by patients' underlying disease and prior therapies. In oncology studies, anti-infective prophylaxis should be implemented as clinically indicated, including appropriate prophylaxis for viral, fungal, bacterial, or pneumocystis carinii pneumonia infections.

See Section 5.1.5.4 and Table 5 for management of cytopenias.

5.1.2.5 Effects on Fertility and Reproductive Toxicity

There were no effects of venetoclax on female or male mouse fertility; however, a risk to human male fertility exists based on the testicular toxicity (germ cell depletion) observed at all dose levels in the repeat-dose dog studies. Reversibility of this finding has not been demonstrated. It is not known whether the dog testicular findings translate to humans. Male patients should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the respective periods of organogenesis. In pregnant mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (approximately 1.2 times the human AUC exposure at the 400-mg human dose). No fetal toxicity was observed in rabbits up to the highest dose tested (approximately 0.2 times the human AUC exposure at the-400 mg human dose).

Due to the risk of decreased spermatogenesis, male patients considering preservation of fertility should bank sperm before treatment with venetoclax and should agree to refrain from donating sperm during the treatment period and for at least 90 days after the last dose of venetoclax.

5.1.2.6 Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies have been reported across the venetoclax oncology program. No pattern has been observed. Because venetoclax is being evaluated in patients with relapsed or refractory disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored. Second primary malignancy is an important potential risk for venetoclax.

5.1.2.7 Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions. Oral venetoclax should be taken with water within 30 minutes of completion of a meal. The tablets for oral suspension should be taken within 30 minutes after completion of any meal.

5.1.3 Risks Associated with Chemotherapy

5.1.3.1 Risks with Cyclophosphamide and Topotecan

The most common risks with cyclophosphamide treatment include infections, myelosuppression (including anemia, [febrile] neutropenia, leukopenia, and thrombocytopenia), immunosuppression, and urinary/renal toxicity. Cyclophosphamide may also have effects on fertility in both males and females, and men should be informed about sperm preservation prior to starting treatment.

The most common risks with topotecan treatment include infections, myelosuppression (including anemia, [febrile] neutropenia, leukopenia, and thrombocytopenia), and GI effects (including diarrhea, vomiting, and nausea). *Use of granulocyte colony stimulating factors is recommended for patients who are receiving the combination of idasanutlin and cyclophosphamide/topotecan per routine local practice.*

In neuroblastoma, the combination of cyclophosphamide and topotecan has been shown to be tolerable in children with no unexpected significant toxicities. The most common toxicities were infections, neutropenia, and thrombocytopenia (London et al. 2010).

5.1.3.2 Risks with Fludarabine and Cytarabine

The most common risks with fludarabine treatment include myelosuppression (including neutropenia, anemia, and thrombocytopenia), infections, and GI effects (including diarrhea, vomiting, and nausea). Fludarabine also has the potential to cause fetal harm.

The most common risks with cytarabine treatment include infections, myelosuppression (including anemia, leukopenia, and thrombocytopenia), GI effects (including diarrhea, vomiting, and nausea) and abnormal hepatic function.

In pediatric patients with AML, the combination of fludarabine and cytarabine has been shown to be tolerable with the most common toxicities being hematologic (including thrombocytopenia, neutropenia, and anemia), infections, fever, and nausea (Kaspers et al. 2013).

5.1.4 Risk of Overlapping Toxicities

The likely potential overlapping toxicities for the combination idasanutlin and venetoclax are primarily hematologic, including partial to complete decrease in lymphocyte counts and/or total WBC depletion and decreased red cell mass. Rapid, marked depletion of WBCs (total lymphocytes for venetoclax) could lead to increased cases of tumor lysis syndrome and infection, and recovery of normal WBC counts may require a prolonged period without treatment. In addition, idasanutlin reduced WBC counts, most severely reducing neutrophils. The combination of venetoclax and idasanutlin could therefore cause overlapping toxicities to WBC counts, concomitant immunosuppression, increase susceptibility to infections, and prolong recovery time.

Other potential overlapping toxicities for the combination are GI toxicities, including diarrhea and nausea/vomiting.

There is the potential for the venetoclax–idasanutlin combination to cause overlapping reproductive and embryo-fetal toxicities (see contraception requirements in Section 4.1.1).

Similarly, the likely potential overlapping toxicities for the combination of idasanutlin and the chemotherapy regimens are primarily hematologic, GI toxicity, and infections. A robust risk minimization plan is in place to monitor and mitigate these risks.

All above toxicities are expected to be clinically manageable in this clinical trial, with the potential benefit to the patient outweighing the risk.

5.1.5 Management of Patients Who Experience Adverse Events

5.1.5.1 Dose Modifications

Guidelines for management of specific adverse events are outlined in Table 5. Additional guidelines are provided in the subsections below.

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

Please refer to Section 3.1.1.3 for details of idasanutlin dose reductions or withdrawals required as a result of defined DLTs during the initial dose escalation and safety run-in stages of the study.

The dose of idasanutlin can be reduced by 20% up to two times (or by 50% once) for management of drug-related toxicities (not including idasanutlin dose reductions that occur *when transitioning from single agent idasanutlin to combination regimens or* after morphologic CR/CRp/CRi is achieved). If further dose reduction is indicated after two dose reductions, the patient must discontinue study therapy *unless treatment continuation/dose reduction is approved by the Medical Monitor*. After dose reduction, idasanutlin may be re-escalated by a maximum of one dose level at the investigator's discretion, provided there are no safety concerns.

If the investigator views that therapeutic toxicity warrants dose modification of venetoclax, fludarabine, cytarabine, cyclophosphamide, topotecan, or IT therapy, the investigator must consult the Medical Monitor for further guidance, unless specific dose modification guidance is provided elsewhere in this protocol.

5.1.5.2 Treatment Interruption

Please refer to Section 3.1.1 for details of dose interruption and re-treatment following DLTs during the dose-escalation phase.

Investigators are permitted to suspend treatment with idasanutlin, venetoclax, or other required chemotherapy agents in patients who experience toxicity considered to be

related to study therapy. All treatment related toxicities should be resolved to Grade ≤ 1 or to baseline grade prior to beginning the next cycle. Patients are 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. If study therapy has been withheld beyond Day 56 because of toxicity, the patient should be discontinued from study therapy, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Study therapy may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

The requirement for the minimum criteria for starting next cycle of therapy:

- Absolute neutrophil count
  - Solid tumors, 0.75×10^9/L
  - Leukemia, 0.5×10^9/L
- Platelet count of 75×10^9/L (exceptions apply for patients with leukemia; see Table 5)

If blood count recovery is delayed beyond Day 42, the patient will receive therapy with idasanutlin at a 50% dose reduction. Further dose reduction guidance for hematologic toxicity specific to diseases is provided in Table 5.

5.1.5.3 Hospitalization Requirements

The following patients are required to be hospitalized:

- During the dose-escalation phase, the first 3 patients must be hospitalized for 24 hours after receiving the first dose of idasanutlin to monitor for diarrhea. Following review of the first 3 patients, subsequent patients may be dosed without this requirement for hospitalization.
- Patients with leukemia are required to be hospitalized in Cycle 1 at least until the Day 5 dose of idasanutlin has been administered, because of the risk of tumor lysis syndrome (see Section 5.1.1.3 for background and Table 5 for management guidelines).
- Patients with *neuroblastoma* receiving venetoclax are required to be hospitalized during the ramp-up phase (Days 1 and 2) because of the risk of tumor lysis syndrome (see Section 5.1.2.1 for background and Table 5 for management guidelines).

Investigators should otherwise follow institutional practice, clinical judgment, and recommendations in Table 5 to determine situations warranting hospitalization. Note that hospitalization required for observation mandated either by the study protocol or

institutional practice would not be considered a serious adverse event (see Section 5.3.5.9).

5.1.5.4 Management Guidelines for Specific Adverse Events

Any toxicities associated with or possibly associated with study treatment should be managed with symptomatic treatment, dose interruptions (maximum allowable length of treatment interruption is 28 days), and/or dose reductions. The decision to extend the dose delay will be made on the basis of the investigator's assessment of ongoing clinical benefit and in consultation with the Medical Monitor.

Guidelines for management of specific adverse events are outlined in Table 5.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Diarrhea Grade 1–2	• Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, antacids), infection by C. difficile, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber. • Monitor electrolytes closely and correct as appropriate. • Implement the following dietary modifications for patient: – Stop all lactose-containing products and eat small meals. – Encourage bland diet. Encourage adequate hydration. • Implement anti-diarrheal therapy based on age and local institutional practice. Loperamide treatment (per local dosing standard) is recommended therapy in patients if permitted according to the regional label or if consistent with institutional standard. • If event persists after 48–72 hours despite maximal supportive care, consider second line anti-diarrheal agents, if applicable. • No change in study drug dosing for Grade ≤2 diarrhea, patients should receive maximal supportive care as described above.
Diarrhea Grade 3+	• Provide maximal supportive care as described above. • If Grade ≥3 diarrhea persists despite adequate supportive care, hold idasanutlin (and, if applicable, venetoclax) until diarrhea improves to Grade ≤ 1. • If no improvement is observed within 24 hours despite best supportive care and anti-diarrheal treatment (if permitted based on patient's age), test for *C. difficile*. If bowel movement characteristics improve to baseline or Grade ≤ 1 within 28 days, restart study drug, with idasanutlin at a 50% dose reduction (or, if applicable, venetoclax reduced by 1 dose level), with continued supportive care or prophylaxis. If the diarrhea is confirmed to be infectious on the basis of results from the stool culture, study treatment may be resumed at the same dose level if approved by the Medical Monitor. • If bowel movement characteristics have NOT improved to Grade ≤ 1 or baseline with maximal supportive care by 28 days, permanently discontinue study therapy. • If Grade ≥ 3 diarrhea recurs despite supportive care and idasanutlin or venetoclax dose reduction, permanently discontinue all study therapy.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Vomiting	• Administer rescue medication according to standard institutional practice. Caution: o For patients receiving venetoclax, only administer Aprepitant (Emend® Oral) if medically necessary and with 50% venetoclax dose reduction, as it is a moderate CYP3A inhibitor. o Avoid agents such as metoclopramide, which may stimulate GI motility. • Re-dosing of study treatment after vomiting: – If vomiting occurs within 15 minutes of administering idasanutlin and/or venetoclax and all expelled tablets are still intact (if applicable), another dose may be administered, and the second dose must be recorded in the drug log. Otherwise, no replacement dose is to be administered.
Tumor lysis syndrome	• Monitor clinical chemistry for signs or symptoms of TLS according to local institutional practice. • Administer recombinant urate oxidase (i.e., rasburicase) for hyperuricemia per institutional practice if available and not otherwise contraindicated. • Withhold study treatment and consult Medical Monitor 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

Table 5 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Tumor lysis syndrome (cont.)	• Permanently discontinue study treatment in the case of Grade 4 events. • Ensure appropriate hydration, as strongly recommended for all patients especially patients considered at risk. • Correct relevant clinical chemistry abnormalities promptly. • Maintain a low threshold for treatment with IV fluids and consideration of uric acid reducing agents. • If all laboratory and clinical signs of TLS are stable for at least 24 hours, study treatment may be restarted following the below guidelines, which are based on the presentation of the event: – For clinical TLS, defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, seizures, idasanutlin and venetoclax may be resumed at a reduced dose as described below: o The dose of idasanutlin can be reduced by 20% up to two times (or by 50% once) for management of drug-related toxicities (see Section 5.1.5.1). o The dose of venetoclax should be reduced by 50%. – For laboratory TLS that is transient, lasting <48 hours, restart study treatment at the same dose. – For laboratory TLS that lasts longer than 48 hours, idasanutlin and venetoclax may be resumed at a reduced dose as described below: o The dose of idasanutlin can be reduced by 20% up to two times (or by 50% once) for management of drug-related toxicities (see Section 5.1.5.1). o The dose of venetoclax should be reduced by 50%. • TLS related abnormalities should be managed per institutional guidelines
LFT elevations: Grade 1 or 2	• No action required.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

LFT elevations: Grade 3 (> 5.0–20.0 × ULN)	• For Grade 3 AST/ALT elevation, study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice. LFTs should be monitored every 3 days until return to baseline values. • If duration of Grade 3 AST/ALT elevation ≥ 3 days, hold idasanutlin (and venetoclax, if applicable) until levels resolve to Grade ≤ 1. – For patients with baseline elevation of AST/ALT due to metastasis or leukemic infiltrate, hold idasanutlin (and venetoclax if applicable) if AST/ALT are ≥ 5× to <10× baseline for > 3 days, or for any AST/ALT above ≥ 10 × baseline, until levels resolved to baseline. – Venetoclax and idasanutlin may be resumed at the current dose or at a dose reduction at the discretion of the investigator and after discussion with the Medical Monitor. • Discontinue study drugs permanently if Hy's Law criteria (defined in Section 5.3.5.5) are met or AST/ALT do not resolve to Grade 1 or baseline) within 28 days.
LFT elevations: Grade 4 (> 20 × ULN)	• Hold study drugs until levels return to Grade ≤ 1. If study drug is resumed: Resume venetoclax and idasanutlin at the reduced dose (please refer to guidance in Section 3.1.1.4) at the discretion of the investigator and after discussion with the Medical Monitor. • Permanently discontinue study drugs if Hy's Law criteria (defined in Section 5.3.5.5) are met, AST/ALT do not resolve to Grade 1 or baseline within 28 days, or if Grade 4 AST/ALT recurs.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Cytopenias	**Patients with Solid Tumors:** If any of the following adverse events occur (whether as single agent or in combination), reduce idasanutlin (and, if applicable, *topotecan/cyclophosphamide or* venetoclax) by at least 20% for the following cycle: • Grade 4 neutropenia lasting at least 7 days Treatment with cytokines is *recommended per routine local practice.* • Grade 4 anemia • Thrombocytopenia Grade 4 (i.e., platelet count $< 25.0 \times 10^9$/L) *lasting at least 14 days and assessed on at least 2 separate days* or requiring *at least 2* platelet transfusion *on separate days* • Delay in starting Cycle 2 beyond Day 28 due to slow recovery from thrombocytopenia (platelet count $< 75 \times 10^9$/L) or neutrophil count $< 0.75 \times 10^9$/L Patients with delayed blood count recovery beyond Day 42 should undergo 50% idasanutlin dose reduction. Patients with delayed blood count recovery beyond Day 56 should discontinue study therapy.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Cytopenias (cont.)	**Patients with Leukemia:** • If blood counts have not recovered (ANC $\geq 0.5 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L) by Day 28, interrupt dosing with venetoclax (if applicable) to allow for count recovery. • If blood count recovery is delayed by $>$ 42 days (between Day 42 and Day 56), administer idasanutlin at a 50% dose reduction for the next cycle. – Patients whose ANC is $\geq 0.5 \times 10^9$/L but who have not recovered platelet counts may start therapy at Day 56. – If ANC $< 0.5 \times 10^9$/L on Day 56, discontinue patient from treatment.
	Growth factors will be permitted for neutropenic sepsis according to local practice, and patients will be monitored and treated promptly in case of infections. Dose interruptions or reductions will be allowed based on toxicity. • In cases of fever in neutropenic patients: Consider a medical emergency. Administer initial doses of antibacterial therapy within 1 hour of triage for febrile neutropenic patients (Grade 3 and higher) (Flowers et al. 2013). Refer to institutional and published guidelines for optimal management of febrile neutropenia for $\geq$ 18 year olds (Flowers et al. 2013; de Naurois et al. 2010) and $<$ 18 year olds (Lehrnbecher et al. 2017). Follow the below recommended transfusion thresholds for all patients: • 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 HLA sensitization, administer HLA-compatible platelet transfusions. • Packed red blood cell transfusion is recommended if hemoglobin $<$ 7 g/dL (or $<$ 9 g/dL in patients with documented cardiac insufficiency) or if patient has symptomatic anemia (e.g., profuse asthenia).

Table 5 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Infections	Patients should be closely monitored for infections and prompt therapy will be instituted, as necessary. Due to the high incidence of diarrhea, *Clostridium difficile* infection (CDI) may occur undetected (refer to above diarrhea guidance for recommended CDI testing). CDI once confirmed should be treated as per standard institutional practice.
Other Grade ≥ 3 non-hematologic adverse events or Grade 4 hematologic adverse events considered to be related to study treatment	• Do not administer study treatment until recovery to Grade ≤ 1. Resume idasanutlin and venetoclax at a reduced dose level. • If patient experiences two episodes of the toxicity, or the toxicity persists for > 14 days despite adequate supportive care, discontinue study treatment permanently. Note: A hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia.

AE = adverse event; CDI = *Clostridium difficile* infection; GI = gastrointestinal; HLA = human leukocyte antigen; TLS = tumor lysis syndrome; ULN = upper limit of normal.

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, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.1.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- 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.
- Any tumor lysis syndrome (per Howard criteria, see Appendix 12)
- Febrile neutropenia (Grade ≥ 3)
- Thrombocytopenia (Grade ≥ 3 if associated with hemorrhage or bleeding)
- Diarrhea (Grade ≥ 2)
- Infections (Grade ≥ 3)
- *C. difficile* infection (Grade ≥ 2)
- *Mucosal inflammation (Grade ≥3)*

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.1.3, 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).

5.3 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 5.3.5.10–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

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, or the use of mandatory prophylactic medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 30 days after completion of the last treatment cycle, with the following exception:

- For patients with AML, all adverse events up to 56 days after the last dose of study treatment should be reported

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 clinic visit?"

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal 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 (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 adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5 Abnormal Liver Function Tests

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

- Treatment-emergent ALT/ AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT/ 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 5.3.5.2) 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).

5.3.5.6 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An IMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.7 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").

5.3.5.8 Lack of Efficacy or Worsening of AML, ALL, or Solid-Tumor Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the applicable response assessments (see Appendix 5–Appendix 8 for details). 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.

5.3.5.9 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient 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
- Hospitalization for observation as per institutional practice following administration of study treatment
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

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

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

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

5.3.5.10 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

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

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

  In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

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

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

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

In addition, all special situations associated with idasanutlin and venetoclax, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

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

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

5.3.5.11 Patient-Reported or Observer-Reported Outcome Data

Adverse event reports will not be derived from patient-reported outcome (PRO) or observer-reported outcome (ObsRO) data by the Sponsor, and safety analyses will not be performed using PRO or ObsRO data. Sites are not expected to review the PRO or ObsRO data for adverse events.

5.3.5.12 Safety Biomarker Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- DLTs during the DLT assessment window (defined in Section 5.2.4; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible: [redacted] M.D., Ph.D. (Primary)

Mobile 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, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported 30 days after the final dose of study drug for patients with solid tumors or ALL, and 56 days after the final dose of study drug for patients with AML. DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur $>$6 weeks after the final dose of idasanutlin or $>$30 days after the last dose of venetoclax after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 6 weeks after the final dose of idasanutlin, 30 days after the final dose of venetoclax, 12 months after final treatment for patients receiving cyclophosphamide/topotecan (or longer if required according to national prescribing information), 6 months after final treatment for patients receiving FLA (or longer if

required according to national prescribing information), or in accordance with national prescribing information guidance regarding abstinence, contraception, and egg donation for any non-Investigational Medicinal Products listed in Section 4.3. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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 90 days after the final dose of idasanutlin, 12 months after final treatment with cyclophosphamide/topotecan (or longer if required according to national prescribing information), 6 months after final treatment with fludarabine (or longer if required according to national prescribing information), or in accordance with national prescribing information guidance regarding abstinence, contraception, and sperm donation for any non-Investigational Medicinal Products listed in Section 4.3. *The investigator should report the pregnancy on the* paper Clinical Trial Pregnancy Reporting Form *and submit the form* 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 *with additional* information on the *pregnant partner and the* course and outcome of the pregnancy *as it* 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).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, the idasanutlin oral dispenser (syringe) is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in 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 can be reported.

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 30 days after the last dose of study drug for patients with solid tumors or ALL, and 56 days after the last dose of study drug for patients with AML), all deaths, regardless of cause, should be reported on the Survival Follow-Up eCRF.

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

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

- Idasanutlin Investigator's Brochure
- Venetoclax Investigator's Brochure
- Cyclophosphamide SmPC
- Topotecan SmPC
- Fludarabine SmPC
- Cytarabine SmPC

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

For purposes of analysis, the following populations are defined below:

- Intent-to-treat (ITT) population: All enrolled patients in the study, regardless of whether they were dosed

  All other populations will be a subset of the ITT population.

- Safety evaluable (SE) population: All patients who received any amount of the study treatment, whether prematurely withdrawn from the study or not
- DLT-evaluable (DE) population: All patients enrolled in Part 1 and Part 2 who either have completed at least 80% of the prescribed dose of idasanutlin *and the DLT observation window* in Cycle 1 ***OR*** have experienced a DLT in Cycle 1 of the dose-escalation phase
- PK population: All patients who have received at least one dose of study treatment and who have data from at least one postdose sample

  Patients will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol, or if data are unavailable or incomplete, which may influence the PK analysis.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for the dose-escalation phase of this study is based on the mCRM-EWOC design. The study will enroll approximately 9–*24 DLT-evaluable* patients in dose escalation to reach the MTD/MAD and approximately 3–9 patients in each cohort in the safety run-in phase to reach RP2D. Explicit power and type I error considerations are not factored into the design of the MTD/MAD or RP2D determination, as the dose-escalation and safety run-in phases are designed to obtain preliminary safety and PK information for the study drug.

An early response assessment (Gate 1B), will be performed for the neuroblastoma cohorts at the end of Study Part 1b after six patients have been treated at the RP2D for the combination. Additional response assessment*s* of patients enrolled in Part 2 *(also including patients treated at the RP2D in Part 1b for the neuroblastoma cohorts) (Gate 2)* and of patients enrolled in Part 2 and Part 3 *(again including patients treated at the RP2D in Part 1b for the neuroblastoma cohort) (Gate 3)* are planned in order to make a preliminary assessment of the efficacy of the study drug.

At least 50% of patients with TP53 wild-type tumors treated at the RP2D in Study Part 1b for the neuroblastoma cohorts (Gate 1b) must have an observed objective response prior to advancing to the next phase of the study. If this benchmark is not reached, the cohort will be discontinued for futility. The minimum number of patients in the response assessment *at Gate 2* and the minimum number of responders required for advancement to the additional response assessment *(Part 3)* are presented by tumor type in Table 8, taking into account historical control ORRs for neuroblastoma and CRR for leukemias. For neuroblastoma and AML, up to one combination regimen may advance to Part 3 for each tumor type, taking into account the preliminary efficacy (i.e., response criteria in Table 8), safety, biomarker data, and enrollment feasibility. The ALL cohort will be considered for expansion similarly, if either morphologic response or MRD-negative response criteria are met.

The sample size and minimum number of responders for the additional response assessment for each tumor type cohort were determined based on 90% confidence interval (CI) for the appropriate response rate parameter for each disease cohort. Part 3 of this trial will be able to detect a large benefit of the idasanutlin in combination with chemotherapy or venetoclax in terms of the appropriate response rate for the disease. For example, an observed response rate of 45% in 40 patients with neuroblastoma will have a 90% confidence interval excluding the 32% historical response rate. Similarly, an observed CRR of 53% in 30 patients with ALL will have a 90% confidence interval excluding 40%.

Table 8 Sample Size for Initial and Additional Response Assessment

Tumor Type	Response Assessment	Control CRR/ORR	Initial Response Assessment (Part 2)		Additional Response Assessment (Parts 2 and 3)
			Minimum No. of Patients Enrolled	Minimum No. of Responders Needed for Tumor Type Cohort Expansion	No. of Patients Enrolled [a]
NBL	INRC	32% [b]	10[c]	5	40
AML	AML [d]	55% [e]	10	7	35
ALL [f]	ALL (morphologic response)	40% [g]	10	6	30
	ALL (MRD-negative response) [h]	20% [i]	10	4	30

ALL = acute lymphocytic leukemia: AML = acute myeloid leukemia; CRR = complete remission rate; FLAG = Fludarabine, cytarabine, and G-CSF; INRC = International Neuroblastoma Response Criteria; MRD = minimal residual disease; NBL = neuroblastoma; No. = number; ORR = overall response rate.

[a] Includes patients from initial response assessment.

[b] London et al. 2010 (TOPO/CTX vs. TOPO).

[c] *including patients treated in Part 1b* at RP2D.

[d] See Appendix 7.

[e] Kaspers et al. 2013 (combination FLAG).

[f] ALL cohort considered for expansion if either morphologic response or MRD-negative response criteria are met.

[g] Ko et al. 2010; Messinger 2012; Bertaina 2017.

[h] MRD negative defined as <0.01% blasts in the bone marrow detected by nucleic acid-based methods, such as next-generation sequencing.

[i] von Stackelberg 2016.

6.2 SUMMARIES OF CONDUCT OF STUDY

All major protocol deviations will be captured. The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics, including age, sex, race/ethnicity, medical history, and prior cancer treatment, will be summarized overall and by each cohort type. Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

All demographic and baseline characteristics analyses will be based on the ITT population.

6.4 SAFETY ANALYSES

Safety will be characterized by incidence of adverse events and DLTs, as well as change from baseline in ECG parameters and clinical laboratory results. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All safety analyses will be based on the SE population.

Incidence and nature of DLTs assessed during the first cycle of study treatment will be summarized using descriptive statistics. All DLT analyses will be based on the DE population.

6.4.1 Primary Safety Model (mCRM-EWOC) for Single-Agent Dose Finding

An mCRM-EWOC model will be utilized to inform decision-making regarding the MTD of idasanutlin in Study Part Ia. The MTD is defined as the dose that maximizes the posterior probability of a DLT being in the targeted toxicity interval of 20%–35%, while controlling the probability of a DLT being in the excessive toxicity interval of 35%–100% to be $<$25%.

The mCRM-EWOC model will adaptively estimate the MTD after gathering cumulative DLT data including newly completed cohorts and calculate a recommended next dose for the next cohort. The mCRM-EWOC design parameters and operating characters are described in Appendix 11.

6.5 PHARMACOKINETIC ANALYSES

Standard non-compartmental analysis will be applied for calculating PK parameters and population methods may be considered.

Analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) separately by disease cohorts and sub-grouped by drug combinations, when applicable.

Individual and mean serum idasanutlin (and M4 metabolite RO6802287, where relevant) concentration versus time data will be tabulated and plotted by dose-level in dose-escalation phase and by drug combination and disease cohorts in later phases of the study. Graphical displays of PK data will also be provided. The PK of idasanutlin (and M4 metabolite RO6802287, where relevant) will be summarized by estimating total exposure (AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), total clearance, volume of distribution at steady-state (V_{ss}), and $t_{1/2}$ when available data permits. Estimates for these parameters will be tabulated and summarized. Inter-patient variability and drug accumulation will be evaluated.

6.6 EFFICACY ANALYSES

All efficacy analyses will be performed on SE population.

Interim response assessments will be performed in centrally-confirmed *TP53* wild-type patients from each tumor type and combination following *Part 1b of the neuroblastoma cohorts and* Part 2 *for all cohorts*. The IMC-SOC will review the safety and efficacy data and recommend whether to expand or stop further enrollment for a tumor type *and combination*.

Tumor response data will be reported using descriptive statistics. The exact binomial CIs will be calculated using Clopper-Pearson method.

6.6.1 Primary Efficacy Endpoints

The primary endpoint for efficacy in neuroblastoma is ORR in patients with *TP53* WT tumors (see Section 2.3.1). Patients with no postbaseline tumor assessments will be counted as non-responders. The ORR and its 95% CI will be calculated for patients enrolled in *Part 1b (neuroblastoma cohorts only),* Part 2*,* and Part 3 by combination regimen.

The primary endpoint for efficacy in AML is CRR in patients with *TP53* WT tumors (see Section 2.3.1). Patients with no postbaseline tumor assessments will be counted as non-responders. The CRR and 95% CI will be calculated by combination regimen.

The co-primary endpoints for efficacy in ALL are CRR and MRD-negative rate in patients with *TP53* WT tumors (see Section 2.3.1). Patients with no postbaseline tumor

assessments will be counted as non-responders in the CRR analysis and MRD-positive patients in the MRD-negative rate analysis, respectively. The CRR and MRD-negative rate, and their corresponding 95% CI will be calculated.

6.6.2 Secondary Efficacy Endpoints

6.6.2.1 Solid Tumors including Neuroblastoma

CBR, DOR, PFS, and OS are defined in Section 2.3.2 and will be calculated in patients with *TP53* WT tumors in *Part 1b,* Part 2*,* and Part 3, by combination regimen.

DOR will be calculated for patients who achieve an objective response. Data for patients without disease progression or death will be censored at the date of the last tumor assessment at which the patient was known to be progression-free or, if no tumor assessment is performed after the baseline visit, at the date of initiation of study drug. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be estimated using Brookmeyer and Crowley method.

For PFS calculation, data for patients without disease progression or death will be censored at the date of the last tumor assessment at which the patient was known to be progression-free or, if no tumor assessment is performed after the baseline visit, at the date of initiation of study drug. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be estimated using Brookmeyer and Crowley method.

ORR and its 95% CI will be calculated for all patients and by dose level in Part 1, as well as in patients in Part 2 and Part 3 regardless of their tumors' *TP53* mutation status.

6.6.2.2 Leukemias

Rate of patients receiving transplant after study treatment, OS, and CRR will be calculated in patients with TP53 WT tumors, by tumor type and combination regimen.

DOR and EFS are defined in Section 2.3.2 and will be calculated in patients with *TP53* WT tumors, by tumor type and combination regimen.

MRD-negative rate and its 95% CI will be calculated for patients with *TP53* WT AML by combination regimen.

CRR and its 95% CI will be calculated for all patients by tumor type and combination regimen, regardless of their tumors' *TP53* mutation status.

6.7 BIOMARKER ANALYSES

Exploratory biomarker analyses may be performed in an effort to better understand response to idasanutlin as a single agent or in combination with chemotherapy or venetoclax at a molecular level and identify potential mechanisms of resistance. These analyses will be descriptive and exploratory in nature and results will be presented in a

separate report. The potential exploratory biomarker assessments for this study requiring statistical considerations may include, but will not be limited to, the following:

- Alterations in DNA and RNA, including DNA mutational status (such as *TP53* mutations), RNA expression levels (such as Bcl-2 and MDM2 transcripts), and DNA copy number may be assessed on pre-study, on-study, and end-of-study tissue samples and/or BMAs to better understand molecular mechanisms of response and resistance.
- Analysis of serum samples for MIC-1 protein levels by ELISA
- Analysis of ctDNA from plasma isolated from peripheral blood for potential blood-based biomarkers including, but not limited to, *TP53* mutations

6.8 HEALTH STATUS UTILITY ANALYSIS

Analyses will be descriptive, enumerating the number of patients that selected each answer choice.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

Acceptability survey data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO, Clin RO, and ObsRO 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 study results have been reported 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 United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) 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 an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure.

Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

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

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are

also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

Study data, which may include data on genomic mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and implement plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd.

Approximately 10–20 sites globally will participate to enroll approximately *183* patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC and an SOC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study(see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities for Patients with Solid Tumors (Single-Agent Dose-Escalation Cohort)

Assessment	Screen.	Cycle 1 (28 days)						Cycle 2 (28 days)				Cycle ≥3 (28 days each)				Study Treat. Disc.[b]	Follow Up[c]
Day[d]	−28 to −1	1[e]	2	5	8[a]	15[a]	22[a]	1	8[a]	15[a]	22[a]	1	8[a]	15[a]	22[a]		
Informed consent[f]	x																
Demographic data and medical history	x																
Weight[g]	x	x						x				x				x	x
Height[g]	x											x[h]				x	x
Head circumference (< 3 years)[g]	x											x[h]				x	x
Tanner staging[g]	x											x[h]				x	x
Complete physical examination[i]	x																
Limited physical examination[j]		x						x				x				x	x
Performance status[k]	x	x						x				x				x	x
Concomitant medications[l]	x	x	x	x	x	x	x	x	x	x	x	x			x	x	
Adverse events[m]	x	x	x	x	x	x	x	x	x	x	x	x			x	x	
Acceptability Survey				x													
Survival assessment																	x
Investigations																	
Hematology[n]	x	x			x	x	x[o]	x	x[p]	x[p]	x[o,p]	x	x[p]	x[p]	x[o,p]	x	
Chemistry[q]	x	x			x	x	x	x	x[p]	x[p]	x[p]	x	x[p]	x[p]	x[p]	x	
PT, PTT, INR	x																
Viral serology[r]	x																
Pregnancy test[s]	x							x				x				x	
12-lead ECG	x							x				x					
Echocardiogram	x																

Appendix 1: Schedule of Activities for Patients with Solid Tumors (Single-Agent Dose-Escalation Cohort)

Assessment	Screen.	Cycle 1 (28 days)						Cycle 2 (28 days)				Cycle ≥3 (28 days each)				Study Treat. Disc.[b]	Follow Up[c]
Day[d]	–28 to –1	1[e]	2	5	8[a]	15[a]	22[a]	1	8[a]	15[a]	22[a]	1	8[a]	15[a]	22[a]		
~~PK and Biomarker~~																	
PK assessment	See Appendix 4																
Tumor tissue for central *TP53* mutation assessment	x																
Plasma and serum for biomarkers assessment	x	x		x				x								x	
Optional postbaseline tumor tissue sample						x[t]	x[t]									x[t]	
Disease assessment																	
Cross-sectional imaging (CT or MRI)	x						x (D22–D28)								x (D22–D28) Cycles 3, 5, and 7 and every fourth cycle thereafter		
Neuroblastoma only: ^{123}I-MIBG (or FDG-PET/CT if MIBG non-avid)	x						x (D22–D28)								x (D22–D28) Cycles 3, 5, and 7 and every fourth cycle thereafter		
Bilateral bone marrow aspirate and biopsy Both required for neuroblastoma; either aspirates or biopsies for other solid tumors	x						x (D22–D28) If positive at screening and as required by Section 4.5.5.1								x If positive at screening and as required by Section 4.5.5.1		

CT = computed tomography; D = day; Disc. = discontinuation; FDG = ^{18}F-fluorodeoxyglucose; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography; Screen. = screening; Treat. = treatment.

[a] For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, when deemed appropriate by the treating physician and when no assessments require the patient be in clinic, all assessments or procedures at these visits may be performed by a trained nursing professional at the patient's home or another suitable location.

[b] The study treatment discontinuation visit will take place 28 (± 30) days after the final dose of study drug and may be done at the clinical visit where clinical or radiographic progression is first noted.

[c] Patients are expected to complete all follow up investigations unless return visits to the study site are considered onerous for the patient (due to distance from the site, health status, etc.) in the opinion of the investigator; such patients will be followed for survival only. Long-term follow up information will be collected every 3 months until death or end of study, whichever occurs first.

[d] The visit window for each visit is ± 3 days, with the exception of PK samples on Days 2 and 5 of Cycle 1. The window for continuing to the next cycle is ± 3 days, for study treatment discontinuation visit is 30 days, and for follow-up is ± 1 month.

[e] All assessments should be completed prior to dosing, with the exception of certain PK assessments outlined in Appendix 4.

[f] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[g] During the treatment period, weight will be measured at the beginning of each cycle. During the follow-up period, weight should be measured every 3 months. Height, head circumference (until the age of 3 years), and Tanner stage should be measured every three cycles (approximately every 3 months). During the follow up period, height, head circumference, and Tanner stage should be measured every 3 months. Tanner staging should be performed until the patient has reached Tanner Stage V.

[h] Assessments to be obtained every 3 months (i.e., every 3 cycles).

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[j] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits or as clinically indicated. 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.

[k] The Lansky Performance Status should be performed for patients who are < 16 years old, and the Karnofsky Performance Status should be performed for patients who are ≥ 16 years old.

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 30 days after the final dose of study drug.

[m] 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. After initiation of study drug, all adverse events will be reported 30 days after completion of the last treatment cycle. After this period, all deaths, regardless of cause, should be reported on the Long-Term Survival eCRF. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, blasts, and other cells).

[o] Weekly thereafter until able to start next cycle.

[p] Can be omitted for patients who continue with single-agent idasanutlin (i.e. do not combine with chemotherapy) unless clinically indicated in investigator's judgement.

[q] Chemistry panel (serum) includes bicarbonate (or total carbon dioxide), sodium, potassium, chloride, glucose, BUN or urea, creatinine, albumin, phosphate, calcium, total bilirubin [if abnormal, fractionate sample for direct and indirect], alkaline phosphatase, ALT, AST, uric acid, and LDH.

[r] Viral serology includes hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, hepatitis C antibody, and HIV.

[s] All females of childbearing potential will have a serum pregnancy test at screening within 1 week prior to first dose. Urine or serum pregnancy tests will be performed at specified subsequent visits.

[t] If clinically feasible and safe, patients are encouraged to provide an optional on-treatment tissue biopsy for biomarker assessments at Day 15 of Cycle 1 (or on Day 22 of Cycle 1, if not provided on Day 15). Similarly, *at the time of progression and* at the study discontinuation visit, if clinically feasible and safe, patients are also encouraged to provide an end-of-treatment biopsy.

Appendix 2 Schedule of Activities for Patients with Neuroblastoma (*Study Parts 1b, 2 and 3*)

Assessment	Screening	Cycle 1 (28 days)						Cycle ≥ 2 (28 days each)				Study Treat. Disc. [b]	Follow-Up [c]
Day [d]	–28 to –1	1 [e]	2	5	8 [a]	15 [a]	22 [a]	1	8 [a]	15 [a]	22 [a]		
Informed consent [f]	x												
Demographic data and medical history	x												
Weight [g]	x	x						x				x	x
Height [g]	x							x [h]				x	x
Head circumference (< 3 years) [g]	x							x [h]				x	x
Tanner staging [g]	x							x [h]				x	x
Complete physical examination [i]	x												
Limited physical examination [j]		x						x				x	x
Performance status [k]	x	x						x				x	x
Concomitant medications [l]	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	
Acceptability Survey				x									
Survival assessment													x
Investigations													
Hematology [n]	x	x		x	x	x	x [o]	x			x [o]	*x*	
TLS chemistry [t]		x											
Chemistry [p]	x	x		x	x	x	x	x			*x*	*x*	
PT, PTT, INR	x												
Viral serology [q]	x												
Pregnancy test [r]	x							x					
12-lead ECG	x							x					
Echocardiogram	x												

Appendix 2: Schedule of Activites for Patients with Neuroblastoma (*Study Parts 1b, 2, and 3*)

Assessment	Screening	Cycle 1 (28 days)						Cycle ≥ 2 (28 days each)				Study Treat. Disc. [b]	Follow-Up [c]
Day [d]	–28 to –1	1 [e]	2	5	8 [a]	15 [a]	22	1	8 [a]	15 [a]	22[a]		
PK and biomarker													
PK assessment	See Appendix 4												
Tumor tissue for central *TP53* mutation assessment	x												
Plasma and serum for biomarkers assessment	x	x		x				x				x	
Optional postbaseline tumor tissue sample						x [s]	x [s]					x [s]	
Disease assessment													
Cross-sectional imaging (CT or MRI)	x										x (D22–D28) Cycles 2, 4, 6, and 8 and then every 4th cycle thereafter		
^{123}I-MIBG (or FDG-PET/CT if MIBG non-avid)	x										x (D22–D28) Cycles 2, 4, 6, and 8 and then every 4th cycle thereafter		
Bilateral bone marrow aspirate and biopsy	x										x Only if positive at diagnosis and as required by Section 4.5.5.1		

CT = computed tomography; D = day; Disc. = discontinuation; FDG = ^{18}F-fluorodeoxyglucose; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography; Screen. = screening; Treat. = treatment.

[a] For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, when deemed appropriate by the treating physician and when no assessments require the patient be in clinic, this all assessments or procedures at these visits may be performed by a trained nursing professional at the patient's home or another suitable location.

[b] The study treatment discontinuation visit will take place 28 (± 30) days after the final dose of study drug and may be done at the clinical visit where clinical or radiographic progression is first noted.

[c] Patients are expected to complete all follow up investigations unless return visits to the study site are considered onerous for the patient (due to distance from the site, health status, etc.) in the opinion of the investigator; such patients will be followed for survival only. Long-term follow up information will be collected every 3 months until death or end of study, whichever occurs first.

[d] The visit window for each visit is ± 3 days, with the exception of PK samples on Days 2 and 5 of Cycle 1. The window for continuing to the next cycle is ± 3 days, for study treatment discontinuation visit is 30 days, and for follow-up is ± 1 month.

[e] All assessments at should be completed prior to dosing, with the exception of certain PK assessments outlined in Appendix 4.

[f] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[g] During the treatment period, weight will be measured at the beginning of each cycle. During the follow-up period, weight should be measured every 3 months. Height, head circumference (until the age of 3 years), and Tanner stage should be measured every three cycles (approximately every 3 months). During the follow up period, height, head circumference, and Tanner stage should be measured every 3 months. Tanner staging should be performed until the patient has reached Tanner Stage V.

[h] Assessments to be obtained every 3 months (i.e., every 3 cycles).

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[j] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits or as clinically indicated. 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.

[k] The Lansky Performance Status should be performed for patients who are < 16 years old, and the Karnofsky Performance Status should be performed for patients who are ≥ 16 years old.

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 30 days after the final dose of study drug.

[m] 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. After initiation of study drug, all adverse events will be reported until until 30 days after completion of the last treatment cycle. After this period, all deaths, regardless of cause, should be reported on the Long-Term Survival eCRF. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, blasts, and other cells).

[o] Weekly thereafter until able to start next cycle.

[p] Chemistry panel (serum) includes bicarbonate (or total carbon dioxide), sodium, potassium, chloride, glucose, BUN or urea, creatinine, albumin, phosphate, calcium, total bilirubin [if abnormal, fractionate sample for direct and indirect], alkaline phosphatase, ALT, AST, uric acid, and LDH.

[q] Viral serology includes hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, hepatitis C antibody, and HIV.

[r] All females of childbearing potential will have a serum pregnancy test at screening within 1 week prior to first dose. Urine or serum pregnancy tests will be performed at specified subsequent visit.

[s] If clinically feasible and safe, patients are encouraged to provide an optional on-treatment tissue biopsy for biomarker assessments at Day 15 of Cycle 1 (or on Day 22 of Cycle 1, if not provided on Day 15). Similarly, at the *time of progression and at the* study discontinuation visit, if clinically feasible and safe, patients are also encouraged to provide an end-of-treatment biopsy.

[t] Applicable for patients combining with venetoclax only. TLS chemistry includes calcium, phosphorus, BUN (or urea), creatinine, potassium, uric acid on Cycle 1, Day 1 predose and at 4, 8, and 24 hours postdose.

Appendix 3
Schedule of Activities for Patients with ALL and AML

Assessment	Screening	Cycle 1 (28 days)						Cycle ≥ 2 (28 days each)				Study Treat. Disc. [b]	Follow-Up [c]
Day [d]	–28 to –1	1 [e]	2	5	8 [a]	15 [a]	22[a]	1	8 [a]	15 [a]	22[a]		
Informed consent [f]	x												
Demographic data and medical history	x												
Weight [g]	x	x						x				x	x
Height [g]	x							x [h]				x	x
Head circumference (< 3 years) [g]	x							x [h]				x	x
Tanner staging [g]	x							x [h]				x	x
Complete physical examination [i]	x												
Limited physical examination [j]		x						x				x	x
Performance status [k]	x	x						x				x	x
Concomitant medications [l]	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	
Acceptability Survey				x									
Survival assessment													x
Investigations													
Hematology [n]	x	x			x	x	x [o]	x	x	x	x [o]	x	
TLS chemistry [t]		x											
Chemistry [p]	x	x			x	x	x	x	x	x	x	x	
PT, PTT, INR	x												
Viral serology [q]	x												
Pregnancy test [r]	x							x					
12-lead ECG	x							x					
Echocardiogram	x												
PK and biomarker													
PK assessment	See Appendix 4												
Bone marrow aspirate for central *TP53* mutation assessment	x												

Appendix 3: Schedule of Activites for Patients with ALL and AML

Assessment	Screening	Cycle 1 (28 days)						Cycle ≥ 2 (28 days each)				Study Treat. Disc. [b]	Follow-Up [c]
Day [d]	–28 to –1	1 [e]	2	5	8 [a]	15 [a]	22[a]	1	8 [a]	15 [a]	22[a]		
Serum for biomarkers assessment	x	x		x				x				x	
Bone marrow aspirate for MRD biomarker assessment	x [s]						x [s] (D28, D29–42, D43–56)				x [s] (D28,D29–42, D43–56)	x [s]	
Whole blood for MDM2 biomarker	x												
Bone marrow biopsy for TP53 mutation assessment	x [v]												
Blood for TP53 mutation assessment and gene expression	x [v]												
Disease assessment													
Bone marrow aspirate (and biopsy as indicated)	x						x (D28) If ANC < 0.5 × 10^9/L repeat assessment at least weekly until ANC ≥ 0.5x10^9/L				x (D28) [u] If ANC <0.5 x10^9/L repeat assessment at least weekly until ANC≥0.5x10^9/L		
Lumbar puncture	x						x if positive at baseline				x if positive previously		

D = day; Disc. = discontinuation; MRD=minimal residual disease; TLS = tumor lysis syndrome; Treat. = treatment.

[a] For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, when deemed appropriate by the treating physician all assessments or procedures at these visits may be performed by a trained nursing professional at the patient's home or another suitable location.

[b] The study treatment discontinuation visit will take place 28 (± 30) days after the final dose of study drug and may be done at the clinical visit where clinical or radiographic progression is first noted.

[c] Patients are expected to complete all follow up investigations unless return visits to the study site are considered onerous for the patient (due to distance from the site, health status, etc.) in the opinion of the investigator; such patients will be followed for survival only. Long-term follow up information will be collected every 3 months until death or end of study, whichever occurs first.

[d] The visit window for each visit is ± 3 days, with the exception of PK samples on Days 2 and 5 of Cycle 1. The window for continuing to the next cycle is ± 3 days, for study treatment discontinuation visit is 30 days, and for follow-up is ± 1 month.

[e] All assessments should be completed prior to dosing, with the exception of certain PK assessments outlined in Appendix 4.

[f] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[g] During the treatment period, weight will be measured at the beginning of each cycle. During the follow-up period, weight should be measured every 3 months. Height, head circumference (until the age of 3 years), and Tanner stage should be measured every three cycles (approximately every 3 months). During the follow up period, height, head circumference, and Tanner stage should be measured every 3 months. Tanner staging should be performed until the patient has reached Tanner Stage V.

[h] Assessments to be obtained every 3 months (i.e., every 3 cycles).

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[j] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits or as clinically indicated. 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.

[k] The Lansky Performance Status should be performed for patients who are $<$ 16 years old, and the Karnofsky Performance Status should be performed for patients who are $\geq$16years old.

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 30 days after the final dose of study drug.

[m] 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. After initiation of study drug, all adverse events will be reported until until 30 days after completion of the last treatment cycle, with the following exception: For patients with AML, all adverse events up to 56 days after the last dose of study treatment should be reported. After this period, all deaths, regardless of cause, should be reported on the Long-Term Survival eCRF. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, blasts, and other cells).

[o] Weekly thereafter until able to start next cycle.

[p] Chemistry panel (serum) includes bicarbonate (or total carbon dioxide), sodium, potassium, chloride, glucose, BUN or urea, creatinine, albumin, phosphate, calcium, total bilirubin [if abnormal, fractionate sample for direct and indirect], alkaline phosphatase, ALT, AST, uric acid, and LDH. On Day 1 of Cycle 1, chemistry must be collected pre-dose and 4, 8 and 24 hours post-dose due to the risk of tumor lysis syndrome. Pre-dose chemistry results must be reviewed before dosing.

[q] Viral serology includes hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, hepatitis C antibody, and HIV.

[r] All females of childbearing potential will have a serum pregnancy test at screening within 1 week prior to first dose. Urine or serum pregnancy tests will be performed at specified subsequent visits.

[s] BMA for MRD should be collected at any timepoint during the study at which BMA and/or BMB is collected as part of hematological response assessments. BMA collections in Cycle1 and Cycle 2 are mandatory as per the specific instructions detailed in Section 4.5.5.1.1. If any MRD assessments are done locally, record this information in the eCRF.

[t] TLS chemistry includes calcium, phosphorus, BUN (or urea), creatinine, potassium, uric acid on Cycle 1, Day 1 predose and at 4, 8, and 24 hours postdose.

[u] Assessments will take place every two cycles after Cycle 2.

[v] If BMA cannot be obtained or is not evaluable (e.g., dry tap or no spicules are obtained), both BMB and blood collection are required.

Appendix 4
Schedule of Pharmacokinetic Samples

Assessment	Screening	Cycle 1 (28 days)													Cycles 2, 3, 8, 12, 16, and every 8 cycles thereafter (28 days each)		Study Treat. Disc. [b]
Day [a]	–28 to –1	1					2	5					8	15	22	1		
Timepoints		Pre	1h	2h	4h	6h	Pre	Pre	1h	2h	4h	6h	NA	NA	NA	Pre	4h [c]	
Plasma for idasanutlin PK		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Plasma for venetoclax PK (only for patients receiving venetoclax)		x	x	x	x	x	x	x	x	x	x	x		x		x	x	x

D = day; Disc. = discontinuation; NA = not applicable as no drug administered on that day; Pre = predose; Treat. = treatment

[a] All study visits and assessments during the treatment period should be performed within ± 3 days, with the exception of assessments to be performed on Day 1 of Cycle 1, and with the exception of PK sample collections on Days 2 and 5 of Cycle 1. The window for continuing to the next cycle is ± 3 days, for study treatment discontinuation visit is 30 days, and for follow-up is ± 1 month.

[b] The study treatment discontinuation visit will take place 28 (± 30) days after the final dose of study drug and may be done at the clinical visit where clinical or radiographic progression is first noted.

[c] PK samples taken 4 hours post-dose are optional for Cycle 3 and beyond.

Appendix 5
International Neuroblastoma Response Criteria

The criteria presented below are based on the revisions to the International Neuroblastoma Response Criteria (INRC) (Park et al. 2017).

Overall response in the revised INRC integrates tumor response in the primary tumor, soft tissue and bone metastases, and bone marrow. Primary and metastatic soft tissue sites will be assessed using RECIST v1.1 (see Appendix 6) and metaiodobenzylguanidine (MIBG) scans or fluorodeoxyglucose-positron emission tomography (FDG-PET) scans if the tumor is MIBG non-avid. Bone marrow will be assessed by histology or immunohistochemistry and cytology or immunocytology. Bone marrow with ≤5% tumor involvement will be classified as minimal disease. Urinary catecholamine levels will not be included in response assessment.

PRIMARY (SOFT TISSUE) TUMOR RESPONSE [a]	
Response	**Anatomic + MIBG (FDG-PET [b]) imaging**
Complete Response	< 10 mm residual soft tissue at primary site AND Complete resolution of MIBG or FDG-PET uptake (for MIBG non-avid tumors) at primary site
Partial Response	≥ 30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved
Stable Disease	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site
Progressive Disease	> 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND Minimum absolute increase of 5 mm in longest dimension [c]

CR = complete response; FDG-PET = fluorodeoxyglucose-positron emission tomography; MIBG = metaiodobenzylguanidine; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Not for use in assessment of metastatic sites.

[b] Used for MIBG non-avid tumors.

[c] Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.

Appendix 5: International Neuroblastoma Response Criteria

TUMOR RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES	
Response	**Anatomic + MIBG (FDG-PET [a]) imaging**
Complete Response	Resolution of all sites of disease, defined as: Non-primary target and non-target lesions measure < 10 mm AND Lymph nodes identified as target lesions decrease to a short axis < 10 mm AND MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely
Partial Response	≥ 30% decrease in sum of diameters [b] of non-primary target lesions compared with baseline AND all of the following: Non-target lesions may be stable or smaller in size AND No new lesions AND ≥ 50% reduction in MIBG absolute bone score (relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET–avid bone lesions [b, c]
Stable Disease	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions
Progressive Disease	Any of the following: Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma Any new bone site that is MIBG avid A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions Relative MIBG score ≥ 1.2 [d]

CR = complete response; FDG-PET = fluorodeoxyglucose-positron emission tomography; MIBG = metaiodobenzylguanidine; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Used for MIBG non-avid tumors.

[b] Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non–lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.

[c] For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

[d] Relative MIBG score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions. The same scoring method (e.g., Curie or International Society of Paediatric Oncology European Neuroblastoma) must be used at all assessment timepoints. MIBG single-photon emission computed tomography (SPECT) or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

Appendix 5: International Neuroblastoma Response Criteria

BONE MARROW METASTASIS RESPONSE [a]	
Response	**Cytology [b]/Histology [c]**
Complete Response	Bone marrow with no tumor infiltration on reassessment, independent of baseline tumor involvement
Minimal Disease	Any of the following: Bone marrow with ≤ 5% tumor infiltration and remains > 0 to ≤ 5% tumor infiltration on reassessment OR Bone marrow with no tumor infiltration that has ≤ 5% tumor infiltration on reassessment OR Bone marrow with > 20% tumor infiltration that has > 0 to ≤ 5% tumor infiltration on reassessment
Stable Disease	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria
Progressive Disease	Any of the following: Bone marrow without tumor infiltration that becomes > 5% tumor infiltration on reassessment OR Bone marrow with tumor infiltration that increases by > 2-fold and has > 20% tumor infiltration on reassessment

CR = complete response; MD = minimal disease; PD = progressive disease; SD = stable disease.

Note: In the case of discrepant results between aspirations or core biopsies from two or more sites taken at the same time, the highest infiltration result should be reported using the criteria in this table.

[a] Response will be compared with baseline disease evaluation at study enrollment.

[b] Accompanied by immunocytology (recommended, not mandatory).

[c] Accompanied by immunohistochemistry; specific recommendations by Burchill et al. (2016).

Appendix 5: International Neuroblastoma Response Criteria

DETERMINATION OF OVERALL RESPONSE Combine response of Soft Tissue, Bone, and Bone Marrow Disease	
Response	**Criterion**
Complete Response	All components meet criteria for CR
Partial Response	PR in at least one component and all other components are either CR, MD [a] (bone marrow), PR (soft tissue or bone), or NI [b]; no component with PD
Minimal Response	PR or CR in at least one component but at least one other component with SD; no component with PD
Stable Disease	SD in one component with no better than SD or NI [b] in any other component; no component with PD
Progressive Disease	Any component with PD

CR = complete response; MD = minimal disease; NI = not involved; PD = progressive disease; SD = stable disease.

[a] For bone marrow assessment only.

[b] Site not involved at study entry and remains uninvolved.

REFERENCES

Burchill SA, Beiske K, Shimada H, et al: Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma: On behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group. Cancer [epub ahead of print on December 16, 2016].

Appendix 6
Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Eisenhauer et al. 2009) are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

MEASURABILITY OF TUMOR AT BASELINE
DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative

of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded

as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint (see Table 3). If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 7
AML Response Assessment

Adapted from Cheson et al. (2003)

Response to Therapy for AML	
Category	**Definition**
Complete remission	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0×10^9/L (1000/μL); platelet count > 100×10^9/L (100,000/μL); independence of transfusions for a minimum of 1 week. No duration of response is required for CR.
Complete remission with incomplete hematological recovery	All CR criteria except for residual neutropenia (< 1.0×10^9/L [1000/μL]) or thrombocytopenia (< 100×10^9/L [100,000/μL]). No duration of response is required for CR.
Morphologic leukemia-free state	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required.
Partial remission	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent. A value of ≤ 5% blasts may also be considered a PR if Auer rods are present. No duration of response is required for CR.
Cytogenetic complete remission	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow.
Molecular complete remission	In addition to above CRc criteria, normalization of previously detected molecular cytogenetic abnormality.
Stable disease	A subject who has no CR/CRi/PR nor has progressive disease for a period of at least 2 months should be considered SD.

Appendix 7: AML Response Assessment

Treatment Failure	
Progressive disease	Increase of at least 25% in the absolute number of circulating leukemic cells, development of new sites of extra-medullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets
Molecular reappearance	A reconversion after MRD negativity to reproducible MRD positivity. A reconfirmation is strongly recommended. This finding does not fulfil the conditions for the definition of subsequent relapse
Relapse	Only in patients who achieved a CR/CRp/CRi and who subsequently develop: • Bone marrow blasts ≥ 5%; or • reappearance of blasts in the blood ≥ 1%; or • development of extra-medullary disease

CR = complete remission; CRc = cytogenetic complete remission; CRi = Complete remission with incomplete hematological recovery; CRm = molecular complete remission; MRD = minimal residual disease; PD = progressive disease; PR = partial remission; SD = stable disease.

Appendix 8
ALL Response Assessment

The assessment of the response to therapy in the bone marrow and cerebral spinal fluid is solely based on cytological criteria.

Bone marrow status categories:

- **M0:** Representative bone marrow aspirate with only few nucleated cells (mostly lymphocytes, cellularity resembles a normal blood count in cytological analysis) without signs of regenerating normal haematopoiesis and with residual leukemic cells $<5\%$
- **M1:** Representative bone marrow aspirate with <5% lymphoblasts, satisfactory cellularity and signs of regenerating normal haematopoiesis
- **M2:** Bone marrow with $\geq 5\%$ and $<25\%$ of lymphoblastic leukemic blasts irrespectively of the cellular content
- **M3:** Bone marrow with $\geq 25\%$ of lymphoblastic leukemic blasts irrespectively of the cellular content

Response to Therapy for ALL	
Category	Definition
Non-representative bone marrow	Markedly reduced cellularity despite signs of regeneration in the peripheral blood and differential count of nucleated cells in the marrow largely corresponding to that in the peripheral blood. It should be repeated particularly when therapeutic decisions are taken based on the results
Complete response	Attainment of M1 bone marrow status with no evidence of circulating blasts (must be $< 1\%$) or extra-medullary disease and with recovery of peripheral counts (ANC $> 1 \times 10^9$/L [1000/μL] and platelet count $> 100 \times 10^9$/L [100,000/μL]), with no platelet and/or neutrophil transfusions less than or equal to 7 days before the date of the peripheral blood sample for disease assessment. The detection of leukemic cells below the threshold of cytological detection using molecular or flow cytometric methods is compatible with the definition of CR.
Complete response with incomplete hematological recovery	Attainment of M1 bone marrow status with no evidence of circulating blasts or extra-medullary disease and with no recovery of peripheral counts (ANC $< 1 \times 10^9$/L [1000/μL]) and/or insufficient recovery of platelets ($< 100 \times 10^9$/L [100,000/μL]), or with platelet or neutrophil transfusion less than or equal to 7 days before date of the peripheral blood sample for disease assessment.
Complete response without platelet recovery	Attainment of M1 bone marrow status with no evidence of circulating blasts or extra-medullary disease and with recovery of peripheral counts (ANC $> 1 \times 10^9$/L [1000/μL]) but with insufficient recovery of platelets ($< 100 \times 10^9$/L [100,000/μL]), or with platelet transfusion less than or equal to 7 days before date of the peripheral blood sample for disease assessment. All patients with CRp qualify as CRi.

Response to Therapy for ALL (cont.)	
Category	Definition
Partial response	It is defined as the complete disappearance of circulating blasts and achievement of M2 bone marrow status without new sites of extramedullary disease, and with recovery of the ANCs ($> 1 \times 10^9$/L [1000/μL])
Stable disease	Disease response that does not meet criteria for CR, CRp, CRi, PR, or PD
Progressive disease	Increase of at least 25% in the absolute number of circulating leukemic cells, development of new sites of extra-medullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets
Molecular reappearance	A reconversion after MRD negativity to reproducible MRD positivity. A reconfirmation is strongly recommended. This finding does not fulfil the conditions for the definition of subsequent relapse
Relapse	Only in patients who achieved a CR/CRp/CRi and who subsequently develop: • Bone marrow blasts ≥ 5%; or • reappearance of blasts in the blood ≥ 1%; or • development of extra-medullary disease

CR = complete response; CRc = cytogenetic complete remission; CRi = complete response with incomplete hematological recovery; CRp = complete response without platelet recovery; MRD = minimal residual disease; PD = progressive disease; PR = partial response; SD = stable disease.

Appendix 9
Lansky Performance Status Scale (Patients <16 years of age)

Score	Description
100	Fully active; normal
90	Minor restrictions in physically strenuous activity
80	Active but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed

Appendix 10
Karnofsky Performance Status Scale (Patients ≥16 years of age)

Score	Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated; death not imminent
20	Very sick; hospitalization indicated; death not imminent
10	Moribund; fatal processes progressing rapidly

Appendix 11
Modified Continual Reassessment Method of Escalation with Overdose Control Design

Details of the modified continual reassessment method of escalation with overdose control (mCRM-EWOC) design used in the study are descripted in this appendix. In addition, the design operating characteristics are evaluated through comprehensive simulations in this section. In this study, the maximum tolerated dose (MTD) is defined as the dose maximizing the posterior probability that the dose-limiting toxicity (DLT) rate belongs to [0.20, 0.35], while keeping the probability of overdose below 0.25. Calculations are done using R package crmPack 0.2.7 (https://cran.r-project.org/web/packages/crmPack/index.html).

Dose-Response Model

The probability of DLTs over doses (dose-DLT response curve) will be described by a two-parameter logistic regression model:

$$logit(p(d)) = \alpha + \beta\left(\frac{d}{d^*}\right)$$

where *p(d)* stands for the DLT rates under a dose level *d*, and *d** is set to 20 mg/kg (i.e., 4 mg/kg QD × 5 days per cycle) in the study as the reference dose. Thus, the dose-DLT response curve follows a sigmoidal shape and can be flexibly adjusted by a parameter.

$$\theta = \begin{pmatrix} \alpha \\ log\beta \end{pmatrix} \sim N(\mu, \Sigma)$$

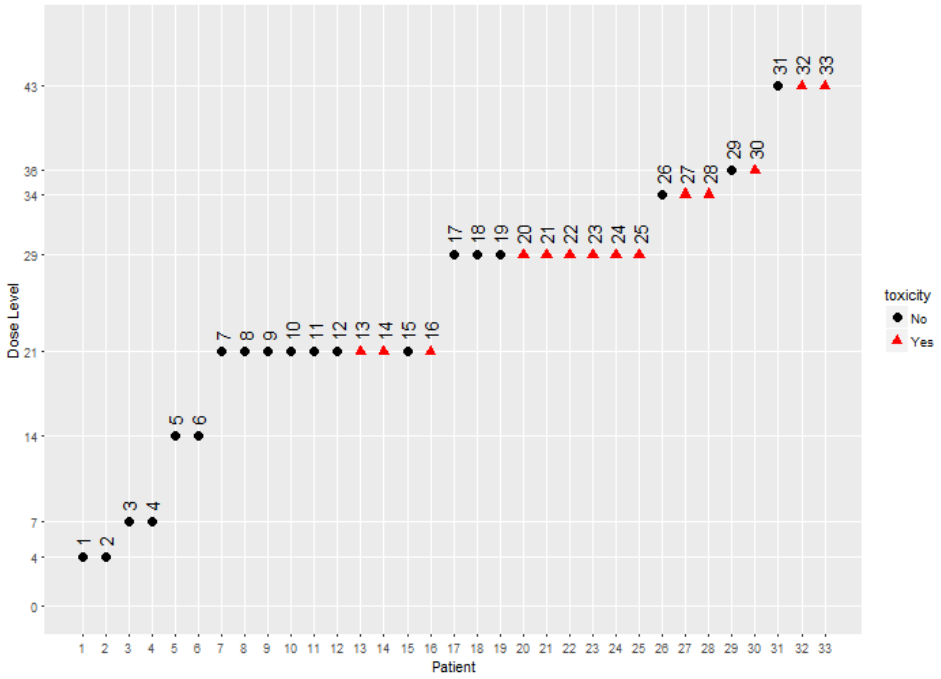
It is common to assume such a sigmoidal curve since usually the DLT rate increases monotonically while dose levels go up, but not in a linear way because it has a minimal level 0 and will reach a plateau when dose is very high. It is anticipated that idasanutlin would have a similar dose-DLT relationship.

Prior setting

In particular, a moderately informative prior is chosen for the log logistic models parameters. The parameters of this prior distribution θ are estimated from a posterior distribution utilizing DLT data collected from Study NP27872, which was a Phase I dose-escalation study for idasanutlin in adult patients with advanced malignancies except leukemia. Data were available from 30 DLT-evaluable patients on Schedule B (QD dosing × 5 days per cycle) portion of this Phase I study. The MBP formulation was used and the tested dose levels ranged from 500 mg to 6000 mg per cycle with DLT distribution as follows: 3 of 10 patients experiencing DLTs at 3000 mg, 6 of 9 patients at 4000 mg, 2 of 3 patients at 4800 mg, 1 of 2 patients at 5000 mg, and 2 of 3 patients at 6000 mg. The RP2D was 2500 mg MBP (500 mg QD × 5 days), which is considered equivalent to 1250 mg SDP formulation (see Figure 1).

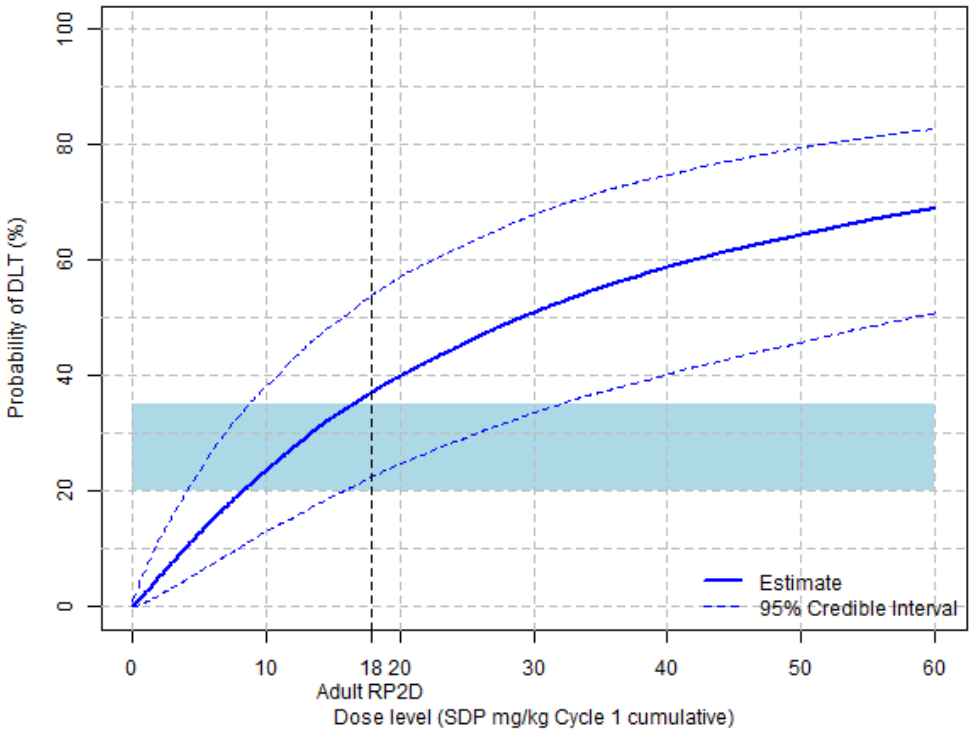
The posterior distribution of the log logistic model using this DLT data from the adult population was estimated based on mCRM. The mCRM design includes a statistical model to describe the DLT-dose relationship by a DLT-dose response curve.

Figure 1DLT Distribution at Different Dose Levels of Idasanutlin from Study NP27872



DLT = dose-limiting toxicity.

Figure 2Posterior Distribution of the Dose-DLT Response Curve according to Patient DLT data from Study NP27872 in Adult Population



DLT = dose-limiting toxicity; RP2D = Recommended Phase 2 Dose; SDP = solid dispersion powder.

The parameters of the log logistic model are listed below based on estimation from Study NP27872:

$$\mu = (-0.41709244 \quad -0.09044227)$$

$$\Sigma = \begin{pmatrix} 0.133065782 & 0.002678115 \\ 0.002678115 & 0.001752474 \end{pmatrix}$$

This prior will be informative as illustrated by the relatively narrow confidence bands. In order to have a less informative prior, the variance is artificially increased by multiplying the covariance matrix by a factor of 6. This factor is chosen to be the factor such that the desired maximum increments (50%) are reached (a smaller factor leads to smaller increments because of the high prior toxicity curve and a larger factor leads to

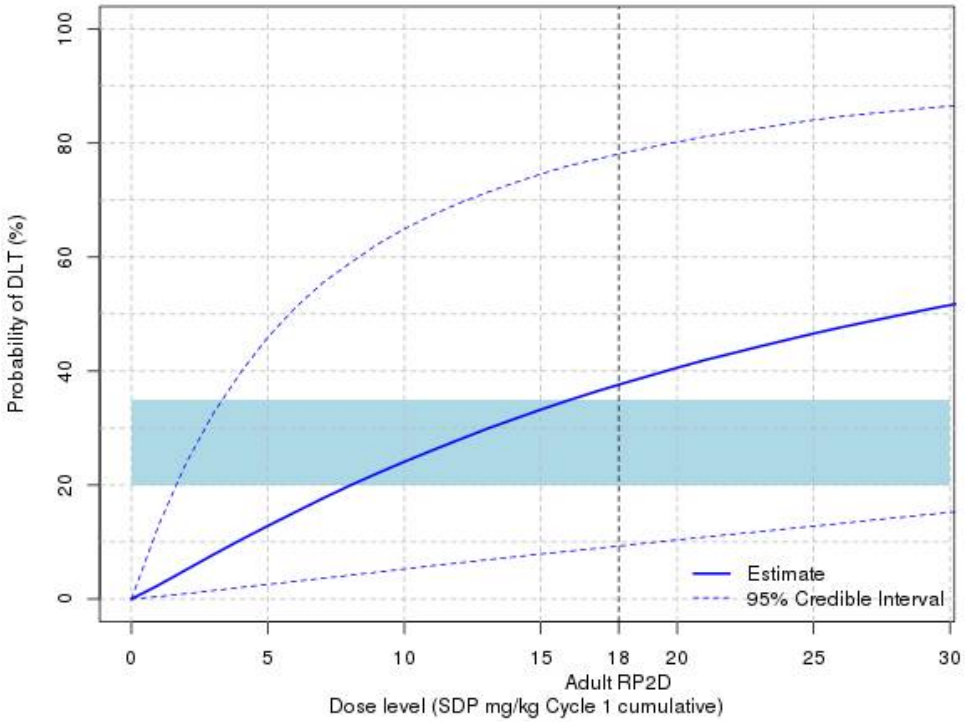
larger increments because of the higher variability of the posterior estimates). The parameters of the prior are listed below:

$$\mu = (-0.41709244 \quad -0.09044227)$$

$$\Sigma = \begin{pmatrix} 0.79839469 & 0.01606869 \\ 0.01606869 & 0.01051484 \end{pmatrix}$$

The prior distribution displayed in Figure 3 assumes: it would be unlikely that a 3-mg/kg dose (0.6 mg/kg QD × 5 days per cycle) corresponds to a 35% or higher DLT rate, and a 30-mg/kg dose (6 mg/kg QD x5 days per cycle) corresponds to a 15% or lower DLT rate.

Figure 3Prior Distribution of the mCRM-EWOC Design for Study GO40871



DLT = dose-limiting toxicity; mCRM-EWOC = modified continual reassessment method of escalation with overdose control; RP2D = Recommended Phase 2 Dose; SDP = solid dispersion powder.

Cohort size

At least 3 patients will be enrolled in each cohort, which, if required, may be expanded with additional patients in order to collect additional data on pharmacokinetics, pharmacodynamics, or safety. If 2 of 3 patients in a cohort (or 2 of 2 patients in a cohort if the third one become non-evaluable) already experienced DLT, no further expansion will be done. See details in Section 3.1.

Maximum Allowable Dose Increments

The maximum allowable dose increment is 50%.

Next Dose Selection

The selection dose for the next cohort will be guided by the mCRM-EWOC model, subject to clinical judgment and mandated safety constraints that limit the size of maximum allowable dose increments. Clinical judgment always overrides model estimates in the selection of the next dose. The Sponsor, in consultation with the investigators, can modify the dose to be used in the next cohort of patients as deemed appropriate at any time during the trial.

mCRM-EWOC Stopping rules

The dose-escalation trial will continue until the RP2D has been determined or the following pre-specified precision rules have been fulfilled:

- At least 6 subjects have been observed at a dose close to MTD (i.e., a dose within a 20% range of the estimated MTD).
- The maximal posterior probability of a dose being in the target DLT range is above 40%.

The Sponsor in consultation with the investigators may decide to stop the escalation prior to above stopping criteria being met if an RP2D has been determined. Also, based on clinical judgement and after discussion and agreement by IMC-SOC, dose escalation may continue despite meeting stopping rule criteria.

The mCRM-EWOC Algorithm

Patients in the first cohort will be treated with the starting dose of 10 mg/kg (2 mg/kg QD $\times$ 5 days per cycle), as recommended by PBPK modeling. Prior to opening a new cohort, the available DLT data will be used to update the mCRM-EWOC model through a Bayesian approach. That is, the posterior probability of parameter $\boldsymbol{\theta}$ from the logistic model will be estimated by using the DLT data from all patients in DLT-evaluable population. A recommended dose, d_r, for the next cohort will be calculated using the updated mCRM-EWOC model, i.e., $P(d_r)_{\text{overdose}} < 25\%$ and $d_r = \min(d_{rmax}, \max\{d_i: P(p(d_i) \in [0.2,0.35])\})$ where d_{rmax} is the highest next dose which subjects to the maximal increment rule.

Patients in the next cohort will be treated at the dose recommended by such an algorithm (possibly adjusted based on clinical judgment). This process is repeated until the stopping criterion is met.

Hypothetical trials

Several hypothetical trials are reported here to illustrate the behavior of the design in specific situations.

The first scenario illustrates how dose will be escalated assuming no DLTs are observed. The mCRM-EWOC model considered doses under a dose grid from 0 to 30 mg/kg (6 mg/kg QD × 5 days per cycle) by every 1 mg/kg (0.2 mg/kg QD × 5 days per cycle). The same dose grid applies in the simulation study.

Table 1 shows the different levels suggested by the mCRM-EWOC design. The results show that, in the absence of observed DLTs, the design will reach high doses based in 3 cohorts but also that the increments are 50% or below to protect the safety of patients.

Table 1 Simulated Dose Escalation Path in Absence of Observed Dose-Limiting Toxicities

Cohort	Dose (mg/kg)	Next Dose (mg/kg)	Increment
1	10	15	50%
2	15	22	47%
3	22	30	36%

Besides the impact on dose-escalation of the occurrence of a first DLT is examined, i.e., for cohorts of 3 subjects, all possible DLT frequencies (1 to 3) are examined assuming that no DLTs occur until the given dose for demonstration purpose. The recommended next doses suggested by the design after the DLTs are reported in the following table. Assuming that no DLTs are observed at this reduced dose, the dose suggested after the reduced dose is also computed.

The results show that the design will adequately adapt the dose in the presence of observed DLTs.

Table 2 Impacts on Dose-Escalation of the Occurrence of First Dose-Limiting Toxicities (Cohort of 3 Patients)

First DLT at Dose (mg/kg)	DLTs/Cohort Size	Next Dose (mg/kg)	Increment	Dose after the Next Cohort (mg/kg)
10	1/3	9	−10%	13
	2/3	5	−50%	7
	3/3	3	−70%	4
15	1/3	15	0%	19
	2/3	10	−33%	13
	3/3	7	−53%	9
22	1/3	20	−9%	28
	2/3	16	−27%	18
	3/3	11	−50%	14

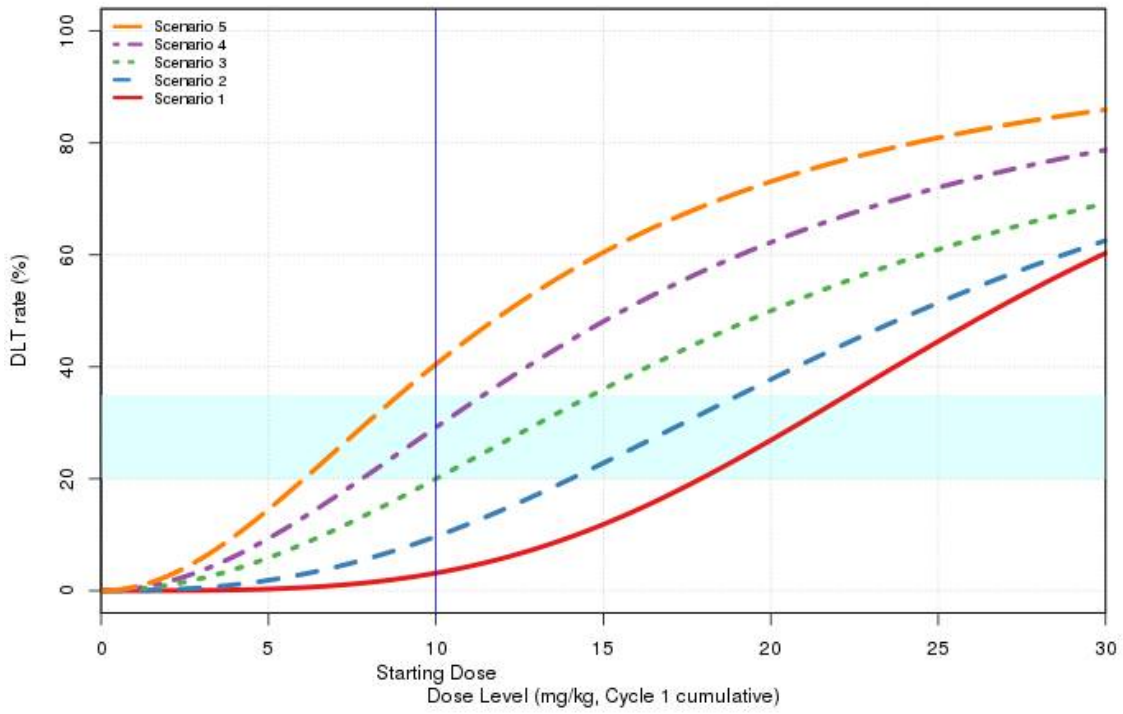
DLT = dose-limiting toxicity.

Simulations

A simulation study is conducted to evaluate the operating characteristics (sample size, estimated MTD, number of patients treated for overdose, etc.) for the chosen design parameters (priors, reference dose, stopping rules). For evaluation purposes, a maximum sample size of approximately 24 is used in the simulation.

Scenarios with different toxicity profiles are simulated with hypothetical MTDs from 7 mg/kg (low MTD) to around 20 mg/kg (illustrating a scenario for which a high MTD are expected). The starting dose is 10 mg/kg, which is marked by the vertical line in Figure 4 in this appendix. The 20% and 35% DLT range is marked by the blue area in Figure 4 in this appendix.

Figure 4 "True" Scenarios Used for Simulations



DLT = dose limiting toxicity.

Each scenario uses 1000 simulated trials, analyzed by generating a Markov chain Monte Carlo (MCMC) algorithm for 10000 iterations following a 1000-iteration burn-in period. Every one out of 2 iterations are saved after the burn-in (i.e., step = 2). Random manual checks revealed no significant MCMC convergence issues using standard convergence diagnostics.

The design is evaluated using the following criteria: the MTD chosen, the number of subjects treated at doses higher than the MTD, and the sample size of the trials. The following table demonstrates the simulation study result.

According to the simulation study, overall approximate 12−14 DLT-evaluable patients will be needed to reach to the MTD. The number of patients who may be treated above doses with 35% DLT rate is below 7 on average depending on the MTD. The most often selected MTD according to the mCRM-EWCO are all located within or very near the true target dose range. Overall, the mCRM-EWOC design has a relatively good performance in terms of controlling the safety and identifying MTD efficiently (Table 3 in this appendix).

Table 3 Operating Characteristics of the mCRM-EWOC Design with Respect to the Chosen Scenarios

Scenarios	Target Dose Range From the "True" Scenario (mg/kg)	Overall Number of Patients [a]	Number of Patients Treated Above Target Toxicity Interval [a]	Doses Selected as MTD (mg/kg) [a]	True Toxicity at Doses Selected as MTD [a]	Dose Most Often Selected as MTD (mg/kg)	Fitted Toxicity Rate at Dose Most Often Selected [a]
1	18–22	14 (12, 18)	2 (0, 6)	19 (14, 25)	24% (10%, 45%)	20	30% (22%, 35%)
2	14–19	13 (9, 18)	2 (0, 6)	15 (10, 21)	24% (10%, 41%)	14	30% (20%, 34%)
3	10–15	11 (9, 15)	3 (0, 9)	12 (9, 17)	26% (17%, 42%)	9	20% (16%, 28%)
4	8–11	11 (6, 15)	3 (0, 6)	10 (7, 14)	29% (17%, 45%)	9	30% (19%, 33%)
5	6–9	12 (6, 15)	7 (3, 9)	8 (5, 12)	32% (15%, 50%)	9	30% (22%, 40%)

mCRM-EWOC = Modified Continual Reassessment Method of Escalation with Overdose Control; MTD = maximum tolerated dose.

[a] Values in the table are means, followed by 10% and 90% quantile.

Appendix 12
Howard Definition and Classification of Tumor Lysis Syndrome

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	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 × (4 – albumin in grams per deciliter).

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

REFERENCES

Table copied from: Howard SC, Jones P, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364:1844–54.

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 13
Acceptability Survey for Patients

Instructions: Please answer the questions below to help us understand your experience with the study medication (idasanutlin). For questions with a face, indicate which of the faces best matches how you felt about the medication.

For children who cannot read yet, parents or caregiver, please help us understand your child's experience with the medication. Invite your child to look at the cartoon, ask him or her the questions, and record his or her answer. If your child cannot answer the question, please leave the question blank.

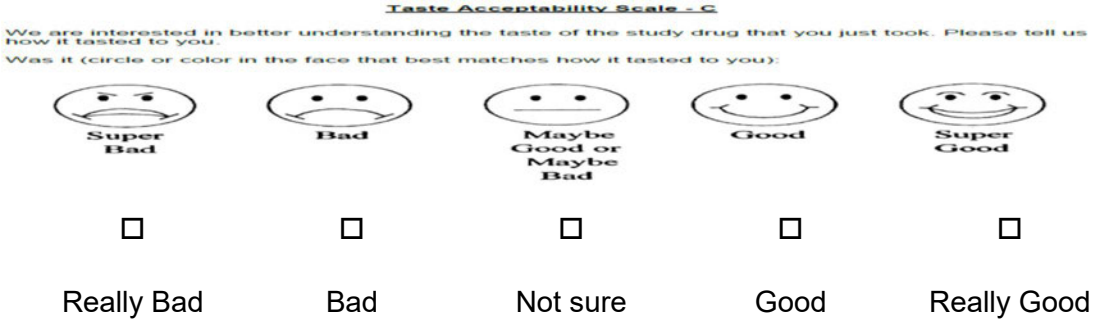
1. How did you take the medication?

   ☐ As a tablet (pill)

   ☐ As a suspension (pills dissolved in water)

For children who cannot answer for themselves, parents or caregiver, please go directly to Questions 8 and 9.

2. How much did you like the taste of the medication?



☐	☐	☐	☐	☐
Really Bad	Bad	Not sure	Good	Really Good

3. What was the taste of the medication?

   ☐ Bitter

   ☐ Sweet

   ☐ Sour

   ☐ Salty

4. How much did you like the feeling of the medication in your mouth?

☐ Really Bad ☐ Bad ☐ Not sure ☐ Good ☐ Really Good

5. How difficult was it to swallow the medication?

☐ Really Bad ☐ Bad ☐ Not sure ☐ Good ☐ Really Good

6. After the medication was not in your mouth anymore, could you still taste the medication?

   ☐ Yes

   ☐ No

7. What was the taste you had in your mouth after the medication was gone?

   ☐ Bitter

   ☐ Sweet

   ☐ Sour

   ☐ Salty

For parent or caregiver of children who cannot answer for themselves:

8. At any time did you have a problem in giving the medication to your child because he or she refused to take it?

   ☐ Yes

   ☐ No

9. At any time did you have a problem in giving the planned dose of the medication to your child because he or she threw it up?

   ☐ Yes

   ☐ No

Additional questions for participants receiving and caregivers administering suspension (tablets dispersed in water):

Instructions: Please answer the questions below to help us understand your experience giving the study medication (idasanutlin).

10. How easy or difficult was it to fill the medication dispenser (syringe) with water?

    ☐ Very easy

    ☐ Somewhat easy

    ☐ Somewhat difficult

    ☐ Very difficult

11. Did all of the tablets dissolve completely in the water?

    ☐ Yes

    ☐ No

12. Were there any undissolved tablets left in the syringe?

    ☐ Yes

    ☐ No

Thank You

Appendix 14
Age and Weight Adjusted Adult-Equivalent Venetoclax Dosing Table

For ≤2 Years						For >2 Years					
Dose Groups: Age	2-day Ramp-up (Solid Tumors)		3-Day Ramp-up (Hematologic Malignancies)			Dose Groups: Weight	2-day Ramp-up (Solid Tumors)		3-Day Ramp-up (Hematologic Malignancies)		
	Day 1	Day 2 & On	Day 1	Day 2	Day 3 & On		Day 1	Day 2 & On	Day 1	Day 2	Day 3 & On
400 mg Adult Equivalent Dose											
newborn to <1 month	2.5[a]	5[a]	2.5[a]	2.5[a]	5[a]	10 to <20 Kg	60	120	30	60	120
1 to <3 months	5[a]	10	2.5[a]	5[a]	10	20 to <30 Kg	80	170	40	80	170
3 to <6 months	10	25	5[a]	10	25	30 to <45 Kg	120	250	60	120	250
6 months to <1 year	25	50	10	25	50	≥45 Kg	200	400	100	200	400
1 to <2 years	30	75	20	40	75						
600 mg Adult Equivalent Dose											
newborn to <1 month	2.5[a]	7.5[a]	2.5[a]	2.5[a]	7.5[a]	10 to <20 Kg	80	150	40	80	150
1 to <3 months	10	20	5	10	20	20 to <30 Kg	120	250	50	120	250
3 to <6 months	20	40	10	20	40	30 to <45 Kg	170	350	80	170	350
6 months to <1 year	30	75	20	40	75	≥45 Kg	300	600	150	300	600
1 to <2 years	60	120	30	60	120						

[a] Dose can only be administered using the $2.5\ mg$ tablet for oral suspension formulation.

Appendix 15
Dosing Tables for Intrathecal Therapy

AML: CNS negative	
Age	Cytarabine
< 1 year	20 mg
≥ 1–< 2 years	30 mg
≥ 2–< 3 years	50 mg
≥ 3 years	70 mg

ALL: CNS negative	
Age	Methotrexate
< 1 year	6 mg
≥ 1–< 2 years	8 mg
≥ 2–< 3 years	10 mg
≥ 3 years	12 mg

AML and ALL: CNS positive or post-traumatic lumbar puncture			
Age	Methotrexate	Cytarabine	Hydrocortisone
< 1 year	6 mg	18 mg	12 mg
≥ 1–< 2 years	8 mg	24 mg	16 mg
≥ 2–< 3 years	10 mg	30 mg	20 mg
≥ 3 years	12 mg	36 mg	24 mg