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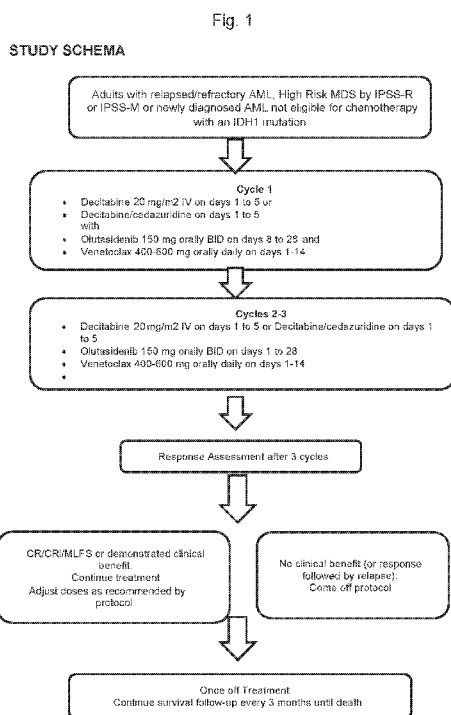
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(54) Title: TREATMENT OF ACUTE MYELOID LEUKEMIA WITH OLUTASIDENIB, VENETOCLAX AND A HYPOMETHY-
LATING AGENT



(57) Abstract: Provided are methods of treating a subject having a hematologic malignancy or pre-malignancy that involve administering an effective amount of olutasidenib, venetoclax, and a hypomethylating agent. In some cases, the patient has an IDH1 mutation.

TREATMENT OF ACUTE MYELOID LEUKEMIA WITH OLUTASIDENIB,
VENETOCLAX AND A HYPOMETHYLATING AGENT

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/525,639, filed on July 7, 2023, which is incorporated herein by reference in its entirety.

INTRODUCTION

[0002] Mutant IDH1 is a genetically validated target in hematologic cancers, including AML. Mutations of IDH1 present in certain cancer cells can result in a new ability of this enzyme to catalyze the NADPH-dependent reduction of α -ketoglutarate to 2-hydroxyglutarate (2HG), usually the enantiomer (R)-2-hydroxyglutarate (R-2HG). 2HG is not formed by wild-type IDH. The presence of mutations at codon 132 in IDH1 imparts a neomorphic activity to the enzyme, resulting in the production of the “oncometabolite” 2HG, which has pleotropic roles in tumorigenesis. Excess production of 2HG has been shown to inhibit α -KG-dependent enzymes involved in epigenetic regulation, collagen synthesis, and cell signaling, thereby leading to a block in normal differentiation of progenitor cells and the subsequent development of cancer mutations in IDH1 associated with 2HG neomorphic activity, specifically R-2HG neomorphic activity, including mutations at residues 97, 100, and 132, e.g. G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. IDH mutation-specific inhibitors have been shown to reduce aberrantly elevated levels of the oncometabolite 2HG, resulting in antitumor efficacy in preclinical models.

SUMMARY

[0003] Provided are methods of treating a subject having a hematologic malignancy or pre-malignancy that involve administering an effective amount of olutasidenib, venetoclax, and a hypomethylating agent. For instance, the hypomethylating agent can be azacytidine or decitabine. In some cases, the malignancy or pre-malignancy has an IDH1 mutation. In certain embodiments the hematologic malignancy comprises acute myeloid leukemia (AML).

BRIEF DESCRIPTION OF THE FIGURES

[0004] **FIG. 1** illustrates the design of a clinical trial.

DETAILED DESCRIPTION

[0005] Before the present invention is described in greater detail, it is to be understood that this invention is not limited to particular embodiments described, as such may vary. It is also to be

understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0006] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0007] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some potential and exemplary methods and materials may now be described. Any and all publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

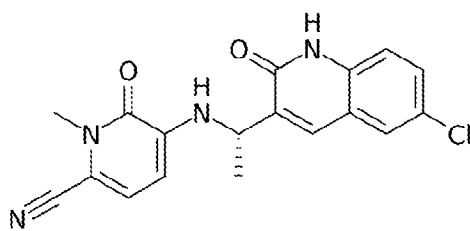
[0008] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a droplet" includes a plurality of such droplets and reference to "the discrete entity" includes reference to one or more discrete entities, and so forth. It is further noted that the claims may be drafted to exclude any element, e.g., any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or the use of a "negative" limitation.

[0009] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed. To the extent the definition or usage of any term herein conflicts with a definition or usage of a term in an application or reference incorporated by reference herein, the instant application shall control.

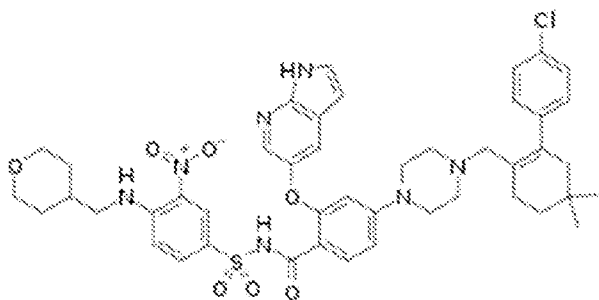
[0010] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

DEFINITIONS

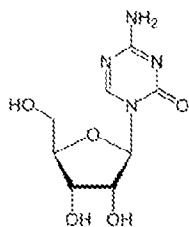
[0011] Olutasidenib is a compound with the Chemical Abstract Services (CAS) number of 1887014-12-1 and the structure:



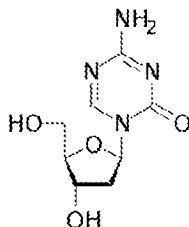
[0012] Venetoclax is a compound with the CAS number 1257044-40-8 and the structure:



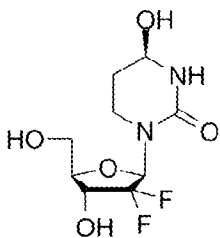
[0013] Azacitidine is a compound with the CAS number 320-67-2 and the structure:



[0014] Decitabine is a compound with the CAS number 2353-33-5 and the structure:



[0015] Cedazuridine is a compound with the CAS number 1141397-80-9 and the structure:



[0016] The term “standard of care” or “SOC” refers to treatment that is accepted by skilled artisans as proper treatment for a certain type of disease, e.g. medical treatments that are widely used by healthcare professionals. In certain embodiments, the National Comprehensive Cancer Network (NCCN) guidelines may be the source for standard of care for AML, MDS and other hematologic malignancies and pre-malignancies.

[0017] The terms active agent, active pharmaceutical ingredient, pharmacologically active agent, and drug are used interchangeably herein to refer to a chemical material or compound which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action.

[0018] The terms “QD” and “BID,” mean once daily and twice daily, respectively.

[0019] The terms “individual,” “host,” “subject,” and “patient” are used interchangeably herein, and refer to an animal, including, but not limited to, human and non-human primates, including simians and humans; rodents, including rats and mice; bovines; equines; ovines; felines; canines; and the like. “Mammal” means a member or members of any mammalian species, and includes, by way of example, canines; felines; equines; bovines; ovines; rodentia, etc. and primates, e.g., non-human primates, and humans. Non-human animal models, e.g., mammals, e.g. non-human primates, murines, lagomorpha, etc. may be used for experimental investigations.

[0020] As used herein, the term “remission,” includes complete remission (“CR”), complete remission with partial hematologic recovery (“CRh”), complete remission with incomplete recovery (“CRi”), morphologic leukemia-free state (“MLFS”), partial remission (“PR”) and stable disease (“SD”). CR includes complete remission, complete cytogenetic remission (“CRc”) and complete molecular remission (CRm). Remission status determined by investigator assessment, using modified response criteria of the International Working Group in AML (Cheson et al., *J Clin Oncol.* 2003;21:4642–4649). CRh was defined as bone marrow blasts <5% with absolute neutrophil count $>0.5 \times 10^9/\text{L}$ and platelet count $>50 \times 10^9/\text{L}$.

[0021] As used herein, the terms “treatment,” “treating,” and the like, refer to obtaining a desired pharmacologic and/or physiologic effect, such as reduction of viral titer. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. “Treatment,” as used herein, covers any treatment of a disease in a

mammal, particularly in a human, and includes: (a) preventing the disease or a symptom of a disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it (e.g., including diseases that may be associated with or caused by a primary disease (as in liver fibrosis that can result in the context of chronic HCV infection); (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease (e.g., reduction in viral titers).

[0022] A “therapeutically effective amount”, “effective amount”, a “therapeutically effective dose” or “therapeutic dose” is an amount sufficient to effect desired clinical results (i.e., achieve therapeutic efficacy, achieve a desired therapeutic response, etc.). A therapeutically effective dose can be administered in one or more administrations. For purposes of this disclosure, a therapeutically effective dose of a compositions is an amount that is sufficient, when administered to the individual, to palliate, ameliorate, stabilize, reverse, prevent, slow or delay the progression of a disease state (e.g., cancer, etc.) present in the subject.

[0023] As used herein, the terms “determining,” “measuring,” “assessing,” and “assaying” are used interchangeably and include both quantitative and qualitative determinations.

[0024] The term “unit dosage form,” as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of a compound (e.g., an aminopyrimidine compound, as described herein) calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for unit dosage forms depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

[0025] A “pharmaceutically acceptable excipient,” “pharmaceutically acceptable diluent,” “pharmaceutically acceptable carrier,” and “pharmaceutically acceptable adjuvant” means an excipient, diluent, carrier, and adjuvant that are useful in preparing a pharmaceutical composition that are generally safe, non-toxic and neither biologically nor otherwise undesirable, and include an excipient, diluent, carrier, and adjuvant that are acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable excipient, diluent, carrier and adjuvant” as used in the specification and claims includes both one and more than one such excipient, diluent, carrier, and adjuvant.

[0026] As used herein, a “pharmaceutical composition” is meant to encompass a composition suitable for administration to a subject, such as a mammal, especially a human. In general a “pharmaceutical composition” is sterile, and preferably free of contaminants that are capable of eliciting an undesirable response within the subject (e.g., the compound(s) in the pharmaceutical composition is pharmaceutical grade). Pharmaceutical compositions can be designed for

administration to subjects or patients in need thereof via a number of different routes of administration including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, intracheal, intramuscular, subcutaneous, and the like.

[0027] The terms "co-administration" and "in combination with" include the administration of two or more therapeutic agents either simultaneously, concurrently or sequentially within a treatment plan, such as a treatment cycle. Typically, a treatment cycle is a period of time wherein a drug or combination of drugs is administered, followed by a period of rest. In the present methods, the period of rest between cycles is optional. Accordingly, co-administration in the present methods, such as co-administration of olutasidenib, venetoclax, and a hypomethylating agent, refers to administration of the three components within a treatment plan. The treatment cycle (or dosing cycle) follows a dosing schedule. As used herein, a dosing schedule describes the frequency a drug is administered at a particular dosage. In one embodiment, co-administration means administration of three components within twenty-eight days of one another, such as on the same or different days within a twenty-eight day treatment cycle. In one embodiment, the agents are present in the cell or in the subject's body at the same time or exert their biological or therapeutic effect at the same time. In one embodiment, the therapeutic agents are in the same composition or unit dosage form. In other embodiments, the therapeutic agents are in separate compositions or unit dosage forms. In certain embodiments, a first agent can be administered prior to (e.g., minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, or 4 weeks) the administration of one or more additional therapeutic agents.

[0028] The term "unfit" refers to an assessment of unfitness to receive chemotherapy and is made by one skilled in the art, such as a clinical hematologist or hematologist-oncologist. For example, Ferrara et al. discusses a consensus based definition of unfitness to intensive and non-intensive chemotherapy in AML (*Leukemia*, 2013, 27, 997, doi: 10.1038/leu.2012.303). Unfitness is also described in Samra et al. (*Frontier in Oncology*, 2020, 10, 562558, doi:10.3389/fonc.2020.562558). In some cases, the patient is unfit because they are over 65 years of age, have organ dysfunction (e.g. cardiac, pulmonary, renal, hepatic), or a combination thereof. In some cases, a determination of unfitness includes an assessment that the chemotherapy is more likely to cause harm or death than leaving the cancer untreated.

[0029] The terms "IDH1-mediated diseases or disorders" shall include diseases associated with or implicating IDH1 activity, for example, the overactivity of IDH1, and conditions that

accompany with these diseases. It is known that overactivity of IDH-1 has been implicated in the pathogenesis of a number of diseases, including inflammatory and autoimmune diseases, cell proliferative disorders, neoplastic disorders and cancers as described herein.

[0030] The term “proliferative disorder or disease” refers to unwanted cell proliferation of one or more subset of cells in a multicellular organism resulting in harm (i.e., discomfort or decreased life expectancy) to the multicellular organisms. A proliferative disorder or disease can occur in different types of animals and humans. For example, as used herein, “proliferative disorder or disease” includes neoplastic disorders and other proliferative disorders.

[0031] The term “neoplastic disorder or disease” or “cancer” refers to a tumor resulting from abnormal or uncontrolled cellular growth. Examples of neoplastic disorders include, but are not limited to, hematopoietic disorders, such as the myeloproliferative disorders, thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes; cancers, such as glioma cancers, lung cancers, breast cancers, colorectal cancers, prostate cancers, gastric cancers, esophageal cancers, colon cancers, pancreatic cancers, ovarian cancers, and hematologic malignancies.

[0032] The term “hematologic malignancy” refers to cancer of the body's blood-forming and immune system-the bone marrow and lymphatic tissue. Examples of hematological malignancies include, for instance, myelodysplasia, lymphomas, leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, such as acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma, (MM).

[0033] The term “pre-malignancy,” as used herein, refers to somatic mutations that may give rise to or increase the risk of the development of a hematologic malignancy. Certain hematopoietic mutations confer a fitness advantage that favors their disproportionate expansion. Examples of pre-malignancies that can be treated as described herein include, without limitation, clonal hematopoiesis of indeterminate potential (CHIP), cytopenia of undetermined significance (CCUS), pre-malignant or low-risk MDS, and the like. Other premalignant conditions are characterized by particular mutations and are known to those of skill in the art.

[0034] The term “leukemia” refers to malignant neoplasms of the blood-forming tissues, including, but not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia.

METHODS

[0035] As discussed above, provided are methods of treating a subject having a hematologic malignancy, such as acute myeloid leukemia (AML) or MDS. In one embodiment, the hematologic malignancy comprises MDS, AML, or both. Accordingly provided herein are methods for treating MDS. Likewise provided are methods for treating AML. Such methods include administering olutasidenib, venetoclax, and a hypomethylating agent. Such methods may result in a beneficial remission in the AML and improvement of symptoms of the patient.

[0036] In some embodiments, the MDS is characterized by an isocitrate dehydrogenase 1 (IDH1) mutation. In one embodiment, the IDH1 mutation is detected in the patient’s blood, bone marrow, or both.

[0037] In some embodiments, the AML is characterized by an isocitrate dehydrogenase 1 (IDH1) mutation. The cancer patient can be diagnosed with AML characterized by the detection of IDH1 mutations in blood, bone marrow or both. AML patients without IDH1 mutations at diagnosis can be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse. In some cases, the administration can inhibit the IDH1 mutant, e.g. as those leading to increased levels of 2HG in leukemia cells. The most common of such mutations are R132H and R132C substitutions. Thus, in some cases the patient has an IDH1 mutation, e.g. a R132H mutation, a R132C mutation, or a combination thereof.

[0038] In some cases, the administration of olutasidenib, venetoclax, and a hypomethylating agent is repeated for multiple days, e.g. for 10 or more days, 50 or more days, 100 or more days, 200 or more days, or 400 or more days. In some instances, the administration is repeated to slow the proliferation of the cancer or to reduce the amount of cancer. Thus, the administration can be repeated for extended periods of time.

[0039] DiNardo et al. have described the use of decitabine or azacitidine in combination with venetoclax in a Phase 1b dose escalation and expansion study in elderly patients with untreated AML (DiNardo et al. *Blood*. 2015-12-03 00:00:00 2015;126(23):327-327). In this study, venetoclax was co-administered daily with 20 mg/m² of decitabine on days 1-5 or 75 mg/m² of azacitidine on days 1-7, each 28-day cycle. Venetoclax was dosed at 400, 800, or 1200 mg in the escalation phase, and 400 or 800 mg in the expansion phase.

[0040] In some instances, the amount of olutasidenib administered per day is about 300 mg. The olutasidenib can be administered in a single dose, e.g. a 300 mg dose, or in multiple doses

that give an overall daily dose of about 300 mg, e.g. a dose of 150 mg that is administered twice a day. In some cases, the administration of “about 300 mg” of olutasidenib is an administration ranging from 200 mg to 400 mg, such as from 250 mg to 350 mg or from 275 mg to 325 mg. In some cases, the administration is 300 mg of olutasidenib. In one embodiment, olutasidenib is administered in a 150 mg dose twice daily.

[0041] In some cases, the amount of venetoclax administered per day ranges from about 400 mg to about 800 mg. For example, the administration of venetoclax per day can range from 300 mg to 900 mg, such as from 400 mg to 800 mg, from 500 mg to 700 mg, or from 550 mg to 650 mg. The venetoclax can be administered as a single dose during a single day, or it can be administered as multiple doses during a single day. In certain embodiments, the dosage of venetoclax is reduced in a course of treatment. By way of example, the dosage of venetoclax on day 1 may be 800 mg and the dosage on a subsequent day may be lower, such as from about 400 mg to about 700 mg, such as 400 mg, 500 mg or 600 mg. Venetoclax typically is introduced to a patient in an initial “ramp up” phase. The ramp up dosing varies depending on the malignancy being treated, however, by way of example, treatment for AML with venetoclax involves an initial ramp up, depending on the combination regimen used. In certain embodiments, the venetoclax ramp up phase consists of 100, 200, and 400 mg given on days 1, 2, and 3, respectively; for day 4 and beyond, the venetoclax dose is 400 mg/day when given in combination with azacitidine or decitabine and 600 mg/day when given in combination with low-dose cytarabine. The three-day ramp up is illustrated in Table 1:

Table 1: Three-day ramp up

	VENCLEXTA Oral Daily Dose	
Day 1	100 mg	
Day 2	200 mg	
Day 3	300 mg	
Days 4 and beyond	400 mg orally once daily of each 28-day cycle in combination with azacitidine or decitabine	600 mg orally once daily of each 28-day cycle in combination with low-dose cytarabine

[0042] In certain embodiments, venetoclax ramp up is to manage the risk of tumor lysis syndrome (TLS). In certain embodiments, patients are assessed for patient-specific factors for level of risk of TLS, for example, as described in the VENCLEXTA® USPI, and provided prophylactic hydration and anti-hyperuricemics to patients prior to first dose of venetoclax to reduce risk of TLS. Venetoclax is administered according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg as shown in Table 2. The 5-week ramp-up dosing

schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS. Patients are instructed to take venetoclax tablets with a meal and water at approximately the same time each day, and to swallow whole and not chew, crush, or break prior to swallowing. The dosing schedule for the 5-week ramp up phase is provided in Table 2:

Table 2: Five-week ramp up phase

Week	Venetoclax Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

[0043] In certain embodiments, venetoclax is administered after a one-day ramp up of 100 mg once daily, at 200 mg once daily. In yet certain embodiments, venetoclax is administered at 200 mg once daily without a ramp-up phase. In one aspect of the present embodiments, venetoclax is dosed after ramp up at 400 mg per day. In another aspect, venetoclax is dosed after ramp up at 600 mg per day. In yet another aspect, venetoclax is dosed after ramp up at 800 mg per day. In one embodiment herein, the ramp up of venetoclax is optional as is understood by those of ordinary skill in the art of treating hematologic malignancies, such as AML. In such an embodiment, the patient is dosed at 400 mg or 600 mg once daily of each 28-day cycle. In another embodiment, the patient is dosed at 400 mg or 800 mg once daily of each 28-day cycle. In yet certain other embodiments, venetoclax is administered at 400 mg once daily or 600 mg once daily without a ramp-up phase.

[0044] In certain embodiments, venetoclax and azacytidine are both administered in a dosing cycle. In yet certain embodiments, venetoclax and azacytidine are administered in a 28-day cycle where venetoclax is administered at 400 mg PO QD at Day 1 to 28 and azacitidine administered 75 mg/m² IV/SC at Day 1 to 7. In yet certain embodiments, during cycle 1, the dose of venetoclax is 100 mg PO QD at Day 1, 200 mg PO QD at Day 2; 400 mg PO QD at Day 3, and remains 400 mg PO QD subsequently until Day 28, while azacitidine is administered 75 mg/m² IV/SC at Day 1 to 7; and in cycle 2 and subsequent 28-day cycles, the dose of venetoclax is 400 mg PO QD while azacitidine is administered 75 mg/m² IV/SC at Day 1 to 7.

[0045] In certain embodiments, venetoclax and decitabine are administered in a dosing cycle. In certain embodiments of a 28-day cycle, decitabine is administered on days 1 – 5 of the cycle, and venetoclax is administered on days 1 – 28 of the cycle or on a subset of days 1 – 28, such as days 1 – 7, 1 – 10, 1 – 14, or 1 – 21. In one embodiment, decitabine is administered intravenously

at a dosage of 20 mg/m² on days 1 – 5 of a 28 day cycle and venetoclax is administered at from 300 to 800 mg daily, such as 400 mg daily, 600 mg daily, or 800 mg daily. In such embodiments, olutasidenib is administered on days 1 – 28 of the 28-day cycle, or a subset of days, such as days 1 – 7, 8 – 21 or 8 – 28. Olutasidenib is administered once or twice daily for a total of 300 mg/day, such as 150 mg twice daily. Embodiments of a dosing schedule for co-administration of decitabine, venetoclax and olutasidenib are illustrated in the following Table 3.

Table 3: Embodiment of triplet therapy dosing schedule

Dose Level	IV decitabine	Venetoclax	Olutasidenib
2	20 mg/m ² IV on days 1-5	600 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)
1	20 mg/m ² IV on days 1-5	400 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)
-1	15 mg/m ² IV on days 1-5	400 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)

[0046]

[0047] The terms “optimal dose” and “suboptimal dose” are also used herein. The meaning of these terms can be understood by considering a hypothetical example where olutasidenib is the only medication being used to treat the patient for AML, i.e. the patient does not receive any other medications for the AML. In such an example, the medical professional can determine the dose of olutasidenib to give to the patient. An “optimal dose of olutasidenib” is the amount of olutasidenib that will produce the maximum improvement in AML when olutasidenib is the only medication being administered for the AML. Therefore, if the actual olutasidenib dose was below the optimal level, then the dose is considered “suboptimal”, and patient’s medical improvement will be less than the medical improvement with the optimal dose.

[0048] In some embodiments of the presently described methods, the patient is administered a suboptimal dose of olutasidenib. Since the present methods also include administration of venetoclax and a hypomethylating agent (e.g. azacitidine or decitabine), a lower dosage of olutasidenib can be used because the venetoclax and the hypomethylating agent are also helping to improve the AML.

[0049] Similarly, in some cases the venetoclax is administered in a suboptimal dose absent the contribution of combination treatment with olutasidenib. If venetoclax was administered under

standard of care conditions for AML, then an optimal dose of venetoclax would provide the best medical outcome. However, in one embodiment, combination therapy with olutasidenib also allows a reduction in the dosage of venetoclax without reducing the benefit to the patient. Reduction in venetoclax dosage in amount, frequency or duration is desirable in view of the toxicity associated with SOC treatment with venetoclax.

[0050] In some cases, the hypomethylating agent is azacitidine. For example, the amount of azacitidine can be about 75 mg/m², such as from 60 mg/m² to 90 mg/m², or from 70 mg/m² to 80 mg/m². The azacitidine can be administered in a single dose or in multiple doses during a single day.

[0051] In some embodiments, the hypomethylating agent is decitabine, e.g. which can be administered in an amount of about 35 mg per day, such as from 20 mg to 50 mg or from 30 mg to 40 mg per day. The decitabine can be administered in a single dose or multiple doses during a single day.

[0052] The compounds can be administered over multiple days according to a dosing schedule. As such, the amount of each compound administered each day can be planned before the commencement of the dosing schedule. In certain embodiments, the combination therapy is administered over a set period of time according to the dosing schedule. In certain embodiments, the combination therapy is administered over a 28-day dosing schedule. For instance, the olutasidenib can be administered on days 1 to 28 of the dosing schedule. Stated in another manner, the olutasidenib can be administered during each day ranging from day 1 to day 28. Additionally, the venetoclax can be administered daily on days 1 to 14 of the dosing schedule. In some cases, the hypomethylating agent is azacitidine and the azacitidine is administered daily on days 1 to 7 of the dosing schedule. In some embodiments, the hypomethylating agent is decitabine and the decitabine is administered on days 1 to 5 of the dosing schedule. In certain embodiments, the combination therapy is administered over the course of one or more 28-day dosing schedule, optionally with a period of non-treatment between two 28-day dosing schedule.

[0053] In some embodiments, the method further includes administering cedazuridine to the subject. In one such embodiment, the hypomethylating agent comprises a combination of decitabine and cedazuridine, such as is sold under the trade name INQOVI®. In one such embodiment, the hypomethylating agent comprises a dose of 35 mg decitabine and 100 mg of cedazuridine. The combination of decitabine and cedazuridine is typically given orally in tablet form. In certain embodiments, venetoclax and a combination of decitabine and cedazuridine are administered in a dosing cycle. In certain embodiments of a 28-day cycle, decitabine and cedazuridine are administered on days 1 – 5 of the cycle, and venetoclax is administered on days 1 – 28 of the cycle or on a subset of days 1 – 28, such as days 1 – 7, 1 – 10, 1 – 14, or 1 – 21. In

one embodiment, decitabine and cedazuridine is administered orally in a single tablet. In one such embodiment, 35 mg decitabine and 100 mg of cedazuridine is administered on days 1 – 5 of a 28 day cycle and venetoclax is administered at from 200 to 800 mg once daily, such as 200 mg once daily, 400 mg once daily, 600 mg once daily, or 800 mg once daily. In one such embodiment, 35 mg decitabine and 100 mg of cedazuridine is administered on days 1 – 5 of a 28 day cycle and venetoclax is administered at from 300 to 800 mg daily, such as 400 mg daily, 600 mg daily, or 800 mg daily. In such embodiments, olutasidenib is administered on days 1 – 28 of the 28-day cycle, or a subset of days, such as days 1 – 7, 8 – 21 or 8 – 28. Olutasidenib is administered once or twice daily for a total of 300 mg/day, such as 150 mg twice daily. Embodiments of a dosing schedule for co-administration of 35 mg decitabine and 100 mg of cedazuridine., venetoclax and olutasidenib are illustrated in the Table 4.

Table 4: Embodiment of triplet therapy dosing schedule

Dose Level	Oral decitabine/cedazuridine	Venetoclax	Olutasidenib
2	1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1-5	600 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)
1	1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1-5	400 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)
-1	1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1-4	400 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)

[0054] With reference to the dosing embodiments set forth above, the dosages can be modified as is known to those of skill in the art upon the occurrence of adverse events or dose-related toxicity.

[0055] In one embodiment, the dose of a the hypomethylating agent is reduced. By way of example, a first (“-1”) dose reduction for patients exhibiting decitabine-related adverse events is 15 mg/m² IV on days 1 – 5; the second (“-2”) dose reduction is 15 mg/m² IV on days 1 – 4; and the third (“-3”) dose reduction is 15 mg/m² IV on days 1 – 3.

[0056] In another embodiment, wherein the hypomethylating agent is decitabine/cedazuridine, the first dose reduction for patients exhibiting decitabine/cedazuridine-related adverse events, such as myelosuppression, is 1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1 – 4; the second dose reduction is 1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1 – 3;

and the third dose reduction is 1 tablet (35 mg decitabine and 100 mg cedazuridine) on days on days 1, 3 and 5.

[0057] In the event of venetoclax-related adverse events, a first dose reduction for patients starting at 400 mg of venetoclax is 400 for 10 days duration, and the second dose reduction is 400mg of venetoclax for 7 days duration. Similarly, a first dose reduction for patients starting at 600 mg of venetoclax is 600mg for 10 days duration, and the second dose reduction is 600mg of venetoclax for 7 days duration.

[0058] In one embodiment, where olutasidenib-related adverse events are observed, the first dose reduction is from 150mg twice daily to 150mg once daily.

[0059] In some embodiments, the hypomethylating agent is administered orally. In some embodiments, decitabine, azacytidine, cedazuridine, or a combination of the foregoing, may be administered orally. By way of example, decitabine, cedazuridine, or both may be administered orally.

[0060] In some cases, the method includes diagnosing the subject with the AML. The cancer patient can be diagnosed with AML characterized by the detection of IDH1 mutations in blood or bone marrow. As such, the diagnosing can comprise taking a sample of bone marrow from the patient and examining the bone marrow sample. AML patients without IDH1 mutations at diagnosis can be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse. Methods of diagnosing AML are described in US Patent Application Publication 2008/028077 and US 2007/0287163. Methods for characterizing AML by IDH1 mutation status are described by Mardis *et al. N. Engl. J. Med.* **2009**, 361, 1058 – 1066.

[0061] In some cases, the dosage schedule includes an initial “ramp up” phase followed by a “constant” phase. During the initial ramp-up phase, the dosage being administered is increased from zero to one or more intermediate values. For example, the dosage of olutasidenib could be 100 mg on the first day and then 200 mg on the second day. Afterwards, the “constant dosage” is administered for each day of the constant phase. For example, 300 mg of olutasidenib could be administered for the third day, the fourth day, the fifth day, and every subsequent day. As such, in some cases the administration involves an initial administration during the initial phase and a constant administration during the constant phase, wherein the dosage during the initial phase is one or more increasing intermediate values, whereas the constant phase involves administration of a single, constant dosage.

[0062] The term “ramp up phase” is used interchangeably with the terms “initial phase” and “increasing phase”. In some cases, the increasing phase ranges in length from 1 day to 10 weeks, such 4 weeks to 6 weeks or from 1 day to 3 days. In some cases, the constant phase ranges in length from 1 day to 500 days, such as from 2 days to 250 days, or from 14 days to 28 days.

[0063] Also provided is a method for treating acute myeloid leukemia (AML), comprising treating a subject having AML with venetoclax until the subject is in remission; and treating the subject in remission with olutasidenib. As such, the initial treatment involves administration of venetoclax but does not involve administration of olutasidenib. Similarly, the secondary treatment when the subject is in remission involves the administration of olutasidenib but does not involve the administration of venetoclax. Such methods can be referred to as “switch maintenance” treatment. The aspects described above (e.g. dosages of venetoclax and olutasidenib) can also be employed in the switch maintenance method.

CERTAIN EMBODIMENTS

[0064] The present disclosure contemplates, among other things, the following numbered embodiments:

1. A method of treating a subject having a hematologic malignancy or pre-malignancy, comprising administering an effective amount of olutasidenib in combination with venetoclax and a hypomethylating agent.
2. The method of embodiment 1, wherein the hematologic malignancy is acute myeloid leukemia (AML).
3. The method of embodiment 1, wherein the hematologic malignancy or pre-malignancy is characterized by an IDH1 mutation.
4. The method of any one of embodiments 1 – 2, wherein the administration is repeated each day for 10 days or more.
5. The method of any one of embodiment 1 – 4, wherein the amount of olutasidenib administered per day is about 300 mg.
6. The method of any one of embodiments 1 – 5, wherein the amount of venetoclax administered per day ranges from about 400 mg to about 800 mg.
7. The method of any one of embodiments 1 – 6, wherein the hypomethylating agent comprises azacitidine.
8. The method of embodiment 7, wherein the amount of azacitidine administered per day is about 75 mg/m².
9. The method of any one of embodiments 1 – 6, wherein the hypomethylating agent comprises decitabine.
10. The method of embodiment 9, wherein the amount of decitabine administered per day is about 35 mg.
11. The method of any one of embodiments 1 – 10, wherein the olutasidenib is administered daily on days 1 – 28 of a dosing schedule.

12. The method of any one of embodiments 1 – 11, wherein the venetoclax is administered daily on days 1 – 14 of the dosing schedule.
13. The method of any one of embodiments 1 – 11, wherein the venetoclax is administered daily on days 1 – 28 of the dosing schedule.
14. The method of any one of embodiments 1 – 13, wherein the hypomethylating agent is azacitidine and the azacitidine is administered daily on days 1 – 7 of the dosing schedule.
15. The method of any one of embodiments 1 – 14, wherein the hypomethylating agent is decitabine and the decitabine is administered on days 1 – 5 of the dosing schedule.
16. The method of any one of embodiments 1 – 15, wherein olutasidenib, venetoclax, or both are administered at a suboptimal dose.
17. The method of any one of embodiments 1 – 16, further comprising administering cedazuridine to the subject.
18. The method of any one of embodiments 1 – 17, further comprising diagnosing the subject with the AML.
19. A method for treating acute myeloid leukemia (AML), comprising treating a subject having AML with venetoclax until the subject is in remission; and treating the subject in remission with olutasidenib.
20. The method of embodiment 19, wherein the AML is characterized by an IDH1 mutation.
21. The method of any one of embodiments 19 – 20, wherein the amount of olutasidenib administered per day is about 300 mg.
22. The method of any one of embodiments 19 – 21, wherein the amount of venetoclax administered per day ranges from about 400 mg to about 800 mg.
23. The method of any one of embodiments 19 – 22, wherein the amount of venetoclax administered is 400 mg per day.
24. The method of any one of embodiments 19 – 22, wherein the amount of venetoclax administered is 800 mg per day.
25. The method of any one of embodiments 19 – 24, further comprising diagnosing the subject with the AML.
26. The method of any one of embodiments 19 – 25, further comprising treating the subject with a hypomethylating agent.
27. The method of embodiment 24, wherein the hypomethylating agent comprises azacitidine or decitabine.

28. A method of treating a subject having a hematologic malignancy or pre-malignancy, comprising administering to the subject an effective amount of venetoclax and a hypomethylating agent for one or more 28-day dosing schedule, followed by administering olutasidenib in combination with the hypomethylating agent for one or more 28-day dosing schedule.
29. The method of embodiment 28 wherein the hypomethylating agent is azacytidine.
30. The method of embodiment 28 or 29 wherein the venetoclax is administered 400 mg once daily.
31. The method of embodiment 29 or 30 wherein the azacytidine is administered at 75 mg/m² IV/SQ once daily.
32. The method of embodiments 28 to 31 wherein olutasidenib is administered 300 mg daily.
33. The method of embodiments 28 to 32 wherein olutasidenib is administered at 150 mg twice daily.

[0065] The present disclosure further contemplates, among other things, the following additional numbered embodiments:

1. A method of treating a subject having a hematologic malignancy or pre-malignancy, comprising administering an effective amount of olutasidenib in combination with venetoclax and a hypomethylating agent.
2. The method of embodiment 1, wherein the hematologic malignancy is acute myeloid leukemia (AML).
3. The method of embodiment 1, wherein the hematologic malignancy or pre-malignancy is characterized by an IDH1 mutation.
4. The method of any one of embodiments 1 – 3, wherein the administration is repeated each day for 10 days or more.
5. The method of any one of embodiments 1 – 4, wherein the amount of olutasidenib administered per day is about 300 mg.
6. The method of any one of embodiments 1 – 5, wherein the amount of venetoclax administered per day ranges from about 400 mg to about 800 mg.
7. The method of any one of embodiments 1 – 6, wherein the hypomethylating agent comprises azacitidine.
8. The method of embodiment 7, wherein the amount of azacitidine administered per day is about 75 mg/m².

9. The method of any one of embodiments 1 – 6, wherein the hypomethylating agent comprises decitabine.
10. The method of embodiment 9, wherein the amount of decitabine administered per day is about 35 mg.
11. The method of any one of embodiments 1 – 6, 9 and 10, wherein the hypomethylating agent comprises cedazuridine.
12. The method of any one of embodiments 1 – 11, wherein the olutasidenib is administered daily on days 1 – 28 of a dosing schedule.
13. The method of any one of embodiments 1 – 12, wherein the venetoclax is administered daily on days 1 – 7 of the dosing schedule.
14. The method of any one of embodiments 1 – 12, wherein the venetoclax is administered daily on days 1 – 10 of the dosing schedule.
15. The method of any one of embodiments 1 – 12, wherein the venetoclax is administered daily on days 1 – 14 of the dosing schedule.
16. The method of any one of embodiments 1 – 12, wherein the venetoclax is administered daily on days 1 – 28 of the dosing schedule.
17. The method of any one of embodiments 13 – 16, wherein the venetoclax administered daily is about 600 mg.
18. The method of any one of embodiments 1 – 17, wherein the hypomethylating agent is azacitidine and the azacitidine is administered daily on days 1 – 7 of the dosing schedule.
19. The method of any one of embodiments 1 – 17, wherein the hypomethylating agent comprises decitabine and the decitabine is administered on days 1 – 5 of the dosing schedule.
20. The method of any one of embodiments 1 – 17, wherein the hypomethylating agent comprises decitabine and cedazuridine and the hypomethylating agent is administered on days 1 – 5 of the dosing schedule.
21. The method of any one of embodiments 1 – 20, wherein olutasidenib, venetoclax, or both are administered at a suboptimal dose.
22. The method of any one of embodiments 1 – 10, further comprising administering cedazuridine to the subject.
23. The method of any one of embodiments 1 – 22, further comprising diagnosing the subject with the AML.

24. A method for treating acute myeloid leukemia (AML), comprising treating a subject having AML with venetoclax until the subject is in remission; and treating the subject in remission with olutasidenib.

25. The method of embodiment 24, wherein the AML is characterized by an IDH1 mutation.

26. The method of any one of embodiments 24 – 25, wherein the amount of olutasidenib administered per day is about 300 mg.

27. The method of any one of embodiments 24 – 26, wherein the amount of venetoclax administered per day ranges from about 400 mg to about 800 mg.

28. The method of any one of embodiments 24 – 27, wherein the amount of venetoclax administered is 400 mg per day.

29. The method of any one of embodiments 24 – 27, wherein the amount of venetoclax administered is 800 mg per day.

30. The method of any one of embodiments 24 – 29, further comprising diagnosing the subject with the AML.

31. The method of any one of embodiments 24 – 30, further comprising treating the subject with a hypomethylating agent.

32. The method of embodiment 31, wherein the hypomethylating agent comprises azacitidine or decitabine.

33. The method of embodiment 31, wherein the hypomethylating agent comprises decitabine and cedazuridine.

34. A method for treating AML, comprising co-administering to a subject having an IDH1 mutant AML an effective amount of olutasidenib, venetoclax and a hypomethylating agent.

35. The method of embodiment 34, wherein co-administering comprises administering the olutasidenib, venetoclax and the hypomethylating agent in a 28-day treatment cycle.

36. The method of embodiment 35, wherein olutasidenib is administered daily on days 1 – 28 of the treatment cycle.

37. The method of embodiment 35, wherein the venetoclax is administered daily on days 1 – 7 of the treatment cycle.

38. The method of embodiment 35, wherein the venetoclax is administered daily on days 1 – 10 of the treatment cycle.

37. The method of embodiment 35, wherein the venetoclax is administered daily on days 1 – 14 of the treatment cycle.

39. The method of any one of embodiments 34 – 37, wherein the venetoclax administered daily is about 400 mg to about 800.
40. The method of any one of embodiments 34 – 39, wherein the venetoclax administered daily is about 600 mg.
41. The method of any one of embodiments 35 – 40, wherein the hypomethylating agent comprises decitabine and the decitabine is administered on days 1 – 5 of the treatment cycle.
42. The method of any one of embodiments 34 – 40, wherein the hypomethylating agent comprises decitabine and cedazuridine and the hypomethylating agent is administered on days 1 – 5 of the treatment cycle.
43. The method of any one of embodiments 34 – 42, wherein the olutasidenib administered daily is about 150 mg.
44. The method of any one of embodiments 34 – 42, wherein the olutasidenib is administered twice daily in a dosage of about 150 mg.
45. The method of any one of embodiments 34 – 44, wherein olutasidenib, venetoclax, or both are administered at a suboptimal dose.

EXAMPLES

[0066] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for.

[0067] Clinical trials for determining the effect of the administration of olutasidenib, venetoclax, and hypomethylating agent are described herein.

Example 1: Phase 1b/2 clinical trial

[0068] Phase 1b/2 is an evaluation of the safety and PK/PD of olutasidenib, venetoclax, and azacitidine or decitabine in IDH1m+ (IDH1 mutation positive) AML and MDS.

[0069] Objectives of phase 1b/2 are:

[0070] dose optimization of venetoclax in triplet combination;

[0071] safety and tolerability;

[0072] determine a recommended dose;

- [0073] PK and PD assessment; and
- [0074] evaluate signal of activity.
- [0075] Inclusion Entry Criteria: IDH1 m+ AML/MDS
- [0076] Cohort A will be given venetoclax DL1 + INQOVI® + olutasidenib, followed by venetoclax DL2 + INQOVI® + olutasidenib
- [0077] Cohort B will be given venetoclax DL1 + azacitidine + olutasidenib, followed by venetoclax DL2 + azacitidine + olutasidenib.
- [0078] Treatment A: Venetoclax is 400 mg (at dose level 1 or DL1) or 800 mg (at dose level 2 or DL2) PO QD (following three day ramp up in cycle 1) Day 1-14+; INQOVI® 1 tab (35 mg decitabine/100 mg cedazuridine) PO QD Day 1-5 + olutasidenib 150 mg PO BID Day 1-28
- [0079] Treatment B: venetoclax 400 mg (DL1) or 800 mg (DL2) PO QD (following three day ramp up in cycle 1) Day 1-14+; azacitidine 75 mg/m² IV/SC QD Day 1-7+; olutasidenib 150 mg PO BID Day 1-28.
- [0080] Treatments are continued until disease progression, intolerability, or withdrawal.
- [0081] Phase 1b is open label and single arm
- [0082] 3+3 dose escalation design
- [0083] N = up to 36
- [0084] Study duration of 36 months, individual patient follow up 12 months.
- [0085] Primary endpoint: safety and PK/PD, and identify a RP2D
- [0086] Secondary endpoints:
- response rates including CR, CRi, CRh, MLFS, and PR
 - time to response, DOR (duration of response), EFS (event-free survival), and OS (overall survival).
- [0087] Exploratory:
- evaluate MRD (measurable residual disease) and VAF (variant allele frequency)
 - evaluate 2HG levels.

Example 2: Phase 3

- [0088] Phase 3 is a randomized open label evaluation of olutasidenib+venetoclax+decitabine versus olutasidenib+venetoclax+azacitidine in treatment naïve unfit IDH1m+ AML and MDS.
- [0089] Endpoints of phase 3 include:
- [0090] Key primary: mEFS (median event-free survival)
- [0091] Key secondary:
- CR, composite CR (CR, CRi, CRh);
 - time to response, duration of response, mOS (median overall survival); and

- incidence and severity of AEs, dose interruptions or discontinuation
- [0092] Exploratory: incidence of MRD negativity, clearance of IDH1m clone.
- [0093] Key Entry Criteria: treatment naïve unfit IDH1 m+ AML
- [0094] N = 200 and randomize 1:1 into Cohort A and B.
- [0095] Cohort A: SOC venetoclax + azacitidine. Venetoclax 400 mg PO QD Day 1-28 + azacitidine 75 mg/m² IV/SQ WD Day 1-7
- [0096] Cohort B: venetoclax 400 mg PO QD Day 1-28* + azacitidine 75 mg/m² IV/SC QD Day 1-7 + olutasidenib 150 mg PO BID Day 1-28
- [0097] Day 1-3 dose ramp-up of venetoclax in Cycle 1
- [0098] Continue until disease progression, intolerability, or withdrawal
- [0099] Phase 3, open label, randomized. N = 200 (100 per arm) up to 55 sites in the US
- [00100] Study duration ~ 4 years (first patient in, to last patient evaluated)
- [00101] Individual subject study duration 24 months
- [00102] Primary Endpoint: EFS
- [00103] Secondary endpoints:
- response rates including CR, Cri, CRh, MLFS, and PR
 - time to response, DOR, and OS
 - incidence and severity of AEs and SAEs

Example 3: Phase 3 trial of Maintenance with Venetoclax vs. Maintenance with Olutasidenib

- [00104] This study is a randomized, phase 3, open label investigation of venetoclax + azacitidine vs. olutasidenib + azacitidine in patients experiencing remission after treatment with venetoclax.
- [00105] Newly diagnosed IDH1 mutant AML patients will receive two cycles of venetoclax + azacitidine
- [00106] Subjects (240) in remission after two cycles are randomized into two maintenance phase cohorts:
- [00107] Cohort 1 (120 subjects) is treated with olutasidenib + azacitidine
- [00108] Cohort 2 (120 subjects) is treated with venetoclax + azacitidine
- [00109] Maintenance phase is 28 days/cycle
- [00110] Cohort 1 receives olutasidenib 150 mg BID days 1 – 28 and azacitidine 75 mg/m² IV/SC QD days 1 – 7
- [00111] Cohort 2 receives venetoclax 400 mg PO QD days 1 – 28 and azacitidine 75 mg/m² IV/SC QD days 1 – 7

- [00112] Primary Endpoint: regression free survival (RFS)
- [00113] Secondary Endpoints time to response, DOR, and OS
- [00114] Response rates including CR, CRi, CRh, MLFS and PR
- [00115] Incidence and severity of AEs and SAEs

Example 3: Phase 1b/2 study of decitabine and venetoclax in combination with the targeted mutant IDH1 inhibitor olutasidenib

[00116] Olutasidenib has demonstrated efficacy in the treatment of relapsed or refractory AML and was approved for the treatment of this disorder in 2022 (de Botton S, Fenaux P, Yee K, et al. Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory IDH1-mutated AML. *Blood Adv.* **2023**;7(13):3117-3127 (de Botton). However evidence for the efficacy of this agent in combination therapy is lacking.

[00117] A clinical study is conducted in adults in AML or MDS having IDH1 mutations. The design for this study is outlined in FIG. 1. This study will be a Phase 1b/2 single center, open-label, non-randomized clinical trial with the dual primary objectives of assessing the safety and efficacy of IV or oral decitabine/cedazuridine in combination with the BCL2 inhibitor venetoclax (VEN) and the mutant targeted IDH1 inhibitor olutasidenib for IDH1 mutated AML.

[00118] The maximum number of patients treated on this investigational study will be 78.

[00119] Patients will continue treatment on study until discontinuation due to relapse, unacceptable toxicity, withdrawal of consent, or disease progression.

[00120] This will be the first study to evaluate the efficacy of the triplet regimen of the IDH1 inhibitor olutasidenib in combination with hypomethylating plus venetoclax therapy.

[00121] Objectives of this study are:

[00122] Phase 1b: To determine the safety and tolerability and recommended phase 2 dose (RP2D) of decitabine (either IV or oral decitabine/cedazuridine (ASTX727, INQOVI®)) and venetoclax in combination with olutasidenib.

[00123] Phase 2: To determine the composite remission rate (CR, CRh and CRi) of decitabine (IV or oral decitabine/cedazuridine (ASTX727, INQOVI®)) and venetoclax in combination with olutasidenib for newly diagnosed (Arm A) or relapsed/refractory (Arm B) patients with IDH1-mutated myeloid malignancy.

[00124] To determine duration of response (DOR), event-free survival (EFS), and overall survival (OS)

[00125] To evaluate occurrence of minimal residual disease (MRD) negative status by multiparameter flow cytometry and molecular evaluation.

[00126] To determine the overall response rate (CR, CRh, CRi, MLFS, and PR).

[00127] To characterize the pharmacokinetic (PK) profiles of venetoclax and olutasidenib in plasma samples (Phase 1b only).

[00128] To investigate global gene expression profiles, DNA methylation profiles, BH3 profiling and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment.

[00129] **Inclusion criteria**, must satisfy all of the following:

1. age of 18 years or more;
2. subjects must have a documented IDH1 gene mutation;
3. patients with a diagnosis of relapsed or refractory AML (including biphenotypic or bilineage leukemia including a myeloid component or isolated extramedullary AML), high-risk MDS by IPSS-R (the International Prognostic Scoring System–Revised developed by the International Working Group for Prognosis in MDS (IWG-PM)) or IPSS-M (the Internal Prognostic Scoring System – Molecular, a clinical-molecular prognostic model – See Bernard et al. 2022 *NEJM Evid* 2022;1(7)); OR

4. Patients with newly diagnosed AML not eligible or appropriate for intensive chemotherapy are also eligible.(Phase 2 portion only);

5. To be considered not eligible for intensive chemotherapy, participants must be defined by the following: Age 75 years or older, or Age 18 to 74 years with at least one of the following comorbidities:

- a) Severe cardiac disorder (e.g., congestive heart failure requiring treatment, ejection fraction less than or equal to 50%, or chronic stable angina).

- b) Severe pulmonary disorder (e.g., DLCO less than or equal to 65% or forced expiratory volume in 1 second [FEV1] less than or equal to 65%.

- c) Creatinine clearance greater than or equal to 30 mL/min to less than 45 mL/min.

- d) Moderate hepatic impairment with total bilirubin >1.5 to ≤ 3.0 x upper limit of normal (ULN)

- e) ECOG performance status of 2 or 3

- f) Any other comorbidity that per the investigator renders a patient inappropriate for intensive chemotherapy.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2 (unless age 18 to 74 years of age with newly diagnosed AML not eligible for intensive chemotherapy as per “e)” above).

7. Adequate renal function including creatinine < 1.5 , unless related to the disease or unless age 18 to 74 years of age with newly diagnosed AML not eligible for intensive chemotherapy as per “c)” above.

8. Adequate hepatic function (direct bilirubin $< 2\times$ upper limit of normal (ULN) unless increase is due to Gilbert’s disease or leukemic involvement, and AST and/or ALT $< 3\times$ ULN unless considered due to leukemic involvement, in which case direct bilirubin or AST and/or ALT $< 5\times$ ULN will be considered eligible, or unless age 18 to 74 years of age with newly diagnosed AML not eligible for intensive chemotherapy as per “d)” above).

9. In the absence of rapidly proliferative disease, the interval from prior treatment to time of initiation will be at least 14 days for cytotoxic or non-cytotoxic (immunotherapy agent(s), or an interval of 5 half-lives of the prior therapy. Oral hydroxyurea and/or cytarabine (up to 2 g/m²) for patients with rapidly proliferative disease is allowed before the start of study therapy, as needed, for clinical benefit as is judged by those of skill in the art. Concurrent intrathecal therapy for central nervous system (CNS) prophylaxis or continuation of therapy for controlled CNS disease is permitted.

10. Male subjects who are sexually active with a women of childbearing potential (WOCBP) and who have not had vasectomies must be willing to use a barrier method of contraception and refrain from sperm donation from initial study drug until 90 days after last dose of study drug.

[00130] Exclusion criteria, must not have any of the following: Patients with t(15;17) karyotypic abnormality or acute promyelocytic leukemia (French-American-British [FAB] class M3-AML).

1. Patients with t(15;17) karyotypic abnormality or acute promyelocytic leukemia (French-American-British [FAB] class M3-AML).

2. Patients with any concurrent uncontrolled clinically significant medical condition including life-threatening severe infection, or psychiatric illness, which could place the patient at unacceptable risk of study treatment.

3. Patients with active, uncontrolled leukemia involvement of the CNS.

4. Patients with active graft-versus-host-disease (GVHD) status post stem cell transplant (patients without active GVHD on chronic suppressive immunosuppression and/or phototherapy for chronic skin GVHD are permitted).

5. Patients with any severe gastrointestinal or metabolic condition which could interfere with the absorption of oral study medications.

6. Known active hepatitis B (HBV) or Hepatitis C (HCV) infection or known HIV infection.

7. Subject has a white blood cell count $> 25 \times 10^9/L$. (Note: Hydroxyurea and cytarabine is permitted to meet this criterion).

8. Nursing women, women of childbearing potential (WOCBP) with positive urine pregnancy test, or women of childbearing potential who are not willing to maintain adequate contraception.

[00131] Treatment plan (Phase 1b Portion): Patients with relapsed/refractory disease only will be enrolled in cohorts of 3 beginning with dose level 1. The starting dose will evaluate the approved doses of decitabine (or oral decitabine/cedazuridine), venetoclax, and olutasidenib.

[00132] Dose level 2 will evaluate venetoclax at 600 mg daily, due to the potential drug-drug interaction of olutasidenib on lowering venetoclax exposure, related to the in vitro evidence that olutasidenib functions as a CYP3A inducer, and thus is anticipated to lead to a considerably decreased venetoclax AUC.

[00133] Cycle 1 Venetoclax Ramp Up

[00134] In patients with a goal venetoclax level of 400 mg daily, venetoclax will be administered at a dose of 100 mg (or equivalent) on day 1, 200 mg (or equivalent) on day 2, and 400 mg (or equivalent) on day 3-14 of the first cycle.

[00135] In patients with a goal venetoclax level of 600 mg daily, venetoclax will be administered at a dose of 100 mg (or equivalent) on day 1, 200 mg (or equivalent) on day 2, 400 mg (or equivalent) on day 3, and 600mg (or equivalent) on day 4-14 of the first cycle.

[00136] During cycle 1 venetoclax dosing ramp up, TLS lab monitoring (K+, uric acid, phosphorus, calcium, and creatinine) should occur at pre- dose, 6-8 hours post dose, and 24 hours post dose.

[00137] The combination RP2D will be selected at the end of the Phase 1b portion based on an analysis of safety and efficacy. Once the RP2D has been identified, the study will transition to the Phase 2 portion.

[00138] Phase 2 Treatment Plan: Patients with relapsed/refractory disease only will be enrolled in cohorts of 3 beginning with dose level 1 as shown in Table 1. The starting dose will evaluate the approved doses of decitabine (or oral decitabine/cedazuridine), venetoclax, and olutasidenib.

[00139] Dose level 2 will evaluate venetoclax at 600 mg daily, due to the potential drug-drug interaction of olutasidenib on lowering venetoclax exposure, related to the in vitro evidence that olutasidenib functions as a CYP3A inducer, and thus is anticipated to lead to a considerably decreased venetoclax AUC.

[00140] The combination RP2D will be selected at the end of the Phase 1b portion based on an analysis of safety and efficacy. Once the RP2D has been identified, the study will transition to the Phase 2 portion.

[00141] Triplet Therapy Administration:

[00142] Phase 1b will commence with the triplet therapy dosage schedule set forth in Table 1:

[00143] **Table 1: Phase 1b dose levels**

Dose Level	IV decitabine or Oral decitabine/cedazuridine	Venetoclax	Olutasidenib
2	20 mg/m ² IV on days 1-5 or 1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1-5	600 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)
1	20 mg/m ² IV on days 1-5 or 1 tablet (35 mg decitabine and 100 mg cedazuridine) on days 1-5	400 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)
-1	15 mg/m ² IV on days 1-5 or 1 tablet (35 mg decitabine and 100 mg cedazuridine) days 1-4	400 mg daily on days 1-14	150 mg twice daily on days 1-28 (days 8-28 for cycle 1 only)

[00144] Dose Modifications

[00145] CYP3 Inducers and Inhibitors

[00146] CYP3A inhibitors are discouraged but allowed with appropriate venetoclax dose reduction at all study timepoints according to the U.S. Prescribing Information including an 82.5% dose reduction for posaconazole (i.e. venetoclax 70 mg QD instead of 400 mg) and 75% dose reduction for other strong CYP3A inhibitors (i.e. venetoclax 100 mg QD instead of 400 mg in combination with voriconazole).

[00147] If a moderate CYP3A inhibitor is prescribed on study, a 50% dose reduction of venetoclax will be required (i.e. 200 mg instead of 400 mg, 300 mg instead of 600 mg, etc).

[00148] Differentiation Syndrome (DS) and/or Leukocytosis

[00149] Subjects treated with olutasidenib may develop signs and symptoms of a differentiation-like syndrome and/or leukocytosis. Differentiation Syndrome (DS) may include any of the following: unexplained fever, skin rash, leukocytosis, thrombocytosis, hypoxia, respiratory distress, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, weight gain, or

clinical deterioration. No single sign or symptom should be considered per se as diagnostic of DS. It is recommended that the prophylactic and therapeutic measures indicated below be undertaken at the earliest manifestations of suspected differentiation-like syndrome:

Prompt initiation of hydroxyurea. Taper hydroxyurea only after leukocytosis improves or resolves.

If DS is suspected or diagnosed, withhold olutasidenib until signs and symptoms improve

Prompt administration of systemic corticosteroids until the disappearance of symptoms and signs, and for a minimum of 3 days

Initiation of furosemide if clinically required

Prompt initiation of leukapheresis or administration of cytarabine, if clinically required

Resume olutasidenib at 150 mg BID after resolution of differentiation syndrome.

If a recurrence of DS is suspected, withhold olutasidenib and institute treatment as per above guidance. After resolution of symptoms, olutasidenib may be resumed at reduced dose of 150 mg QD for minimum of 7 days, after which it can be increased to 150 mg BID. Once the signs and symptoms resolve and the subject's clinical condition improves, olutasidenib (if previously held) may be reinitiated as outlined above.

[00150] Hepatotoxicity with Olutasidenib

[00151] Subjects treated with olutasidenib may develop liver toxicity. Blood chemistries including liver function tests should be assessed during screening, at least once weekly for the first 2 cycles, every 2 weeks for the third cycle, And then at least once per cycle thereafter.

[00152] In the event of grade 3 hepatotoxicity including liver function test elevations, hold olutasidenib and monitor LFTs twice per week until values have returned to baseline or grade 1 toxicity. Restart olutasidenib at a dose of 150 mg once daily and continue monitoring. Olutasidenib may be re-increased to 150 mg twice daily if hepatotoxicity resolves to baseline for at least 28 days. If grade 3 hepatotoxicity recurs at 150 mg once daily, olutasidenib should be discontinued.

[00153] In the event of grade 4 hepatotoxicity or AST or ALT > 3x ULN and total bilirubin > 2x ULN and alkaline phosphatase < 2x ULN in the absence of a clear alternative explanation, permanently discontinue olutasidenib.

[00154] Recommended dose modification for other Grade 3 or higher toxicity considered related to olutasidenib treatment

[00155] Interrupt olutasidenib until toxicity resolves to Grade 2 or lower. Resume olutasidenib at 150 mg once daily (dose level -1); may increase to 150 mg twice daily (dose level 1/starting

dose) if toxicities resolve to grade 1 or lower for at least 1 week. If grade 3 or higher toxicity recurs at 150 mg once daily, discontinue olutasidenib

[00156] A patient who has had a dose reduction should have their dose re-escalated provided the patient has remained free of toxicity requiring dose adjustments for one month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month.

[00157] Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator.

[00158] Management of Myelosuppression

[00159] Myelosuppression and related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML. In addition, based on clinical experience with BCL-2 inhibition, patients treated with venetoclax may experience increased rates of neutropenia.

[00160] If a patient achieves a clinical response including CR, CRh, or MLFS while on study and they have not recovered an ANC > 500/uL within 14 days of venetoclax drug interruption, unless it is thought to be due to the underlying disease, venetoclax dosing may be further interrupted until ANC recovery to > 500/uL. Additionally, GCSF may be administered if in the best interest of the patient.

[00161] Recommended ASTX727/INQOVI Dose Reductions for Myelosuppression is a first dose reduction of administering 1 oral tablet for a reduced dose duration of Days 1 through 4, a second dose reduction of administering 1 oral tablet for a reduced dose duration of Days 1 through 3, and third dose reduction of administering 1 oral tablet on Days 1, 3 and 5, of a given cycle.

[00162] Recommended dose modifications for decitabine-related AEs comprises a first dose reduction of decitabine administered at 15 mg/m² IV on days 1-5, a second dose reduction of decitabine administered at 15 mg/m² IV on days 1-4 and a third dose reduction of decitabine administered at 15 mg/m² IV on days 1-3.

[00163] Recommended dose modifications for venetoclax-related AEs, for patients starting at 400 mg venetoclax, comprises a first dose reduction (DL-1) of 400 mg for 10 days and a second dose reduction (DL-2) of 400 mg for 7 days, of a given cycle.

[00164] Recommended dose modifications for venetoclax-related AEs, for patients starting at 600 mg venetoclax, comprises a first dose reduction (DL-1) of 600 mg for 10 days and a second dose reduction (DL-2) of 600 mg for 7 days, of a given cycle.

[00165] A reduction of 2 dose levels at once may be considered if the toxicity was deemed severe and life threatening by the treating physician, and/or if it is in the patient's best interest.

[00166] Additional or alternative dose modifications are acceptable when deemed to be in the patient's best interest, after a discussion by the investigator and PI and with appropriate documentation.

[00167] General Concomitant Medication and Supportive Care Guidelines

[00168] Supportive care measures including blood products, infection prophylaxis and growth factors should be administered according to institutional and departmental guidelines.

[00169] Concomitant intrathecal chemotherapy is permitted for treatment or prophylaxis of extramedullary disease.

[00170] Investigational agents or supportive care studies (even if under an IND) that are not designed for treatment of the leukemia per se (e.g. anti-infective prophylaxis or therapy) will be allowed.

[00171] Because there is a potential for interaction of venetoclax with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently updated medical reference for a list of drugs to avoid or minimize use of.

[00172] Duration of Therapy

[00173] All subjects must complete a screening visit, day 1 visits for each new cycle, cycle 1 day 15 visit, and an end-of-treatment visit.

[00174] Treatment will continue until discontinuation due to relapse, unacceptable toxicity, withdrawal of consent, or disease progression. Reasons for study treatment discontinuation include:

- clinically significant progressive disease at any time, or
- possibility of undergoing allogeneic stem cell transplantation
- intercurrent illness that prevents further administration of treatment, or
- unacceptable adverse event(s), or
- patient decision for study withdrawal, or
- general or specific changes in the patient's condition that render the patient

unacceptable for further treatment in the judgment of the investigator

[00175] Patients may remain on study as long as the patient continues to demonstrate clinical benefit and no excessive toxicity (i.e. no clinically significant study-drug related grade > 3 toxicity).

[00176] Dose modifications and interruptions are permitted as necessary for the clinical benefit of the patient. If side effects or toxicity are related to one study drug only; patients may proceed

with dose modification and/or discontinuation of that agent and continue treatment with the remaining study agents, if in the investigator's assessment the patient continues to demonstrate clinical benefit and all protocol-specified criteria for continuation of study treatment are met. All dose modifications should be discussed with the PI and clearly documented in the medical record. Treatment may be held as long as clinically necessary for resolution, after discussion with the PI.

[00177] For patients with study-drug related clinically significant toxicities, the following dose adjustment rules apply:

[00178] For Grade 0-2 non-hematological toxicities, no dose reduction is required. For grade 2 toxicities that are persistent and/or intolerable (e.g. stomatitis), patients may have a treatment interruption or dose reduction to the next lower dose level.

[00179] For Grade 3-4 clinically significant non-hematological toxicity, hold until recovery to Grade 0-1, or to baseline if Grade 2 at study entry. Dose should be reduced to -1 dose level, if applicable.

[00180] All patients discontinued from study treatment for any reason other than withdrawal of consent for treatment and follow-up will continue to be assessed for survival. Reasons for study discontinuation include:

- Disease progression

- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)

- Patient decides to withdraw from the study

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

- Clinical progression

- Patient non-compliance

- Pregnancy (All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.)

- Termination of the study by ind/ide sponsor

- The drug manufacturer can no longer provide the study agent

[00181] The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

[00182] Duration of Follow-Up

[00183] Patients will be followed for Survival information (i.e. the date and cause of death) will be collected via telephone calls and/or clinical visits at 3-month intervals for a period of 3 years after the last subject has enrolled on the study.

[00184] Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

[00185]

[00186] Study assessments and procedures

[00187] Screening

[00188] The following activities – complete medical history, physical examination, performance status, documentation of measurable disease, CBC with differential, creatinine, total bilirubin, ALT and/or AST measures, pregnancy test, bone marrow aspirate and/or biopsy, and correlatives on bone marrow - will be performed within 14 days prior to study drug administration and during screening, staging and workup.

[00189] A complete physical examination and documentation of concomitant medications will be done on day 1 of each cycle (+/- 7 days).

[00190] CBC with differential, creatinine, total bilirubin, ALT or AST will be done at least once weekly (+/- 4 days) for the first 2 cycles, then every 2 weeks for cycle 3, and then every 2-4 weeks on subsequent cycles.

[00191] Pregnancy test either urine or plasma should be done in women of childbearing potential 72 hours before initiation of protocol therapy.

[00192] Bone marrow aspiration and/or biopsy must be done within 28-days (+/- 7 days) of initiation of therapy; then after cycle 3, after cycle 5, every 3 cycles thereafter, and end of study. Cytogenetics and molecular annotation may be used from prior bone marrow analysis if these were not reported on the screening bone marrow. See section 8.3 for studies to be completed on bone marrow specimens.

[00193] Correlative studies will be collected on peripheral blood at Day 1 (prior to dosing), between days 21 to 28 on cycle 1 and at the end of cycle 3 and cycle 5. Subsequently, peripheral blood will be obtained at progression if possible. All these tests can be +/- 5 days.

[00194] Correlative studies will be collected on bone marrow at baseline (prior to dosing), on day 28 (+/- 7 days), at the end of cycle 3 and cycle 5, and at progression.

[00195] EOS visits (30 days post last dose) include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, AST or ALT). A bone marrow aspiration may be done if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood.

[00196] At subsequent cycles bone marrow (aspiration and/or biopsy) will be performed every 3 cycles at the discretion of the treating physician. See section 8.3 for studies to be completed on bone marrow specimens.

[00197] TLS lab monitoring (potassium, uric acid, phosphorus, calcium and creatinine) should occur at pre- dose, 6-8 hours post dose, and 24 hours post dose during cycle 1 ramp up (inpatient AM labs may substitute for the 24 hour post-dose labs)

[00198] Phase 1b portion only: For the evaluation of plasma concentrations of venetoclax and olutasidenib, blood samples will be obtained on cycle 1 day 7, cycle 1 day 15, cycle 2 day 7, and cycle 2 day 15. See Section 6.3.

[00199] The same screening procedures will be performed for both the Phase 1b and Phase 2.

[00200]

[00201] Cycle 1 day -1

[00202] To mitigate the risk for TLS, subjects must be receiving tumor lysis prophylaxis, including hydration (oral and/or intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) per institutional guidelines prior to and during the venetoclax ramp-up period of Cycle 1.

[00203]

[00204] Cycle 1 Venetoclax Ramp Up

[00205] Venetoclax will be administered at a dose of 100 mg (or equivalent) on day 1, 200 mg (or equivalent) on day 2, and 400 mg (or equivalent) on day 3-14 of the first cycle. For patients intended to reach a venetoclax level of 600 mg daily, venetoclax will be administered at a dose of 100 mg (or equivalent) on day 1, 200 mg (or equivalent) on day 2, 400 mg (or equivalent) on day 3, and 600mg (or equivalent) on day 4-14 of the first cycle.

[00206] During cycle 1 venetoclax dosing ramp up, TLS lab monitoring (K+, uric acid, phosphorus, calcium, and creatinine) should occur at pre- dose, 6-8 hours post dose, and 24 hours post dose (inpatient AM labs may substitute for the 24-hour post-dose labs).

[00207] Treatment Schedule

[00208] All subjects must complete a screening visit, cycle 1 day 1, day 1 visits for each new cycle, and an end-of-treatment visit.

[00209] Bone marrow aspirate and/or biopsy on day 28 (+/- 7 days); if no morphologic evidence of leukemia, bone marrow should be repeated 2 weeks (+/- 7 days) in the absence of count recovery. Bone marrow aspirate and/or biopsy will also be performed after cycle 3 and cycle 5; subsequent bone marrow aspirate and/or biopsy will be every 3 cycles or as clinically indicated. No on-study bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests.

[00210] Cytogenetics should be performed if abnormal pre-therapy, at any time a bone marrow exam is performed. Molecular testing including IDH1 analysis should be performed depending on

the positive tests pre-study (specific mutations, whole genome sequencing) and should be followed any time a bone marrow exam is performed.

[00211] Multi-parameter flow cytometry for the presence of leukemia associated immunophenotype (minimal residual disease) should be performed any time a remission bone marrow exam is performed.

[00212] Olutasidenib is a continuous twice daily medication. In the absence of toxicity, if cycle length is prolonged beyond 28 days, treatment with olutasidenib should continue.

[00213] After completion of 12 cycles of therapy, patients must return at least once every 3 months to MDACC. Virtual monthly visits with their MDACC physician may be performed in the interim, with investigational supply shipped directly to the patient after each virtual visit.

[00214]

[00215] PK Sample Collection

[00216] Phase 1b portion only: For the evaluation of plasma concentrations of venetoclax and olutasidenib, blood samples will be obtained at the following timepoints in reference to venetoclax dose administration: pre-dose (Time 0 or within 90 minutes before dosing), 2 hours ($\pm$ 5 min), 4 hours ($\pm$ 5 min), 6 hours ($\pm$ 15 min), 8 hours ($\pm$ 30 min), 24 hours ($\pm$ 30 min), to be collected on the following days: C1D7/cycle 1 day 7 (prior to initiation of olutasidenib), C1D15/cycle 1 day 15, C2D7/cycle 2 day 7 and C2D15/cycle 2 day 15. The actual study days may shift as long as the following criteria are met:

[00217] a. The C1D7 PK serial sampling is intended to be drawn the day before starting olutasidenib and after at least 3 consecutive days of venetoclax dose being maintained at the same dose level (i.e., after the ramp-up phase)

[00218] b. The C1D15 and C2D15 pre-dose samples are intended to be drawn 24-hour after the last venetoclax dose in each cycle.

[00219] c. The C2D7 PK serial sampling is intended to be drawn after at least 7 consecutive days of olutasidenib and venetoclax dosing.

[00220] Primary Safety Analysis:

[00221] The overall incidence and severity of all adverse events using Common Toxicity Criteria v 5.0.

[00222] An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

[00223] Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

[00224] Exploratory Biomarker Analysis:

[00225] Peripheral blood and bone marrow aspirate samples will be obtained at study specified time points. Biomarker assays may include, but are not limited to the following:

1. Leukemia mutation panel: As a standard of care all AML patients at MDACC are evaluated for karyotype and molecular mutation profile using a CLIA-certified next-generation gene sequencing platform. The effects of the combination will be compared not only to historical outcomes in matched groups of patients, but also at the molecular and cellular level by correlating with karyotype and molecular mutation profile. The Leukemia mutation panel will be performed on the screening BM aspirate and the progression/relapse BM aspirate. An aliquot of DNA will be stored for additional analysis of DNA mutations in responding patients.

2. Minimal Residual Disease assessment by flow-cytometry: As a standard of care all remission BM aspirates will be evaluated for MRD by validated 17-color multiparameter multicolor flow-cytometry.

3. Gene expression signatures by RNA sequencing and/or RT-PCR: This will be performed on BM aspirate on the screening BM sample.

4. Pharmacokinetics: Plasma concentrations and PK parameters of olutasidenib and venetoclax will be tabulated for each subject, visit, and dose level, and summary statistics will be computed for each sampling time and each parameter. Pharmacokinetic parameters will be estimated using non-compartmental methods.

[00226]

[00227] Primary Efficacy Analysis: Clinical activity is assessed based on revised IWG response criteria for AML. The primary endpoint is the composite remission rate (CRc), defined as the proportion of patients who had CR (complete remission), CRh (complete remission with incomplete hematologic recovery), and/or CRi (complete remission with incomplete count recovery), within 5 cycles of treatment initiation among adult patients with AML.

[00228] CR: Absolute neutrophil count $> 10^3/\mu\text{L}$, platelets $\geq 10^5/\mu\text{L}$, red cell transfusion independence, absence of extramedullary disease, and bone marrow with $< 5\%$ blasts.

[00229] CRi: Bone marrow with $< 5\%$ blasts, with peripheral neutrophils of $< 1000/\mu\text{L}$ OR platelets $\leq 100,000/\mu\text{L}$.

[00230] CRh: Bone marrow with $< 5\%$ blasts, with peripheral neutrophils of $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$.

[00231] PR: All of the hematologic values for a CR, but with a decrease of at least 50% in the percentage of blasts, to 5% to 25%, in the bone marrow aspirate.

[00232] HR: Improvement in hematologic parameters that do not meet criteria for PR (i.e., transfusion independence and /or decline in incidence of febrile neutropenia and related hospitalizations).

[00233] MLFS Bone marrow with < 5% blasts, absence of extramedullary disease, no hematologic recovery required.

[00234] Analyses of overall response rate (ORR) as defined by CR + CRh + CRi + PR + MLFS, as well as CR rate, CR/CRi rate, CR/CRh rate will be performed for enrolled subjects, with laboratory response assessment occurring +/- 10 days from bone marrow evaluations. The depth of remission such as with exploratory analyses of MRD negativity by flow cytometry and/or concomitant molecular analysis will also be performed.

[00235] For each subject, response to therapy, duration of response, event-free survival, and overall survival will be calculated. The duration of response is defined as the number of days from the date of initial response to the date of first documented disease progression/relapse or death, whichever occurs first. Event-free survival is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented treatment failure, relapse, or death from any cause, whichever occurs first, and will be calculated for all patients. In the event that neither disease progression nor death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last tumor assessment date.

[00236] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

[00237] Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function,

regardless of structure. Moreover, nothing disclosed herein is intended to be dedicated to the public regardless of whether such disclosure is explicitly recited in the claims.

[00238] The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims. In the claims, 35 U.S.C. §112(f) is expressly defined as being invoked for a limitation in the claim only when the exact phrase "means for" or the exact phrase "step for" is recited at the beginning of such limitation in the claim; if such exact phrase is not used in a limitation in the claim, then 35 U.S.C. § 112 (f) is not invoked.

CLAIMS

What is claimed is:

1. A method of treating a subject having a hematologic malignancy or pre-malignancy, comprising administering an effective amount of olutasidenib in combination with venetoclax and a hypomethylating agent.
2. The method of claim 1, wherein the hematologic malignancy is acute myeloid leukemia (AML).
3. The method of claim 1, wherein the hematologic malignancy or pre-malignancy is characterized by an IDH1 mutation.
4. The method of any one of claims 1 – 3, wherein the administration is repeated each day for 10 days or more.
5. The method of any one of claims 1 – 4, wherein the amount of olutasidenib administered per day is about 300 mg.
6. The method of claim 5, wherein the olutasidenib is administered at 150 mg twice daily.
7. The method of any one of claims 1 – 6 wherein the amount of venetoclax administered per day ranges from about 200 mg to about 800 mg.
8. The method of claim 7, wherein the amount of ventoclax administered per day is about 200 mg.
9. The method of claim 7, wherein the amount of ventoclax administered per day is about 400 mg.
10. The method of claim 7, wherein the amount of ventoclax administered per day is about 600 mg.
11. The method of claim 7, wherein the amount of ventoclax administered per day is about 800 mg.
12. The method of any one of claims 7 – 11, wherein the venetoclax is administered once daily.
13. The method of any one of claims 1 – 12, wherein the hypomethylating agent comprises azacitidine.
14. The method of claim 13, wherein the azacitidine is administered per day is about 75 mg/m².
15. The method of claim 14, wherein the azacitidine is administered once daily.
16. The method of any one of claims 1 – 12, wherein the hypomethylating agent comprises decitabine.

17. The method of claim 16, wherein the decitabine administered per day is about 35 mg.
18. The method of claim 17, wherein the decitabine is administered once daily.
19. The method of any one of claims 16 – 18, wherein the hypomethylating agent comprises cedazuridine.
20. The method of claim 19 wherein the cedazuridine is administered at 100 mg once daily.
21. The method of any one of claims 1 – 20, wherein the olutasidenib is administered daily on days 1 – 28 of a dosing schedule.
22. The method of any one of claims 1 – 20, wherein the olutasidenib is administered daily on days 8 – 28 of a dosing schedule.
23. The method of any one of claims 1 – 22, wherein the venetoclax is administered once daily on days 1 – 7 of the dosing schedule.
24. The method of any one of claims 1 – 22, wherein the venetoclax is administered once daily on days 1 – 10 of the dosing schedule.
25. The method of any one of claims 1 – 22, wherein the venetoclax is administered once daily on days 1 – 14 of the dosing schedule.
26. The method of any one of claims 1 – 22, wherein the venetoclax is administered once daily on days 1 – 28 of the dosing schedule.
27. The method of any one of claims 1 – 26, wherein the hypomethylating agent is azacitidine and the azacitidine is administered daily on days 1 – 7 of the dosing schedule.
28. The method of any one of claims 1 – 26, wherein the hypomethylating agent comprises decitabine and the decitabine is administered on days 1 – 5 of the dosing schedule.
29. The method of any one of claims 1 – 26, wherein the hypomethylating agent comprises decitabine and cedazuridine and the hypomethylating agent is administered on days 1 – 5 of the dosing schedule.
30. The method of any one of claims 1 – 29, wherein olutasidenib, venetoclax, or both are administered at a suboptimal dose.
31. The method of any one of claims 1 – 28, further comprising administering cedazuridine to the subject.
32. The method of any one of claims 1 – 31, further comprising diagnosing the subject with the AML.
33. A method for treating acute myeloid leukemia (AML), comprising treating a subject having AML with venetoclax until the subject is in remission; and treating the subject in remission with olutasidenib.

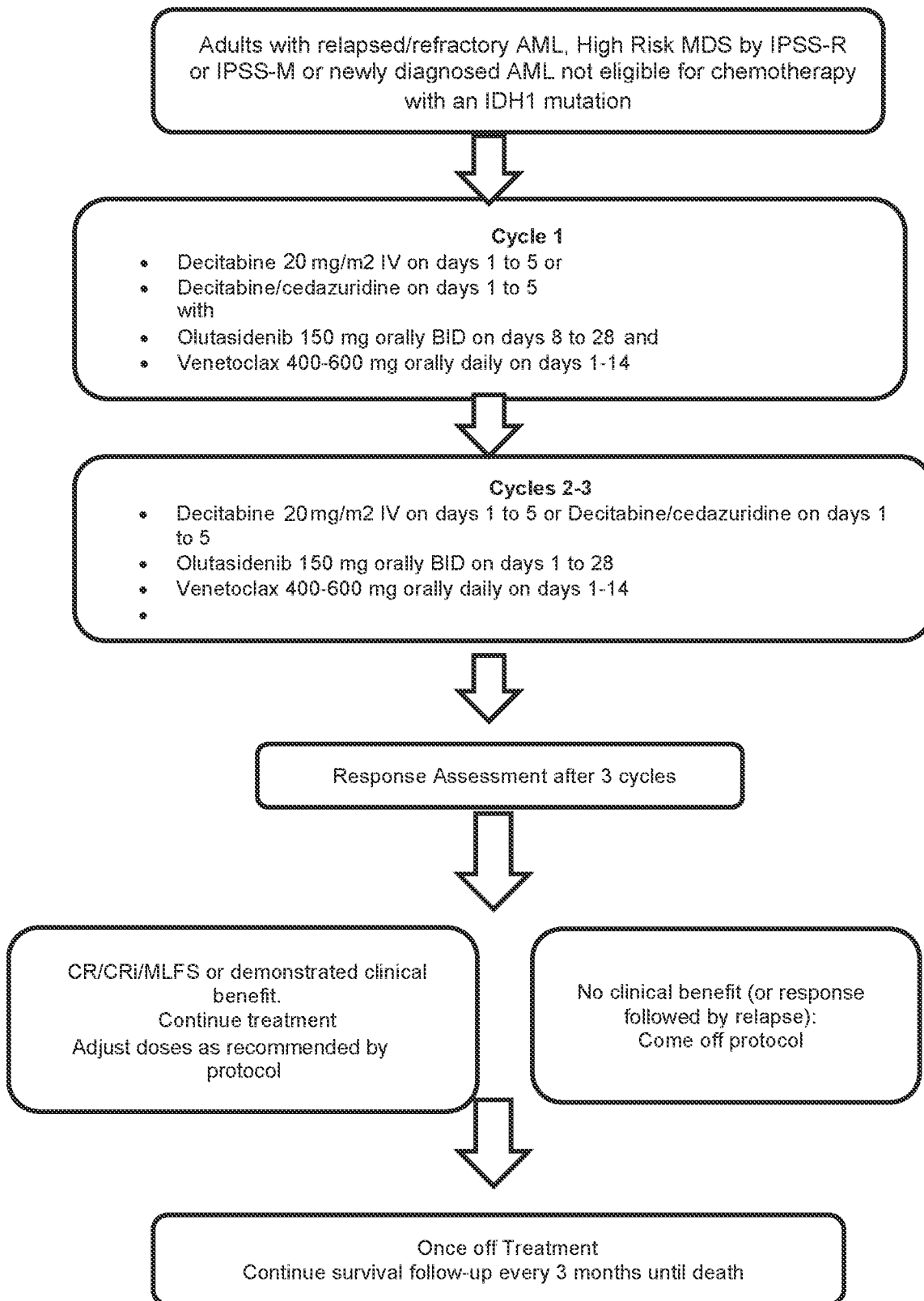
34. The method of claim 33, wherein the AML is characterized by an IDH1 mutation.
35. The method of any one of claims 33 – 34, wherein the amount of olutasidenib administered per day is about 300 mg.
36. The method of claim 35, wherein the olutasidenib is administered at about 150 mg twice daily.
37. The method of any one of claims 33 – 36, wherein the amount of venetoclax administered per day ranges from about 200 mg to about 800 mg.
38. The method of any one of claims 33 – 37, wherein the amount of venetoclax administered is 200 mg per day.
39. The method of any one of claims 33 – 37, wherein the amount of venetoclax administered is 400 mg per day.
40. The method of any one of claims 33 – 37, wherein the amount of venetoclax administered is 600 mg per day.
41. The method of any one of claims 33 – 37, wherein the amount of venetoclax administered is 800 mg per day.
42. The method of any one of claims 33 – 41, wherein the venetoclax is administered once daily.
43. The method of any one of claims 33 – 42, further comprising diagnosing the subject with the AML.
44. The method of any one of claims 33 – 43, further comprising treating the subject with a hypomethylating agent.
45. The method of claim 44, wherein the hypomethylating agent comprises azacitidine or decitabine.
46. The method of claim 45, wherein the hypomethylating agent comprises decitabine and cedazuridine.
47. A method for treating a hematologic malignancy, comprising co-administering to a subject having an IDH1 mutant AML an effective amount of olutasidenib, venetoclax and a hypomethylating agent.
48. The method of claim 47, wherein co-administering comprises administering the olutasidenib, venetoclax and the hypomethylating agent in a 28-day treatment cycle.
49. The method of claim 48, wherein olutasidenib is administered daily on days 1 – 28 of the treatment cycle.
50. The method of claim 48 or 49, wherein the venetoclax is administered daily on days 1 – 7 of the treatment cycle.

51. The method of claim 48 or 49, wherein the venetoclax is administered daily on days 1 – 10 of the treatment cycle.
52. The method of claim 48 or 49, wherein the venetoclax is administered daily on days 1 – 14 of the treatment cycle.
53. The method of any one of claims 47 – 53, wherein the venetoclax administered daily is about 200 mg to about 800.
54. The method of any one of claims 47 – 53, wherein the venetoclax administered daily is about 200 mg.
55. The method of any one of claims 47 – 53, wherein the venetoclax administered daily is about 400 mg.
56. The method of any one of claims 47 – 53, wherein the venetoclax administered daily is about 600 mg.
57. The method of any one of claims 47 – 53, wherein the venetoclax administered daily is about 800 mg.
58. The method of any one of claims 53 – 57, wherein the venetoclax is administered once daily.
59. The method of any one of claims 47 – 58, wherein the hypomethylating agent comprises decitabine and the decitabine is administered on days 1 – 5 of the treatment cycle.
60. The method of any one of claims 47 – 59, wherein the hypomethylating agent comprises decitabine and cedazuridine and the hypomethylating agent is administered on days 1 – 5 of the treatment cycle.
61. The method of any one of claims 47 – 60, wherein the olutasidenib administered daily is about 150 mg.
62. The method of any one of claims 47 – 60, wherein the olutasidenib is administered twice daily in a dosage of about 150 mg.
63. The method of any one of claims 47 – 62, wherein olutasidenib, venetoclax, or both are administered at a suboptimal dose.
64. The method of any one of claims 47 – 63, wherein the hematologic malignancy comprises AML.
65. The method of any one of claims 1 and 3 – 63, wherein the hematologic malignancy comprises MDS.
66. The method of claim 64, wherein the AML is relapsed or refractory AML or newly-diagnosed AML not eligible for chemotherapy.
67. The method of claim 65, wherein the hematologic malignancy is high risk MDS.

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Fig. 1

STUDY SCHEMA



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/036827

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/4709 A61K31/635 A61K31/706 A61K45/06 A61P35/02 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE BOTTON STÉPHANE ET AL: "Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory IDH1 -mutated AML", BLOOD ADVANCES, vol. 7, no. 13, 30 June 2023 (2023-06-30), pages 3117-3127, XP093212903, ISSN: 2473-9529, DOI: 10.1182/bloodadvances.2022009411 Retrieved from the Internet: URL:https://ashpublications.org/bloodadvances/article-pdf/7/13/3117/2062965/bloodadv-2022-009411-main.pdf>	1 - 67
Y	Key Points Introduction Study Design page 3124, right-hand column, paragraph 2 ----- - / - -	1 - 67
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 10 October 2024		Date of mailing of the international search report 30/10/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Hörtner, Michael

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/036827

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	PERL ED - PERL: "The role of targeted therapy in the management of patients with AML", HEMATOLOGY. AMERICAN SOCIETY OF HEMATOLOGY. EDUCATION PROGRAM,, vol. 2017, no. 1, 8 February 2017 (2017-02-08), pages 54-64, XP002793133, table 1 -----	1 - 67
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		US 2022125776 A1	28-04-2022
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