Ziftomenib in Combination With Chemotherapy for Children With Relapsed/Refractory Acute Leukemia

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 0 years to 21 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

- Age: 0-21 years (and at least 5 kg body weight), with a minimum of 80% of participants under 18 years of age.
- Diagnosis: KMT2A-r, NPM1-m, or NUP98-r acute leukemia in first or greater relapse or refractory to standard (re-) induction treatment (including HSCT). Please note that genetic alteration must be confirmed by the central laboratory, or the participant will discontinue protocol therapy.
- Eligible participants also must fulfill one of the following conditions:

1. Bone marrow relapse is defined as:

    1. A single bone marrow sample showing ≥ 5% leukemic blasts by flow cytometry, fluorescence in situ hybridization (FISH) testing, or other molecular method.

    * a single bone marrow sample with at least two tests showing ≥ 1% leukemic blasts, examples of tests (confirmed by central lab) include: Flow cytometry showing leukemia ≥ 1% by multiparameter flow cytometry (MFC) confirmed by central lab.
    * Karyotypic abnormality as confirmed by central cytogenetic review.
    * FISH abnormality identical to one present at diagnosis (must be above level of sensitivity of specific FISH probe; central cytogenetic review required).
    * Polymerase chain reaction (PCR) or next generation sequencing (NGS)-based demonstration of validated leukemogenic lesion (e.g., fusion, mutation) in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory that matches initial diagnosis and is quantifiable as ≥1% confirmed by central lab.

    1. Participants with combined extramedullary and bone marrow relapse (defined as above) are eligible.
    2. Participants with isolated extramedullary disease (EMD) are not eligible. EMD relapse is defined as biopsy-proven extramedullary disease without bone marrow disease after documented complete response (CR) following initial therapy. Participants with isolated central nervous system (CNS) relapse are not eligible. Participants with a combined medullary/extramedullary relapse, including CNS disease, are eligible.
    3. Participants with asymptomatic CNS3 disease are eligible if they do not have isolated CNS3 extramedullary relapse.
    4. For participants unable to undergo bone marrow assessment, a peripheral blood absolute blast count ≥ 1,000 cell/microliter is sufficient to diagnose relapsed or refractory disease and facilitate confirmation of required genetic alterations for protocol therapy.
2. Refractory disease/induction failure:

    1. Acute myeloid leukemia (AML): The bone marrow contains ≥ 1% leukemic blasts by MFC at the end of 2 cycles of induction therapy.
    2. Acute lymphoblastic leukemia (ALL)/mixed-phenotype acute leukemia (MPAL)/acute undifferentiated leukemia (AUL): The bone marrow contains ≥ 1% leukemic blasts by MFC at the end of induction and consolidation, or persistent MRD prior HSCT (defined as > 0.01%).
    3. For participants unable to have bone marrow assessed, a peripheral blood absolute blast count ≥ 1,000 cell/microliter is sufficient to diagnose relapsed or refractory disease.
3. Molecular refractory disease in infant ALL, defined as MRD >0.05% after primary induction and consolidation therapy measured by MFC or PCR.

    - Performance status: Participants must have a performance status corresponding to Eastern Cooperative Oncology Group (ECOG) scores of 0, 1 or 2 (≥ 50% Lansky or Karnofsky score). Use ECOG for adult participants (≥18 to 21 years), Karnofsky for participants ≥16 to 18 years of age, and Lansky for participants < 16 years of age. Participants who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
    - Adequate organ function:
4. Renal function defined as: Creatinine clearance (CrCl) ≥60 mL/min (as measured by a nuclear glomerular filtration rate [GFR] scan or calculated by the Schwartz formula and normalized to a body surface area of 1.73 m^2).

5. Liver function defined as:

    1. Direct bilirubin < 3 x upper limit of normal (ULN) and Serum glutamic pyruvic transaminase (SGPT) (alanine transaminase [ALT]) ≤ 5 x ULN.
    2. If liver abnormality is due to radiographically identifiable leukemia infiltrate, the participant will remain eligible.
6. Cardiac function defined as: Pre-treatment left ventricular function on echocardiography: Fractional shortening (FS) ≥ 25% or ejection fraction (EF) ≥ 40%, and no signs of congestive heart failure within 4 weeks before start of screening.

    - Prior therapy: Participants must have recovered from the acute toxic effects of all prior anti-cancer therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment.
7. Cytotoxic chemotherapy: Must not have received within 14 days or within 5 drug half-lives (whichever is longer), of entry onto this study, except for hydroxyurea or corticosteroids. Use of steroids and hydroxyurea for other purposes such as differentiation syndrome, or to premedication to prevent allergic reaction or during anesthesia is allowed.

8. Intrathecal cytotoxic therapy: No washout or waiting period is required for participants having received any combination of intrathecal cytarabine, methotrexate, and/or hydrocortisone.

9. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of an antibody-drug conjugate. For unmodified antibodies or T cell engaging antibodies, 2 half-lives must have elapsed before enrollment. Any toxicity related to prior antibody therapy must be recovered back to baseline.

10. Interleukins, interferons and cytokines (other than hematopoietic growth factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than hematopoietic growth factors).

11. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g., peg-filgrastim) or 7 days for short-acting growth factor.

12. Radiation therapy (RT): 14 days have elapsed for local palliative RT (small port); ≥ 84 days must have elapsed if prior craniospinal RT or if ≥ 50% radiation of pelvis; ≥ 42 days must have elapsed if other substantial bone marrow (BM) radiation.

13. Stem cell infusions:

    1. Participants who have relapsed after allogeneic (non-autologous) BM or stem cell transplant (with or without total body irradiation [TBI]) or boost infusion (any stem cell product; not including donor lymphocyte infusion [DLI]) must be at least 84 days post HSCT and without evidence of graft versus host disease (GVHD) of any severity except: the use of topical steroids for cutaneous GVHD is allowed and stable steroid doses less than or equal to 10 mg of prednisone daily is permitted. Prednisone dose must be adjusted for body surface area (BSA) in young children. Physiologic doses of hydrocortisone for participants with adrenal insufficiency is allowed.
    2. Participants who after relapse and continue to receive cyclosporine, tacrolimus or other agents to treat or prevent either GVHD post BM transplant or organ rejection post-transplant are not eligible for this trial. In the relapse setting, participants must be off medications to treat or prevent either GVHD post BM transplant or organ rejection post-transplant for at least 14 days prior to enrollment. A stable steroid dose as mentioned above is allowed.

14. Cellular therapy: ≥ 30 days after the completion of DLI or any type of cellular Therapy (e.g., modified T cells, NK cells, dendritic cells, etc.).

15. Prior exposure to a different menin inhibitor: Participants who received previous treatment with a different menin inhibitor are allowed to enrol in the study with the exception of those who experienced a severe adverse event attributable to the strong anti-proliferative/pro-differentiation effects of other menin inhibitors (such as severe differentiation syndrome). Participants who experienced a severe adverse event, which can directly be attributed to specific effects (e.g., long QT syndrome) observed with other menin inhibitors can participate in the study if they fulfill the inclusion criteria.

    - Informed consent: Written, signed and dated informed consent and pediatric assent (if applicable) according to local law and legislation should be collected before start of any study procedures.
    - Female participants of childbearing potential must have a negative urine or serum pregnancy test confirmed prior to enrollment.
    - Female participants with infants must agree not to breastfeed their infants while on this study.
    - Contraception:

16. Participants of reproductive potential, starting from menarche and onwards, may not participate unless they have agreed to use a highly effective contraceptive method per Clinical Trial Facilitation Group (CTFG) guidelines for the duration of study therapy and for 6 months after the completion of all study therapy. For further guidance please review the CTFG website.

17. Male participants must use a condom during intercourse and agree not to father a child or donate sperm during therapy and for the duration of study therapy and for 4 months after the completion of all study therapy.

    - Enrollment APAL2020SC trial (US and Canada only): Participants in the US and Canada must have enrolled in the APAL2020SC trial prior to enrollment in the APAL2020K trial.

Exclusion Criteria:

- Participants who in the opinion of the investigator may not be able to comply with the study requirements of the study.
- Participants with Down syndrome.
- Participants with EMD are not eligible. EMD relapse is defined as biopsy proven extramedullary disease without bone marrow disease after documented CR following initial therapy.
- Participants with isolated CNS relapse are not eligible, as well as symptomatic CNS3 disease.
- Participants with acute promyelocytic leukemia (APL) or juvenile myelomonocytic leukemia (JMML).
- Participants with malabsorption syndrome or any other condition that precludes enteral administration of a menin inhibitor.
- Concomitant therapy: Gastric pH has great influence on absorption of ziftomenib; therefore, the use of proton pump inhibitors is prohibited, if necessary H2 Blockers may provide an alternative treatment option.
- Participants who are currently receiving another investigational drug.
- Participants with any known congenital bone marrow failure syndrome.
- Participants with known prior allergy to any of the medications used in protocol therapy.
- Participants with documented active, uncontrolled infection at the time of study entry.
- Active/uncontrolled known human immunodeficiency virus (HIV) infection, hepatitis B virus (HBV) and hepatitis C virus (HCV). Note: HIV testing does not need to be conducted at screening unless it is required per local guidelines or institutional standard.
- Post menarche female participants with positive pregnancy test, and a lactating female participant.
- Participant has a pre-existing disorder predisposing the participant to a serious or life-threatening infection (e.g., cystic fibrosis, congenital or acquired immunodeficiency, bleeding disorder, or cytopenia not related to the leukemia or its treatment).
- Participants must not be receiving other investigational medications (defined as medicinal products not yet approved for any indications, including alternative/herbal therapies) within 30 days of first dose of study drug or while on study.
- Significant congenital cardiovascular disease including, but not limited to conditions such as long QT syndrome, fundamental uncorrected cardiac defect (e.g., coarctation of the aorta) that poses a significant risk to the participant (ventricular septal defect or atrial septal defect are considered non-significant).
- Underlying medical condition that, in the Principal Investigator's opinion, will make the administration of study treatment hazardous or

obscure the interpretation of toxicity determination or AEs.
- For fludarabine and cytarabine: Hypersensitivity to the active substance or to any of the excipients.
- Recent live vaccinations for at least 6 months.

Conditions & Interventions

Interventions:
DRUG: Ziftomenib, DRUG: Cytarabine, DRUG: Fludarabine
Conditions:
Relapsed/Refractory KMT2A-r Acute Leukemia, Relapsed/Refractory NUP98-r Acute Leukemia, Relapsed/Refractory NPM1-m Acute Leukemia
Keywords:
Ziftomenib, Acute leukemia, KMT2A-r, NUP98-r, NPM1-m

More Information

Description:
The primary objective of the study is to determine the recommended phase 2 dose (RP2D) of ziftomenib in combination with chemotherapy (FLA) in children with relapsed or refractory KMT2A-r, NUP98-r, or NPM1-m acute leukemia based on safety and pharmacokinetics (PK).

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