A Study to Find the Highest Dose of Imetelstat in Combination With Fludarabine and Cytarabine for Patients With AML, MDS or JMML That Has Come Back or Does Not Respond to Therapy

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 1 year to 18 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

- Patients must be ≥ 1 year and ≤ 18 years of age at the time of study enrollment
- Patients, with or without down syndrome (DS), and with acute myeloid leukemia, therapy-related AML, MDS or JMML and meet one of the following:
    - Second or greater relapse or refractory AML, including isolated extramedullary disease (EMD), but excluding isolated central nervous system (CNS) or isolated testicular relapse
    - First or greater relapse of MDS
    - First or greater relapse of JMML
- For flow cytometry, it's strongly recommended to enroll onto APAL2020SC or to send samples to Hematologics, Inc. Otherwise, assessments must be performed at a College of American Pathologists (CAP)/Clinical Laboratory Improvement Act (CLIA) certified lab that has expertise in AML.
    - For fluorescence in situ hybridization (FISH)/Karyotype, samples must be sent to a Children's Oncology Group (COG)-approved Cytogenetics Lab
- Bone marrow relapse AML: (patients must meet one of the following criteria to be defined as having relapsed disease)
    - 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 with at least two tests showing ≥ 1% leukemic blasts; examples of tests include:
    - Flow cytometry showing ≥ 1% leukemic blasts by multidimensional flow cytometry (MDF)
    - Karyotypic abnormality with at least one metaphase similar or identical to diagnosis
    - FISH abnormality identical to one present at diagnosis
    - Polymerase chain reaction (PCR) or next generation sequencing (NGS)-based demonstration of leukemogenic lesion identical to diagnosis and ≥ 1%
    - In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy. A complete blood count documenting the presence of at least 1,000/uL (i.e., a white blood cell [WBC] count ≥ 10,000/uL with ≥ 10% blasts or a WBC count of ≥ 5,000/uL with ≥ 20% blasts) circulating leukemic cells (blasts) can also be used if a bone marrow aspirate or biopsy cannot be performed
- Extramedullary relapse: Biopsy proven extramedullary disease after documented complete remission
- Refractory disease AML: Following a re-induction cycle after a second relapse, or refractory to two reinduction attempts after either primary induction failure or first relapse with:
    - 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 with at least two tests showing ≥ 1% leukemic blasts: examples of tests include:
    - Flow cytometry showing ≥ 1% leukemic blasts by multidimensional flow cytometry (MDF)
    - Karyotypic abnormality with at least one metaphase similar or identical to diagnosis.
    - FISH abnormality identical to one present at diagnosis
    - Polymerase chain reaction (PCR) or next generation sequencing (NGS)-based demonstration of leukemogenic lesion identical to diagnosis and ≥ 1%
    - In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy. A complete blood count documenting the presence of at least 1,000/uL (i.e., a WBC count ≥ 10,000/uL with ≥ 10% blasts or a WBC count of ≥ 5,000/uL with ≥ 20% blasts) circulating leukemic cells (blasts) can also be used if a bone marrow aspirate or biopsy cannot be performed
- Extramedullary refractory disease:
    - Biopsy proven persistent extramedullary disease
- In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy. A complete blood count documenting the presence of at least 1,000/ µL (i.e., a WBC count ≥ 10,000/µL with ≥ 10% blasts or a WBC count of ≥ 5,000/µL with ≥ 20% blasts) circulating leukemic cells (blasts) can also be used if a bone marrow aspirate or biopsy cannot be performed
- Central nervous system disease: Patients with relapsed or refractory disease with central nervous system (CNS) 1 and CNS 2 status are eligible
- MDS: Bone marrow relapse: (patients must meet one of the following criteria to be defined as having relapsed disease)

    - A single bone marrow sample showing ≥ 5% leukemic blasts by flow cytometry, FISH, or other molecular method
    - A single bone marrow with at least two tests showing ≥ 1% leukemic blasts; examples of tests include:
    - Flow cytometry showing ≥ 1% leukemic blasts by multidimensional flow cytometry (MDF)
    - Karyotypic abnormality with at least one metaphase similar or identical to diagnosis
    - FISH abnormality identical to one present at diagnosis
    - Polymerase chain reaction (PCR) or next generation sequencing (NGS)-based demonstration of MDS associated lesion identical to diagnosis and ≥ 1%
    - In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy
- JMML: Diagnosis: Patients must have had histologic verification of juvenile myelomonocytic leukemia (JMML) at original diagnosis and currently have relapsed or refractory disease. The diagnosis is made based on the following criteria

    - JMML category 1 (all of the following):
    - Splenomegaly
    - > 1000 (1 x 10^9 /uL) circulating monocytes
    - < 20% Blasts in the bone marrow or peripheral blood
    - Absence of the t(9;22) or BCR/ABL fusion gene
    - The diagnostic criteria must include all features in category 1 and either (i) one of the features in category 2 or (ii) two features from category 3 to make the diagnosis
    - JMML category 2 (at least one of the following if at least two category 3 criteria are not present):
    - Somatic mutation in RAS or PTPN11
    - Clinical diagnosis of NF1 or NF1 gene mutation
    - Homozygous mutation in CBL
    - Monosomy 7
    - JMML category 3 (at least two of the following if no category 2 criteria are met):
    - Circulating myeloid precursors
    - White blood cell count, > 10,000 (10 x 10^9 / uL)
    - Increased hemoglobin F for age
    - Clonal cytogenetic abnormality
    - Granulocyte-macrophage-colony-stimulating factor (GM-CSF) hypersensitivity
- Patients with relapsed JMML must have had at least one cycle of intensive frontline therapy or at least 2 cycles of a deoxyribonucleic acid (DNA) hypomethylating agent with persistence of disease, defined by clinical symptoms or the presence of a clonal abnormality. Frontline therapy is defined as one cycle of intravenous chemotherapy that includes of any of the following agents: fludarabine, cytarabine, or any anthracycline but specifically excludes oral 6-mercaptopurine. Frontline therapy will also include any conditioning regimen as part of a stem cell transplant. Patients who transform to AML at any point with more than 20% blasts are eligible for this trial per the AML specific criteria

- Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life

- Patients must have a performance status corresponding to Eastern Cooperative Oncology Group (ECOG) scores of 0, 1 or 2. Use Karnofsky (≥ 50) for patients > 16 years of age and Lansky for patients ≤ 16 years of age (≥ 50)

- Patients must have fully recovered (grade < 2) from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required time frame, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately

    - NOTE: IT therapy does not require a washout period
- Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive: See DVL homepage on the COG Members site for commercial and investigational agent classifications (https://cogmembers.org/uploadedFiles/Site/Disc/DVL/Documents/TableOfMyelosuppressiveAnti-CancerAgents.pdf). For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned research coordinator prior to enrollment

    - ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea, for patients not receiving standard maintenance therapy. Additionally, patients must have fully recovered from all acute toxic effects of prior therapy
    - Note: Cytoreduction with hydroxyurea must be discontinued ≥ 24 hours prior to the start of protocol therapy
- Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or absolute neutrophil [ANC] counts):

    - ≥ 7 days after the last dose of agent. See the DVL homepage on the COG Members site for commercial and investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned research coordinator prior to enrollment
- Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to grade ≤ 1

- Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur

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

- Stem cell Infusions (with or without total body irradiation [TBI]):

    - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusion (DLI) or boost infusion: ≥ 84 days after infusion and no evidence of graft-versus-host disease (GVHD)
    - Patients must be off calcineurin inhibitors for at least 28 days prior to the date of enrollment. Patients may be on physiological doses of steroids (equivalent to ≤ 10 mg prednisone daily for patients ≥ 18 years or ≤ 10mg/m^2/day [up to a maximum of 10 mg/day] for

patients < 18 years)
    - Autologous stem cell infusion including boost infusion: ≥ 30 days
- Cellular Therapy: ≥ 30 days after the completion of any type of cellular therapy (eg, modified T cells, natural killer [NK] cells, dendritic cells, etc.)
- External Beam Radiation (XRT)/external beam irradiation including protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial bone marrow (BM) radiation
- Radiopharmaceutical therapy (eg, radiolabeled antibody, 131I MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy
- Patients must not have received prior exposure to imetelstat
- For patients with leukemia:
    - Platelet count ≥ 25,000/uL (may receive platelet transfusions). These patients must not be known to be refractory to red cell or platelet transfusion
    - Hemoglobin >= 8.0 g/dL at baseline (may receive red blood cell [RBC] transfusions)
- Adequate renal function defined as:
    - Estimated glomerular filtration rate (GFR) (eGFR) ≥ 70 mL/min/1.73 m^2 OR
    - a 24 hour urine creatinine clearance ≥ 70 mL/min/1.73 m^2 OR
    - a GFR ≥ 70 mL/min/1.73 m^2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard)
- Adequate liver function defined as:
    - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
    - Serum glutamic-pyruvic transaminase (SGPT) (alanine aminotransferase [ALT]) ≤ 3 x ULN, unless attributed to leukemia involvement
    - AST ≤ 3 x ULN, unless attributed to leukemia involvement
    - Albumin ≥ 2 g/dL
- Shortening fraction of ≥ 27% by echocardiogram, or ejection fraction of ≥ 50% by gated radionuclide study

Exclusion Criteria:

- Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, or because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two effective methods of birth control, including a medically accepted barrier or contraceptive method (eg, male or female condom) for the duration of the study. Abstinence is an acceptable method of birth control. Women of childbearing potential must use highly effective contraception in addition to a barrier method during treatment and for at least 1 month after the last dose of imetelstat or longer if required by the institutional guidelines for conventional chemotherapy (fludarabine/cytarabine). Male patients who can father a child should use contraception during treatment and for 3 months after the last dose of imetelstat or longer if required by the institutional guidelines for conventional chemotherapy (fludarabine/cytarabine). Imetelstat should not be administered to nursing mothers
- Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. Patients may be on physiological doses of steroids (equivalent to ≤ 10 mg prednisone daily for patients ≥ 18 years or ≤ 10mg/m^2/day [up to a maximum of 10 mg/day] for patients < 18 years). If used to modify immune adverse events related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid
- Investigational drugs: Patients who are currently receiving another investigational drug are not eligible
- Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible except patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy
- Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial
- Specific to MDS patients: Low-grade MDS/refractory cytopenia of childhood (RCC) - MDS with less than 2% blasts in peripheral blood (PB) or less than 5% blasts in the bone marrow (BM) by morphology
- Uncontrolled seizure disorder that is not stabilized with anti-convulsants
- Patient has undergone surgery that requires general anesthesia within 3 weeks before enrollment (line placement/removal/revision or tissue collection is allowed)
- Known hypersensitivity to the study drug or excipients of the preparation
- Patients with acute promyelocytic leukemia (APL) with PML-RARA genetic abnormality according to World Health Organization (WHO) classification or t(15;17) are not eligible
- Patients known to have a congenital bone marrow failure syndrome where increased risk of toxicity may be expected as judged by the Investigator, for example dyskeratosis congenita, are not eligible
- Patients with isolated or refractory CNS or isolated or refractory testicular relapse are not eligible
- Patients who have an uncontrolled infection are not eligible
- Patients who have received a prior solid organ transplantation are not eligible
- Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible

Conditions & Interventions

Interventions:
PROCEDURE: Biospecimen Collection, PROCEDURE: Bone Marrow Aspiration, PROCEDURE: Bone Marrow Biopsy, DRUG: Cytarabine, PROCEDURE: Echocardiography Test, DRUG: Fludarabine, DRUG: Hydrocortisone Sodium Succinate, BIOLOGICAL: Imetelstat, DRUG: Leucovorin Calcium, PROCEDURE: Lumbar Puncture, DRUG: Methotrexate
Conditions:
Recurrent Childhood Acute Myeloid Leukemia, Recurrent Childhood Myelodysplastic Syndrome, Recurrent Juvenile Myelomonocytic Leukemia, Refractory Childhood Acute Myeloid Leukemia, Refractory Childhood Myelodysplastic Syndrome, Refractory Juvenile Myelomonocytic Leukemia

More Information

Description:
This phase I trial tests the safety, side effects, and best dose of imetelstat in combination with fludarabine and cytarabine in treating patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or juvenile myelomonocytic leukemia (JMML) that has not responded to previous treatment (refractory) or that has come back after a period of improvement (recurrent). Imetelstat may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth. Chemotherapy drugs, such as fludarabine and cytarabine, work in different ways to stop the growth of cancer cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Giving imetelstat in combination with fludarabine and cytarabine may work better in treating patients with refractory or recurrent AML, MDS, and JMML.

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