A Phase I/II Study of Trametinib and Azacitidine for Patients With Newly Diagnosed Juvenile Myelomonocytic Leukemia

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 1 month to 21 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

Age

• Patients must be ≥ 1 month and ≤21 years of age at enrollment.

Diagnosis • Patients must meet the 2022 International Consensus Classification criteria for JMML. The diagnosis is made based on the following criteria:.

Clinical and hematologic features (the first 2 features are present in most cases; the last 2 are required):

- Peripheral blood monocyte count ≥ 1 × 109/L*
- Splenomegaly†
- Blast percentage in PB and BM < 20%
- Absence of BCR::ABL1
    - This monocyte threshold is not reached in approximately 7% of cases. †Splenomegaly is absent in 3% of cases at presentation.

II. Genetic studies (1 finding required):

- Somatic mutation in PTPN11‡ or KRAS‡ or NRAS‡ or RRAS or RRAS2‡
- Clinical diagnosis of neurofibromatosis type 1 or germline NF1 mutation and loss of heterozygosity of NF1 or somatic biallelic loss of NF1
- Germline CBL mutation and loss of heterozygosity of CBL, or somatic mutation(s) in CBL§
    - Germline mutations (indicating Noonan syndrome) need to be excluded. §Occasional cases with heterozygous splice site mutations.

Performance Level

- Karnofsky > 50% for patients ≥ 16 years of age
- Lansky > 50% for patients < 16 years of age.

Prior Therapy

- No prior leukemia directed therapy is permitted with the exception of:

1. Cytoreduction with hydroxyurea can be initiated and continued for up to 24 hours prior to the start of trametinib.
2. Cytoreduction with 6-mercaptopurine (6-MP) 6-MP can be initiated and continued for up to 72 hours prior to the start of trametinib.
3. Intrathecal (IT) cytarabine, IT methotrexate or triple IT therapy (cytarabine, methotrexate and hydrocortisone) within 7 days of enrollment as part of a diagnostic evaluation.

   No prior hematopoietic stem cell transplant is permitted.

   Adequate Renal Function Defined as:
    - Patient must have a calculated creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73m2 OR a normal serum creatinine based on age/gender in the chart below:

Maximum Serum Creatinine (mg/dL):

- 1 month to < 6 months old - Male: 0.4, Female 0.4
- 6 months to <1 year old - Male 0.5, Female 0.5
- 1 to < 2 years old - Male: 0.6, Female: 0.6
- 2 to < 6 years old - Male:0.8, Female: 0.8
- 6 to < 10 years old - Male: 1, Female: 1
- 10 to < 13 years old - Male: 1.2, Female: 1.2
- 13 to < 16 years old - Male: 1.5, Female: 1.4
- ≥ 16 years old - Male: 1.7, Female: 1.4 The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

Adequate Liver Function Defined as:

- Direct bilirubin < 1.5 x upper limit of normal (ULN) for age or normal, AND alanine transaminase (ALT) < 5 x ULN for age.
- The hepatic requirements are waived for patients with known or suspected liver involvement by leukemia and will not be evaluable for

hepatotoxicity. This must be reviewed and approved by the study chair or vice chair.

Adequate Cardiac Function Defined as:

- Ejection fraction of > or = to 50% by echocardiogram, OR
- Ejection fraction of > or = to 50% by radionuclide angiogram (MUGA).

Reproductive Function

- Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed within 2 weeks prior to enrollment.
- Female patients with infants must agree not to breastfeed their infants while on this study.
- Male and female patients of child-bearing potential must agree to use an effective method of contraception approved by the investigator during the study and for a minimum of 6 months after study treatment.

Exclusion Criteria:

- Patients cannot have a known allergy to any of the drugs used in the study.
- Patients cannot have a systemic fungal, bacterial, viral, or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient needs to be off pressors and have negative blood cultures for 48 hours.
- Patients cannot have a plan to administer non-protocol chemotherapy, radiation therapy, or immunotherapy during the study period.
- Patients cannot have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with the protocol treatment or procedures, interfere with consent, study participation, follow up, or interpretation of study results.
- Patients cannot have a clinical or molecular diagnosis of Noonan syndrome. Note: patients with either neurofibromatosis type 1 or Casitas B-lineage lymphoma (CBL) syndrome (also known as Noonan-like syndrome), are eligible to enroll. Patients with Down syndrome are excluded from the study.
- Patient cannot have had prior use of hematopoietic growth factors, biologics (anti-neoplastic agent), or XRT.
- Patients cannot be taking any medications for treatment of left ventricular systolic dysfunction.
- Patients cannot have a history of or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR).
- Patients cannot have had prior use of any MEK inhibitor.

Conditions & Interventions

Interventions:
DRUG: Trametinib, DRUG: Azacitidine, DRUG: Fludarabine, DRUG: Cytarabine
Conditions:
Leukemia, Juvenile Myelomonocytic, JMML, JCML, Neurofibromatosis 1, CBL Syndrome

More Information

Description:
This clinical trial will test the safety and efficacy of combining trametinib and azacitidine in patients with juvenile myelomonocytic leukemia (JMML). Newly diagnosed lower-risk JMML patients will receive trametinib and azacitidine. High-risk JMML patients will receive trametinib, azacitidine, fludarabine, and cytarabine.

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IRB Number:
System ID: NCT05849662