Tagraxofusp in Pediatric Patients With Relapsed or Refractory CD123 Expressing Hematologic Malignancies

Status: RECRUITING

Eligibility Criteria

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

Age

- Patients must be ≥ 1 and ≤21 years of age at the time of study enrollment.

Diagnosis

- Relapsed and/or refractory hematologic malignancy (including, but not limited to, acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplastic syndrome, mixed phenotype acute leukemia, acute undifferentiated leukemia, blastic plasmacytoid dendritic cell neoplasm, Hodgkin lymphoma, and non-Hodgkin lymphoma).
- Tumor cells must demonstrate surface expression of CD123 at the time of enrollment by flow cytometry or immunohistochemistry, as defined by the local institution.

Disease Status:

Monotherapy, Part 1

- Second or greater relapse; or
- Refractory after 2 or more chemotherapy cycles; or
- First relapse after primary chemotherapy-refractory disease; or
- BPDCN in first relapse or refractory after 1 or more chemotherapy cycles

Combination therapy, Part 2

- First or greater relapse; or
- Refractory after 2 or more chemotherapy cycles; or
- BPDCN in first relapse or refractory after 1 or more chemotherapy cycles

For relapsed/refractory leukemia, patients must have:

- >5% blasts in the bone marrow aspirate or biopsy by morphology or flow cytometry
- Patients with 1% - 5% blasts are eligible for Part 2, Cohort C (only), if A single bone marrow sample with flow cytometry and at least one other test (e.g. karyotype, FISH, PCR, or NGS) shows ≥ 1% leukemic blasts and/or flow cytometry demonstrates a stable or rising level of disease on two serial bone marrows.

For relapsed/refractory non-Hodgkin or Hodgkin lymphoma, patients must have:

- Histologic verification of relapse
- Measurable disease documented by radiographic criteria or bone marrow
- Patients in Part 1 may have sites of non-CNS extramedullary disease, but no CNS disease. Patients in Part 2 may have CNS disease and/or other non-CNS extramedullary disease. No cranial irradiation is allowed during the protocol therapy.
- Patients with Down syndrome are eligible to participate in Part 1 only.

Performance Level

- Karnofsky > 50% for patients > 16 years of age and Lansky > 50% for patients ≤ 16 years of age (See Appendix I for Performance Scales). Patients 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.

Prior Therapy

- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy, defined as resolution of all such toxicities to ≤ Grade 2 or lower per the inclusion/exclusion criteria.

Myelosuppressive chemotherapy: Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. At least 14 day must have elapsed since the completion of myelosuppressive therapy. However, individuals may receive any of the following medications within 14 days without a "wash-out period":

- Hydroxyurea: Hydroxyurea can be initiated and/or continued for up to 24 hours prior to the start of protocol therapy.
- "Maintenance-style" therapy: therapy including vincristine (dosed a maximum of one-time weekly), oral 6-mercaptopurine, oral methotrexate (dosed a maximum of one-time weekly), intrathecal therapy (dosed a maximum of one-time weekly) and/or dexamethasone (dosed at ≤3 mg/m2/dose twice daily) or prednisone (dosed at ≤20 mg/m2/dose twice daily) can be continued for up to 24 hours prior to entering the

mg/m2/dose twice daily) or prednisone (dosed at ≤20 mg/m2/dose twice daily) can be continued for up to 24 hours prior to entering the study.
- Hematopoietic stem cell transplant: Patients who have experienced their relapse after a HSCT are eligible, provided they have no evidence of acute or chronic Graft-versus-Host Disease (GVHD) and are at least 100 days post-transplant at the time of enrollment.
- Hematopoietic growth factors: It must have been at least 7 days since the completion of therapy with granulocyte colony stimulating factor (GCSF) or other growth factors at the time of enrollment. It must have been at least 14 days since the completion of therapy with pegfilgrastim (Neulasta®).
- Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. 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. The duration of this interval must be discussed with the study chair.
- Monoclonal antibodies: Maximum of 3 half-lives of the antibody or 21 days (whichever is shorter) must have elapsed after the last dose of monoclonal antibody.
- Immunotherapy: At least 30 days from last infusion of chimeric antigen receptor T cell (CART) therapy or tumor vaccine.
- Radiation Therapy (XRT):

1. ≥ 84 days must have passed, from the end of therapy, if patient received prior total body irradiation (TBI).
2. ≥ 42 days must have passed, from the end of therapy, if patient received craniospinal irradiation (CSI).
3. ≥ 14 days must have passed after whole brain radiotherapy or stereotactic radiation therapy.
4. No washout period is required for:

i. Extramedullary site other than CNS that is a maximum 10 x 10 cm total radiation non-CNS field. If the field is > 10 x 10 cm, a 14-day washout period is required. ii. Local ocular radiotherapy as long as subject has measurable/evaluable disease outside the radiation port.
* Patients that have received other non-tagraxofusp CD123 targeting agents are eligible. Patients that have previously received tagraxofusp are not eligible.

Organ Function Requirements

Adequate Bone Marrow Function Defined as:

- Patients should not be known to be refractory to red blood cell or platelet transfusions.
- Blood counts are not required to be normal prior to enrollment on trial. However, platelet count must be ≥20,000/mm3 to initiate therapy (may receive platelet transfusions).

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 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:

- Total bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x institutional upper limit of normal for age
- SGPT (ALT) and SGOT (AST) must be less than 3x institutional upper limit of normal.
- Serum albumin ≥3.2 g/dL (albumin infusion independent).

Adequate Cardiac Function Defined as:

- Shortening fraction of ≥27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study/echocardiogram.

Adequate Pulmonary Function Defined as:

- Pulse oximetry > 94% on room air (> 90% if at high altitude)
- No evidence of dyspnea at rest and no exercise intolerance.

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 12 weeks after the last dose of tagraxofusp.

Exclusion Criteria

Disease Status:

- Patients with CNS disease are not eligible for Part 1.
- Patients with isolated CNS disease are not eligible for Part 1 or Part 2.
- Patients with isolated non-CNS disease are eligible for Part 1 and Part 2.

Concomitant Medications

- Corticosteroids - Patients receiving corticosteroids for disease control who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible.
- Investigational Drugs - Patients who are currently receiving another investigational drug are not eligible. The definition of "investigational" for use in this protocol means any drug that is not licensed by the FDA, Health Canada or the Therapeutic Goods Administration to be sold in the countries they govern. (United States, Canada and Australia)
- Anti-cancer Agents - Patients who are currently receiving or may receive while on therapy, other anti-cancer agents, radiation therapy or immunotherapy are not eligible [with the exceptions being laid out in the inclusion criteria under 'Prior Therapy']. Intrathecal chemotherapy (at the discretion of the primary oncologist) may be given up to one week prior to the initiation of study treatment (day 1 therapy).
- Anti-GVHD or agents to prevent organ rejection post-transplant - Patients who are receiving cyclosporine, tacrolimus or other agents to prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant are not eligible for this trial. At least 4 weeks must have elapsed after the last dose of GVHD meds.

Infection Criteria - Patients are excluded if they have:

- Positive blood culture within 48 hours of study enrollment;
- Fever above 38.2 within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability.
- A positive fungal culture within 30 days of study enrollment.
- Active fungal, viral, bacterial, or protozoal infection requiring IV treatment. Chronic prophylaxis therapy to prevent infections is allowed.
- Patients will be excluded if they have a known allergy to any of the drugs used in the study.
- Patients will be excluded if they 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 with DNA fragility syndromes (such as Fanconi anemia, Bloom syndrome) are excluded.

Conditions & Interventions

Interventions:
DRUG: Tagraxofusp, DRUG: Fludarabine, DRUG: Cytarabine, DRUG: Dexamethasone, DRUG: Vincristine, DRUG: Azacitidine, DRUG: Methotrexate, DRUG: Cytarabine IT, DRUG: Hydrocortisone
Conditions:
Hematologic Malignancy, AML, ALL, BPDCN, MDS, Lymphoblastic Lymphoma, Lymphoma, B-Cell, Lymphoma, T-Cell, Hodgkin Lymphoma, Mixed Phenotype Acute Leukemia, Acute Undifferentiated Leukemia

More Information

Description:
Tagraxofusp is a protein-drug conjugate consisting of a diphtheria toxin redirected to target CD123 has been approved for treatment in pediatric and adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). This trial aims to examine the safety of this novel agent in pediatric patients with relapsed/refractory hematologic malignancies. The mechanism by which tagraxofusp kills cells is distinct from that of conventional chemotherapy. Tagraxofusp directly targets CD123 that is present on tumor cells, but is expressed at lower or levels or absent on normal hematopoietic stem cells. Tagraxofusp also utilizes a payload that is not cell cycle dependent, making it effective against both highly proliferative tumor cells and also quiescent tumor cells. The rationale for clinical development of tagraxofusp for pediatric patients with hematologic malignancies is based on the ubiquitous and high expression of CD123 on many of these diseases, as well as the highly potent preclinical activity and robust clinical responsiveness in adults observed to date. This trial includes two parts: a monotherapy phase and a combination chemotherapy phase. This design will provide further monotherapy safety data and confirm the FDA approved pediatric dose, as well as provide safety data when combined with chemotherapy. The goal of this study is to improve survival rates in children and young adults with relapsed hematological malignancies, determine the recommended phase 2 dose (RP2D) of tagraxofusp given alone and in combination with chemotherapy, as well as to describe the toxicities, pharmacokinetics, and pharmacodynamic properties of tagraxofusp in pediatric patients. About 54 children and young adults will participate in this study. Patients with Down syndrome will be included in part 1 of the study.

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