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Inutuzumab

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Title	**A phase I/II study of Inotuzumab Ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/refractory Acute Lymphoblastic Leukemia (Study ITCC-059)**
Disease	Stratum 1: relapsed/refractory CD22 positive B-cell precursor (BCP)-ALL Stratum 2: other CD22 positive B-cell malignancies
Type	Phase 1-2, multicenter, international, single-arm, open-label study
Therapy / Study arms	**In stratum 1, the BCP-ALL stratum, three different cohorts of patients are planned:** **Stratum 1A**: To establish the maximum tolerated dose of single agent InO when administered in children with CD22-positive relapsed/refractory BCP-ALL. **Phase 2 cohorte**: To explore the safety and tolerability of InO as a single agent in children with relapsed/refractory other CD22 positive B-cell malignancies. **Stratum 1B**: in this cohort we will determine the recommended phase 2 dose (RP2D) of InO in combination with reinduction chemotherapy using a Rolling-6 design. This cohort will be added to the protocol via an amendment at a later stage. **Stratum 2:** To explore the safety and tolerability of InO as a single agent in children with relapsed/refractory other CD22 positive B-cell malignancies.

Inclusion Criteria	• **Stratum 1A: Diagnosis**: Patients must have either: First relapse of BCP-ALL post allogeneic HSCT; or second or greater relapsed or refractory BCP-ALL, or refractory disease: refractory is defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission, AND must meet the following criteria: • Patients must have M2 or M3 marrow status (≥ 5% blasts by morphology) • The malignant clone needs to be CD22 surface antigen positive (in either the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. • The first 6 patients must have M3 marrow status (≥ 25% blasts by morphology). • **Phase 2 Cohort: Diagnosis**: Patients must have either: First relapse of BCP-ALL post allogeneic HSCT, OR second or greater relapsed or refractory BCP-ALL, OR refractory disease: refractory is defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission. AND must meet the following criteria: • Patients must have M2 or M3 marrow status (≥ 5% blasts by morphology) • The malignant clone needs to be CD22 surface antigen positive (in either the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. • **Stratum 2: Diagnosis**: Patients must have second or greater relapsed or refractory CD22-positive B-cell malignancy including but not limited to diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), Burkitt lymphoma, Burkitt leukemia or B-cell precursor lymphoblastic lymphoma: • There must be histologic verification of disease at original diagnosis or subsequent relapse. • Patient must have evaluable or measurable disease documented by radiographic criteria or bone marrow disease present at study entry. • The malignant cells need to be CD22 surface antigen positive (in either biopsy material, the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory. • **Performance Level and Life Expectancy**: Karnofsky > 60% for patients > 16 years of age and Lansky > 60% for patients ≤ 16 years of age. (See Appendix I for Performance Scales). • Patient must have a life expectancy of at least 6 weeks. • **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 non-hematologic toxicities to ≤ Grade 2 per the CTCAE 4.03 prior to entering this study, with the exception of the authorized laboratory abnormalities as defined in the inclusion/exclusion criteria. • a.Chemotherapy: At least 7 days must have elapsed since the completion of cytotoxic therapy, with the exception of hydroxyurea, 6-mercaptopurine and steroids which are permitted up until 48 hours prior to initiating protocol therapy. Patients may have received intrathecal therapy at any time prior to study entry. Patients who relapse while receiving maintenance chemotherapy will not be required to have a waiting period before enrollment onto this study. • b. Radiotherapy: At least 28 days must have elapsed since any prior radiation therapy. • c. Hematopoietic Stem Cell Transplant: At least 180 days must have elapsed since previous allo-HSCT. Patient must have no evidence of active graft vs. host disease. Patient must not be receiving GVHD prophylaxis or treatment. • d. Hematopoietic growth factors: At least 7 days must have elapsed since the

completion of therapy with GCSF or other growth factors at the time of enrollment. At least 14 days must have elapsed since the completion of therapy with pegfilgrastim (Neulasta®).

- e. Immunotherapy: At least 42 days must have elapsed after the completion of any type of immunotherapy, e.g. tumor vaccines or chimeric antigen receptor T cell (CART) therapy. Patients may not have received prior CD22-targeted therapy (immunotoxin or CART therapy).
- f. Monoclonal antibodies: At least 3 half-lives of the antibody must have elapsed after the last dose of a monoclonal antibody (ie: Rituximab = 66 days, Epratuzumab = 69 days), with the exclusion of blinatumomab. Patients must have been off blinatumomab infusion for at least 14 days and all drug-related toxicity must have resolved to grade 2 or lower as outlined in the inclusion and exclusion criteria.
- g. Investigational drugs: At least 7 days or 5 drug half-lives (whichever is longer) must have elapsed since prior treatment with any experimental drug (with the exception of monoclonal antibodies) under investigation. No residual toxicities should be observed following previous treatment. An experimental drug is defined as any drug that is not approved and licensed for sale by the FDA for institutions in the United States, by the EMA for institutions in Europe, by Health Canada for institutions in Canada and by The Therapeutic Goods Administration for institutions in Australia.
- h. Prior calicheamicin exposure: Patient has not received prior treatment with a calicheamicin-conjugated antibody (e.g. gemtuzumab ozogamicin).
- **Renal and Hepatic Function**: Patient's serum creatinine must be ≤ 1.5 x institutional upper limit of normal (ULN) according to age. If the serum creatinine is greater than 1.5 times normal, the patient must have a radioisotope GFR ≥ 70mL/min/1.73m2. Patient's AST and ALT must be ≤ 2.5 x institutional ULN. Patient's total bilirubin must be ≤ 1.5 x institutional ULN unless the patient has documented Gilbert syndrome, and AST and ALT are 2.5 x ULN.
- **Cardiac Function**: Patient must have a shortening fraction ≥ 30% by echocardiogram or an ejection fraction > 50% by MUGA.
- **Reproductive Function**: Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed 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 highly effective method of contraception approved by the investigator during the study and for 90 days after the last dose of InO. Highly effective methods of contraception include (but not exclusively) the following contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), sexual abstinence.

Exclusion Criteria	• **Isolated extramedullary relapse**: Patients with isolated extramedullary disease are excluded (not applicable to lymphoma patients except for isolated CNS-relapse) • **VOD/SOS**: Patients with any history of prior or ongoing VOD/SOS per the modified Seattle criteria are excluded, as specified in appendix 3, or prior liver-failure [defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5)]. • **Infection**: Patients will be excluded if they 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 may not have: A requirement for vasopressors; 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 or oral treatment. Chronic crophylaxis therapy to prevent infections is allowed. • **Other anti-cancer therapy**: Patients will be excluded if there is a plan to administer non-protocol anti-cancer therapy including but not limited to chemotherapy, radiation therapy, or immunotherapy during the study period. • **Allergic reaction**: Patients with prior Grade 3/4 allergic reaction to a monoclonal antibody are excluded. • **Concurrent disease**: Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with protocol therapy, interfere with consent, study participation, follow up, or interpretation of study results. • Children with Down syndrome are excluded from participation in the dose finding part (stratum 1A), but not in the stratum 1 phase 2 cohort.
Status	Start 2018
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