SWOG 1905: A Phase II Study of Akr1c3-Activated Prodrug Obi‐3424 (Obi-3424) In Patients with Relapsed/Refractory T‐Cell Acute Lymphoblastic Leukemia (T-All)/T-Cell Lymphoblastic Lymphoma (T-Lbl)

ELIGIBILITY CRITERIA

5.1 Disease Related Criteria

a. Patients must have a diagnosis of relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) based on WHO classification. Patients with relapsed/refractory T-cell lymphoblastic lymphoma are eligible if lymphoblasts are $\geq$ 5% in the bone marrow or in the peripheral blood.

b. Patients must have evidence of acute leukemia in their peripheral blood or bone marrow. Patients must have $\geq$ 5% lymphoblasts in the peripheral blood or bone marrow within 14 days prior to registration. Patients with only extramedullary disease are not eligible.

c. Patients must be refractory to or have relapsed following a standard induction chemotherapy. A standard chemotherapy induction regimen is defined as any program of treatment that includes: (1) vincristine and corticosteroids plus at least one more chemotherapy agent, (2) cytarabine and anthracycline, or (3) high dose cytarabine (defined as at least 1 gr/m2 per individual dose unless adjustments were required for renal/liver function).

d. Patients must have no evidence of central nervous system disease within 28 days prior to registration based on CSF studies. Patients with clinical signs or symptoms consistent with CNS involvement must have a lumbar puncture which is negative for CNS involvement; the lumbar puncture must be completed within 28 days prior to registration. The Steinherz/blyer Algorithm will be used to interpret CNS involvement in the presence of circulating blasts in the peripheral blood.

Steinherz/Bleyer algorithm method of evaluating traumatic lumbar punctures:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains $\geq$ 5 WBC/ μ L and blasts, the following algorithm should be used to distinguish between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2\times \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

e. Note that the patients may receive intrathecal chemotherapy with the initial lumbar puncture; see Section 7.1a.4.

5.2 Prior/Concurrent Therapy Criteria

a. Prior nelarabine therapy is not required. In addition, patients who receive nelarabine during initial induction or post-remission treatment are eligible only if the physician does not feel they would benefit from other, multi-agent chemotherapy.

b. Patients must not have had chemotherapy or investigational agents within 14 days prior to registration except for steroids, oral 6-mercaptopurine, oral methotrexate, vincristine, intrathecal chemotherapy, or hydroxyurea. See Section 7.4 for pretreatment discontinuation instructions. For participants who have received radiation therapy, at least 7 days must have elapsed from the end of radiation prior to registration and participants must not currently be experiencing toxicities from radiation therapy.

c. Patients must not have undergone allogeneic hematopoietic transplant within 90 days prior to registration.

d. Patients must have no evidence of ≥ Grade 2 acute graft versus host disease (GVHD) or moderate or severe limited chronic GVHD and must have no history of extensive GVHD of any severity within 90 days prior to registration. Patients posttransplant must be off calcineurin inhibitors for at least 21 days to be eligible. Extensive GVHD is defined as 1) generalized skin involvement or 2) localized skin involvement and/or hepatic dysfunction plus liver histology or cirrhosis or involvement of eye or minor salivary organ or oral mucosa or any other target organ. See Section 18.4 for the Global severity scoring.

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have a Zubrod Performance Status of 0 - 3 (see Section 10.11).

c. Patients must not have systemic fungal, bacterial, viral or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) within 14 days prior to registration.

d. Patients must have creatinine clearance > 30 mL/min within 14 days prior to registration according to the Cockcroft Gault equation.

$$*CCr = \frac{\{(140 - \text{age}) \times \text{weight (kg)}\} \times (0.85 \text{ (if female)})}{(72 \times \text{Serum Creatinine (mg/dL)})}$$

e. Patients must have direct bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) within 14 days prior to registration.

f. Patients must have AST and ALT $\leq$ 3.0 x institutional ULN or $\leq$ 5.0 x ULN (if thought to be related to leukemic involvement) within 14 days prior to registration.

g. Patients must have the following tests within 14 days prior to registration to obtain baseline measurements. The results do not determine eligibility:

- PT/PTT (or a PTT)/Fibrinogen (as clinically indicated).
- From Comprehensive Metabolic Panel: sodium, potassium, chloride, CO2, and BUN.

h. Patients with known human immunodeficiency virus (HIV)-infection are eligible providing they are on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test within 6 months prior to registration. (HIV viral load testing is required only for patients with known HIV infection.) Patients must not be receiving antiviral therapies that are known strong inhibitors or inducers of CYP3A4.

i. Patients with evidence of chronic hepatitis B virus (HBV) infection may be eligible provided that they have an undetectable HBV viral load within 28 days prior to registration. Patients may be currently receiving HBV treatment. (HBV viral load testing is required only for patients with known HBV infection.) Patients must not be receiving antiviral therapies that are known strong inhibitors or inducers of CYP3A4.

j. Patients with known history of hepatitis C virus (HCV) infection may be eligible provided that they have an undetectable HCV viral load within in 28 days prior to registration. Patients may be currently receiving treatment. (HCV viral load testing is required only for patients with known HCV infection.) Patients must not be receiving antiviral therapies that are known strong inhibitors or inducers of CYP3A4.

k. Patients must not have a known history of prolonged QTcF (interval > 450 msec for males; > 470 msec for females).

l. Patients must not be pregnant or nursing due to the teratogenic potential of the drug used on this study. Females of reproductive potential must have a negative serum pregnancy test within 14 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method during and up to 6 months after treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

m. Patients must not have other active malignancies for which they have received treatments within 6 months prior to registration excluding localized malignancies that do not

require systemic treatment.

5.4 Specimen Submission Criteria

a. Patients must agree to have bone marrow and blood specimens submitted for MRD testing as outlined in Section 15.2.

b. Patients must be offered the opportunity to participate in specimen banking. With patient consent, residuals from specimens submitted per Section 15.2 will be retained and banked for future research.

SCHEMA

Patients receive AKR1C3-activated prodrug OBI-3424 intravenously (IV) over 30 minutes on days 1 and 8. Treatment repeats every 21 days for up to 17 cycles in the absence of disease progression or unacceptable toxicity.

The maximum tolerated dose (MTD) of OBI-3424 was determined to be 12 mg/m^2. Please refer to Section 7.2.a of the protocol for treatment instructions.