COG-ANHL2121: Phase 2 Study of Tovorafenib (DAY101) in Relapsed and Refractory Langerhans Cell Histiocytosis

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

___2. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.**
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section.

___3. Laboratory Studies
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy* if > 7 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT), albumin, and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies
Clinical studies (e.g., cardiac imaging, pulmonary function tests, bilateral BMA/BX and CSF analysis), if applicable, must be obtained within 28 days prior to enrollment and start of protocol therapy (repeat if necessary). Disease/Staging Imaging Disease/staging imaging studies, if applicable, must be obtained within 28 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

Disease/Staging Imaging
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___4. Age
180 days- <22 years (at time of study enrollment).

___5. Diagnosis

Patients with multifocal progressive, relapsed, or recurrent LCH with measurable disease at study entry.

- Patients must have had histologic verification of LCH (from either original diagnosis or relapse/progression) at the time of study entry.
  - Tissue confirmation of relapse is recommended but not required.
  - Pathology report must be submitted for central confirmation of diagnosis within 7 days of enrollment.
  - FFPE blocks or unstained slides (initial diagnosis and/or subsequent biopsies) will be required for retrospective central confirmation of diagnosis and molecular studies.
  - Patients with mixed histiocytic disorders (e.g., LCH with juvenile xanthogranuloma) may be included.
- Patients must have measurable disease, documented by radiographic imaging (LCH- specific response criteria, See Section 10.0).
- Patients must have progressive or refractory disease or experience relapse after at least one previous systemic chemotherapy treatment strategy.
- Pathogenic somatic mutation detected in genes encoding tyrosine kinase receptors (*CSFR1*, *ERBB3* or *ALK*), RAS or RAF (may be from original or subsequent biopsy or peripheral blood/bone marrow aspirate). Clinical mutation reports may include quantitative PCR (e.g., BRAFV600E) and/or Sanger or Next Generation sequencing. Immunohistochemistry (e.g., VE1 antibody for BRAFV600E) alone is not sufficient.

___6. Participant must be able to take an enteral dose and formulation of medication. Study medication is only available as an oral suspension or tablet, which may be taken by mouth or other enteral route such as nasogastric, jejunostomy, or gastric tube.

___7. Performance Level

Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50% for patients ≤ 16 years of age.

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See "Performance Status Scales Scoring".

___8. Prior Therapy

- Myelosuppressive chemotherapy: Patients must not have received within 14 days of entry onto this study.
- Investigational agent or any other anticancer therapy not defined above: Patients must not have received any investigational agent for at least 14 days prior to planned start of tovorafenib (DAY101).
- Radiation therapy (RT): Patient must not have received RT within 2 weeks after the last dose fraction of RT.
- Patients must have fully recovered from any prior surgery.
- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy with toxicities reduced to Grade 1 or less ((CTCAE) version 5.0).

___9. Concomitant Medications Restrictions

- Steroids: <0.5 mg/kg/day of prednisone equivalent (maximum _20_mg/day) averaged during the month prior to study enrollment is permissible but must be discontinued fourteen (14) days prior to study enrollment. Patients with documented brain lesions receiving corticosteroids for management of cerebral edema must be on a stable dose for fourteen (14) days prior to study enrollment.
- Strong **inducers** or **inhibitors** of CYP2C8 are prohibited for 14 days before the first dose of tovorafenib (DAY101) and from planned administration for the duration of study participation. See Appendix VII and Section 4.1.7 for list of agents.
- Medications that are breast cancer resistant protein (BCRP) substrates that have a narrow therapeutic index are prohibited for 14 days before the first dose of tovorafenib (DAY101) and for the duration of study participation (See Appendix VII for a list of agents).
  Please see Section 4.1.7 for the concomitant therapy restrictions for patients during treatment.

___10. Organ Function Requirements

- Adequate Bone Marrow Function Defined As:
  - Peripheral absolute neutrophil count (ANC) ≥ 750/µL unless secondary to bone marrow involvement; in such cases bone marrow involvement must be documented.
  - Platelet count ≥ 75,000/µL (unsupported/without transfusion within the past 7 days).
  - Patients with marrow disease must have platelet count of ≥ 75,000/µL (transfusion support allowed) and must not be refractory to platelet transfusions. Bone marrow involvement must be documented.
  - Hemoglobin ≥ 8 g/dL (unsupported/without transfusion within the past 7 days). Patients with marrow disease must have hemoglobin ≥ 8 g/dL (transfusion support allowed). Bone marrow involvement must be documented.
  - Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g., Neulasta®) or 7 days for short-acting growth factor
- Adequate Renal Function Defined As:
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR child length and stature data published by the CDC.

OR - a 24 hour urine Creatinine clearance ≥ 50 mL/min/1.73 m^2

OR - a GFR ≥ 50 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).

Note: Estimated GFR (eGFR) from serum creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

- Adequate Liver Function Defined As:
  - Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
  - ALT ≤ 3 x ULN for age.
  - Serum albumin ≥ 2 g/dl
  - For patients with liver disease caused by their histiocytic disorder (as evaluated on radiographic imaging or biopsy): Patients may be enrolled with abnormal bilirubin, AST, ALT, and albumin with documentation of histiocytic liver disease.
- Adequate Cardiac Function Defined As:
  - Fractional shortening (FS) of ≥ 25% or ejection fraction of > 50%, as determined by echocardiography or multigated acquisition scan (MUGA) within 28 days prior to study enrollment. Depending on institutional standard, either FS or left ventricular ejection fraction (LVEF) is adequate for enrollment if only one value is measured; if both values are measured, then both values must meet criteria above
- Adequate Pulmonary Function Defined As:
  No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination; unless it is due to underlying pulmonary LCH 3.2.7.6

- Central Nervous System Function Defined As:
  - Patients with seizure disorder may be enrolled if well controlled.
  - CNS toxicity ≤ Grade 2
- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial unless antiretroviral therapy interacts with the metabolism of tovorafenib (DAY101) and cannot safely be changed to antivirals that do not interact with study medication.

The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix V.

EXCLUSION CRITERIA:

___1. LCH arising along with other hematologic malignancy (e.g., mixed LCH with acute lymphoblastic leukemia) or any history of non-histiocytic malignancy.

___2. Disease scenarios as below will be excluded
- Skin-limited disease
- Single bone lesion
- GI tract involvement only (those that have disease that can be determined by endoscopic biopsies only)
- LCH-associated neurodegeneration (LCH-ND) without parenchymal lesions or other systemic lesions

___3. Patients with activating mutations in MAP2K1 are not eligible for this study due to drug target specificity. Mutation status will be submitted to study team within 7 days of enrollment.

___4. <u>Prior Therapy</u>
Patient must not have received any prior MAPK pathway inhibitor therapy.

___5. Exclusions for other illness
- Refractory nausea and vomiting, malabsorption, or external biliary shunt that would preclude adequate absorption of tovorafenib (DAY101).
- Uncontrolled systemic bacterial, viral, or fungal infection.
- Major surgical procedure or significant traumatic injury within 14 days prior to study enrollment, or anticipation of need for major surgical procedure during the course of the study. Placement of a vascular access device or minor surgery is permitted within fourteen (14) days of study enrollment (provided that the wound has healed).
- History of significant bowel resection that would preclude adequate absorption or other significant malabsorptive disease.
- Ophthalmologic considerations: Patients with known significant ophthalmologic conditions or known risk factors for retinal vein occlusion (RVO) or central serous retinopathy (CSR) are not eligible.
- History of solid organ or hematopoietic bone marrow transplantation
- Clinically significant active cardiovascular disease, or history of myocardial infarction, or deep vein thrombosis/pulmonary embolism within 6 months prior to enrollment, ongoing cardiomyopathy, or current prolonged QT interval > 440 ms based on triplicate ECG average.
- History of Grade ≥ 2 CNS hemorrhage or history of any CNS hemorrhage within 28 days of study entry.
- History of any drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome or Stevens Johnsons syndrome (SJS) or who are allergic to tovorafenib (DAY101) or any of its components.
- CTCAE V. 5.0 Grade 3 symptomatic CPK elevation (> 5 x ULN).

___6. Pregnancy and Breastfeeding
- Female patients who are pregnant are ineligible. A pregnancy test is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants are ineligible.
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation are ineligible. Participants (male and female) who are sexually active must use two forms of an acceptable method of birth control (for men, one form must be a barrier method) from start of therapy through 180 days following last dose of tovorafenib (DAY101).

REQUIRED OBSERVATIONS:

Required Observations – Tovorafenib (DAY101) Monotherapy Cycle 1

All baseline studies (a-t below) must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam with vital signs
b. Height, weight, and BSA
c. Performance Status
d. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment. Serum or urine hCG both acceptable.
e. CBC, differential and platelets
f. AST, ALT, Albumin, Bilirubin, ALP (alkaline phosphatase)
g. Electrolytes, BUN, Creatinine, Ca^{++}, PO_4, Mg^{++}
h. Creatinine Phosphokinase (CPK)
i. Serum and urine osmolality, urinalysis
j. ECG
k. MUGA or ECHO
l. *BRAF V600E* qPCR blood (Only required for those with known lesional *BRAF V600E* mutation).
m. Lumbar puncture, Cerebrospinal Fluid (CSF) for protein, glucose, cytology, document opening pressure (Only required for patients with confirmed or suspected neurodegenerative disease, confirmed or suspected pituitary involvement and/or CNS mass lesions (parenchymal lesions or invasion of dura).
n. Bilateral bone marrow biopsy and aspirate (Only required for patients < 2 years of age, patients with known or suspected risk organ involvement (liver, spleen, bone marrow), or patients with unexplained cytopenias. Aspirate and biopsy may be done within 28 days of enrollment and start of protocol therapy
o. BRAF qPCR bone marrow. Only required for patients receiving a bone marrow biopsy/aspirate per n above and with known LCH lesion tissue BRAFV600E positivity.
p. Tumor disease evaluation. Combined whole body FDG-PET/CT or diagnostic CT neck/abdomen pelvis along with a PDG-PET scan for patients at baseline. Organ specific imaging based on patient's sites of disease should be performed.
q. Dermatologic examination. Required at baseline and subsequent assessments as symptom directed. Baseline and subsequent (if performed) should be performed by the investigator and/or a dermatologist.
r. Neurologic examination with Scale for Assessment and Rating of Ataxia (SARA) See Appendix IX. Only required for patients with CNS lesions and/or neurodegeneration.
s. Ophthalmologic examination. Should include slit lamp examination for corneal/lens abnormalities, fundus examination with comment on retinal abnormalities and visual acuity testing.
t. Research blood (Optional). See Section 7.2.
u. TSH. Baseline only. If TSH is abnormal, T3 and free T4 should be evaluated.
v. PK Samples. See Section 16.0.

TREATMENT PLAN:

Dose Confirmation

Up to 12 patients will first be enrolled using the Rolling 6 design and observed for safety of tovorafenib (DAY101) in this population. If there are < 2 DLTs in 6 subjects treated at these doses (Dose Level 1) during the first 2 cycles of therapy, these will be considered the RP2Ds, and all subsequent patients will be enrolled at these doses. If 6 patients tolerate the RP2D (Dose level 1 or –1), then the Phase 2 study cohort will be initiated. Patients for the Phase 2 study may be included for analysis at the RP2D from the dose-finding cohort.

Please refer to Section 5.0 for evaluations of toxicities known to be associated with MAPK inhibitors. Additionally, all toxicities will be graded by the NCI Common Toxicity Criteria (CTCAE) Version 5.0. All Grade 3 and above will be collected. Toxicities will be considered DLT as specified in Section 5.2. If ≥ 2 DLTs are observed in the first 6 subjects, then the –1 dose level(s) will be studied in a new cohort (Table 4). Refer to Section 5.0 for dose modifications.

Table 4: DAY101 dose levels

Dose Level	Tovorafenib (DAY101)	# Events to change
1*	420 mg/m^2 (max 600 mg/dose)	≥ 2 of 6
-1	350 mg/m^2 (max 500 mg/dose)	≥ 2 of 6; stop

*Starting dose level

Drug Administration

Treatment Schedule Table	
Days 1-28	Once weekly, on Days 1, 8, 15, 22
Day 28	End of Cycle

A cycle of therapy is considered to be 28 days

At Dose Level 1, tovorafenib (DAY101) is administered as an oral tablet or reconstituted liquid suspension at 420 mg/m^2 /dose enterally once weekly (not to exceed 600 mg/dose). If using tablets, doses should be rounded to the nearest 100 mg tablet. Patients with BSA < 0.84 m^2 should receive suspension formulation. Patients with BSA ≥ 0.84 m^2 may receive tablet or suspension formulation (if unable to swallow tablets). Refer to Appendix VI for Dosing Nomograms.

Therapy may continue for up to a total of 12 cycles provided the patient meets the criteria for starting subsequent cycles and does not meet any of the criteria for removal from protocol therapy.

Treatment compliance

The study diary will be completed by the patient, or patient's parent or legal guardian, for every dose of study drug administered starting at Cycle 1 Day 1 (C1D1). The Investigator or study coordinator should review diary entries for compliance, in particular for any potential missed doses. Patients will return the pill diary to clinic at the start of every cycle.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

Submission of Scans for Central Review:
Pre-Treatment, PET/CT, CT, and MRI
Also see Section 17.6.1

Response Criteria:
Response and progression will be evaluated using RECIST criteria.
Also see Section 10.2 and Appendix X

SPECIMEN REQUIREMENTS:
Diagnosis Confirmation
The pathology report will be required to submit for central confirmation of diagnosis within 7 days of enrollment.

SPECIMENS TO SUBMIT FOR RETROSPECTIVE CENTRAL PATHOLOGY REVIEW

List of Specimen Types

Materials must be submitted for retrospective pathology review from either tumor biopsy at original diagnosis and/or time of relapse (if applicable). If possible, please submit the following materials to the COG Biopathology Center (BPC):

1. 1 to 2 representative blocks. If blocks are unavailable, submit the following:
    a. 1 H&E
    b. 15 unstained plus-charged slides. Sections should be cut on positively charged slides (Superfrost® Plus, slide will have + at the bottom). Do not bake slides.
    c. 15 unstained uncharged slides from non-decal block. Sections should be cut on non-charged slides (Superfrost® and Colorfrost®; will not have + at the bottom). Do not bake slides.
2. 1 H&E slide from each available block.

Also see Section 14.2.

BIOLOGY REQUIREMENTS:
Optional Blood in EDTA, Marrow in EDTA, CSF.
Also see Section 15.0