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FROM: Juvianee Ibrahim Estrada-Veras, M.D. National Human Genome Research Institute, 10 Center Drive Building Ten Room 3-2551 Bethesda, MD 20892-1851

SUBJECT: A Phase 2 Therapeutic Trial of the Use of Dabrafenib and Trametinib in Patients with BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease. NIH Clinical Center and NHGRI local number: 15-HG-0006.

TO: Kathleen Brewer, President ECD Global Alliance.

The following is to inform you that the NIH Clinical Center, CTEP-NCI, GSK, NHGRI and FDA have reviewed and approved the proposal titled **"A Phase 2 Therapeutic Trial of the Use of Dabrafenib and Trametinib in Patients with BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease"**

This study has a ceiling of 18 patients aged 18yrs-80yrs, male and female with ECD and BRAF V600E confirmed mutation. Patients will have to go through a series of screenings prior to acceptance to the trial and must have been off therapy for at least 4 weeks prior to baseline visit to the NIH Clinical Center.

Below is the clinicaltrials.gov link for the trial:

https://clinicaltrials.gov/ct2/show/NCT02281734?term=erdheim&rank=3

Below is a list of inclusion and exclusion criteria that all patients must meet:

Inclusion Criteria:

- All patients will be previously or simultaneously enrolled in the natural history ECD protocol #11-HG-0207, "Clinical and Basic Investigations into Erdheim Chester disease"; eligible patients must have been diagnosed with Erdheim Chester disease, confirmed by pathological evaluation of the affected tissue with adequate staining; affected tissue must harbor the BRAF V600E or V600K mutation
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >= 20 mm with conventional techniques or as >= 10 mm with spiral CT scan, MRI, or calipers by clinical exam

- Prior treatment, involving interferon, anakinra, imatinib, steroids, chemotherapy with, but not limited to cladribine, vinblastine, 6-mercaptopurine and etoposide, or other medications used empirically for the treatment of ECD, will be acceptable; these therapies should have been completed and discontinued 4 weeks or more prior to enrollment in this study
- Eastern Cooperative Oncology Group (ECOG) performance status =< 2 (Karnofsky >= 60%)
- Life expectancy of greater than 3 months
- Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels
- Patients must have BRAFV600E or BRAFV600K mutations, identified by a Food and Drug Administration (FDA)-approved test at a Clinical Laboratory Improvement Amendments (CLIA)-certified lab; if test at CLIA-certified lab used a non-FDA approved method, information about the assay must be provided; (FDA approved tests for BRAF V600 mutations in melanoma include: THxID BRAF Detection Kit and Cobas 4800 BRAF V600 Mutation Test)
- Absolute neutrophil count (ANC) >= 1.2 x 10^9/L
- Hemoglobin >= 9 g/dL
- Platelets >= 100 x 10^9/L
- Albumin >= 2.5 g/dL
- Serum bilirubin =< 1.5 x institutional upper limit of normal (ULN) except subjects with known Gilbert's syndrome
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) =< 2.5 x institutional ULN
- Serum creatinine =< 1.5 mg/dL OR calculated creatinine clearance (Cockcroft-Gault formula) >= 50 mL/min
- Prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) =< 1.3 x institutional ULN; subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization
- Left ventricular ejection fraction >= institutional lower limit of normal (LLN) by echocardiogram (ECHO)
- Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration or randomization

- Women of child-bearing potential must agree to use adequate contraception (barrier method of birth control, or abstinence; hormonal contraception is not allowed) for the duration of study participation, and for at least 2 weeks after treatment with dabrafenib or for 4 months after dabrafenib in combination with trametinib; should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately

- Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR by the site; exposure may be decreased due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR; consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate; prophylactic low dose warfarin may be given to maintain central catheter patency

- Ability to understand and the willingness to sign a written informed consent document

Exclusion Criteria:

- Inability to provide informed consent

- Prior systemic anti-cancer therapy (chemotherapy with delayed toxicity, extensive radiation therapy, immunotherapy, biologic therapy, or vaccine therapy) within the last 3 weeks; chemotherapy regimens without delayed toxicity within the last 2 weeks preceding the first dose of study treatment

- Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of study treatment and during the study; patients that have used other BRAF or mitogen-activated protein kinase kinase (MEK) inhibitor are excluded

- Current use of a prohibited medication; patients receiving any medications or substances that are strong inhibitors or inducers of cytochrome P450, family 3, subfamily A (CYP3A) or cytochrome P450, family 2, subfamily C, polypeptide 8 (CYP2C8) are ineligible; current use of, or intended ongoing treatment with: herbal remedies (e.g., St. John's wort), or strong inhibitors or inducers of P-glycoprotein (Pgp) or breast cancer resistance protein 1 (Bcrp1) should also be excluded

- Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) grade 2 or higher from previous anti-cancer therapy, except alopecia, at the time of randomization

- Human immunodeficiency virus (HIV)-positive patients on combination antiretroviral therapy are ineligible

- A history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (with the exception of cleared HBV and HCV infection, which will be allowed)

- Presence of malignancy other than the study indication under this trial within 5 years of study enrollment
- Patients with history of rat sarcoma (RAS) mutation-positive tumors are not eligible regardless of interval from the current study; note: prospective RAS testing is not required; however, if the results of previous RAS testing are known, they must be used in assessing eligibility
- Leptomeningeal or brain metastases or metastases causing spinal cord compression that are symptomatic or untreated or not stable for >= 3 months (must be documented by imaging) or requiring corticosteroids; subjects on a stable dose of corticosteroids > 1 month or who have been off of corticosteroids for at least 2 weeks can be enrolled with approval of the Cancer Therapy Evaluation Program (CTEP) medical monitor; subjects must also be off of enzyme-inducing anticonvulsants for > 4 weeks
- History or evidence of cardiovascular risks, except stable ECD cardiac lesion, including any of the following:
    - QT interval corrected for heart rate using the Bazett's formula (QTcB) >= 480 msec
    - History of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within the past 24 weeks prior to randomization
    - History or evidence of current class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
    - Intra-cardiac defibrillators
    - Abnormal cardiac valve morphology (>= grade 2) documented by ECHO; (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study); subjects with moderate valvular thickening should not be entered on study
    - History or evidence of current clinically significant uncontrolled cardiac arrhythmias; clarification; subjects with atrial fibrillation controlled for > 30 days prior to dosing are eligible
    - Treatment refractory hypertension defined as a blood pressure of systolic > 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO)
- Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures

- Pregnant women are excluded from this study; breastfeeding should be discontinued prior to treatment with dabrafenib/trametinib
- History of retinal vein occlusion (RVO)
- Interstitial lung disease or pneumonitis not secondary to ECD
- Central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or visible pathology (e.g., evidence of optic disc cupping, evidence of new visual field defects on automated perimetry, or intraocular pressure > 21 mmHg as measured by tonography) as assessed by ophthalmic examination
- Inability to travel to the National Institutes of Health (NIH) Clinical Center
- Patients with wild type BRAF gene molecular results on ECD affected tissue
- Patients with confirmed diagnosis of ECD that are asymptomatic and with no visceral involvement are not eligible for this trial (patients with no target lesions as per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria

Interested patients can contact me OR Kevin O'Brien NP for further information. We will encourage the patients to involve their doctors as well since we will have to have close communication with their medical team. We will need medical records for those patients unknown to us, but not as extensive as with the natural history protocol. A detailed summary written by their doctor can be used as referral and base line history, though physician referral is not needed, patients can self-refer and have more info from us. We will need a true and updated medications list, since there are certain medications that will exclude the patients from the trial due to known side effects and interactions.

There is more information available upon request. Logistical and administrative matters will be the same as with the natural history study.

Thank you and if any questions, please contact me.

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