KPCRTF State Funded Projects Reporting Template

University of Louisville
Eflornithine/DFMO as Maintenance Therapy for SHH Pathway
Program Director: Dr. Michael Huang

Reporting Period: April 1, 2021 to June 30, 2021

Below please provide a brief summary of the status of the Project listed as well as for each Objective listed below. Include any barriers, how and if they were overcome, and successes achieved.

Please provide a short overall summary of the status of your project here.

Whereas the initial application for state grant funding was for a Phase 1 relapsed or refractory medulloblastoma study, the initial collaboration with the pharmaceutical company Cancer Prevention Pharmaceuticals has since been abandoned. In its stead, this project was adopted in mid-March 2019 by the Beat Childhood Cancer (BCC) consortium in its initial intended iteration to use DFMO in a Phase 2 setting as a maintenance strategy for molecular high risk medulloblastoma. The only major revisions were: 1) the addition of a third cohort for relapsed medulloblastoma patients who have achieved a second complete remission status, and 2) the addition of cancer stem cell and circulating tumor DNA as biomarkers for disease burden and treatment response.

The significant expansion of the trial from a single institution to 30 participating BCC sites, from a single cohort of patients with a limited number of subjects (N=15) to 3 patient cohorts with a total number of subjects of 120, and from an expected accrual period of 2 years to now 4 to 5 years has expectantly resulted in delays in moving the study forward, largely owing to insufficient funding to support a now large trial. After discussion with the KPCRTF board at the meeting on July 23, 2019, we requested and received approval for reallocation of the existing UofL FY2018-2020 budget in the amount of $28,000, which covered the following costs to jump start the BCC016 trial: 1) research salary effort for the primary investigator, and 2) site initiation costs for the lead site (Norton Children's Cancer Institute) and BCC home institution (Atrium Health). We also applied for and received state grant funding for a project extension for FY20-22 to cover the first 2 years of the study.

The COVID pandemic and BCC's move from Michigan State in Grand Rapid, MI to Atrium Health also contributed to further delays. The BCC016 study protocol was approved by the FDA, central and local IRB (WIRB) as of December 2020, and has been assigned the ClinicalTrials.gov identifier NCT04696029 and posted online in early January 2021. The study has now opened at 3 of an initial planned 15 sites: 1) Levine Children's Hospital/Atrium Health in Charlotte, NC, 2) Norton Children's Cancer Institute, and 3) St. Joseph's Children's Hospital in Tampa, FL. To date, two patients have been enrolled and another are being screened for enrollment. Of note, the first patient was enrolled mid-March 2021.

Primary Objective: Evaluate the maximum tolerated dose (MTD) of Difluoromethylornithine (DFMO) as a single agent in patients with relapsed or refractory Sonic Hedgehog (Shh) activated, Group 3 or other Myc-amplified medulloblastoma.

Please provide a brief summary of the status of this objective here as well as the other objectives below. The objectives that you provided in your last progress report should be included under the appropriate objective listed here as these are the objectives that are listed in your contract.

As this project has been completely revamped from a phase I to a phase II trial, unfortunately, the listed project title as well as primary and secondary objectives herein are null and void. Please refer to the Phase 2 DFMO project for updated primary and secondary objectives.

Secondary Objectives:

1. ***Verify peak serum concentrations (Cmax), time at max drug concentration (Tmax), and Area under the Curve (AUC) in medulloblastoma patients after administration of DFMO. Serum will be collected at hours 0, 0.5, 1, 3 and 6 hours of first dose administration.***

2. ***Document Cerebrospinal Fluid (CSF) and urine concentrations after DFMO administration. CSF will be collected at hour 24 following first dose administration. Urine polyamine measurements to be obtained at baseline and weekly for 3 total measurements after starting DFMO.***

3. ***Determine overall response rate (complete responses + partial responses + stable disease) in relapsed/refractory Shh activated, Group 3 or other MYC-amplified medulloblastoma after receiving DFMO for up to 13 cycles. Complete response (CR) is defined by the disappearance of all lesions whereas partial response (PR) is defined by a greater than 30% decrease in tumor size.***

Deliverables (check when completed)	**Month 1-3**	**Month 4-6**	**Month 7-9**	**Month 10-12**	**Month 13-15**	**Month 16-18**	**Month 19-21**	**Month 22-24**	**√**
Describe the disease status analysis including brain and spine MR imaging at 3-month intervals while receiving the study drug and until 2 years from end of treatment									

Unfortunately, the deliverable listed herein is null and void. Please refer to the Phase 2 DFMO Project for accurate, updated information.

Reports should be returned to:
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