

SCHEMA

This is a Phase I and Phase II study for children with pediatric low-grade glioma who have a molecularly-confirmed diagnosis that is recurrent or progressive.

Pediatric low-grade gliomas (pLGGs) comprise a heterogeneous group of grades I and II tumors that collectively represent the most common central nervous system tumors in children. Though response to initial chemotherapy therapy is good (25-50%), it may be short-lived, requiring the use of multiple therapies over many years. Radiation therapy while effective, is associated with high morbidity, including neurocognitive, endocrine, visual, and auditory deficits, vasculopathy, and secondary tumors.

Tumor biology plays a role in the clinical behavior of pLGGs, which harbor a variety of genetic aberrations leading to activation of the mitogen-activated protein kinase (MAPK) pathway. The most common MAPK-activating alterations are BRAF fusion/tandem duplication, present in 70-95% of pilocytic astrocytomas (PAs), and BRAF V600E mutations, found in 17% of all pLGGs and 75% and 50% of pleomorphic xanthoastrocytomas (PXAs) and gangliogliomas (GGs), respectively. Independent of histological subtype, extent of resection, or therapy, BRAF V600E negatively impacts the outcome of patients with pLGG.

Clinical development of RAF inhibitors (RAF_i) such as Dabrafenib has dramatically altered clinical management of BRAF V600E-driven tumors, including melanoma, papillary craniopharyngioma, multiple myeloma, Langerhans cell histiocytosis, and astrocytoma. Similarly, MEK inhibitors (MEK_i), such as trametinib have demonstrated strong clinical utility in BRAF fusion and wild type (WT) tumors which likely have other MAPK activating aberrations).

Hydroxychloroquine (HCQ; Plaquenil) is FDA-approved for treatment of malaria, systemic and discoid lupus, and rheumatoid arthritis (including use in children and adolescents). HCQ deacidifies lysosomes, inhibiting the last step in autophagy, which causes cells reliant on autophagy to increase the generation of autophagosomes and undergo either apoptotic or non-apoptotic cell death. Evidence in mouse models and human cancer cell lines suggest HCQ may have significant anti-tumor activity by inhibiting autophagy induced by cancer therapy.

In this phase I/II study, we will investigate the safety and efficacy of dabrafenib + trametinib + HCQ (D+T+HCQ) and trametinib + HCQ (T+HCQ) in pediatric and young adult patients with BRAF-altered or NF1-associated gliomas who have previously received a RAF and/or MEK inhibitor. The goal of this study is to optimize the clinical effect of dabrafenib and trametinib by addressing intrinsic and acquired resistance that is well-described in V600E-mutant melanoma and for which early preclinical and clinical evidence exists in pediatric gliomas. Aside from overlapping skin toxicity of dabrafenib and trametinib, which preliminarily does not appear worse in the D+T combination in adults and children, potential for ocular toxicity, which has been observed with each agent as monotherapy, will require close monitoring. An important outcome of this study will be improved understanding of resistance mechanisms and the role of autophagy in BRAF-altered or NF1-associated gliomas through sequencing of pre- and post-RAF_i or MEK_i tumor (when available) and measurement of autophagy inhibition in PBMCs throughout protocol therapy.

Phase I:

The primary objective of the Phase I component is to estimate the maximum tolerated doses (MTD) and recommended Phase II doses (RP2D) of D+T+HCQ and T+HCQ in children and young adults with recurrent or progressive glioma treated with prior RAF and/or MEK inhibitor therapy.

Patients with BRAF V600E LGG or HGG will receive the combination of D+T+HCQ given orally in the form of capsules which must be taken whole, or an oral solution made from tablets. Hydroxychloroquine will only be administered by oral suspension. Within each combination, Dabrafenib and Hydroxychloroquine will be administered twice a day in a 28-day course. Trametinib will be administered once a day for 28 days during each course. One course is equivalent to 28 days. Therapy with either combination may continue for up to 2 years (26 courses) in the absence of disease progression or unacceptable toxicity.

BRAF V600E LGG or HGG (Stratum 1)

Dose Level	Dabrafenib + Trametinib	Hydroxychloroquine
1*	<u>Dabrafenib</u> (max 300 mg/day div BID) Age ≥12 years: 4.5 mg/kg/day div BID Age <12 years: 5.25 mg/kg/day div BID <u>Trametinib</u> (max 2 mg/day) Age ≥6 years: 0.025 mg/kg once daily Age <6 years: 0.032 mg/kg once daily	8 mg/kg/day div BID (max 600 mg/day div BID)
2		15 mg/kg/day div BID (max 1000 mg/day div BID)
3		20 mg/kg/day div BID (max 1200 mg/day div BID)
*Starting dose		

BRAF fusion/duplication or NF1- associated LGG (Stratum 2)

Dose Level	Trametinib	Hydroxychloroquine
1*	Age ≥6 years: 0.025 mg/kg once daily (max 2mg) Age <6 years: 0.032 mg/kg once daily (max 2mg)	8 mg/kg/day div BID (max 600 mg/day div BID)
2		15 mg/kg/day div BID (max 1000 mg/day div BID)
3		20 mg/kg/day div BID (max 1200 mg div BID)
*Starting dose		

Phase II

Potential patients for the Phase II portion of the trial must provide the following for central review for screening prior to enrollment. The required prior treatment scans include (1) prior targeted MEK/RAF therapy baseline, (2) prior MEK/RAF therapy best response, (3) scan at off treatment, and if different from off treatment (4) scan documenting PD associated with prior MEK/RAF targeted therapy. Additional scans may be requested from the site if the required eligibility assessments cannot be completed based on these minimal imaging requirements.

In the Phase II portion of the trial, patients will continue to receive either the D +T+HCQ or T+HCQ combination at the RP2D defined in the Phase I portion. All drugs will be given continuously without a break unless required for excess toxicity. For Phase I subjects who are treated at the MTD a similar review will take place retrospectively to determine whether the patients meet the criteria to be included in the Phase II cohort.

OBJECTIVES

Primary Objectives Phase I

- To estimate the maximum tolerated doses (MTD) and recommended Phase II doses (RP2D) of dabrafenib + trametinib + hydroxychloroquine (D+T+HCQ) and T+HCQ in children and young adults with recurrent or progressive glioma treated with prior RAF and/or MEK inhibitor therapy.
- To characterize the pharmacokinetics of D+T+HCQ and T+HCQ in children with recurrent or progressive glioma.

Primary Objectives Phase II

- To assess the sustained objective response rate (ORR) of recurrent/progressive BRAF V600E LGG/HGG to D+T+HCQ, and BRAF fusion/duplication positive or NF1-associated LGG to T+HCQ, respectively, at the combination RP2D in children and young adults who previously did not respond (achieved < PR) or who progressed on RAF and/or MEK inhibitor therapy.

Secondary Objectives Phase I

- To define the toxicity profile and define the DLTs of D+T+HCQ or T+HCQ in children with recurrent or progressive glioma

Secondary Objectives Phase II

- To estimate progression free survival (PFS) distributions of patients receiving D+T+HCQ or T+HCQ at the RP2D who are stratified by WHO grade and NF status and who previously had suboptimal response to RAF and/or MEK inhibitor

Exploratory Objectives

- To describe the response rate of recurrent or progressive BRAF-altered gliomas to protocol therapy in the context of a phase I trial
- To explore the pharmacogenetic polymorphisms in D, T, and HCQ metabolizing enzymes and transporters and relate these polymorphisms to D, T, and HCQ

pharmacokinetics.

- To assess visual outcomes of children with tumors involving the visual pathway using Teller acuity cards, HOTV (if developmentally able to perform), and visual field assessment
- To assess the association between clinical outcomes (e.g. PFS and response) and apparent diffusion coefficient (ADC) histogram metrics as measured using MR diffusion imaging in children and young adults with BRAF V600E-mutant recurrent or progressive gliomas undergoing treatment with dabrafenib, trametinib, and hydroxychloroquine (HCQ) and BRAF fusion/duplication-positive or NF1-associated recurrent or progressive gliomas undergoing treatment with trametinib and HCQ.
- To assess autophagy inhibition by evaluating:
 - accumulation of LC3II and p62 in PBMCs by Western blot analysis
 - accumulation of autophagic vesicles in PBMCs by electron microscopy
 - levels of IL-8, IL-1 Beta, LIF, DKK3, and FAM3C in plasma by ELISA1
- To assess archival tumor tissue for MAPK pathway aberrations (other than BRAF) using WES and RNASeq
- To explore markers of resistance to RAF or MEK inhibition by performing WES and RNASeq on archival tumor tissue from diagnosis and/or relapse after single-agent RAFi, or single-agent MEKi, or combination RAFi/MEKi inhibitor therapy
- To evaluate mutant allele frequency of BRAF V600E (ctDNA) in plasma (and CSF if clinically appropriate) from patients receiving D+T+HCQ and to describe the correlation between BRAFV00E ctDNA and tumor response

PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within three weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

Screening

- Phase II patients who are candidates for enrollment must complete a release of medical information to provide previous Brain and/or Spine MRIs for central review as well as limited dated related to their prior treatment. The required prior treatment scans for central review include (1) prior targeted MEK/RAF therapy baseline, (2) prior MEK/RAF therapy best response, (3) scan at off treatment, and if different from off treatment (4) scan documenting PD associated with prior MEK/RAF targeted therapy. Additional scans may be requested from the site if the required eligibility assessments cannot be completed based on these minimal imaging requirements.
 - Data related to prior treatment should include agent names of prior MEK/RAF treatment, start and end dates of prior therapy and date of progression while on or following MEK/RAF treatment and reason for ending treatment.
- Phase I patients will have these same images and associated prior MEK/RAF treatment data reviewed retrospectively to determine if they will be eligible for inclusion in the Phase II cohort.

Eligibility Criteria for Enrollment

Inclusion Criteria

➤ Tumor/Diagnosis

Patients must have one of the following histologies with molecularly-confirmed diagnosis that is recurrent or progressive. Patients enrolled will be stratified as follows:

Phase I:

- Stratum 1 LGG or HGG with BRAF V600E/D/K mutation
- Stratum 2 LGG with BRAF duplication or fusion with any partner or LGG with Neurofibromatosis Type 1

Phase II:

- Stratum 3 LGG with BRAF V600E/D/K mutation
- Stratum 4 HGG with BRAF V600E/D/K mutation
- Stratum 5 LGG with BRAF duplication or fusion with any partner
- Stratum 6 LGG with Neurofibromatosis Type 1

BRAF alterations will be locally determined using molecular methods in a CLIA-certified laboratory. Immunohistochemistry for BRAF V600E alone is not adequate and must be confirmed molecularly.

➤ Age

Patient must be ≥ 1 but ≤ 30 years of age at the time of enrollment.

➤ Disease Status

Phase II patients must have bi-dimensionally measurable disease defined as at least one lesion that can be accurately measured in at least two planes. A target lesion should be chosen.

➤ **Weight Restrictions**

Patients are required to have weight ≥ 9 kg to enroll on any stratum in the Phase I or Phase II.

Phase I only

Patients enrolled on the 8 mg/kg/day (dose level 1) must have a weight < 90 kg.

Patients enrolled on the 15 mg/kg/day (dose level 2) must have a weight < 80 kg.

Patients enrolled on the 20 mg/kg/day (dose level 3) must have a weight < 68 kg.

➤ **Prior Therapy**

Patients must have received prior therapy other than surgery and must have fully recovered from the acute treatment related toxicities (defined as \leq Grade 1) of all prior chemotherapy, immunotherapy, radiotherapy or any other treatment modality prior to entering this study.

- Prior RAF and/or MEK inhibitor Therapy

Only applicable to LGG patients on Phase I and all patients on Phase II

Patients must have received prior RAF and/or MEK inhibitor therapy and meet one of the following criteria:

- Did not experience an objective response (defined as $< PR$)

OR

- Achieved an objective response (CR or PR) but progressed while on active therapy

HGG patients on Phase I: may be enrolled regardless of prior MEK /RAF treatment.

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- Relevant imaging

Imaging must be available for central review to confirm eligibility for LGG patients on the Phase I study and all patients on the Phase II study.

- Patients with HGG on the phase I study do not require central imaging review for eligibility.
- Patients with LGG on the Phase I study will not require real-time central imaging review, but imaging must be available for retrospective review in case eligible to be considered enrolled at the RP2D and may be counted as part of the phase II study

- Chemotherapy

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea.

- Biologic or investigational agent (anti-neoplastic):

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment. For biologic agents with a prolonged half-life, at least three half-lives must have elapsed prior to enrollment.

- Monoclonal antibody treatment and agents with known prolonged half-lives:

At least three half-lives must have elapsed prior to enrollment.

- Radiation

Patients must have had their last fraction of:

- Craniospinal irradiation, whole brain radiation, total body irradiation or radiation to $\geq 50\%$ of pelvis or spine ≥ 6 weeks (42 days) prior to enrollment.
- Focal irradiation ≥ 14 days prior to enrollment.

➤ Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 7 days prior to enrollment. A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of enrollment.
- Patients with seizure disorders may be enrolled if seizures are controlled. Patients may take non-enzyme inducing anti-epileptic medications, such as felbamate, valproic acid, gabapentin, lamotrigine, tiagabine, topiramate, zonisamide, or levetiracetam.
- Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to enrollment.

➤ Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 7 days of enrollment must be ≥ 50 .

- Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for assessing the performance score.

➤ Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count $\geq 1.0 \times 10^9$ cells/ L
- Platelets $\geq 100 \times 10^9$ cells/ L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin ≥ 8 g/dl (may receive transfusions)
- Total bilirubin ≤ 1.5 times institutional upper limit of normal (ULN)
- ALT(SGPT) < 3 x institutional upper limit of normal (ULN)
- Albumin ≥ 3 g/dl
- Serum creatinine based on age/gender as noted in Table 3. Patients that do not meet these criteria but have a 24-hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m² are eligible.

Table 3:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

➤ Cardiac Function:

- Left Ventricular Ejection Fraction greater than the institutional lower limit of normal by echo (while not receiving medications for cardiac function)
- QTc \leq 480 msec

➤ Pregnancy

Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

➤ Pregnancy Prevention

Females of child-bearing potential must use a highly effective method of contraception during dosing of study treatment and for 16 weeks after stopping study medication. Effective contraception methods include:

- Total abstinence. Periodic abstinence and withdrawal are not acceptable methods of contraception
- Placement of a non-hormonal intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).
Note: Hormonal-based methods (e.g., oral contraceptives) are not permitted as contraception due to potential drug-drug interactions with dabrafenib and there is a possibility of decreased efficacy of hormonal contraceptives.
- Sexually active males must use a condom during intercourse while on study and for 16 weeks after stopping study treatment and agree not to father a child during this period.

➤ Informed Consent

The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

Exclusion Criteria

➤ Breast-feeding females

Breast-feeding women are excluded from this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies.

➤ Concurrent Illness

Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results:

- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational

regimen are eligible for this trial. Patients with NF1 and history of plexiform neurofibroma will be permitted to enroll.

- Patients with a previously documented retinal vein occlusion or severe retinopathy.
- Presence of active GI disease or other condition (e.g., small bowel or large bowel resection) that will interfere significantly with the absorption of drugs.

➤ Concomitant Medications

- Patients who are unable to discontinue prohibited medications or herbal preparations within 7 days of enrollment and 14 days of starting study therapy.
- Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.

➤ Allergy

Patients with a history of a known hypersensitivity to dabrafenib, trametinib, HCQ, or any of their excipients or compounds of similar chemical or biologic composition.

➤ Prisoners

Prisoners will be excluded from this study.

➤ Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.